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Gap Detection Measured with Electrically-Evoked Auditory Event-Related Potentials and Speech Perception Abilities in Children with Auditory Neuropathy Spectrum Disorder

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Abstract

Objective—This study aimed 1) to investigate the feasibility of recording the electrically evoked auditory event-related potential (eERP), including the onset P1-N1-P2 complex and the electrically evoked auditory change complex (EACC) in response to temporal gaps, in children with auditory neuropathy spectrum disorder (ANSD); and 2) to evaluate the relationship between these measures and speech perception abilities in these subjects.

Design—Fifteen ANSD children who are Cochlear Nucleus device users participated in this study. For each subject, the speech processor microphone was bypassed and the eERPs were elicited by direct stimulation of one mid-array electrode (electrode 12). The stimulus was a train of biphasic current pulses 800 ms in duration. Two basic stimulation conditions were used to elicit the eERP. In the *no-gap condition*, the entire pulse train was delivered uninterrupted to electrode 12, and the onset P1-N1-P2 complex was measured relative to the stimulus onset. In the *gapped condition*, the stimulus consisted of two pulse train bursts, each being 400 ms in duration, presented sequentially on the same electrode and separated by one of five gaps (i.e. 5, 10, 20, 50, and 100 ms). Open-set speech perception ability of these subjects with ANSD was assessed using the Phonetically Balanced Kindergarten (PBK) word lists presented at 60 dB SPL using monitored live voice in a sound booth.

Results—The eERPs were recorded from all subjects with ANSD who participated in this study. There were no significant differences in test-retest reliability, root mean squared (RMS) amplitude or P1 latency for the onset P1-N1-P2 complex between subjects with good (> 70% correct on PBK words) and poorer speech-perception performance. In general, the EACC showed less mature morphological characteristics than the onset P1-N1-P2 response recorded from the same subject. There was a robust correlation between the PBK word scores and the EACC thresholds for gap detection. Subjects with poorer speech-perception performance showed larger EACC thresholds in this study.

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Conclusions—These results demonstrate the feasibility of recording eERPs from implanted children with ANSD using direct electrical stimulation. Temporal processing deficits, as demonstrated by large EACC thresholds for gap detection, might account in part for the poor speech-perception performances observed in a subgroup of implanted subjects with ANSD. This finding suggests that the EACC elicited by changes in temporal continuity (i.e. gap) holds promise as a predictor of speech perception ability among implanted children with ANSD.

Keywords

Auditory Neuropathy Spectrum Disorder; Auditory cortical evoked potential; electrical stimulation; speech perception

INTRODUCTION

Auditory neuropathy spectrum disorder (ANSD) is a form of a hearing impairment characterized by normal hair cell functions as indicated by cochlear microphonics (CMs) and/or otoacoustic emissions (OAEs) and absent or grossly abnormal auditory brainstem responses (ABRs). Patients with ANSD often have difficulty hearing in noise, demonstrate fluctuating hearing sensitivity, and exhibit speech perception abilities that are disproportionately poor relative to the severity of hearing loss as measured by pure tone audiometry (Rance et al., 2005). Although the site of lesion and underlying pathological mechanisms are yet to be determined for any individual patient with ANSD, it is generally believed that the abnormal neural transmission is likely to result from disruptions in the phase locking ability of the peripheral auditory neurons, and/or prolonged neural conduction time (Starr et al., 1996, 2003). As a consequence, patients with ANSD often demonstrate significant auditory processing deficits for temporal cues (Starr et al., 1991; Berlin et al., 1993; Starr et al., 1996; Hood, 1999; Zeng et al., 1999; Kraus et al., 2000; Rance et al., 2004; Zeng et al., 2005). For example, temporal resolution is referred to as the ability of the auditory system to detect changes in stimuli over time. It can be evaluated by measuring how well the listener can identify a silent interval embedded within a stimulus (i.e. gap detection). It has been shown that gap detection thresholds are similar between normal-hearing (NH) subjects and cochlear implant (CI) users with sensorineural hearing loss (e.g. Shannon, 1989, 1992). By contrast, subjects with ANSD have larger gap detection thresholds than NH subjects (Michalewski et al., 2005; Zeng et al., 1999, 2001, 2005; Starr et al., 2008), probably due to a temporally smeared neural representation of the gap caused by desynchronized neural discharge and/or conduction of the auditory nerve (Zeng et al., 2005). Results of several studies have shown that the severity of these temporal processing deficits strongly correlates with speech perception abilities in patients with ANSD (Starr et al., 1991; Zeng et al., 1999; Zeng et al., 2001; Rance et al., 2004; Zeng et al., 2005).

The auditory event-related potentials (ERP), including the onset P1-N1-P2 complex and the acoustic change complex (ACC), are cortically generated potentials that can be recorded from surface electrodes placed on the scalp. The onset P1-N1-P2 complex is typically evoked by a brief stimulus and its presence indicates sound detection. The ACC is elicited by stimulus change(s) that occur within an ongoing, long-duration stimulation. The ACC provides evidence of discrimination capacity across various stimulus dimensions at the level of the auditory cortex (Martin et al., 2008).

The onset P1-N1-P2 complex shows age-dependent morphological changes due to maturations of the central auditory system (Kraus et al., 1993; Ponton et al., 1996, 2000; Wunderlich et al., 2006). In normal-hearing adults the complex consists of three response peaks occurring in sequence: P1, N1 and P2. In infants and young children, the onset response is dominated by a large positive peak (P1) with a latency of approximately 100 ms,

followed by a broad negativity (N2). When mature, the P1 latency is typically around 50 ms and the N1 and P2 latencies are typically around 100 and 150 ms, respectively. The time for the first appearance of the N1 varies with stimulation rate due to neural refractoriness. The N1 can be observed in children between 7 and 9 years of age with a stimulation rate of 0.5 Hz or higher (Gilley et al., 2005; Ponton et al., 2000; Wunderlich et al., 2006) and in younger children using slower rates (Ceponiene et al., 1998; Sharma et al., 1997). Maturation of the ACC response has been investigated in normal-hearing children by Jeon et al. (2011). Their results show that the ACC demonstrates age-dependent morphological changes similar to those observed for the onset P1-N1-P2 complex. However, compared to the onset response, the N1 peak of the ACC appears at an older age.

Despite an absent or grossly abnormal ABR, the onset P1-N1-P2 complex and the ACC have been successfully recorded from patients with ANSD in response to acoustic stimulation (Dimitrijevic et al., 2011; Sharma et al., 2011; Michalewski et al., 2005, 2009; Narne and Vanaja, 2008; Rance et al, 2002; Kraus et al., 2000). In these studies, the onset P1-N1-P2 complex showed a better morphology (Sharma et a., 2011; Rance et al., 2002), larger peak amplitude (Narne and Vanaja, 2008; Sharma et al., 2011), and shorter P1 latency (Narne and Vanaja, 2008; Sharma et al., 2011) in individuals with good speech perception performance when compared to responses recorded from patients with poor speech perception performance. Moreover, the N1 latency of the ACC correlated with speech perception scores and gap detection thresholds in patients with ANSD (Dimitrijevic et al., 2011; Michalewski et al., 2009). Differences in the observed ERP response characteristics between good and poor performers are presumably related to the degree of neural dys-synchronization induced by the various pathological insults. Overall, results of these studies suggest that ERPs might be a promising tool for predicting speech perception performance among patients with ANSD.

