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Acoustically-Evoked Auditory Change Complex in Children with Auditory Neuropathy Spectrum Disorder: A Potential Objective Tool for Identifying Cochlear Implant Candidates

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Abstract

Objective: The overall aim of the study was to evaluate the feasibility of using electrophysiological measures of the auditory change complex (ACC) to identify candidates for cochlear implantation in children with auditory neuropathy spectrum disorder (ANSD). In order to achieve this overall aim, this study 1) assessed the feasibility of measuring the ACC evoked by temporal gaps in a group of children with ANSD across a wide age range; and 2) investigated the association between gap detection thresholds (GDTs) measured by the ACC recordings and open-set speech-perception performance in these subjects.

Design: Nineteen children with bilateral ANSD ranging in age between 1.9 to 14.9 yrs (mean: 7.8 yrs) participated in this study. Electrophysiological recordings of the auditory event-related potential (ERP), including the onset ERP response and the ACC, were completed in all subjects and open-set speech perception was evaluated for a subgroup of sixteen subjects. For the ERP recordings, the stimulus was a Gaussian noise presented through ER-3A insert earphones to the test ear. Two stimulation conditions were used. In the “*control condition*,” the stimulus was an 800-ms Gaussian noise. In the “*gapped condition*,” the stimuli were two noise segments, each being 400 ms in duration, separated by one of five gaps (i.e. 5, 10, 20, 50, or 100 ms). The inter-stimulation interval was 1200 ms. The aided open-set speech perception ability was assessed using the Phonetically Balanced Kindergarten (PBK) word lists presented at 60 dB SPL using recorded testing material in a sound booth. For speech perception tests, subjects wore their hearing aids at the settings recommended by their clinical audiologists. For a subgroup of five subjects, psychophysical gap detection thresholds for the Gaussian noise were also assessed using a three-interval, three-alternative forced-choice procedure.

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Results: Responses evoked by the onset of the Gaussian noise (i.e. onset responses) were recorded in all stimulation conditions from all subjects tested in this study. The presence/absence, peak latency and amplitude, and response width of the onset response did not correlate with aided PBK word scores. The objective GDTs measured with the ACC recordings from seventeen subjects ranged from 10 to 100 ms. The ACC was not recorded from two subjects for any gap durations tested in this study. There was a robust negative correlation between objective GDTs and aided PBK word scores. In general, subjects with prolonged objective GDTs showed low aided PBK word scores. GDTs measured using electrophysiological recordings of the ACC correlated well with those measured using psychophysical procedures in four of five subjects who were evaluated using both procedures.

Conclusions: The clinical application of the onset response in predicting open-set speech-perception ability is relatively limited in children with ANSD. The ACC recordings can be used to objectively evaluate temporal resolution abilities in children with ANSD having no severe comorbidities, and who are older than 1.9 years. The ACC can potentially be used as an objective tool to identify poor performers among children with ANSD using properly fit amplification, and who are thus, cochlear implant candidates.

Keywords

auditory neuropathy spectrum disorders; hearing aid; auditory event-related response; speech perception

INTRODUCTION

Auditory neuropathy spectrum disorder (ANSD) is a form of hearing impairment that is characterized by evidence of cochlear function in conjunction with an aberrant auditory neural system. The diagnosis of ANSD is defined on the basis of present otoacoustic emissions (OAEs) and/or cochlear microphonics (CMs) with absent or abnormal auditory brainstem responses (ABRs). The prevalence of ANSD is about 5-15% of children with newly identified hearing loss (Berlin et al., 2010; Bielecki et al., 2012; Rance et al., 1999). The proposed sites of lesion include inner hair cells (IHCs), the synapse between the IHC and the VIII nerve, and/or the VIII nerve itself (Berlin et al., 2003; Fuchs et al., 2003; Starr et al., 1996). Auditory abilities among children with ANSD are diverse and, in many cases, poorly understood. Pure-tone detection thresholds can range from normal to profound levels (Madden et al., 2002; Rance et al., 1999; Starr et al., 2000). However, unlike children with sensorineural hearing loss (SNHL), speech perception abilities of children with ANSD cannot be predicted based on the degree of pure-tone hearing loss (Rance et al., 2002). In addition, these children often experience excessive difficulties in understanding speech in background noise (e.g. Rance et al., 2007; Zeng & Liu, 2006).

Current intervention protocols for children with ANSD typically include a trial of acoustic amplification (i.e. hearing aids [HAs]). Although well fitted HAs can provide improved audibility of acoustic input to all children with ANSD, appropriate development of auditory function and speech and language skills cannot be guaranteed. Substantial across-patient variations in aided speech perception skills have been reported for children with ANSD. Some patients demonstrate speech perception in quiet and spoken language abilities that are

comparable to their matched peers with SNHL (Berlin et al., 2010; Deltenre et al., 1999; Rance et al., 1999, 2002; Rance & Baker, 2008, 2009; Runge et al., 2011). In contrast, many patients fail to show significant improvement in speech understanding and language development even with appropriately fitted HAs (e.g. Berlin et al., 2010; Rance et al., 2002). The ability to identify these patients at an early stage is critical for making better recommendation for optimal intervention strategies. For these patients, a timely transition from HAs to other intervention strategies such as cochlear implantation may be crucial for the achievement of maximum potential in terms of speech and language development. The availability of effective newborn hearing screening programs allows early identification of ANSD. However, it can be challenging or infeasible to obtain reliable behavioral measures or verbal descriptions of subjective percepts of auditory stimuli in infants and young children. In addition, many children with ANSD have multiple disabilities or medical conditions that limit their ability to provide such responses or descriptions despite advanced age. Therefore, it is important to develop some objective tools that can be used in children with ANSD to identify patients who are unlikely to receive substantial benefits from their HAs in a timely manner.

Understanding daily conversation depends, at least partially, on the ability of the auditory system to detect ongoing changes in the temporal patterns of incoming signals (i.e. temporal resolution). Children with ANSD are known to have temporal resolution deficits, and the severity of these deficits strongly correlates with their speech perception abilities (He et al., 2013a; Michalewski et al., 2005; Rance et al., 2004; Starr et al., 1991; Zeng et al., 1999, 2001, 2005). It is generally believed that the temporal resolution deficits are likely to result from disruptions in the phase locking ability of the peripheral auditory neurons, the synchronicity of the population response, and/or prolonged neural conduction time (Starr et al., 1996, 2003), which cannot be restored through the use of HAs. In adult and older child listeners, temporal resolution abilities can be evaluated by measuring how well the listener can identify a silent interval embedded within a stimulus (i.e. gap detection) using psychophysical measures. It has been shown that subjects with ANSD have larger gap detection thresholds (GDTs) than normal-hearing subjects (Michalewski et al., 2005; Zeng et al., 1999, 2001, 2005; Starr et al., 2008), and their GDTs are strongly associated with their speech perception abilities (He et al., 2013a; Zeng et al., 1999, 2001). Performing these psychophysical measures requires a significant amount of linguistic experience and cognitive ability, which makes it very challenging or impossible to conduct these measures in young children with ANSD. Therefore, the clinical application of these psychophysical measures is relatively limited.

Despite an absent or abnormal ABR, the auditory event-related potentials (ERPs), including the onset response and the auditory change complex (ACC), can often be recorded from patients with ANSD (Demitrijevic et al., 2011; Kraus et al., 2000; He et al., 2013a, 2013b; Michalewski et al., 2005, 2009; Narne & Vanaja, 2008; Pearce et al., 2007; Rance et al., 2002; Sharma et al., 2011; Starr et al., 1996). These two responses are cortically generated potentials that can be recorded from surface electrodes placed on the scalp. The onset ERP response is typically evoked by a brief stimulus. 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 auditory discrimination capacity at the level of the auditory cortex (Martin et al., 2008).

