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The Electrically Evoked Auditory Change Complex Evoked by Temporal Gaps using Cochlear Implants or Auditory Brainstem Implants in Children with Cochlear Nerve Deficiency

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Abstract

Objective—This study aimed to 1) establish the feasibility of measuring the electrically evoked auditory change complex (eACC) in response to temporal gaps in children with cochlear nerve deficiency (CND) who are using cochlear implants (CIs) and/or auditory brainstem implants (ABIs); and 2) explore the association between neural encoding of, and perceptual sensitivity to, temporal gaps in these patients.

Design—Study participants included five children (S1–S5) ranging in age from 3.8 to 8.2 years (mean: 6.3 years) at the time of testing. All subjects were unilaterally implanted with a Nucleus 24M ABI due to CND. For each subject, two or more stimulating electrodes of the ABI were tested. S2, S3 and S5 previously received a CI in the contralateral ear. For these three subjects, at least two stimulating electrodes of their CIs were also tested. For electrophysiological measures, the stimulus was an 800-ms biphasic pulse train delivered to individual electrodes at the maximum comfortable level (C level). The electrically evoked responses, including the onset response and the eACC, were measured for two stimulation conditions. In the *standard condition*, the 800-ms pulse train was delivered uninterrupted to individual stimulating electrodes. In the *gapped condition*, a temporal gap was inserted into the pulse train after 400 ms of stimulation. Gap durations tested in this study ranged from 2 up to 128 ms. The shortest gap that could reliably evoke the eACC was defined as the objective gap detection threshold (GDT). For behavioral GDT

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measures, the stimulus was a 500-ms biphasic pulse train presented at the C level. The behavioral GDT was measured for individual stimulating electrodes using a one-interval, two-alternative forced-choice procedure.

Results—The eACCs to temporal gaps were recorded successfully in all subjects for at least one stimulating electrode using either the ABI or the CI. Objective GDTs showed inter-subject variations, as well as variations across stimulating electrodes of the ABI or the CI within each subject. Behavioral GDTs were measured for one ABI electrode in S2 and for multiple ABI and CI electrodes in S5. All other subjects could not complete the task. S5 showed smaller behavioral GDTs for CI electrodes than those measured for ABI electrodes. One CI and two ABI electrodes in S5 showed comparable objective and behavioral GDTs. In contrast, one CI and two ABI electrodes in S5 and one ABI electrode in S2 showed measurable behavioral GDTs but no identifiable eACCs.

Conclusions—The eACCs to temporal gaps were recorded in children with CND using either ABIs or CIs. Both objective and behavioral GDTs showed inter- and intra-subject variations. Consistency between results of eACC recordings and psychophysical measures of GDT was observed for some but not all ABI or CI electrodes in these subjects.

Keywords

Auditory brainstem implant; electrically-evoked cortical auditory event-related potentials; auditory temporal processing

INTRODUCTION

The auditory brainstem implant (ABI) is an implantable device that bypasses the auditory nerve and directly stimulates the cochlear nucleus in the auditory brainstem. Recently, under experimental protocols with Investigational Device Exemption (IDE), ABIs with surface electrode arrays have been used in the United States as a treatment option for children with cochlear nerve deficiency (CND) (Buchman et al., 2006). CND refers to a small (hypoplastic) or absent (aplastic) cochlear nerve as revealed by the results of high-resolution magnetic resonance imaging (MRI). Unfortunately, the imaging technique offers limited spatial resolution and provide no information about the functional status of the auditory pathway. Consequently, pre-operative MRI results cannot be used to select or predict outcomes of amplification devices for children with CND (Kutz et al., 2011; Song et al., 2011).

The ABI may be the only treatment option for enabling auditory perception in children with cochlear nerve aplasia. However, there is a standing debate over whether the ABI or the cochlear implant (CI) is the optimal treatment option for children with cochlear nerve hypoplasia. Auditory brainstem implantation is more risky and expensive than cochlear implantation. In addition, due to the novelty of its use and limited access for children, the long-term ABI outcomes in children are unknown. Therefore, selecting the ABI over the CI can be justified only if it provides more benefit than the CI. Unfortunately, there is no indicator for predicting CI or ABI benefit for individual children with CND. As a result, there is no evidence for supporting device selection (i.e. ABI or CI) in these patients.