Cochlear implantation (CI) has been used as a treatment for patients with ANSD who demonstrate limited benefit from conventional amplification. Whereas many implanted children with ANSD receive substantial benefit from their devices (Teagle et al., 2010; Buss et al., 2002; Shallop et al., 2001; Madden et al., 2002; Mason et al., 2003), a sub-group of implanted children fails to show significant improvement in speech perception performance despite prolonged experience (Teagle et al., 2010; Gibson and Sanli, 2007; Miyamoto et al., 1999; Rance et al., 1999). The mechanism responsible for the wide range of speech perception abilities observed among implanted patients with ANSD remains to be determined. In theory, the electrical stimulation provided by a CI could improve neural synchronization along auditory pathways in patients with ANSD. This assumption is supported by results from several studies showing that the electrically evoked ABR (EABR) responses can be recorded from some patients with ANSD (Runge-Samuelson et al., 2008; Walton et al., 2008; Mason et al., 2003; Buss et al., 2002; Sininger and Trautwein, 2002). However, these EABRs demonstrate a wide range of response characteristics, which might reflect various degrees of neural synchronization induced by electrical stimulation in these patients. In addition, it has been shown that the EABR cannot be recorded from a subgroup of patients with ANSD even with electrical stimulation (McMahon et al., 2008). Therefore, it is possible that electrical stimulation might not provide enough neural synchronization to adequately convey speech cues in patients with abnormal or absent EABRs. As a consequence, it is reasonable to expect that the electrically evoked onset P1-N1-P2 complex recorded from this subgroup of patients with ANSD may show different response characteristics from those recorded from patients who receive substantial benefit from their devices. In addition, this subgroup of patients should still have temporal resolution deficits even after cochlear implantation, which can be objectively measured using the electrically evoked ACC (EACC) in response to temporal gaps. However, it remains unknown whether these electrically evoked ERPs (eERPs) can be recorded from pediatric patients with ANSD

who are CI users. In addition, the relationship between the temporal resolution capacities as indicated by the EACC measure and the open-set speech perception skill has not been systematically investigated in patients with ANSD after cochlear implantation.

The purpose of this study was twofold: 1) to investigate the feasibility of measuring the electrically evoked onset P1-N1-P2 complex and the EACC in response to temporal gaps in pediatric subjects with ANSD who show a range of speech perception performance; and 2) to explore the association between temporal acuity, as measured by the EACC, and speech perception performance.

MATERIALS AND METHODS

Subjects

Fifteen pediatric subjects with ANSD (S1 – S15) ranging in age between 5.3 to 17.2 yrs (mean: 9.0 yrs, SD: 3.4 yrs) participated in this study. All subjects were diagnosed with ANSD based on the presence of a CM (+/− OAEs) with absent ABRs None of the subjects in this study had any anatomical labyrinthine malformations or cochlear nerve deficiencies based on results of high-resolution computed tomography (CT) or magnetic resonance imaging (MRI). In addition, none of these subjects had any known cognitive or neurological conditions that might affect central auditory processing. Full electrode insertions were achieved in the test ear for all subjects. Robust electrically evoked compound action potentials (ECAPs) were recorded from at least five electrodes across the electrode array during intra-operative testing in all subjects except for S15. Four subjects were implanted unilaterally (S6, S7, S8, and S15); all others had sequential bilateral cochlear implantation. The first implanted ear was tested for all bilaterally implanted subjects except for S14. Subject S14 received an Advanced Bionics device (Valencia, CA) in her right ear at age 5.0 yrs and received a Nucleus 24RE in her left ear at age 15.6 yrs. Only data from her left ear are included. It should be noted that with her Advanced Bionics device only, S14 obtained scores of 20% correct on phonetically balanced kindergarten (PBK) words presented at 60 dB SPL live voice after more than 12 years of device use. Each subject had been using his/her Cochlear Nucleus device in the test ear for at least 12 mos prior to testing. For 13 subjects with ANSD, English is the only language used in their families. Two subjects (S2 and S9) were learning English as their primary language in school and used a combination of English and Spanish at home. Detailed demographic information for these subjects is listed in Table 1.

All subjects were recruited from the Pediatric Cochlear Implant Clinic of the Carolina Children's Communicative Disorders Program. All subjects and/or their legal guardians provided written consents to the procedures as approved by the University of North Carolina at Chapel Hill Human Subjects Institutional Review Board. All subjects were paid for participating in this study.

General Procedures

The study protocol included open-set speech perception tests and electrophysiological measures. These two tests were undertaken in different sessions scheduled on the same day.

Speech Perception Tests—PBK word lists were used to assess open-set speech perception abilities. The stimuli (25 monosyllabic words) were presented using monitored live-voice at 60 dB SPL through a loudspeaker placed at 0° azimuth in a single-walled sound attenuating booth. Live-voice presentations were necessary for some children to complete the tests due to their young age and/or relatively short attention span. Tests were administered in an auditory-only condition using preferred CI settings; for bilateral implant

subjects, each ear was tested separately. Experienced audiologist phonetically scored the child's response and no corrections for known articulation errors were made. Only scores for the ear that was also used for the eERP measures were included in this study.

Electrophysiological Measures—In this study, the speech processor microphone was bypassed and the electrical stimulus delivered directly to a single electrode using a Nucleus Implant Communicator (NIC) library of subroutines. This technique was originally described by Brown et al. (2008). Compared with presenting the stimulus in the sound field, this technique allows better stimulus control and less contamination from stimulus artifact, which simplifies interpretation of results.

Stimuli: The stimulus was a train of biphasic pulses with a duration of 800 ms and an interstimulus interval of 1200 ms. Individual pulses were 25 μs/phase with an interphase interval of 8 μs. Biphasic pulses were presented at a rate of 1000 pulses per second (pps). The pulse train was presented in a monopolar stimulation mode (MP1) for all subjects. It was presented directly to a mid-array electrode (electrode 12) using NIC routines at the maximum comfortable level that was measured for each subject. There were two stimulation conditions. In the *no-gap condition*, the 800-ms biphasic pulse train was delivered to electrode 12 without any interruption. In the *gapped condition*, a temporal gap (silent interval) was inserted after 400 ms of stimulation. Five gap durations were tested in this study (5, 10, 20, 50, and 100 ms). The presentation order of stimulation condition was randomized across subjects. Figure 1 shows schematic illustrations of the two stimulating conditions. The upper panel shows the *no-gap condition*. The lower panel shows an EACC stimulus with a 100-ms temporal gap.

eERP Recordings: All subjects were tested in a sound-treated booth while seated in a reclining chair and watching a silent movie with captions. Subjects were instructed to ignore the sound that they heard and to remain as quiet and still as possible. Breaks were provided as necessary to ensure that they were able to comply with these instructions. Each evoked potential recording session took approximately two hours to complete.