Electrophysiological measures of the ACC have been used to objectively measure GDTs in normal-hearing adults (Atcherson et al., 2009; He et al., 2012; Lister et al., 2007; Palmer & Musiek, 2013) and in subjects with ANSD (Michalewski et al., 2005). This technique does not require active participation from listeners. Therefore, it is uniquely suited for evaluating temporal resolution abilities in children. Previous studies showed that GDT measured using psychophysical approaches and electrophysiological measures of the ACC are similar in normal-hearing listeners (Atcherson et al., 2009; Pratt et al., 2005). Michalewski et al (2005) reported a reasonable association between the gap durations that could be perceptually detected and those that evoked a reliable ACC in subjects with ANSD. This finding suggests that the ACC can be used as an objective measure of temporal resolution abilities in subjects with ANSD. However, to date, the ACC evoked by temporal gaps has only been reported for three school-aged children with ANSD (Michalewski et al., 2005). It is unknown whether it can be recorded in a large group of children with ANSD across a wide age range. In addition, the association between GDTs measured using the ACC and open-set speech perception ability has not been systematically investigated. As a result, it remains unknown whether the ACC can be used as an objective tool for identifying poor speech perception among ANSD children using hearing aids and thus, a potential indicator of cochlear implant candidacy.

This study aimed 1) to evaluate the feasibility of measuring the ACC evoked by temporal gaps in children with ANSD across a wide age range; and 2) to assess the association between GDTs measured with the ACC and aided open-set speech perception abilities in these subjects. We hypothesized that the ACC evoked by temporal gaps could be recorded from children with ANSD and that temporal resolution capabilities inferred from ACC measures would be associated with speech perception performance. Subjects with longer GDTs measured using the ACC recordings were expected to demonstrate less benefit from their HAs (i.e. worse-aided speech perception performance) than subjects with shorter GDTs.

METHODS

Subjects

Nineteen pediatric subjects with bilateral ANSD (S1 – S19) ranging in age between 1.9 to 14.9 yrs (mean: 7.8 yrs, SD: 3.2 yrs) participated in this study. There were four female and 15 male subjects. All subjects were diagnosed with ANSD based on the presence of a CM (+/- OAEs) with absent or abnormal ABRs. None of these subjects had any known cognitive or neurological conditions that might affect results of this study. Magnetic Resonance Imaging (MRI) revealed no evidence of dysplasia of the inner ear or internal auditory canal in any of these subjects. None of the subjects showed historical or clinical evidence of peripheral neuropathy in other systems. The degree of pure-tone hearing loss ranged from normal to profound. All except two subjects (S5 and S6) were fitted with HAs in the ears tested in this study, and they had a minimum of 6 months of experience with their HAs. For these subjects, HAs were programmed using the manufacturer's fitting software

according to DSL v. 5.0 targets (Bagatto et al. 2005; Scollie et al. 2005) using simulated real-ear measures (S-REM). Whenever possible, real-ear-to-coupler differences (RECDs) were measured. If the child was too active for RECD measures, age appropriate normative values were used. Verification of the HA was performed in a 2-cc coupler using the Audioscan Verifit. Three subjects (S10, S11, and S13) received cochlear implants in the opposite ear. The two youngest subjects (S17 and S18) were referred by their audiologists and/or speech pathologists due to delayed progress in auditory development in contrast with their motor and cognitive development, suggesting that they were only receiving limited benefit from their HAs. There was substantial cross-subject variation in both age at diagnosis and age at HA fitting. All subjects, except for two (S13 and S18), had a medical history of neonatal conditions, including prematurity and hyperbilirubinemia. For 17 of the subjects with ANSD, English was the only language used in their families. Two subjects (S9 and S19) were learning English as their primary language in school and used a combination of English and Spanish at home. For two subjects with symmetric hearing loss (S2 and S19), the right ear was selected as the experimental ear. For all other subjects, the ear with better pure-tone hearing thresholds was selected as the test ear in this study. Detailed demographic information for these subjects is listed in Table 1.

All subjects were recruited from the Ear & Hearing Center within the Department of Otolaryngology-Head and Neck Surgery at the University of North Carolina at Chapel Hill (UNC). The study was approved by the Institutional Review Board (IRB) at UNC, and all subjects and/or their guardians provided written consents/assents using age-appropriate, IRB-approved forms. All subjects received payment for their participation.

General Procedures

Open-set speech perception ability and electrophysiological measures of the ACC were evaluated in sixteen subjects. These two tests were undertaken in two sessions scheduled on the same day. Open-set speech perception testing was conducted by experienced clinical audiologists and the ACC was recorded by electrophysiologists. Results of these two measures were independently scored and evaluated.

For three subjects (S6, S17 and S18), only the ACC in responses to temporal gaps was recorded. For five subjects (S2, S4, S5, S7, and S13), psychophysical measures of GDT were undertaken in a separate session scheduled approximately 12 months after the initial two testing sessions.

Speech Perception Tests

The Phonetically Balanced Kindergarten (PBK) Word test was used to evaluate the open-set speech perception ability. The stimuli (25 recorded monosyllabic words) were presented in an auditory only condition at 60 dB SPL through a loudspeaker placed at 0° azimuth in a single-walled sound attenuating booth. Hearing aids were worn at the settings recommended by their clinical audiologists. The subject was required to repeat the words, and a score indicating the percentage of words (out of 25) in which all phonemes were repeated correctly was obtained. For subjects with bilateral HAs, each ear was tested separately. The ear contralateral to the test ear was occluded when speech stimuli were presented to one ear.

Only scores for the test ear were included in this study. Open-set speech ability was not assessed in three subjects (S6, S17 and S18) due to their young ages.

Electrophysiological Measures

Stimulation Conditions—The stimulus was an 800-ms Gaussian noise gated on and off using 1-msec linear ramps. Two stimulation conditions were used in this study. In the “*control condition*”, the 800-ms Gaussian noise was presented to the test ear without any interruption. In the “*gapped condition*”, a temporal silence (i.e. gap) was inserted after 400 ms of stimulation. The gap durations tested in this study included 5, 10, 20, 50, and 100 ms. A gap duration of 5 ms was not tested in eight subjects (S1, S6, S10, S12, S14, S17, S18 and S19) and a gap duration of 10 ms was not tested in S17 due to time constraints. Figure 1 shows a schematic of the “*control condition*” (upper panel) and the “*100-ms gap condition*” (lower panel). All stimuli were presented through an ER-3A insert earphone at 35 dB SL (RE pure tone average) or at the maximum output level (120 dB SPL) of the Neuroscan Stim2 (Compumedics, Charlotte, NC) if this limit was less than 35 dB SL. The inter-stimulus interval was 1200 ms.

Electrophysiological Recordings—For each subject, electrophysiological recordings were completed in one test session lasting approximately 2 hours. Subjects were tested without their hearing aids in a single-walled sound booth. They were seated in a comfortable chair or a caregiver’s lap watching a silent movie with closed captioning or engaging in quiet play during the recording session. Breaks were provided as necessary.

Electroencephalographic (EEG) activity was recorded using the Neuroscan SCAN 4.4 software and a SynAmpRT amplifier (Compumedics, Charlotte, NC) with a sampling rate of 1000 Hz. Disposable, sterile Ag-AgCl surface recording electrodes were used to record the EEG. Responses were recorded differentially from high forehead (F_z , active) to contralateral mastoid ($A_{1/2}$, reference) relative to body ground at low forehead (F_{pz}). The single-channel recording method with a convenient electrode montage (i.e. F_z) implemented in this study was motivated by the consideration of clinical feasibility with young child participants. Eye blink activity was monitored using surface electrodes placed superiorly and inferiorly to one eye. Responses exceeding 100 μV were rejected from averaging. Electrode impedances were maintained below 5 k Ω for all subjects. The EEG was epoched and baseline corrected online using a window of 2000 ms, including a 100-ms pre-stimulus baseline and a 1900-ms peri/post-stimulus time. Auditory evoked responses were amplified and analog band-pass filtered online between 0.1 and 100 Hz (12 dB/octave roll-off). After artifact rejection, the remaining (at least 100) artifact-free sweeps were averaged and two averaged responses were recorded for each stimulation condition for each subject. These recordings were digitally filtered between 1-30 Hz (12 dB/octave roll-off) offline using custom-designed MATLAB (Mathworks) software before response identification and amplitude measurements.