Currently, children with CNDe are recommended to undergo cochlear implantation prior to auditory brainstem implantation whenever feasible (Yamazaki et al., 2015). For patients who cannot benefit from the CI, a timely transition to the ABI may be crucial for the achievement of maximum potential of speech and language development. Currently, the decision regarding whether individual children shall be implanted with an ABI after a trial of CI is primarily based on the team's assessment of benefit from the CI. This may be challenging because many children with CNDe have multiple disabilities or medical conditions that limit their abilities to provide reliable behavioral responses regardless of age. The absence of reliable predictors of CI benefits in these patients delays appropriate intervention, which may create periods of auditory deprivation that can have lasting detrimental effects on communication skill development. Therefore, there is a clinical need for developing tools that can be used to evaluate benefits provided by the CI and the ABI in children with CNDe.

Successful processing of spectro-temporal stimuli such as speech requires, at a minimum, sufficient abilities to discriminate sound along its frequency and temporal dimensions. The construct of the cochlear nucleus is more complex and less predictably organized tonotopically, compared to the organization of the cochlea. Thus, ABI surface electrodes (arranged in rows) may not approximate a tonotopic axis for stimulation. In addition, many patients with ABIs require high stimulation levels and wide pulse durations to achieve auditory perceptions. The resulting broad neural excitation is expected to provide limited spectral information. Consistent with this prediction, many ABI patients are not able to pitch-rank electrodes regardless of their performance on speech perception tasks (Colletti & Shannon, 2005; McKay et al., 2015; Otto et al., 2002). This inability of ABI stimulation to provide discrete, spectrally-specific auditory stimulation suggests that speech perception among successful ABI users is primarily dependent on temporal cues. Using behavioral procedures, Colletti & Shannon (2005) established a positive association between temporal processing capability and speech perception in adult ABI users. These results support the notion that it will be crucial to evaluate whether the ABI can provide better temporal cues than the CI for children with CNDe. This information could provide an answer to the clinical question regarding whether the ABI or the CI should be selected for these patients. Specifically, if the ABI does not provide better temporal information than the CI, it should not be recommended as the first-line of treatment due to its great risk, high cost, and limited spectral resolution. To date, it has not been investigated how well temporal information is processed and perceived in pediatric ABI users with CNDe or CI users with cochlear nerve hypoplasia, presumably due to the lack of assessment tools that can be used in these patient populations.

Temporal resolution refers to the ability of the auditory system to detect changes in stimuli over time. Gap detection (i.e. identify a silent interval embedded within a stimulus) is one of the most widely used testing paradigms for evaluating temporal resolution acuity. It can be reliably measured in CI users using both psychophysical procedures (e.g. Garadat & Pfingst, 2011; Shannon, 1992) and electrophysiological measures of the electrically evoked auditory change complex (eACC) (He et al., 2013). Prolonged gap detection thresholds (GDTs) are associated with poor speech perception performance in CI users (e.g. Busby & Clark, 1999; He et al., 2013; Sagi et al., 2009). The eACC is a neural response generated in the central auditory system of implanted patients that can be recorded from surface electrodes placed on

the scalp. It can be elicited by stimulus change(s) occurring within an ongoing, long-duration electrical stimulation. The presence of the eACC provides an indication of auditory discrimination capability at the auditory cortex (Martin et al., 2008). Unlike behavioral procedures, measuring the eACC does not require active participation from listeners, which is ideal for testing young children and children with multiple impairments. The feasibility of measuring the eACC evoked by temporal gaps in implanted children has been established in one of our previous studies (He et al., 2013). Their results revealed a robust negative correlation between gap detection thresholds measured using eACC recordings and speech perception scores in these listeners. Therefore, the eACC holds great promise to be used as an objective tool for evaluating neural encoding and processing of temporal cues in children with CNL. However, high electrical charge levels (pulse phase duration $\times$ stimulation level) are typically needed in these patients, which can potentially create excessive stimulus artifact contamination in electrophysiological recordings. To date, the feasibility of measuring the eACC in patients with ABIs or children with CIs who have cochlear nerve hypoplasia has not been established.