Electroencephalographic (EEG) activity was recorded using a Neuroscan system (version 4.4) and a SynAmp 2 amplifier. Disposable, sterile Ag-AgCl surface recording electrodes were placed at the high forehead (Fz), the low forehead (Fpz), and the contralateral mastoid. The EEG was recorded differentially between Fz and the contralateral mastoid with Fpz serving as the ground. Eye movements were monitored using a pair of recording electrodes placed above and below the eye that was contralateral to the CI. Electrode impedances were maintained below 5000 Ohms with an inter-electrode impedance difference of less than 2000 Ohms. The recording window included a 100 ms pre-stimulus baseline and a 2000 ms post-stimulus time. During acquisition, the EEG was digitized at a sampling rate of 1000 Hz, amplified with a gain of X10, and analog band-pass filtered on-line between 0.1-100 Hz (12 dB/octave). Any EEG epochs containing amplitudes exceeding ±100 μV were rejected from averaging. Each response represented the average of 100 artifact-free epochs. For each subject, two responses were recorded for each stimulating condition, and these two replicates were averaged together. Each subject, therefore, generated 6 averaged responses (no-gap, 5-, 10-, 20-, 50-, and 100-ms gaps). These averaged responses were baseline corrected, digitally filtered between 1-30 Hz (12 dB/octave) offline using custom MATLAB software, and smoothed using a 40-ms wide boxcar filter before response analysis.

Data Analysis

Two experienced researchers who were blind to subject identification and stimulation condition independently evaluated responses. For each subject, two replicates were plotted

along with the averaged responses of these replicates for each stimulation condition. Waveform identification for the onset and the EACC was based on peak latency, waveform morphology, and the replicable property of neural responses. Responses were determined to be absent if two replicates recorded for the same stimulation condition were not repeatable regardless of morphology of the averaged response. Grand mean averages were computed for each stimulating condition and used to determine the latency ranges for which the onset P1-N1-P2 complex and the EACC were measured. The windows for the onset P1-N1-P2 and the EACC response were from 20 to 215 ms and from 450 to 640 ms relative to the stimulus onset, respectively. Intra-class correlation tests with a two-way random model evaluating the consistency were used to evaluate 1) the test-retest reliability of every two averaged onset responses recorded from the same subject within the same recording session; and 2) the test-retest reliability of the two EACC replicates recorded for the same stimulating condition for each subject.

Both peak-to-peak and root mean square (RMS) amplitudes were measured for the onset P1-N1-P2 complex and the EACC. For subjects whose responses are dominated by a P1 peak, the peak-to-peak amplitude was measured as the difference in voltage between the P1 and the following trough (i.e. the N2). For subjects whose response consisted of all three peaks (i.e. P1, N1 and P2), the peak-to-peak amplitude was measured as the difference in voltage between the N1 and P2 peaks. The RMS amplitude was computed between 20 to 215 ms for the onset P1-N1-P2 complex and between 450 to 640 ms for the EACC. In addition, the RMS amplitude of a baseline period (1800-2000 ms) was also computed in order to estimate the noise floor for these recording traces. No stimulus-related EEG activity is expected during this baseline period. The presence of the EACC response was determined based on two criteria: 1) a visually detectable EACC response in the recording trace; and 2) an RMS amplitude during the EACC response window that was at least 50% larger than that of the noise floor. The EACC threshold was defined as the shortest temporal gap that could reliably evoke the EACC response. The correlation between the EACC threshold and the PBK word score was evaluated using a one-tailed Spearman's Rank correlation test.

RESULTS

The PBK word scores measured for all subjects with ANSD ranged from 12% to 100% with a median of 80% correct. Results measured from individual subject are listed in Table 2. Previous work has shown that speech perception scores in children may be influenced by age at implantation, age at the time of testing and the amount of listening experience with their devices (Fryauf-Bertschy et al., 1997; Kirk et al., 2002; Moog & Geers, 2003; Petrov and Pisareva, 2011). Results of a multiple linear regression analysis suggested that neither of these factors were significantly correlated with PBK word scores in this study ($p>0.05$).

The eERP responses, including the onset P1-N1-P2 complex and the gap-evoked EACC, were successfully recorded from all subjects with ANSD. Figure 2 shows a collection of eERP responses recorded from all subjects with ANSD for the no-gap (the left panels) and 100-ms gap (the right panels) stimulation conditions. For clarity, the display window for all graphs included only the 100-ms pre-stimulus baseline and 1400 ms after stimulus onset. Waveforms recorded from individual subjects are shown with grey lines and the grand average waveforms are shown with black lines in all graphs. The vertical dashed line indicates the time when the first 400 ms of stimulation ended. Responses with similar morphologies were grouped together. The top panels show responses recorded from ten subjects whose eERPs are dominant by a P1 peak followed by a N2 peak occurring approximately 100 ms later. The bottom panels show responses recorded from the remaining five subjects (S1, S6, S8, S14 and S15) whose onset responses show three peaks (i.e. P1, N1 and P2). For each of the waveforms shown in Figure 2, an onset response is clearly visible

within a time window between 20 to 215 ms after stimulus onset. In the *100-ms-gap condition*, EACC responses occurring within a time window of 450 to 640 ms are evident in individual waveforms and in the grand average waveform. P1 peaks of the onset and the EACC responses are labeled for traces shown in the top panels. P1, N1 and P2 peaks are labeled for onset responses shown in the bottom panels. Unlike the onset response, the EACC recorded from these five subjects except for subject S14 consists of P1 and N2 peaks. For subject S14, the EACC in response to a temporal gap of 100 ms shows the characteristic of a P1-N1-P2 complex. EACC responses recorded from these subjects are indicated using a black rectangle and labeled as the EACC. Individual peaks were not labeled due to variations in response morphology. The eERP in response to the offset of stimulation was also observed for a subgroup of five subjects. However, a careful inspection of responses recorded from individual subjects revealed that the offset response was not reliably recorded for every stimulating condition for these subjects. Therefore, its peak latency and amplitude were not investigated in this study.

In general, the onset responses recorded for different stimulating conditions from the same subjects were relatively consistent. For each subject, the two EACC replicates recorded for the same stimulating conditions also showed good replicability. Intra-class correlation tests were used to evaluate 1) the test-retest reliability of every two averaged onset responses recorded from the same subject within the same recording session; and 2) the test-retest reliability of the two EACC replicates recorded for the same stimulating condition for each subject. The mean intra-class correlation coefficients (ICCs) of the onset response range from 0.63 to 0.98 with a mean of 0.80 (SD: 0.12). The mean ICCs of the EACC range from 0.52 to 0.96 with a mean of 0.77 (SD: 0.13). Figure 3 shows eERP traces with various degrees of test-retest reliability of the onset response recorded from four subjects with ANSD. Each graph shows responses recorded from one subject. Subject number and the mean ICC of the onset response are shown at the bottom of each graph. Responses recorded from subject S10 have the lowest test-retest reliability (ICC=0.63) for the onset response and recordings recorded from subject S5 have the highest test-retest reliability (ICC=0.98) for the onset response among all subjects who participated in this study. The ICCs of the onset response for subject S12 and S14 are 0.81 and 0.91, respectively. The mean ICC of the EACC was 0.96 for S10, 0.56 for S12, 0.93 for S14 and 0.83 for S5. The vertical dashed line indicates the time when the first 400 ms of stimulation ended. Two averaged responses recorded for each stimulation condition were overlapped to show the repeatability. Gap durations used to evoke EACC responses are labeled for these traces. For each graph, response components are labeled for the top trace. Filled and open triangles indicate the P1 peak (N1 peak for S14) of the onset and the EACC response, respectively. Overall, these results showed good repeatability of eERP traces recorded for the same stimulation conditions.