Psychophysical Measures of GDTs

As an addendum to the main study, and occurring about one year later, behavioral GDTs were measured for a subgroup of five subjects (S2, S4, S5, S7 and S13). A three interval,

three alternative forced choice (3AFC) procedure was used that incorporated a two-down one-up adaptive strategy estimating 70.7% correct detection (Levitt, 1971). The experiment was run using custom MATLAB (Mathworks) script that controlled a digital signal processor (RP2, Tucker-Davis Technologies). This platform controlled all signal presentation and response collection. The stimulus was again a broad-band Gaussian noise that was gated on and off using 1-msec linear ramps. It was presented monaurally to the test ear through a Sennheiser HD 265 linear headset at approximately 35 dB SL (RE pure tone average). Durations for listening intervals and inter-stimulus intervals were 500 ms. Based on results reported by Busby and Clark (1999), differences in stimulation duration (500 ms vs. 800 ms) used in psychophysical and electrophysiological measures are unlikely to affect results of this study. Two of the listening intervals contained continuous Gaussian noise whereas the third interval, chosen at random, contained a temporal gap occurring after 250 ms of stimulation. The initial step size of the change in gap duration was 20 msec. This step changed by a factor of $1.414 (\sqrt{2})$ and a factor of $1.189 (4\sqrt{2})$ at the second reversal point and the rest of reversal points, respectively. A threshold track stopped after eight reversals, and the gap duration at the final six reversals was geometrically averaged. At least three estimates were obtained for subject. Behavioral GDT was defined as the average of all estimates obtained for each subject. Animation was used to mark listening intervals on a computer screen. For each correct response, one piece of a jigsaw puzzle was revealed over the course of a track. No feedback was given for any incorrect response. The number of track reversals obtained up to that point was indicated using a progress bar at the top of the screen. Subjects were tested in a double-walled sound-attenuating booth. For each subject, the behavioral GDT measure took approximately 10-15 minutes to complete.

Data Analysis

The ERP responses were independently assessed by two experienced researchers (authors SH and JHG) who were blind to subject identification and subject speech perception abilities. Replicated responses measured for each stimulation condition were overlapped to show their repeatability. Visual identification of the onset ERP response and the ACC was based on peak latency, waveform morphology, and the replicable property of neural responses. A signal-to-noise criterion was also employed (see below). Time windows delimiting the possible occurrence of the onset ERP and the ACC responses were determined based on the grand mean average of all recorded responses. The windows for the onset and the ACC response were from 20 to 250 ms and from 420 to 660 ms, relative to the stimulus onset, respectively. Root mean squared (RMS) amplitudes were measured for both the response segments within these time windows. The RMS amplitude of a baseline period (1800-1900 ms) was also computed in order to estimate the noise floor for these recording traces. The presence of the ACC response was determined based on two criteria: 1) a repeatable neural response within the expected time window for the ACC based on mutual agreement between the two researchers; and 2) an RMS amplitude of the ACC that was at least 50% higher than that of the noise floor. The shortest gap that could reliably evoke the ACC response was defined as the objective GDT. Initial decisions regarding the objective GDT thresholds between the two judges were consistent for responses recorded from 17 subjects (i.e. approximately 90% inter-judge reliability). In two cases where disagreement existed, objective GDTs were taken as the shortest gap duration for which both judges

agreed that the ACC was recorded. The onset ERP and the ACC responses recorded from all subjects tested in this study consisted of a positive peak (P1) followed by a negative peak (N2) occurring around 100 ms later. In this study, the response width was measured as the difference in peak latencies of the P1 and N2 peaks. The peak-to-peak amplitude was measured as the difference in voltage between the P1 and N2 peaks. The dependent variables included objective GDTs, P1 and N2 latencies, response width, and peak-to-peak and RMS amplitudes of the onset response and the ACC. The correlations between the PBK word score and these dependent variables were evaluated using a one-tailed Spearman's rank correlation test.

RESULTS

Subjects participating in this study demonstrated considerable variability in open-set speech perception ability. The aided PBK word scores ranged from 0 to 92% correct with a mean of 55.8% (SD: 30.5%). PBK word scores measured from individual subjects are listed in Table 2. Results of a multiple linear regression analysis suggested that PBK word scores were not correlated with the degree of hearing loss, age at HA fitting, age at the time of testing or the amount of listening experience with their HAs in this study ($p>0.05$).

Figure 2 shows a collection of ERP responses recorded from all subjects with ANSD for the “control condition” (left panel) and 100-ms gap condition (right panel). For clarity, the display window for both graphs extends only from 100 ms pre-stimulus onset to 1300 ms post-stimulus onset. The responses are plotted vertically based on subject age at testing with responses recorded from the oldest subject plotted on the top in each graph. Subject numbers are listed to the left of each response set. Inspection of Figure 2 suggests that the onset ERP response, as indicated with an inverted filled triangle, was recorded from all subjects tested in this study. These onset responses consisted of a P1 followed by a N2 peak occurring approximately 100 ms later regardless of subject age at testing. The mature P1-N1-P2 complex was not observed in any of the subjects. Despite similar morphologies of ERPs observed across subjects, these averaged responses recorded from different subjects, as well as replications recorded from the same subject within the same recording session, demonstrated substantial variations in peak latencies and amplitudes. For example, P1 latencies of the onset ERP replications recorded from S13 ranged from 51 to 126 ms with a mean of 80.5 ms (SD: 25.1 ms). Overall, for the onset response, the mean P1 latency in all stimulation conditions from individual subjects ranged from 47.0 to 189 ms with a mean of 93.7 ms (SD: 28.4 ms); the mean N2 latency ranged from 142 to 316 ms with a mean of 206.4 ms (SD: 33.8 ms); the mean peak-to-peak amplitude (P1-N2) ranged from 1.4 to 10.8 μV with a mean of 5.9 μV (SD: 2.3 μV); and the mean RMS amplitude ranged from 0.5 to 3.8 μV with a mean of 2.1 μV (SD: 0.9 μV). The ACC response was recorded from 17 subjects. These responses are indicated using open triangles in Figure 2. For two subjects (S10 and S17), the ACC was not recorded in any of the stimulation conditions. Similar to the onset ERP response, the ACC consisted of a P1 and a N2 peak and demonstrated substantial inter-subject variations in peak latency and amplitude. For the ACC, the mean P1 latency ranged from 455 to 560 ms with a mean of 499.3 ms (SD: 25.6 ms); the mean N2 latency ranged from 542 to 723 ms with a mean of 610.1 ms (SD: 38.7 ms); the mean peak-to-peak amplitude (P1-N2) ranged from 0.8 to 9.3 μV with a mean of 3.6 μV (SD: 2.1 μV);

and the mean RMS amplitude ranged from 0.4 to 2.9 μV with a mean of 1.3 μV (SD: 0.6 μV). The mean RMS amplitudes of noise floors of these recordings ranged from 0.1 to 1.1 μV with a mean of 0.4 μV (SD: 0.2 μV). The ERP in response to the offset of stimulation was not investigated in this study since it was not reliably recorded for every stimulating condition or in every subject. Peak latencies, peak-to-peak and RMS amplitudes of the onset and the ACC responses, as well as RMS amplitudes of the noise floor measured from individual subjects are listed in Table 3.

Figure 3 shows ERPs, including the onset and the ACC responses, recorded from eight subjects who showed an objective GDT of 10 ms. Figures 4 and 5 show ERP responses recorded from four subjects who showed an objective GDT of 20 ms and three subjects who showed an objective GDT of 50 ms, respectively. In each figure, gray lines indicate replicated ERP recordings and black lines indicate the averaged responses of the two replications. Responses recorded in the same stimulation condition are overlapped to show repeatability. Each trace represents an average of 100 artifact-free sweeps. The dashed line indicates the time point when the first 400-ms of stimulation ended. P1 peaks of the onset and the ACC responses are labeled for these traces. Stimulation conditions are labeled on the top of these panels. In general, substantial inter-subject variations in response morphology, amplitude and peak latency were observed in ERPs recorded in subjects with similar GDTs. For example, ERPs recorded from subjects S4, S11, S15 and S16 were much larger in amplitude than responses recorded from subjects S7 and S9 even though all of these subjects showed an objective GDT of 10 ms. In addition, replications recorded for the same stimulation condition appeared to show better repeatability in some subjects (i.e. S2 and S5) than those recorded in other subjects (i.e. S6 and S16). However, a careful inspection of these responses indicated that the repeatability between replications was not associated with objective GDTs or PBK word test scores in these subjects.