This study aimed to 1) establish the feasibility of measuring the eACC in response to temporal gaps in children with CNL who are using CIs and/or ABIs; and 2) explore the association between neural encoding of, and perceptual sensitivity to, temporal gaps in these patients. It was hypothesized that the eACC could be used to objectively evaluate temporal resolution acuity in children with CNL.

METHODS

Subjects

Study participants included five pediatric ABI users (S1–S5) ranging in age from 3.8 to 8.2 years (Mean = 6.3 yrs, SD = 1.7 yrs) at the time of testing. Each subject participated in multiple testing sessions scheduled on multiple visits. All subjects were pre-lingually deaf and diagnosed with CNL based on diagnostic imaging protocols reported in Buchman et al. (2006). The terms aplasia and hypoplasia are not used to describe subjects tested in this study due to diagnosis uncertainty caused by limited spatial resolution of current MRI technique. All subjects were unilaterally implanted with a Cochlear Nucleus 24M ABI and had at least 12 months of experience with their devices. Electrically evoked intra- and post-operative auditory brainstem responses (eABRs) were recorded for ABI electrodes tested in this study in S1–S4. The presence/absence of the intra- or post-operative eABR in S5 is unknown because she was implanted at another medical center. For all subjects, ABI devices were programmed using a SPEAK processing strategy. The stimuli used in their programming maps were presented with a pulse rate of 250 pulses per second (pps) per channel in monopolar-coupled stimulation mode (MP1+2). The pulse duration ranged from 100 to 300 μ s per phase and the interphase gap was 45 μ s.

S2, S3 and S5 were also implanted with a Cochlear Nucleus Freedom (24RE) CI in the contralateral ear. Their CIs were programmed using a SPEAK processing strategy. The stimulation mode was MP1+2. The pulse rate was 500 pps per channel for S2 and S5; and 250 pps per channel for S3. The pulse duration was 88 μ s per phase for S2 and S3; and 75 μ s per phase for S5. The interphase gap of 45 μ s was used for all CI programming maps.

Detailed demographic information and speech perception scores for these subjects are listed in Table 1. After at least one year of ABI use, S1–S4 demonstrated only limited close-set speech perception capabilities evaluated using the Standard Early Speech Perception (ESP-S) test (Moog & Geers, 1990). S5 developed limited open-set speech perception capability with her CI prior to auditory brainstem implantation and with her ABI alone. Hers scores on the Multisyllabic Lexical Neighborhood Test (MLNT, Kirk et al., 1995) and Common Phrase Test are listed in Table 1.

The study was approved by the local Biomedical Institutional Review Board. All subjects received payment for their participation, and written, informed consent was obtained from all legal guardians prior to participation.

Procedures

In this study, the speech processor was bypassed and the electrical stimulus was directly delivered to individual ABI or CI electrodes. Stimulating electrodes tested for each subject are listed in Table 1. Each subject participated in electrophysiological measures of the eACC. Behavioral measures of GDT were attempted in all subjects except for S3. The stimulus used in this study was created using custom-designed software incorporating Nucleus Interface Communication programming routines (NIC v2). It was presented in a stimulation mode of MP1+2 and was delivered directly to individual stimulating electrodes using a research interface. The stimulus was presented at the maximum comfortable level (C level) measured for each subject and each electrode. Procedures used to measure C levels were similar with those reported in our previous study (He et al., 2016). Pulse rate and pulse phase duration were adjusted for individual subjects based on their programming maps.

Electrophysiological Measures—The stimulus was an 800-ms biphasic pulse train with an inter-stimulus interval of 1200 ms. It was presented at the C level in two stimulation conditions: the *standard* condition and the *gapped* condition. In the *standard* condition, the stimulus was presented to the selected electrode continuously. In the *gapped* condition, a silent interval (i.e. temporal gap) was inserted after 400 ms of stimulation. Gap durations tested in this study ranged from 2 up to 128 ms. All subjects were tested in a sound-treated booth while seated in a comfortable chair and watching a silent movie with captions. Subjects were instructed to remain as quiet and still as possible. Breaks were provided as necessary to ensure compliance with these instructions. For each stimulating electrode, the testing session took approximately 1.5 – 2 hours to complete.