Measurements from the onset responses are summarized on the left side of Table 3. For the 10 subjects with ANSD whose onset responses consist of P1 and N2 peaks, the peak-to-peak amplitude (P1-N2) of the onset response ranged from 2.84 to 14.92 μV with a mean of 7.23 μV (SD: 2.84 μV). The RMS amplitude of the onset response ranged from 0.99 to 5.09 μV with a mean of 2.47 μV (SD: 1.05 μV). The P1 latency ranged from 73 to 161 ms with a mean of 105.90 ms (SD: 20.63 ms). The N2 latency ranged from 143 to 259 ms with a mean of 204.70 ms (SD: 21.57 ms). For the five subjects whose onset responses showed P1, N1 and P2 components, the peak-to peak amplitude (N1-P2) of the onset response ranged from 0.46 to 6.25 μV with a mean of 2.66 μV (SD: 1.95 μV). The RMS amplitude of the onset response ranged from 0.43 to 2.17 μV with a mean of 1.06 μV (SD: 0.53 μV). The P1 latency ranged from 28 to 104 ms with a mean of 67.43 ms (SD: 19.18 ms). The N1 latency ranged from 83 to 168 ms with a mean of 112.46 ms (SD: 19.41 ms). The P2 latency ranged from 134 to 217 ms with a mean of 164.33 ms (SD: 20.05 ms). Table 3 also details means

and standard deviations of latency and amplitude measured for eERP components for each subject.

Figure 4 shows the RMS amplitude of each trace during the onset window (filled square), the EACC window (filled circle), and the noise floor window (open circle) plotted as a function of gap duration. Each panel is for an individual subject. The EACC threshold is indicated by an upward triangle plotted on the abscissa in each panel. In general, the results show that both the onset and the EACC response were recorded at levels that exceeded the noise floor. The difference in RMS amplitude between the onset and the EACC response did not show a consistent trend among all subjects.

Six subjects had an EACC threshold of 5 ms and four subjects showed an EACC threshold of 10 ms. Figures 5 and 6 show individual waveforms recorded for these subjects. In each figure, the left panel shows responses recorded for the *no-gap condition*, the middle panels shows responses measured for their EACC condition associated with threshold (*5-ms-gap* for Figure 5 and *10-ms-gap* for Figure 6), and the right panel shows responses obtained for the *100-ms-gap condition*. Each trace represents an averaged response of 100 artifact-free sweeps. Two replicates recorded for each stimulation condition were overlapped to show the repeatability. Response peaks are labeled for each trace. In general, these responses showed a substantial amount of inter-subject variation in response morphology, amplitude and peak latency. While some subjects showed a P1-N1-P2 complex (i.e. S1, S6 and S8), other subjects showed P1 and N2 peaks for the onset response. However, the EACC show similar morphology in these subjects. It consisted of a P1 followed by a N2 peak regardless of the morphological characteristics of the onset response. Meanwhile, responses recorded from some subjects (e.g. S5) were much larger in amplitude than responses recorded from other subjects (e.g. S7). Results of a repeated measures analysis of variance (ANOVA) showed that the EACC in response to a 100-ms gap was larger in peak amplitude than the EACC recorded at the level of gap detection threshold [$F_{(1,9)} = 8.05$, $p < 0.05$; RMS amplitude: $F_{(1,9)} = 9.07$, $p < 0.05$]. However, there was no significant difference in P1 latency of the EACC recorded for these two conditions [$F_{(1,9)} = 0.01$, $p = 0.94$].

Figure 7 shows eERP responses recorded from five subjects with ANSD whose EACC thresholds were 20 ms or larger. Each panel shows responses recorded from one subject. Subject numbers (and PBK word scores) are listed on the top of each panel. These panels were ordered based on the subject's PBK word scores. Each trace represents an averaged response of 100 artifact-free sweeps. Two replicates recorded for each stimulation condition were overlapped to show the repeatability. The gap duration used to elicit the EACC is labeled for each trace. For each panel, response components are labeled for the top trace. Filled and open triangles indicate the P1 peak (N1 peak for S14) of the onset and the EACC response, respectively. Inspection of Figure 7 suggests that the onset response was robust for each recorded trace for all five subjects regardless of their PBK word scores. Similar to onset responses shown in Figures 5 and 6, these onset responses demonstrate substantial inter-subject variations in waveform morphology, peak amplitude and latency. The mean correlation coefficients of the intra-class correlation test for the onset response range from 0.81 to 0.95 with a mean of 0.88 (SD: 0.06) for these subjects. The EACC is dominated by a P1 component except for subject S14 whose EACC response shows a robust N1-P2 complex. The mean correlation coefficients of the intra-class correlation test for the EACC range from 0.61 to 0.96 with a mean of 0.82 (SD: 0.09) for these subjects. Subjects S11, S12 and S13 showed an EACC threshold of 20 ms; subject S14 had an EACC threshold of 50 ms; and, for subject S15, a temporal gap of 100 ms was necessary to evoke the EACC.

Inspection of Table 2 indicates that these five subjects whose EACC thresholds were 20 ms or longer also had PBK word scores that were lower than 70% correct. Based on these

results, these five subjects were classified as poor performers in this study. In contrast, subjects with a PBK word score higher than 70% correct had EACC thresholds that were 10 ms or shorter; these subjects were classified as good performers. The differences between good and poor performers in P1 latency, RMS amplitude, and intra-class correlation coefficient of the onset response were compared using independent sample Mann-Whitney U tests. Peak-to-peak amplitudes of onset responses were not compared for these two groups due to variation in response morphologies. Results indicated that there was no significant difference in P1 latency ($p=0.29$), RMS amplitude ($p=0.71$), or intra-class correlation coefficient ($p=0.18$) between these two groups. This indicates that onset eERP responses recorded from poor performers did not show different morphologies from those recorded from good performers (compare Figures 5-7).

Regardless of the analysis method used, significant across-subject variation in EACC amplitude is evident. In general, amplitudes of the EACC tended to increase as durations of temporal gap increased. However, this function was not monotonic in all subjects. In addition, there were no obvious differences between EACC RMS amplitude growth functions measured for good performers and those measured for poor performers. This observation was confirmed by results of Mann-Whitney U tests (RMS amplitude: $p=0.79$). EACC peak-to-peak amplitude growth functions were not compared for these two groups due to variation in response morphologies.

Figure 8 shows the EACC threshold plotted as function of PBK word score for all subjects. The black line represents the result of a linear regression fitted to the data. Results of a one-tailed Spearman's Rank correlation test are shown at the left upper corner. These results showed that the EACC gap threshold was significantly correlated with PBK word score ($\rho = -0.81$; $p<0.01$), which suggests that the larger the EACC gap threshold, the poorer the speech perception performance for these subjects.

DISCUSSION

The first aim of the study was to investigate the feasibility of measuring the eERP, including the onset P1-N1-P2 complex and the EACC, in response to temporal gaps in ANSD subjects using direct-in stimulation. Our results showed that both the onset P1-N1-P2 complex and the EACC were recorded from all subjects with ANSD tested in this study. To our knowledge, this is the first study showing that these responses can be measured from pediatric subjects with ANSD using electrical stimulation.