Figure 6 shows ERPs recorded in all stimulation conditions from three subjects (S10, S13 and S17). Each panel shows responses recorded from one subject. The subject number is listed on the top of each panel. Gap durations used to evoke these responses are labeled for these recording traces. Similar to Figures 3-5, responses recorded in the same stimulation condition are overlapped to show repeatability, each replication represents an average of 100 artifact-free sweeps, and the dashed line indicates the time point when the first 400 ms of stimulation ended. Onset ERPs could be identified for individual replications, as well as the averaged response traces in all three subjects despite differences in response morphology, amplitude and latency. P1 peaks of the onset response are labeled for all three subjects. The ACC was only recorded for the gap duration of 100 ms in subject S13, as shown by the labeled P1 peak of the ACC in the top traces of panel (b). For subjects S10 and S17, the ACC was not measured for any gap durations tested in this study.

Objective GDTs measured in 16 subjects and behavioral GDTs measured approximately one year later in a subgroup of five subjects are listed in Table 2. Objective GDTs showed good association with behavioral GDTs in four subjects (S2, S4, S5 and S7). However, S13 showed a behavioral GDT of 10.21 ms, which is notably different from his objective GDT (i.e. 100 ms).

A two-tailed Spearman's rank correlation test was used to evaluate the potential association between 3-frequency averaged pure-tone hearing thresholds and objective GDTs measured in all subjects participated in this study. The results revealed no association between these two measures ($\rho=0.27$, $p=0.26$). Objective GDTs and aided PBK word scores measured from 16 subjects who completed both tests are listed in Table 2. It should be pointed out that the ACC was not recorded from subject S10 in any stimulation conditions. For this subject, the objective GDT was assigned to be 101 ms. Figure 7 shows aided PBK word scores measured in these subjects plotted as a function of objective GDT. Each dot represents data recorded from one subject. The solid line indicates the linear regression fitted to the data. All eight subjects who showed an objective GDT of 20 ms or longer achieved an aided PBK word score that was lower than 70% correct. In contrast, all subjects except for one (S11) who showed an objective GDT of 10 ms achieved an aided PBK word score that was 70% correct or higher. Results of the one-tailed Spearman's rank correlation test are shown at the upper right corner of Figure 7. This result shows that objective GDTs are significantly correlated with aided PBK word scores ($\rho=-0.81$, $p<0.01$). Overall, these data indicate that subjects with longer objective GDTs are less likely to achieve good open-set speech perception scores with HAs.

Results of one-tailed Spearman's rank correlation tests showed that there was no correlation between aided PBK word scores with: P1 latency of either the onset response ($\rho=-0.13$, $p=0.32$) or the ACC ($\rho=-0.06$, $p=0.42$), N2 latencies of either the onset response ($\rho=0.06$, $p=0.41$) or the ACC ($\rho=0.07$, $p=0.40$), response widths of either the onset response ($\rho=0.22$, $p=0.21$) or the ACC ($\rho=0.26$, $p=0.17$), peak-to-peak amplitudes of either the onset response ($\rho=0.26$, $p=0.16$) or the ACC ($\rho=0.12$, $p=0.33$), or RMS amplitudes of either the onset response ($\rho=0.29$, $p=0.14$) or the ACC response ($\rho=0.07$, $p=0.40$).

DISCUSSION

The overall aim of this study was to evaluate the possibility of using electrophysiological measures of the ACC to identify associations with poor speech perception abilities among children with ANSD and thus, their possible audiological candidacy for cochlear implantation. Two specific aims were studied in order to achieve this overall purpose. The first aim was to evaluate the feasibility of measuring the ACC evoked by temporal gaps in children with ANSD. Subjects tested in this study showed a wide age range. The youngest and oldest subjects were 1.92 and 14.89 years of age at the time of testing, respectively. The ACC evoked by temporal gaps was recorded from 17 of 19 subjects tested in this study. Objective GDTs measured with ACC recordings in these subjects were 10 ms or longer, which is consistent with results reported in Michalewski et al. (2005) and Zeng et al. (2005). These results demonstrate the feasibility of measuring the ACC evoked by temporal gaps in children with ANSD who are older than 1.9 years and who do not have any severe comorbidity. The second aim of this study was to assess the association between temporal resolution capabilities (i.e. GDTs) inferred from ACC measures and open-set speech perception abilities in children with ANSD. Our results revealed a statistically significant association between GDTs measured with the ACC recording and aided PBK word scores in children with ANSD who wore appropriately fitted HAs. In general, subjects with long objective GDTs were less likely to demonstrate good open-set speech ability. All subjects

with an objective GDT of 10 ms, except for subject S11, showed higher aided PBK word scores than subjects with longer objective GDTs. These results suggest that the severity of the temporal resolution deficit correlates well with open-set speech perception abilities in children with ANSD, which is consistent with results of previous studies (Michalewski et al., 2005; Rance et al., 2004; Starr et al., 1991; Zeng et al., 1999, 2001, 2005). One exception was subject S11 who had an objective GDT of 10 ms but only obtained 36% correct on PBK word lists. Previous studies showed that patients with ANSD also show deficits in frequency discrimination (Rance et al., 2004; Zeng et al., 2005) and the degree of this deficit is associated with their speech perception performance (Rance et al., 2004). This subject described that male voices were more difficult to understand than female voices. For the recorded PBK word lists, words were spoken by a male talker. One possibility is that this subject might have deficits in spectral processing. However, Rance et al. (2004) showed that patients with poor speech perception performance have deficits in both temporal resolution and frequency discrimination. These results are inconsistent with the speculation that spectral processing deficits might account for poor speech perception performance measured in S11 in this study. Unfortunately, the PBK word lists with a female speaker were not available and frequency discrimination was not evaluated in this study. Therefore, factors that might account for poor speech perception performance in S11 are still unclear. The ACC was not recorded from two subjects (S10 and S17) in any stimulation condition tested in this study despite clearly identifiable onset responses (Figure 6). Subject S10 achieved 0% correct on the aided PBK word test. Parents reported that the HA only provides benefit for sound awareness to this subject in daily life. Subject S17 was referred to this study due to delayed auditory skills. This subject received a cochlear implant in the test ear shortly after finishing the main study and has been showing satisfactory progress in speech understanding and language development.

Results of several studies have shown that the onset ERP cannot be recorded from a subgroup of subjects with ANSD (Narne & Vanaja, 2008; Pearce et al., 2007; Rance et al., 2002; Sharma et al., 2011; Starr et al., 1996). However, Michalewski et al. (2009) reported that the onset ERP was recorded from all subjects with ANSD tested in their study. Similar to the results reported by Michalewski et al. (2009), the onset ERP was recorded from all children tested in the current study. Differences in degree of pure-tone hearing loss are unlikely to be the factor accounting for this discrepancy since all of these studies showed that the presence/absence of the onset ERP was not dependent on the degree of pure-tone hearing loss. One factor that might account for this discrepancy is the potential difference in subjects with ANSD tested in these studies. It is well known that the ANSD phenotype encompasses a number of auditory dysfunctions and underlying conditions. It is possible that subjects tested in these studies had different degrees of neural dys-synchrony, which might contribute to differences observed across studies. This speculation is supported by the fact that even though many studies have shown that the onset ERP cannot be recorded from all subjects with ANSD, there is a large variation in the percentage of subjects with absent ERP responses across studies. For example, Rance et al. (2002) tested 18 children with ANSD and reported that the onset ERP was not recorded from 7 subjects (approximately 40%). Sharma et al. (2011) measured the onset ERP response from 21 children with ANSD and reported that the response was not recorded from only two subjects (approximately

10%). Another factor that might also account for this discrepancy is the difference in the eliciting stimulus used in these studies. A broadband noise with an abrupt onset was used in this study and in Michalewski et al. (2009). In contrast, clicks (Narne and Vanaja, 2008; Starr et al., 1996), tonebursts (Rance et al., 2002) and speech tokens (Pearce et al., 2007; Rance et al., 2002; Sharma et al., 2011) with relatively slow onsets were used in other studies.