For S1 – S4, electroencephalographic (EEG) activity was recorded using a Neuroscan system (version 4.4) and a SynAmp² amplifier (Compumedics, Charlotte, NC). For S5, the EEG was recorded using a Brain Vision system (version 2.1) and a Brain Amp DC amplifier. Disposable, sterile Ag-AgCl surface recording electrodes were used to record the EEG. The EEG was recorded differentially between five active recording electrodes (Fz, FCz, Cz, C3 and C4) and contralateral mastoid (A_{1/2}, reference) relative to a ground electrode placed at the low forehead (Fpz). Electrode impedances were below 5 kΩ. The recording window included a 100-ms pre-stimulus baseline and a 1600-ms post-stimulus time. The EEG was sampled at 1000 Hz, baseline corrected, and online filtered between 0.1 and 100 Hz (12 dB/

octave roll off). Eye movements were monitored using a pair of recording electrodes placed above and below the eye, contralateral to the ABI or the CI. The artifact rejection threshold was $\pm 120 \mu\text{V}$. For each subject, at least two replications with 100 artifact-free sweeps per replication were recorded for each stimulating condition. These replications were digitally filtered between 1 – 30 Hz (12 dB/octave) offline. Replications recorded for the same stimulating condition were averaged together and the averaged response was used for response identification, and peak amplitude and latency measurements.

Psychophysical Measures of GDTs—Behavioral GDT was measured using a one-interval, two-alternative forced-choice (2AFC) procedure that incorporated a two-down, one-up adaptive strategy targeting 70.7% correct gap detection (Levitt, 1971). The stimulus was a train of biphasic pulses presented at the C level. 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. Subjects were asked to decide whether they heard one or two sounds for each stimulus presentation. Initial gap duration and step size were selected based on pulse rate used in programming maps (i.e. 250 vs 500 pps). For ABI electrodes, the initial gap duration was 64 ms and the initial step size was 16 ms. For CI electrodes, the initial gap duration and initial step size was 32 and 8 ms, respectively. The step changed by a factor of 2 until the third reversal point. A threshold track stopped after 12 reversals, and the gap duration at the final six reversals was geometrically averaged. At least three estimates were obtained. Behavioral GDT was defined as the average of all estimates obtained for each electrode in each subject.

Data Analysis—In all subjects, responses recorded at electrode sites that were close to the ABI or the CI (i.e. C3 or C4) were contaminated by electrical artifacts and therefore excluded from data analysis. For each subject, all replications recorded for each stimulation condition were plotted along with the averaged responses of these replications. Responses were independently evaluated by three judges who were blind to subject identification and stimulation condition. Responses were determined to be present only if all replications recorded for the same stimulation condition at all midline-recording sites (i.e. Fz, FCz and Cz) were repeatable. Responses were recorded for 126 stimulating conditions. Initial decisions regarding response identification among these three judges were consistent for 118 stimulation conditions (i.e. approximately 93.6% inter-judge reliability). The disagreements over responses recorded for the other eight stimulation conditions were resolved through discussion.

Responses evoked by the stimulus onset (i.e. the onset responses) recorded for ABI electrodes demonstrated substantial intra- and inter-subject variability in morphological characteristics. Similar to responses reported in our previous study (He et al., 2016), two types of onset responses were recorded in these subjects with their ABIs. Type I responses primarily consisted of a single vertex positive peak followed by a trough occurring within the time window of 40 – 250 ms after stimulus onset. Type II responses consisted of up to three groups of positive and negative peaks within a time window of 25 – 700 ms after stimulus onset. Onset responses recorded for CI electrodes showed a vertex positive peak

with a latency of 100 – 150 ms followed by a trough occurring approximately 50 – 200 ms later.

eACCs recorded in all subjects using either a CI or an ABI showed relatively similar morphological characteristics. It primarily consisted of a vertex positive peak occurring around 460 – 660 ms after stimulus onset followed by a trough occurring about 80 – 180 ms later. Root mean squared (RMS) amplitudes of eACC responses were calculated within the time window of 440 – 750 ms relative to the stimulus onset using custom-designed MATLAB (Mathworks) software. The RMS amplitude of a baseline period (1500 – 1600 ms) was also computed to estimate the level of recording noise in these traces. The eACC was determined to be present only if 1) there was a visually detectable eACC response based on the agreement among three judges; 2) the RMS amplitude of the eACC was at least 50% larger than that of the noise floor; and 3) the eACC was determined to be present for at least two consecutive gap durations. The shortest gap that could reliably evoke the eACC was defined as the objective GDT.