For the onset response, substantial inter-subject variation in morphology, amplitude and peak latency was observed in this study. This variation could be due to many factors including variation in neural synchronization achieved by the electrical stimulation, age at testing, and amount of listening experience with their devices. However, the onset response recorded from the same subject was relatively stable across stimulating conditions. Test-retest reliability of the onset P1-N1-P2 complex was assessed for all subjects using intra-class correlation tests. The mean correlation coefficients across traces range from 0.63 to 0.98, which is consistent with published literature (e.g. Hensch et al., 2008; Friesen and Tremblay, 2006). Unlike previously reported differences between the onset P1-N1-P2 complex measured from good and poor performers using acoustic stimulation (Narne and Vanaja, 2008; Sharma et al., 2011), the onset responses recorded using electrical stimulation in this study did not show differences in morphology, P1 latency, RMS amplitude, or test-retest reliabilitybetween good and poor performers. This discrepancy could be due to differences in stimulation mode used for the recording (electrical vs. acoustic) and/or subject populations tested (implanted children with ANSD vs. non-implanted children with ANSD).

Unlike the onset response, relatively small inter-subject variation in morphology was observed for the EACC. Only one subject (S14) showed a P1-N1-P2 complex, which was similar in morphology to the onset response. The EACC recorded from all other subjects was dominated by a P1 peak followed by a N2 peak regardless of the presence/absence of the N1 peak in the onset response. These results suggest that the EACC was delayed in maturation compared with the onset response in these pediatric subjects with ANSD. This finding is consistent with the developmental characteristics of the ACC observed in normal hearing children (Jeon et al., 2011). Previously published studies have demonstrated the similarity in morphology between the onset and the change response in adult subjects using either acoustic (Martin et al., 2010; Harris et al., 2012) or electrical stimulation (Kim et al., 2009; Brown et al., 2008). The discrepancy between results of these studies and our results might be partially accounted by differences in stimulation paradigms (i.e. interrupted vs. continuous stimuli). In addition, differences in neural refractory properties between children and adults also likely contribute to this discrepancy. It has been suggested that children show greater neural refractoriness than adults (Gomes et al., 1999, 2001; Ceponiene et al., 1998; Gilley et al., 2005; Wunderlich et al., 2006). Specifically, the neural generators of the N1 response undergo significant developmental changes in refractoriness in early childhood (Ceponiene, 1998). However, it has not yet been determined whether the ACC and the onset P1-N1-P2 complex share the same group of neural generators, which makes our explanation speculative. Further studies focusing on neural generators of the ACC, as well as effects of stimulation rate and maturation on the ACC in hearing impaired subjects, are needed.

For nine subjects (S3, S5, S6, S8, S10, S12, S13, S14, and S15), a vertex-positive peak was observed within a time window of 400 to 800 ms (Figure 5, 6 and 7) for all stimulation conditions, including the *no-gap* condition. This positive peak might have caused RMS amplitudes measured for responses occurring within the EACC time window (i.e. 450 to 640 ms) to be higher than those measured for the noise floor even for conditions where EACC responses were determined to be absent (Figure 4). At this time, the origin and significance of this peak are still unknown. However, the presence/absence of this peak seems to be unrelated to speech perception performance since it was observed in both good and poor performers. Further investigation on this vertex-positive peak is warranted.

The second aim of this study was to explore the relationship between the EACC and open set speech perception skills in subjects with ANSD. Our results showed that there was no difference in EACC amplitude between good and poor performers, which suggests that the EACC amplitude is not a good predictor of open set speech perception skills in these subjects. However, the EACC threshold and the PBK word score were strongly correlated with each other. Overall, subjects who showed longer EACC gap thresholds also had poorer PBK word scores. These results suggest that poor performers diagnosed with ANSD can still have temporal resolution deficits after cochlear implantation. The electrical stimulation provided by their CIs presumably does not provide sufficient enhancement in neural synchronization to fully compensate for the reduced phase locking ability of the auditory system in these subjects. Therefore, these results provide some insight into mechanisms underlying the lack of CI benefit in this subgroup of subjects with ANSD. Having an objective means for identifying this sub-group at an early post-implant stage might facilitate timely inclusion of a *supplemental* rehabilitation strategy or communication mode (e.g. visual support for spoken language). Early initiation of appropriate intervention and habilitation strategies is crucial for a child to achieve his or her maximum potential in the development of communication abilities.

One potential limitation of this study is that only PBK word lists presented with monitored live-voice were used to assess open-set speech perception skills. In our center, speech perception skills are evaluated using a hierarchical battery of measures starting with small

closed-set tests and moving to open-set speech perception tests. For the open-set speech perception measure, the PBK work lists and the Lexical Neighborhood tests (MLNT or LNT; Kirk et al., 1995) are the first two tests to be used once a child has achieved an above-chance score on closed-set tests. If subjects are able to achieve 80% or higher on the MLNT and the LNT tests presented at 60 dB SPL, the Hearing In Noise test for Children (HINT-C; Nilsson et al., 1996) and the Bamford-Kowal-Bench Speech-in-Noise Test (BKB-SIN; Etymōtic Research, 2005) is then used. Subjects tested in this study demonstrated a wide range of speech perception abilities. Many of them could not be tested for the HINT-C or the BKB-SIN due to their young age or limited open-set speech perception skills. In this study, 11 subjects were bilaterally implanted. The study protocol called for open-set speech perception performance to be evaluated monaurally. However, the MLNT or LNT has only two test lists. In addition, the PBK word list has been used in studies that evaluated the relationship between the onset P1-N1-P2 complex and speech perception abilities in pediatric ANSD children (Rance et al., 2002) and in children with sensorineural hearing loss (Gordon et al., 2008). Therefore, PBK word lists were chosen over the MLNT or LNT in this study in order to minimize the potential learning effect on the results and to better compare our results with published literature. For normal-hearing children who are older than five years of age, it is fairly easy to evaluate speech perception performance using recorded testing materials. However, hearing-impaired children tend to show lower cognitive function, poorer psychosocial skills and shorter attention spans than their age-matched peers who have normal hearing (Khan et al., 2005; Shin et al., 2007; Le Maner-Idrissi et al., 2008; Corina & Singleton, 2009). Our pilot data collection indicated that it was necessary to present PBK word lists using monitored live-voice to subjects tested in this study in order to obtain accurate results in a timely fashion.

The other potential limitation of this study is that behavioral gap detection thresholds were not measured for these subjects due to time constraints. However, the long-term goal of this research was to identify some objective tools that can be used in clinical settings instead of investigating gap detection *per se*. In addition, previously published studies have shown that the monaural gap detection threshold measured for within-channel conditions using narrow-band noise in school-aged children with normal hearing range from 4 to 10 ms (Lister et al., 2011; Amaral & Collella-Santos, 2010; Shinn et al., 2009; Trehub et al., 1995). In this study, EACC gap detection thresholds ranging from 5 to 10 ms were recorded for all subjects with ANSD with good speech perception performance, which is generally consistent with the normative behavioral gap detection findings.