In normal-hearing listeners, the onset ERP shows age-dependent morphological changes due to maturation of the central auditory system (Kraus et al., 1993; Ponton et al., 1996, 2000; Wunderlich et al., 2006). In particular, ERPs in young children with normal hearing consist of a single broad peak (P1) with a latency of approximately 100 ms, followed by a broad negative peak (N2). In normal-hearing adults, the onset ERP consists of three response peaks occurring in sequence: P1, N1 and P2. The N1 can be observed in children between 7 and 9 years of age using a stimulation rate of 0.5 Hz or higher (Gilley et al., 2005; Ponton et al., 2000; Wunderlich et al., 2006). It initially presents as a small dip between P1 and P2 that continuously increases in size with age. The N1 dominates the onset ERP in adult listeners. In children with hearing loss, the normal cortical maturation can be disrupted due to inadequate auditory stimulation (Ponton et al., 1996; Sharma et al., 2002). As a result, the onset ERP may not demonstrate the age-appropriate morphology. The most common finding is that the N1 fails to emerge or emerges late (Eggermont, 2008; Ponton et al., 1996). In this study, the onset ERP responses recorded from all subjects consisted of a P1 and an N2 peak regardless of age at testing. These findings suggest that neural dys-synchrony disrupts normal maturation of the auditory cortex in children with ANSD, which is consistent with results of Sharma et al. (2011).

The presence/absence of the onset ERP has been reported to be positively correlated with speech perception ability in children with ANSD (Rance et al., 2002). However, several other studies have not observed this association (Lee et al., 2001; Hood, 1999). For example, Lee et al. (2001) reported that robust onset ERP responses were recorded from two children with ANSD who had poor speech discrimination scores. Similarly, our results also show that the onset ERP response was recorded from all subjects regardless of their aided PBK word scores.

Consistent with results reported in previous studies (Michalewski et al., 2005; Narne & Vanaja, 2008; Sharma et al., 2011), there were substantial inter-subject variations in peak latencies and amplitudes of the onset response measured in this study. For example, the mean P1 latencies of averaged responses measured across all stimulation conditions from individual subjects ranged from 62.2 to 159.3 ms. Inspection of Table 3 suggests that there is no consistent trend relating P1 latency and aided PBK word score measured in this study. This observation was confirmed by the result of a one-tailed Spearman's rank correlation test. However, Sharma et al. (2011) reported that P1 latency strongly correlated with auditory skill development in children with ANSD. They suggested that P1 latency is a good predictor of behavioral outcomes in these patients. It is unclear what factors account for the discrepancy between our results and those reported in Sharma et al. (2011). However, differences in methodologies used in these two studies do exist. First of all, the stimuli used in the current study were Gaussian noises gated on and off using 1-msec linear ramps

presented at a stimulation rate of 0.5 Hz. In contrast, the stimulus used in Sharma et al. (2011) was a synthesized speech syllable /ba/ presented at a relatively fast stimulation rate (approximately 1.4 Hz). Second, PBK word lists were used to directly evaluate open-set speech perception abilities of subjects tested in this study. By contrast, the Infant Toddler Meaningful Auditory Integration Scale (IT-MAIS) was used in Sharma et al. (2011). The IT-MAIS is a subjective, parent-driven questionnaire assessing the child's auditory awareness and sound identification rather than speech perception ability. Open-set speech perception requires many aspects of auditory processing, including auditory discrimination and integration, beyond awareness and sound identification. Therefore, information provided by the results of these two tests might not be equivalent.

Previous studies have shown that the duration of the interruption in GDT studies can have an effect on the morphology of the ACC response (Atcherson et al., 2009; Michalewski et al., 2005; Pratt et al., 2005, 2007). For example, Michalewski et al. (2005) showed that the ACC evoked by temporal gaps of 20 ms or longer include two N1 negativities (i.e. a double-peaked ACC) in normal-hearing adults. In contrast, the ACC evoked by shorter gaps consists only of one N1 peak in these subjects. It has been proposed that the double-peaked ACC response measured for long gaps may include a combination of offset and onset responses (Michalewski et al., 2005). However, the double-peaked ACC response was not observed in any subjects for any gaps in this study. Two factors might account for this discrepancy. First, Pratt et al. (2007) showed that the presence/absence of the double-peaked ACC is affected by the duration of the pre-gap noise in normal-hearing listeners. The minimum duration of the pre-gap noise required for evoking the double-peaked ACC is just under 500 ms. Second, previous studies have shown that neural generators of ERPs have longer recovery periods in children than in adults (Ceponiene et al., 1998; Gilley et al., 2005). Therefore, the lack of the extra peak evoked by temporal gaps in children with ANSD could be due to insufficient separation between the offset of the leading noise segment and the onset of the trailing noise segment such that responses evoked by the stimulus offset and onset overlapped, resulting in a single broad peak in children with ANSD as observed in this study.

As an addendum to the main study, and undertaken almost a year later, GDTs were measured using a psychophysical procedure in a subgroup of five subjects from the main study. In four of these subjects, the behavioral results showed a close association to the respective objective GDTs, which is consistent with results reported in Michalewski et al (2005). However, one subject (S13) showed a behavioral GDT of 10.21 ms yet had exhibited an objective GDT of 100 ms. This behavioral GDT is comparable to those of ANSD patients who are good HA users as found both in this study and in other previously published studies (Michalewski et al., 2005; Zeng et al., 1999). In contrast, subject S13 has consistently demonstrated poor speech perception performance (8% PBK word score, Table 2). We can offer no explanation for the disparate behavioral GDT relative to the objective GDT and poor speech performance at the current time; further investigation of this interesting case is warranted.

One potential caveat for this study is that a gap duration of 5 ms was not tested in eight subjects and a gap duration of 10 ms was not tested in subject S17 due to time constraints.

However, previous studies have shown that behavioral GDTs measured in school-aged children with normal hearing for broadband noise range from 5-10 ms (Buss et al., 2014; Amaral & Collella-Santos, 2010; Shinn et al., 2009; Trehub et al., 1995; Zaidan & Baran, 2013) and subjects with ANSD had longer GDTs than normal-hearing listeners (Michalewski et al., 2005; Zeng et al., 1999; 2005). In addition, only one subject (S15) among these eight subjects showed an objective GDT of 10 ms. Objective GDTs measured from all other subjects were 20 ms or longer. Even though it is still possible that S15 had an actual objective GDT of 5 ms, reducing the objective GDT measured from this subject from 10 ms to 5 ms did not diminish the robust correlation between PBK word scores and objective GDTs ($\rho = -0.78$, $p < 0.01$). Therefore, it is unlikely that the omission of these conditions materially affected our results.

Two other potential limitations of this study are that ERPs were recorded using only one midline recording channel, and only 200 artifact-free sweeps were recorded for each stimulation condition. Previous studies have shown that a single-channel recording cannot provide information about differences in EEG pattern across the hemispheres (Pratt et al., 2005; Tremblay et al., 2009). The long-term goal of this research is to develop objective tools that can be used in clinical settings for young pediatric patients. Multi-channel recordings require a significant patient preparation time, which can be prohibitively challenging in pediatric patients in a clinical setting. In keeping with this long-term goal, the recording methodology used in this study represented a compromise between an ideal approach and a practical, yet informative, approach. Response amplitude is likely to be somewhat compromised by the montage (i.e. Fz) used in this study. However, ERPs recorded in this study are still typically robust. In terms of number of sweeps per average, two replications of 100 artifact-free sweeps typically yield ERP recordings with an acceptable signal-to-noise ratio (Brett et al., 2007). However, this number might not be sufficient in subjects with ANSD. In this study, both subjective and objective criteria were used to evaluate these ERP responses in order to minimize measurement error. In addition, S2 and S13 were retested approximately 12 and 24 months after the initial test session, respectively. In these retests, ERPs were recorded using the same stimulus and protocol by the same researcher except that more artifact-free sweeps were collected in S13. The left and right panels of Figure 8 show averaged ERPs recorded for the two recording sessions in S2 and S13, respectively. For both subjects, solid lines indicate averaged ERPs recorded in the initial test session and dashed lines indicate averaged responses recorded in the second test session. The P1 peaks of the onset and the ACC responses are labelled in black and red, respectively. For S2, each trace represents an averaged response of 200 artifact-free sweeps collected in each test session. For S13, two replications of 100 artifact-free sweeps were collected for each stimulation condition in the initial test session. In the second test session, four replications of 100 artifact-free sweeps were collected for the 5 ms-, 10 ms-, 20 ms- and 50 ms-gap conditions. For the control condition and the 100 ms-gap condition, seven replications of 100 artifact-free sweeps were collected. For both subjects, ERP responses replicated very well between recording sessions for the same stimulation conditions. In addition, it is evident that ERPs measured in different recording sessions yielded the same GDT for both subjects (i.e., 20 ms for S2 and 100 ms for S13). These data suggest that averaged ERP responses based on 200 artifact-free sweeps as collected in this study are

robust and informative. It should be emphasized that ERP responses in this study were recorded in subjects with ANSD using acoustic stimuli. These responses may appear to be “noisier” than those typically reported from subjects who do not have ANSD (e.g. normal-hearing listeners). It is possible that ERP responses recorded in subjects with ANSD include a higher background noise than those recorded in subjects without ANSD. However, a robust ERP response requires a high degree of neural synchronization, and it is likely that subjects with ANSD exhibit a wide range of neural synchronization abilities. Therefore, the higher background noise observed in these subjects is likely internal to their auditory systems and can be considered integral to their auditory neural responses.