Peak amplitude and latency of the onset and the eACC were measured using custom-designed MATLAB (Mathworks) software. Peak latency was measured relative to the stimulus onset. The peak-to-peak amplitude was measured as the difference in microvolts (μV) between the vertex positive peak and its following trough. Intra-class correlation (ICC) 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 replications recorded for the same stimulating condition for each subject.

RESULTS

Results of Electrophysiological Measures

The onset and the eACC could be recorded for one or more stimulating electrodes in all subjects using either the ABI or the CI. These responses showed variations in morphological characteristics across subjects, as well as across stimulating electrodes within each subject using either device. Results recorded using the ABI were reported first, followed by responses recorded using the CI. For all figures showing electrophysiological results, each panel shows responses recorded for one stimulating electrode in one subject. The rectangle in each panel indicates the time window (i.e. 440 – 750 ms) of the eACC response. Subject number, device type (i.e. ABI vs CI) and stimulating electrode are indicated at the top of each panel. Gap durations used to evoke these responses are labeled for these traces.

Responses Evoked by Electrical Stimulation of the ABI—Repeatable responses were recorded for all 12 ABI electrodes tested in all five subjects. Responses recorded for nine electrodes included both the onset and the eACC responses. The eACC could not be identified for traces recorded for three ABI electrodes in two subjects (i.e. electrode 21 in S2 and electrodes of 9 and 12 in S5) despite robust responses evoked by the stimulus onset. In this section, results measured for responses including both the onset and the eACC responses were reported first, followed by those measured for traces only showing the onset response.

I. Responses with identifiable eACCs: Figure 1 shows responses recorded for one ABI electrode in each subject. These results were recorded from a recording electrode located at Cz. Responses recorded in S1–S3 are relatively artifact-free. Small positive peaks at 0 ms were observed in some responses recorded in S4, which represent stimulus artifact. Traces recorded in S5 show signs of DC offset at stimulus onset and offset, as well as around 400 ms for responses measured in the *gapped* condition. These DC offsets were probably caused by the capacitive coupling between the RF transmission cable and the recording electrode leads (Hofmann & Wouters, 2012). Despite contaminations of stimulus artifact, repeatable neural responses could still be identified for this subject since they occurred later than artifacts. These results show that repeatable responses were recorded in all subjects. Despite substantial inter-subject variations in morphological characteristics, these responses include the onset response in the time window of 30 – 400 ms after stimulus onset. Onset responses recorded in S1, S4 and S5 consist of a vertex positive peak followed by a trough, which is consistent with morphological characteristics described for the Type I response (He et al., 2015a; He et al., 2016). In comparison, onset responses measured in S2 and S3 show multiphasic morphology, which is consistent with those described for the Type II response (He et al., 2015a; He et al., 2016).

Overall, Type I responses were observed for seven ABI electrodes tested in four subjects. Type II responses were observed for the other five ABI electrodes 18 and 17 in S2 and S3, respectively. The mean ICCs measured for these onset responses ranged from 0.66 to 0.99 (mean = 0.86, SD = 0.13). The average peak-to-peak amplitude of the Type I response ranged from 1.70 to 5.66 μ V. The average latency of the positive peak and the trough ranged from 57.63 to 129.57 ms and 165.00 to 309.50 ms, respectively. Type II responses showed variations in peak amplitudes and latencies. Response types, means and standard deviations of peak amplitudes and latencies measured for different ABI electrodes in all subjects are listed in Table 2.