CONCLUSIONS

The eERP, including the onset P1-N1-P2 complex and the EACC, could be recorded from pediatric ANSD subjects using electrical stimulation. General characteristics of the electrically evoked onset response could not be used to predict speech perception performance in these children. Subjects with limited open set speech perception skills demonstrated temporal resolution deficits as evidenced by larger EACC thresholds for gap stimuli, suggesting that electrical stimulation applied using currently available paradigms is not sufficient to restore neural synchrony in some subjects with ANSD. Importantly, results of this study indicate that measuring the EACC in response to temporal gaps holds great promise as an objective biomarker of speech perception ability and, consequently, as a means for identifying the subgroup of children with ANSD that may require supplemental rehabilitation strategies.

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Summary

This study aimed 1) to investigate the feasibility of recording the electrically evoked auditory event-related potential (eERP), including the onset P1-N1-P2 complex and the electrically evoked auditory change complex (EACC) in response to temporal gaps, in children with auditory neuropathy spectrum disorder (ANSD); and 2) to evaluate the relationship between these measures and speech perception abilities in these patients. eERPs were recorded from 15 children with ANSD who had various speech perception performance. There was a robust correlation between the PBK word scores and the EACC thresholds for gap detection. Subjects with poorer speech performance showed larger EACC thresholds in this study.

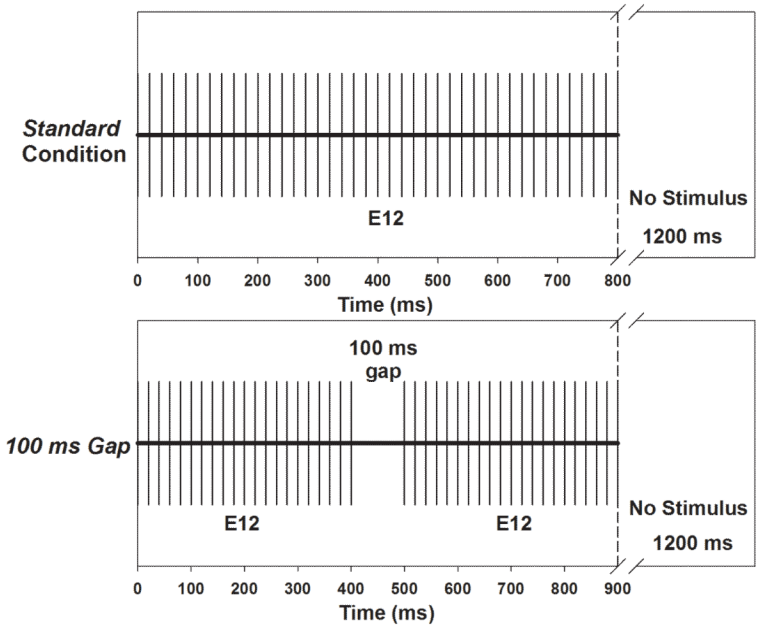

Figure 1.
Schematic illustration of two stimulation paradigms used for the study.

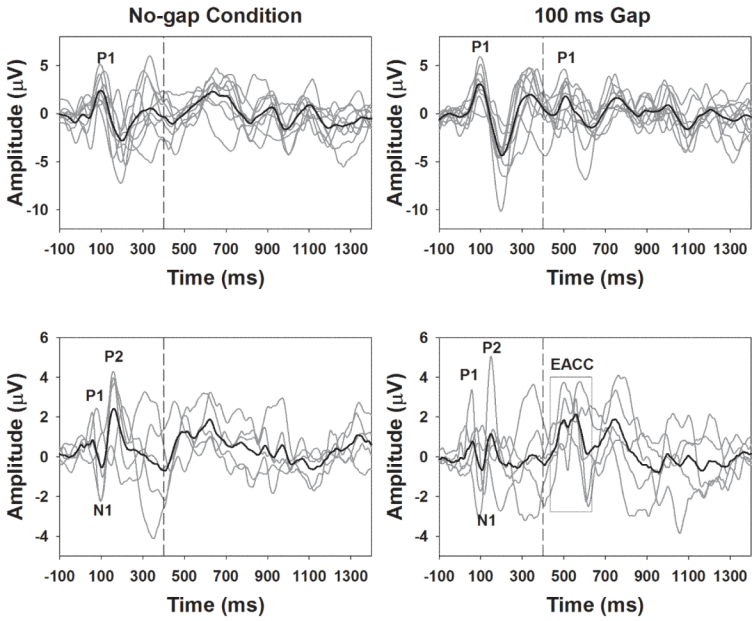

Figure 2.

eERP responses recorded from all subjects for the *no-gap condition* (the left panels) and the *100 ms-gap condition* (the right panels). Responses recorded from ten subjects only showed P1 and N2 peaks. These responses are shown in the top panels. P1 peaks are labeled for onset and EACC responses in graphs shown in the top panels. Graphs in the bottom panels show eERPs recorded from five subjects whose onset responses showed the P1-N1-P2 complex. P1, N1 and P2 peaks are labeled for onset responses in these graphs. The EACC recorded from the 100 ms-gap condition is indicated by a rectangle.

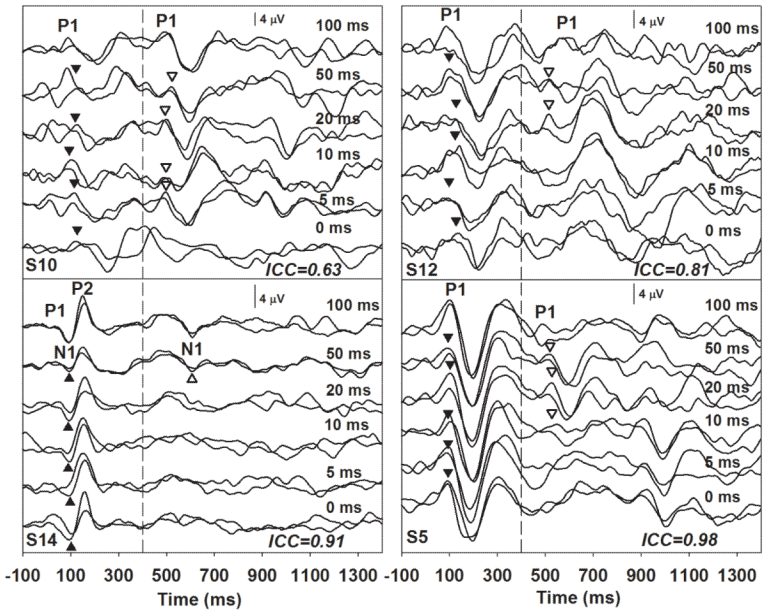

Figure 3.

eERP responses recorded from four subjects with ANSD whose response showed various degree of test-retest reliability of the onset response as indicated by the intra-class correlation coefficients (ICCs). Traces recorded for the same stimulation condition were overlapped to show the repeatability of these responses. Subject number and the ICC of the onset response are shown in each panel.