Finally, it should be pointed out that measuring the ACC in children with ANSD can be time-consuming and challenging. Even though our results demonstrate that it is feasible to objectively measure GDT using the ACC in all subjects with ANSD tested in this study, it is still unknown whether it is feasible to do so in infants and young children, or in patients with severe comorbidities. Therefore, the conclusions of this study should not be generalized beyond the subject profile tested here.

CONCLUSION

The onset ERP response was recorded from all subjects tested in this study. The clinical application of the onset ERP in predicting open-set speech perception ability in children with ANSD is relatively limited. The ACC can potentially be used to objectively assess temporal resolution abilities in children with ANSD, at least in those who are older than 1.9 years and who do not have other severe comorbidities. There was a negative correlation between objective GDTs measured using the ACC and aided PBK word scores. Subjects with long objective GDTs are less likely to receive substantial benefits from their HAs. These results suggest that the ACC can potentially be used as a clinical tool to identify potential candidates for cochlear implantation in children with ANSD.

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REFERENCES

- Amaral MIRD, Colella-Santos MF. Temporal resolution: performance of school-aged children in the GIN –Gaps-in-noise test. *Braz J Otorhinolaryngol*. 2010; 76:745–752. [PubMed: 21180943]
- Atcherson SR, Gould HJ, Mendel MI, et al. Auditory N1 component to gaps in continuous narrowband noises. *Ear Hear*. 2009; 30:687–695. [PubMed: 19675460]
- Berlin CI, Hood LJ, Morlet T, et al. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). *Int J Audiol*. 2010; 49:30–43. [PubMed: 20053155]

- Bielecki I, Horbulewicz A, Wolan T. Prevalence and risk factors for auditory neuropathy spectrum disorder in a screened newborn population at risk for hearing loss. *Int J Pediatr Otorhinolaryngol*. 2013; 76:1668–1670. [PubMed: 22939890]
- Bagatto M, Moodie S, Scollie S, et al. Clinical protocols for hearing instrument fitting in the Desired Sensation Level method. *Trends Amplif*. 2005; 9:199–226. [PubMed: 16424946]
- Busby PA, Clark GM. Gap detection by early-deafened cochlear-implant subjects. *J. Acoust. Soc. Am*. 1999; 105:1841–1852. [PubMed: 10089607]
- Buss E, Hall JW 3rd, Porter H, et al. Gap detection in school-age children and adults: effects of inherent envelope modulation and the availability of cues across frequency. *J. Speech Lang. Hear. Res*. 2014 [Epub ahead of print].
- Ceponiene R, Cheour M, Naatanene R. Interstimulus interval and auditory event-related potentials in children: evidence for multiple generators. *Electroencephalogr Clin Neurophysiol*. 1998; 108:345–354. [PubMed: 9714376]
- Deltenre P, Mansbach AL, Bozet C, et al. Auditory neuropathy with preserved microphonics and secondary loss of otoacoustic emissions. *Int J Audiol*. 1999; 38:187–195.
- Dmitrijevic A, Starr A, Bhatt S, et al. Auditory cortical N100 in pre- and post-synaptic auditory neuropathy to frequency or intensity changes of continuous tones. *Clin Neurophysiol*. 2011; 122:594–604. [PubMed: 20822952]
- Eggermont JJ. The role of sound in adult and developmental auditory cortical plasticity. *Ear Hear*. 2008; 29:819–829. [PubMed: 18941413]
- Fushs H, Glowatzki E, Moser T. The afferent synapse of cochlear hair cells. *Current Opinion Neurobiol*. 2003; 13:452–458.
- Gilley PM, Sharma A, Dorman M, et al. Developmental changes in refractoriness of the cortical auditory evoked potential. *Clin Neurophysiol*. 2005; 116:648–657. [PubMed: 15721079]
- He S, Grose J, Teagle HFB, et al. Gap detection measured with electrically-evoked auditory event-related potentials and speech perception abilities in children with auditory neuropathy spectrum disorder. *Ear Hear*. May 29, 2013a (Epub ahead of print).
- He S, Grose J, Teagle HFB, et al. Objective measures of electrode discrimination with electrically evoked auditory change complex and speech-perception abilities in children with auditory neuropathy spectrum disorder. *Ear Hear*. 2013b (Accepted).
- He S, Grose JH, Buchman CA. Auditory discrimination: the relationship between psychophysical and electrophysiological measures. *Int J Audiol*. 2012; 51:771–782. [PubMed: 22998415]
- Hood L. A review of objective methods of evaluating auditory neural pathways. *Laryngoscope*. 1999; 109:1745–1748. [PubMed: 10569400]
- Kraus N, Bradlow AR, Cheatham J, et al. Consequences of neural asynchrony: a case of auditory neuropathy. *J Assoc Res Otolaryngol*. 2000; 1:33–45. [PubMed: 11548236]
- Kraus N, McGee T, Carrell T, et al. Speech-evoked cortical potentials in children. *J Am Acad Audiol*. 1993; 4:238–248. [PubMed: 8369541]
- Lee JS, McPherson B, Yuen KC, et al. Screening for auditory neuropathy in a school of hearing impaired children. *Int J Pediatr Otorhinolaryngol*. 2001; 61:39–46. [PubMed: 11576630]
- Levitt H. Transformed up-down methods in psychoacoustics. *J. Acoust. Soc. Am*. 1971; 49:467–477. [PubMed: 5541744]
- Lister JJ, Maxfield ND, Pitt GJ. Cortical evoked response to gaps in noise: within-channel and across channel conditions. *Ear Hear*. 2007; 28:862–878. [PubMed: 17982372]
- Madden C, Hilbert L, Rutter M, et al. Pediatric cochlear implantation in auditory neuropathy. *Otol Neurotol*. 2002; 23:163–168. [PubMed: 11875345]
- Martin BA, Tremblay KL, Korczak P. Speech evoked potentials: From the laboratory to the clinic. *Ear Hear*. 2008; 29:285–313. [PubMed: 18453883]
- Martin, BA.; Tremblay, KL.; Stapells, DR. Principles and applications of cortical auditory evoked potentials. In: Burkard, RF.; Don, M.; Eggermont, JJ., editors. *Auditory Evoked Potentials: Basic Principles and Clinical Application*. Lippincott Williams & Wilkins; Philadelphia: 2007. p. 482-507.