In addition to the onset response, eACC responses evoked by temporal gaps were recorded for these electrodes. The mean ICCs measured for eACC replications ranged from 0.46 to 0.96 (mean = 0.65, SD = 0.17). Unlike morphological variations observed for the onset response, all eACCs recorded for ABI electrodes consisted of a vertex positive peak followed by a trough. The averaged latency of the positive peak and the trough ranged from 491.75 to 641.00 ms and from 607.20 to 749.75 ms, respectively. The averaged eACC amplitude ranged from 2.23 to 14.20 μ V. Objective GDTs varied across stimulating electrodes and subjects. Means and standard deviations of amplitudes and latencies of the eACC and objective GDTs measured using ABIs in all subjects are listed in Table 3.

II. Responses without identifiable eACCs: Figure 2 shows responses evoked by electrical stimuli delivered by the ABI electrode 21 in S2 (left panel) and ABI electrodes 9 (middle panel) and 12 (right panel) in S5. Subject and electrode number are shown on the top of each graph. Responses recorded for electrode 12 in S5 show signs of stimulus artifact contamination around 0 and 800 ms. These artifacts had relatively small amplitudes and much shorter latencies compared to those of recorded responses. Therefore, response identification or peak amplitude and latency measures were not affected by these artifacts. Responses recorded for electrode 21 in S2 and electrode 9 in S5 are relatively artifact-free.

A careful inspection of Figure 2 indicates that morphological characteristics of responses recorded for electrode 21 in S2 and electrode 12 in S5 are remarkably similar.

Onset responses shown in Figure 2 demonstrate good repeatability. ICCs measured for these onset responses ranged from 0.95 to 0.97 (mean = 0.96, SD = 0.01). These responses have complicated morphological characteristics and consist of three sets of vertex positive peak and trough within a time window of 100 – 700 ms. The largest peak-to-peak amplitudes ranged from 35.63 to 57.47 μV , which is much larger than those measured for any other stimulating electrodes tested in this study (see Table 2). More importantly, the eACC could not be identified for any trace despite robust onset responses.

Responses Evoked by Electrical Stimulation of the CI—Onset responses were recorded for all eight CI electrodes tested in three subjects (S2, S3 and S5). The eACC was recorded for seven out of these eight electrodes. It was not recorded for electrode 16 in S5 despite the presence of onset responses. Both onset and eACC responses showed a vertex positive peak with a latency of approximately 120 ms (P1) followed by a trough (N2). The mean ICCs measured for these onset responses ranged from 0.66 to 0.96 (mean = 0.81, SD = 0.12). The mean ICCs measured for eACC replications ranged from 0.57 to 0.88 (mean = 0.74, SD = 0.12).

Figure 3 shows responses measured for one CI electrode in S2 (left panel), S3 (middle panel) and S5 (right panel). Results recorded in S3 and S5 are relatively artifact-free. In comparison, traces recorded in S2 show electrical artifact contamination around 0 ms. This early artifact contamination did not affect identifying responses that occurred later for this subject. Despite variations in peak amplitudes and latencies, each trace contains an onset response. The eACC was recorded for all gap durations tested for these electrodes. The objective GDT determined for results shown in this figure was 4 ms for S2, and 2 ms for S3 and S5.

Overall, the averaged latency of P1 of the onset and the eACC response ranged from 77.00 to 129.57 ms and from 507.00 to 528.67 ms, respectively. The averaged latency of N2 of the onset and the eACC response ranged from 175.43 to 237.71 ms and from 586.67 to 686.33 ms, respectively. The averaged peak-to-peak amplitude (P1-N2) of the onset response ranged from 2.17 to 10.8 μV . The averaged P1-N2 amplitude of the eACC ranged from 2.75 μV to 5.29 μV . Results of amplitude and latency measurement of onset responses are listed in Table 2. Amplitudes and latencies of eACCs, and objective GDTs measured for different CI electrodes are included in Table 3.

Objective GDTs Measured for ABI and CI Electrodes—Figure 4 shows objective GDTs measured for different electrodes in each subject using either the ABI (upper panel) or the CI (lower panel). These data suggest that objective GDTs vary across stimulating electrodes of both devices. Objective GDTs shown in these two panels are within a similar range (i.e. 2 – 64 ms). Results of the Wilcoxon signed-rank test showed that there was no statistically significant difference in objective GDTs measured for CI and ABI electrodes ($p = 0.42$).