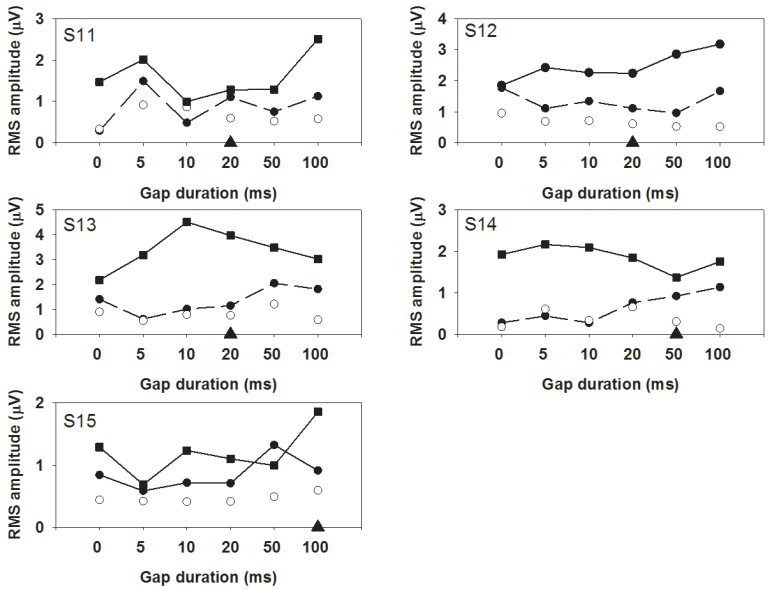

Figure 4.

RMS amplitudes measured for responses recorded within the time window of the onset P1-N1-P2 complex, the EACC, and the noise floor for all subjects. Each graph shows results measured for one subject.

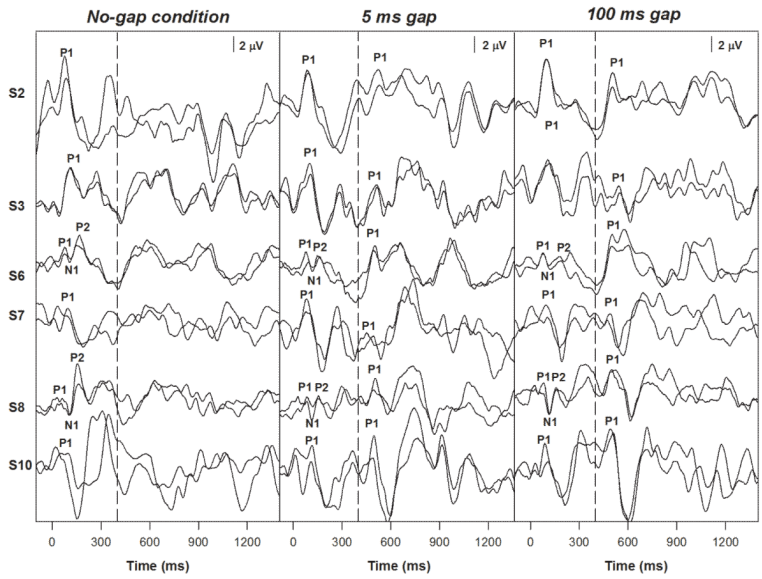

Figure 5.
eERP responses recorded for three stimulation conditions in six subjects with ANSD with EACC threshold of 5 ms. The first dashed line indicates the time when the first 400 ms segment of stimulation ended.

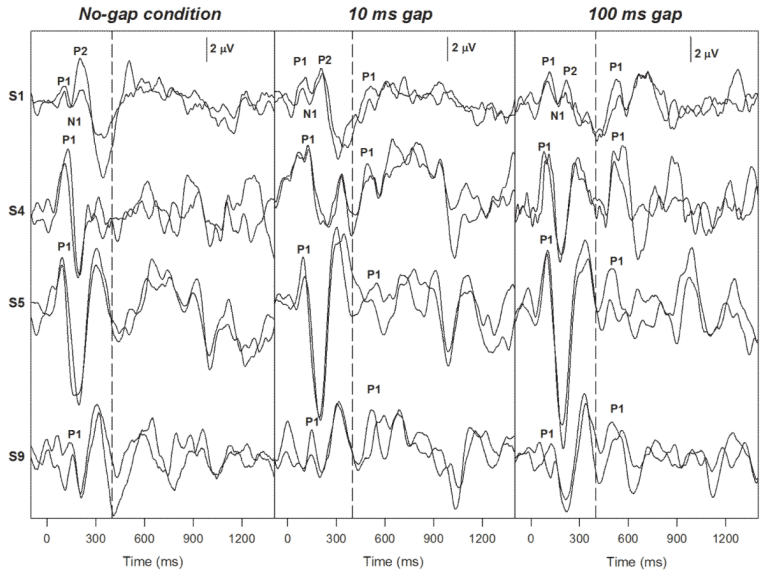

Figure 6.

eERP responses recorded for three stimulation conditions in four subjects with ANSD with EACC threshold of 10 ms. The dashed line indicates the time when first 400 ms of stimulation ended.

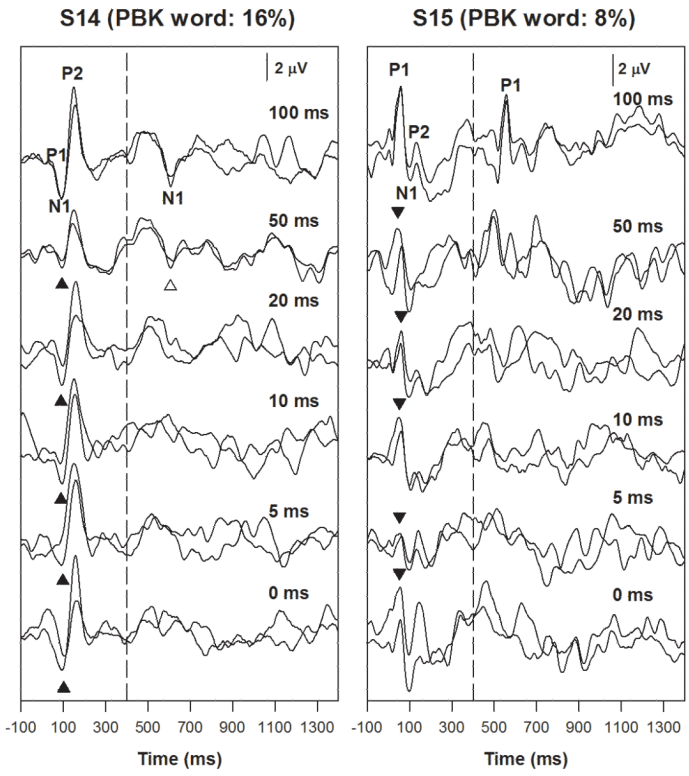

Figure 7.

eERP responses recorded from five subjects with ANSD whose EACC thresholds are 20 ms or larger. Peaks are labeled for the top trace. P1 peaks for responses recorded from S11, S12, S13 and S15 are indicated using filled triangle for the onset response and open triangle for the EACC. For subject S14, the N1 peak is labeled for the onset (filled triangle) and the change potential (open triangle). The dashed line indicates the time point when first 400 ms of stimulation ended.