- Michalewski HJ, Starr A, Zeng FG, et al. N100 cortical potentials accompanying disrupted auditory nerve activity in auditory neuropathy (AN): effect of signal intensity and continuous noise. *Clin Neurophysiol.* 2009; 120:1352–1363. [PubMed: 19535287]
- Michalewski HJ, Starr A, Nguyen TT, et al. Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy. *Clin Neurophysiol.* 2005; 116:669–680. [PubMed: 15721081]
- Narne VK, Vanaja CS. Speech identification and cortical potentials in individuals with auditory neuropathy. *Behavioral Brain Funct.* 2008; 4:15–23.
- Ponton CW, Don M, Eggermont JJ, et al. Maturation of human cortical auditory function: differences between normal-hearing children and children with cochlear implants. *Ear Hear.* 1996; 17:430–437. [PubMed: 8909891]
- Ponton CW, Eggermont JJ, Kwong B, et al. Maturation of human central auditory system activity: evidence from multi-channel evoked potentials. *Clin Neurophysiol.* 2000; 111:220–236. [PubMed: 10680557]
- Palmer SB, Musiek FE. N1-P2 recordings to gaps in broadband noise. *J Am Acad Audiol.* 2013; 24:37–45. [PubMed: 23231815]
- Pearce W, Golding M, Dillon H. Cortical auditory evoked potentials in the assessment of auditory neuropathy: two case studies. *J Am Acad Audiol.* 2007; 18:380–390. [PubMed: 17715648]
- Pratt H, Bleich N, Mittelman N. The composite N1 component to gaps in noise. *Clin. Neurophysiol.* 2005; 116:2648–2623. [PubMed: 16221565]
- Pratt H, Starr A, Michalewski HJ, et al. The N1 complex to gaps in noise: effects of preceding noise duration and intensity. *Clin Neurophysiol.* 2007; 118:1078–1087. [PubMed: 17321795]
- Rance G. Auditory neuropathy/dys-synchrony and its perceptual consequences. *Trends Amplif.* 2005; 9:1–43. [PubMed: 15920648]
- Rance G, Barker EJ. Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *Int J Audiol.* 2009; 48:313–320. [PubMed: 19925339]
- Rance G, Barker EJ. Speech perception in children with auditory neuropathy/dyssynchrony managed with either hearing AIDS or cochlear implants. *Otol Neurotol.* 2008; 29:179–182. [PubMed: 18165792]
- Rance G, Barker EJ, Mock M, et al. Speech perception in noise for children with auditory neuropathy/dys-synchrony type hearing loss. *Ear Hear.* 2007; 28:351–360. [PubMed: 17485984]
- Rance G, Cone-Wesson B, Wunderlich J, et al. Speech perception and cortical event related potentials in children with auditory neuropathy. *Ear Hear.* 2002; 23:239–253. [PubMed: 12072616]
- Rance G, Cone-Wesson B, Shepherd RK, et al. Clinical findings for a group of infants and young children with auditory neuropathy. *Ear Hear.* 1999; 20:238–252. [PubMed: 10386850]
- Rance G, McKay C, Grayden D. Perceptual characterization of children with auditory neuropathy. *Ear Hear.* 2004; 25:34–46. [PubMed: 14770016]
- Runge CL, Jensen J, Friedland DR, et al. Aiding and occluding the contralateral ear in implanted children with auditory neuropathy spectrum disorder. *J Am Acad Audiol.* 2011; 22:567–577. [PubMed: 22192602]
- Sharma A, Cardon G, Henion K, et al. Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder. *Int J Audiol.* 2011; 50:98–106. [PubMed: 21265637]
- Sharma A, Dorman M, Spahr A. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear.* 2002; 23:532–539. [PubMed: 12476090]
- Shinn JB, Chermak GD, Musiek FE. GIN (Gaps-In-Noise) performance in the pediatric population. *J Am Acad Audiol.* 2009; 20:229–238. [PubMed: 19927695]
- Starr A, McPherson D, Patterson J, et al. Absence of both auditory evoked potentials and auditory percepts dependent on timing cues. *Brain.* 1991; 111:1157–1180. [PubMed: 2065245]
- Starr A, Michalewski HJ, Zeng FG, et al. Pathology and physiology of auditory neuropathy with a novel mutation in the MPZ gene. *Brain.* 2003; 121:1604–1619. [PubMed: 12805115]

- Starr A, Picton TW, Sininger Y, et al. Auditory neuropathy. *Brain*. 1996; 119:741–753. [PubMed: 8673487]
- Starr A, Sininger Y, Pratt H. The varieties of auditory neuropathy. *J Basic Physiol Pharmacol*. 2000; 11:215–230.
- Scollie S, Seewald R, Cornelisse L, et al. The Desired Sensation Level multistage input/output algorithm. *Trends Amplif*. 2005; 9:159–197. [PubMed: 16424945]
- Starr, A.; Zeng, FG.; Michalewski, HJ., et al. Perspectives in auditory neuropathy: Disorders of the inner hair cell, auditory nerve, and their synapses. In: Dallos, P.; Oertel, D., editors. *The senses: A comprehensive reference*. Academic Press; San Diego, CA: 2008. p. 397–412.
- Tremblay KL, Shahin AJ, Pitcon T, et al. Auditory training alters the physiological detection of stimulus-specific cues in humans. *Clin. Neurophysiol*. 2009; 120:128–135. [PubMed: 19028139]
- Trehub SE, Schneider BA, Henderson JL. Gap detection in infants, children, and adults. *J Acoust Soc Am*. 1995; 98:2532–2541. [PubMed: 7593935]
- Werner LA, Folsom RC, Mancl LR, et al. Human auditory brainstem response to temporal gaps in noise. *J Speech Lang Hear Res*. 2001; 44:737–750. [PubMed: 11521768]
- Wunderlich JL, Cone-Wesson BK, Shepherd R. Maturation of the cortical auditory evoked potential in infants and young children. *Hear Res*. 2006; 212:185–202. [PubMed: 16459037]
- Zaidan E, Baran JA. Gaps-in-noise (GIN[®]) test results in children with and without reading disabilities and phonological processing deficits. *Int J Audiol*. 2013; 52:113–123. [PubMed: 23167240]
- Zeng FG, Kong YY, Michalewski HJ, et al. Perceptual consequences of disrupted auditory nerve activity. *J Neurophysiol*. 2005; 93:3050–3063. [PubMed: 15615831]
- Zeng FG, Liu S. Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear Res*. 2006; 49:367–380. [PubMed: 16671850]
- Zeng, FG.; Oba, S.; Garde, S., et al. Psychoacoustic and speech perception in auditory neuropathy. In: Sininger, Y.; Starr, A., editors. *Auditory Neuropathy: A new perspective on hearing disorder*. Singular Press; San Diego, CA: 2001. p. 141–164.
- Zeng FG, Oba S, Garde S, et al. Temporal and speech processing deficits in auditory neuropathy. *Neuroreport*. 1999; 10:3429–3435. [PubMed: 10599857]

Figure 1.

Schematic illustrations of the stimulation paradigm used in the “*control condition*” (upper panel) where 800-ms Gaussian noise was delivered to the test ear without any interruption and the “*100ms-gap condition*” (lower panel) where a 100-ms temporal gap was inserted into the stimulus after 400-ms of stimulation. Stimulus onset is denoted by dashed vertical gray line.

Figure 2.

ERP responses recorded in all subjects for the *control condition* (left panel) and the 100 ms gap condition (right panel). Each gray line represents an averaged response of 100 artifact-free sweeps. Two replications recorded for each stimulation condition are overlapped to show the repeatability. Black lines indicate averaged responses of two replications recorded in the same stimulation condition. The dashed line indicates the time point at which the first 400-ms of stimulation ended. Onset P1 marked with filled inverted triangle; ACC P1 marked with unfilled inverted triangle.

Figure 3.

ERP responses recorded from eight subjects with ANSD who had a GDT of 10 ms. Stimulation conditions where these responses were recorded are listed on top of each panel. Subject numbers are listed at the left of panel (a). P1 peaks of the onset and the ACC responses are labeled for these traces. Gray traces are replications of at least 100-sweep averages; solid black trace is the average of the replications. Panel (a) shows responses recorded in the “*control condition*”, panel (b) shows responses recorded in the “*10-ms gap condition*” (i.e. their GDTs), and panel (c) shows responses recorded in the “*100-ms gap condition*”.

Figure 4.

ERP responses recorded from four subjects with ANSD who had a GDT of 20 ms. Panel (a) shows responses recorded in the “control condition”, panel (b) shows responses recorded in the “10-*ms gap condition*”, panel (c) shows responses measured in the “20-*ms gap condition*” and panel (d) shows responses recorded in the “100-*ms gap condition*”. P1 peaks of the onset and the ACC responses are labeled for these traces. Gray traces are replications of at least 100-sweep averages; solid black trace is the average of the replications.

Figure 5.

ERP responses recorded from three subjects with ANSD who had a GDT of 50 ms. Panel (a) shows responses recorded in the “*control condition*”, panel (b) shows responses recorded in the “*20-ms gap condition*”, panel (c) shows responses measured in the “*50-ms gap condition*” and panel (d) shows responses recorded in the “*100-ms gap condition*”. Subject numbers are listed at the left to panel (a). P1 peaks of the onset and the ACC responses are labeled for these traces. Gray traces are replications of at least 100-sweep averages; solid black trace is the average of the replications.