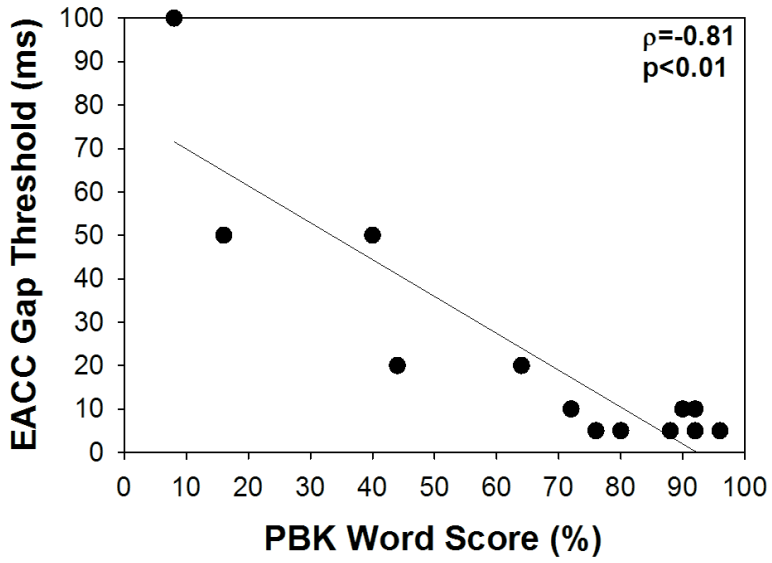

Figure 8.
The relationship between the EACC threshold and the PBK word test score. Result measured for each subject is indicated by a filled dot. The solid line shows the result of linear regression fitted to all data. Results of One-tailed Spearman's Ranked correlation test are shown in the upper right corner of the graph.

Table 1

Demographic information of all subjects who participated in this study.

Subject number	Gender	Risk Factor	Ear tested	Age at testing	Age at implantation	CI type	Processing strategy and rate
S1	M	None	L	6.8	1.6	24R (CA)	ACE 1200
S2	M	Premature	L	7.8	1.9	24R (CA)	ACE 1200
S3	F	None	L	5.6	3.6	24R (CA)	ACE 900
S4	F	None	R	9.4	3.3	24R (CA)	ACE 900
S5	M	Premature	R	5.8	2.4	24R (CA)	ACE 900
S6	M	Premature	L	13.6	2.5	N5	ACE 900
S7	F	None	R	7.1	3.6	N5	ACE 900
S8	M	None	R	12.6	3.5	24R (CS)	ACE 900
S9	M	None	R	9.7	4.3	24RE	ACE 900
S10	M	None	L	7.0	1.1	N5	ACE 900
S11	M	Premature	L	8.8	2.7	24RE (CA)	ACE 900
S12	F	Premature	R	6.8	3.2	24RE	ACE 900
S13	M	None	L	5.3	1.8	24RE (CA)	ACE 900
S14	F	None	L	17.2	15.6	24RE	ACE 900
S15	F	None	R	12.1	2.5	24R (CS)	ACE 900

CI: cochlear implant

Table 2

PBK word scores and EACC thresholds for all subjects.

Subject number	PBK word score (%)	EACC threshold (ms)
S1	96	5
S2	100	5
S3	92	5
S4	92	10
S5	80	10
S6	80	5
S7	80	5
S8	72	5
S9	72	10
S10	80	5
S11	64	20
S12	44	20
S13	40	50
S14	20	50
S15	12	100
Median	80	10

PBK: Phonetically Balanced Kindergarten Words test

EACC: electrically evoked auditory change complex

Table 3

Means and standard deviations (parentheses) for latency and amplitude of eERP components.

Subject number	Onset response						EACC						Noise floor
	Latency (ms ± SD)				Amplitude (μV ± SD)		Latency (ms ± SD)				Amplitude (μV ± SD)		RMS amplitude (μV± SD)
	P1	N1	P2	N2	Peak to peak	RMS	P1	N1	P2	N2	Peak to peak	RMS	
S1	91.2 (9.7)	145.8 (13.8)	208.7 (5.3)		1.5 (0.8)	0.7 (0.2)	547.4 (45.4)			592.6 (56.9)	0.6 (0.4)	0.7 (0.1)	0.5
S2	91.2 (5.2)			**206.5 (46.7)**	7.8 (1.7)	2.5 (0.5)	522 (10.4)			587.4 (22.9)	3.2 (2.9)	1.5 (0.7)	0.8
S3	110.8 (7.4)			200.5 (8.2)	6.8 (2.0)	2.4 (0.7)	540.6 (22.5)			601 (19.6)	3.5 (1.3)	1.4 (0.3)	1.0
S4	112.5 (14.9)			201.5 (8.9)	8.1 (1.3)	2.9 (0.4)	524.5 (33.9)			615.8 (31.1)	2.9 (2.5)	1.1 (0.5)	0.6
S5	102.0 (5.6)			197.6 (4.5)	12.5 (1.5)	4.7 (0.5)	517.5 (11.2)			602.8 (5.3)	3.7 (2.4)	1.3 (0.5)	0.7
S6	71.2 (5.6)	107.2 (4.4)	157.3 (7.9)		1.1 (0.6)	0.6 (0.2)	596.2 (46.8)			803.7 (5.1)	6.2 (1.8)	1.2 (0.2)	0.5
S7	92.5 (5.6)			190.3 (4.8)	5.8 (1.3)	2.1 (0.5)	500.4 (41.8)			561.6 (30.6	1.5 (0.9)	0.8 (0.3)	0.4
S8	75.2 (14.0)	112.8 (5.5)	158.7 (2.9)		3.8 (1.3)	1.1 (0.4)	498.8 (7.6)			579.8 (28.4)	3.8 (1.5)	1.3 (0.5)	0.6
S9	152.3 (5.0)			213.7 (11.7)	3.5 (0.4)	1.2 (0.2)	513.8 (14.7)			603.8 (31.8)	2.9 (1.2)	1.1 (0.2)	0.8
S10	99.0 (18.2)			202.3 (29.0)	5.7 (1.1)	1.9 (0.3)	503 (10.2)			598 (11.5)	8.4 (3.0)	3.0 (1.2)	1.3
S11	84 (9.1)			208.8 (28.7)	4.6 (1.1)	1.6 (0.6)	500.3 (12.7)			577 (19.1)	2.6 (0.4)	1.0 (0.2)	0.6
S12	113.2 (21.5)			218.7 (17.3)	8.1 (1.7)	2.5 (0.5)	533.7 (28.0)			618.7 (42.4)	2.8 (0.2)	1.2 (0.4)	0.7
S13	98.2 (5.0)			207.0 (17.8)	9.6 (2.3)	3.4 (0.8)	521			621.5	5.5	1.9	0.9
S14	37.5 (13.6)	93.8 (5.8)	156.2 (4.9)		5.6 (0.7)	1.9 (0.3)	512	620	685		1.3	1.0	0.4

Subject number	Onset response						EACC						Noise floor
	Latency (ms ± SD)				Amplitude (μV ± SD)		Latency (ms ± SD)				Amplitude (μV ± SD)		RMS amplitude (μV± SD)
	P1	N1	P2	N2	Peak to peak	RMS	P1	N1	P2	N2	Peak to peak	RMS	
S15	58.8 (1.8)	102.7 (3.7)	140.8 (6.0)		1.4 (0.8)	1.2 (0.4)	529	577.5	658.5		0.3	1.1	0.5
Group	96.6 (27.8)	112.5 (19.4)	164.3 (24.1)	204.7 (21.6)	5.8 (3.4)	2.4 (1.1)	525.3 (36.3)	598.8 (26.8)	671.8 (50.1)	613.4 (67.8)	3.5 (2.6)	1.3 (0.8)	0.7 (0.4)

eERP: electrically evoked event-related potential

EACC: electrically evoked auditory change complex

SD: standard deviation