Figure 6.

ERP responses recorded from three subjects with ANSD who had a GDT of 100 ms or longer. Each panel shows responses recorded from one subject. Subject numbers are listed on the top of these panels. Gap durations used to evoke these ERP responses and P1 peaks of the onset response are labeled for these traces. The ACC was only recorded from subject S13 in the “100-ms gap condition”. P1 peak of this change potential is also labeled. Gray traces are replications of at least 100-sweep averages; solid black trace is the average of the replications.

Figure 7.

Scattergram of individual GDTs measured with the ACC against PBK word test score. The solid line shows the linear regression fitted to all data. Results of a one-tailed Spearman's rank correlation test are shown in the upper right corner of the graph.

Figure 8.

ERPs recorded in subjects S2 and S13 in two recording sessions separated by 12 and 24 months, respectively. Subject number is indicated in the lower left corner of each graph. Gap duration tested in each stimulation condition is labeled for these traces.

Table 1

Demographic information of all subjects who participated in this study.

Subject number	Gender	Risk factor	Ear tested	Age at diagnosis (year)	Age at hearing aid fitting (year)	Age at testing (year)	3-Frequency Pure-Tone Average (dB HL)
1	M	Prematurity, hyperbilirubinemia	L	1.07	1.08	5.79	53.33
2	F	Prematurity, hyperbilirubinemia	R	0.04	1.29	9.45	71.67
3	M	Prematurity, hyperbilirubinemia	R	0.57	0.84	9.07	73.33
4	M	Prematurity	R	0.59		6.84	25.00
5	M	Prematurity	R	5.68		6.16	23.33
6	M	Prematurity	L	0.45	0.97	3.79	91.67
7	M	Prematurity	L	0.49	5.40	12.28	43.33
8	M	Prematurity, hyperbilirubinemia	R	3.47	3.24	8.01	58.33
9	M	Prematurity	L	1.74	1.74	8.68	35.00
10	F	Prematurity, hypoxia	L	2.53	2.53	10.81	61.67
11	M	Prematurity, hyperbilirubinemia	L	0.78	0.78	7.25	73.33
12	F	Prematurity	L	2.03	2.08	5.39	80.00
13	M	none	L	5.03	3.20	14.89	80.00
14	M	Prematurity	L	0.88	2.96	9.80	46.67
15	M	Prematurity, hyperbilirubinemia	R	1.50	1.50	10.87	85.00
16	M	Prematurity	R	1.70	1.82	6.09	58.33
17	M	Prematurity,	L	0.86	1.17	1.92	55.00
18	M	Unknown	R	2.13	2.04	3.12	60.00
19	F	Prematurity, hyperbilirubinemia	R	0.42	2.00	7.18	56.67

Table 2

Gap detection thresholds (GDTs) and Phonetically Balanced Kindergarten (PBK) word scores measured from 16 subjects tested in this study.

Subject number	PBK word (%)	Objective GDT (ms)	Behavioral GDT (ms)
1	44	50	DNT ♦
2	56	20	27.42
3	84	10	DNT
4	92	10	13.64
5	84	10	11.73
7	92	10	10.32
8	68	20	DNT
9	44	10	DNT
10	0	101 [*]	DNT
11	36	10	DNT
12	52	50	DNT
13	8	100	10.21
14	81	10	DNT
15	70	10	DNT
16	76	10	DNT
19	8	50	DNT

* The auditory change complex was not recorded for temporal gaps with duration of 100 ms or less. For this subject, the gap detection threshold was assigned to be 101 ms.

♦ DNT: did not test

Table 3

Means and standard deviations (parentheses) for latency and amplitude of the onset ERP and the ACC responses.

Subject Number	Onset Response				ACC				Noise Floor
	Latency (ms SD)		Amplitude (μ V SD)		Latency (ms SD)		Amplitude (μ V SD)		RMS Amplitude (mV SD)
	P1	N2	Peak-to-Peak	RMS	P1	N2	Peak-to-Peak	RMS	
S1	70.4 (15.5)	192.4 (27.1)	5.3 (1.1)	2.0 (0.5)	498.7 (18.6)	616.3 (25.4)	3.64 (0.9)	1.2 (0.3)	0.2 (0.2)
S2	103.5 (3.8)	203.8 (11.3)	8.9 (1.2)	3.0 (0.4)	495.7 (10.8)	579.7 (11.0)	1.9 (0.4)	0.9 (0.1)	0.1 (0.1)
S3	92.8 (12.6)	177.3 (16.5)	5.3 (1.5)	2.0 (0.5)	496.7 (14.6)	634.3 (24.6)	3.0 (1.6)	1.1 (0.3)	0.4 (0.2)
S4	72.7 (9.4)	200 (16.0)	8.6 (0.7)	3.4 (0.3)	484.7 (3.2)	619 (33.3)	5.7 (2.3)	1.7 (0.8)	0.4 (0.2)
S5	88.7 (2.5)	183.8 (10)	7.0 (1.2)	2.4 (0.5)	513.7 (39.5)	600 (64.6)	1.4 (0.4)	0.6 (0.1)	0.4 (0.1)
S6	125.2 (23.2)	228.2 (18.6)	3.1 (1.0)	1.2 (0.5)	499.0 (27.9)	571.7 (13.1)	2.4 (1.7)	0.8 (0.4)	0.4 (0.1)
S7	69.0 (16.8)	218.7 (16.7)	4.8 (0.8)	1.7 (0.3)	507.0 (22.1)	644.8 (24.0)	2.0 (1.3)	0.7 (0.1)	0.4 (0.2)
S8	74.3 (6.7)	158.7 (13.8)	6.9 (1.5)	2.9 (0.5)	498.3 (21.4)	604.7 (19.9)	2.7 (1.1)	1.6 (0.4)	0.3 (0.2)
S9	87.8 (20.2)	173.7 (16.4)	3.2 (1.2)	1.2 (0.4)	488.0 (51.8)	604.0 (8.8)	1.7 (1.0)	0.9 (0.3)	0.4 (0.2)
S10	159.3 (24.9)	260.5 (16.3)	2.3 (0.4)	0.7 (0.2)					0.4 (0.2)
S11	82.3 (7.3)	199.0 (11.2)	8.6 (1.0)	3.1 (0.2)	501.5 (13.0)	567.3 (14.8)	1.3 (0.1)	0.6 (0.1)	0.2 (0.1)
S12	105.8 (14.9)	219.2 (12.9)	8.3 (1.5)	2.5 (0.6)	541	638.5	4.1	1.1	0.6 (0.2)
S13	80.5 (25.1)	192.2 (6.2)	3.5 (0.9)	1.1 (0.2)	556	615	2	0.7	0.3 (0.1)
S14	77.6 (8.4)	260.4 (14.1)	4.1 (1.8)	1.1 (0.5)	495.7 (2.5)	590.7 (15)	4.7 (0.4)	1.6 (0.2)	0.6 (0.3)
S15	97.0 (11.5)	218.7 (21)	7.1 (0.9)	2.4 (0.4)	511 (17.8)	624.5 (27.3)	4.9 (0.5)	1.5 (0.4)	0.3 (0.1)
S16	88.8 (17.4)	206.8 (7.1)	6.7 (1.4)	2.5 (0.6)	484.8 (4.0)	570.0 (26.8)	5.2 (1.2)	1.6 (0.5)	0.4 (0.4)
S17	152.8 (14.7)	287.0 (29.5)	5.0 (1.5)	1.2 (0.8)					0.7 (0.1)
S18	102.2 (5.0)	193.2 (10.0)	7.3 (1.4)	2.5 (0.5)	499.7 (16.1)	684.7 (35.1)	6.4 (0.5)	2.1 (0.2)	0.6 (0.3)
S19	62.2 (19.5)	180.6 (10.6)	5.4 (1.6)	2.0 (0.6)	456	645	7.24	2.3	0.3 (0.1)
Group	90 (4.5)	197.3 (17.5)	4.6 (0.2)	1.8 (0.1)	481 (9.1)	589.5 (14.0)	1.7 (0.9)	0.6 (0.3)	0.1 (0.1)