Results of Psychophysical Measures

Reliable behavioral GDTs were measured for one ABI electrode (i.e. electrode 21) in S2 and for multiple ABI and CI electrodes in S5. All other subjects could not complete behavioral GDT measures due to the lack of understanding of task instruction despite our best efforts of explanation. For S2, the behavioral GDT measured for ABI electrode 21 was 15.13 ms. For S5, means and standardized errors of behavioral GDTs measured for ABI (filled circles) and CI (open circles) electrodes are shown in Figure 5. For this subject, behavioral GDTs measured for ABI electrodes ranged from 9.2 to 59.33 ms (mean: 23.81 ms, SD: 14.67 ms). In comparison, behavioral GDTs measured for CI electrodes ranged from 2.73 to 3.33 ms (mean: 3.07 ms, SD: 0.31 ms), which is much shorter than those measured for her ABI electrodes.

Comparison of Electrophysiological and Psychophysical Results

Results of both electrophysiological and psychophysical measures were obtained for four ABI electrodes (electrode 5, 7, 9 and 12) and two CI electrodes (electrodes 7 and 16) in S5, and for one ABI electrode (electrode 21) in S2. Consistency between results of these two measures was observed for ABI electrodes 5 and 7, and CI electrode 7 in S5. Specifically, eACCs evoked by temporal gaps were recorded for these electrodes, which suggest that these temporal cues were transmitted to, and encoded by the central auditory system. Being consistent with these electrophysiological results, this subject showed behavioral sensitivity to temporal gaps delivered by these electrodes. As a result, objective and behavioral GDTs measured for these electrodes appeared to be comparable (see Table 3).

Discrepancies between results of electrophysiological and psychophysical measures was observed for three ABI electrodes (i.e. electrodes 9 and 12 in S5, and electrode 21 in S2) and one CI electrode (electrode 16 in S5). For these three ABI electrodes, behavioral GDTs ranged from 8 to 32 ms (mean = 18.37 ms, SD = 12.32 ms). In contrast, the eACC evoked by temporal gaps could not be identified for any trace (see Figure 2). It should be pointed out that onset responses of these traces were broad and had large amplitudes. It is possible that the eACC was recorded for these electrodes but simply could not be identified because it was masked by the onset response.

The left and right panel of Figure 6 shows responses recorded for CI electrodes of 7 and 16 in S5, respectively. Electrode number and behavioral GDT are shown on the top of each graph. Despite almost identical behavioral GDTs (3.13 ms vs 3.33 ms), responses recorded for these two electrodes are notably different. Specifically, robust onset and eACC responses with age-appropriate morphology (i.e. the P1-N2 complex) were recorded for electrode 7. Onset responses occurred within a time window of 30 – 230 ms. The eACC could be identified within a time window of 425 – 650 ms for traces evoked by gap durations of 2 ms or longer. These responses demonstrate good test-retest reliability. The mean ICCs of onset responses ranged from 0.66 to 0.99 (mean = 0.90, SD = 0.08). The mean ICCs of eACC replications ranged from 0.47 to 0.88 (mean = 0.69, SD = 0.14). The objective GDT was determined to be 2 ms. In comparison, responses recorded for electrode 16 show poorly defined morphology and have much smaller amplitudes than those measured for electrode 7. Onset responses could be identified within a time window of 20 – 190 ms. However, these

responses showed the worst overall repeatability, as evidenced by the lowest mean ICC (i.e. 0.66), among all onset responses recorded for CI electrodes. More importantly, the eACC could not be identified for traces evoked by temporal gaps of 2, 4, 16, 32 and 128 ms due to poor repeatability between replications recorded for the same stimulation condition. Even though traces evoked by temporal gaps of 8 and 64 ms appeared to contain repeatable responses within the time window of 425 – 680 ms, the eACC response was determined to be absent due to relatively small RMS amplitudes compared with those measured for the noise floor. Therefore, the eACC was determined to be absent for electrode 16, which is inconsistent with the relatively good behavioral GDT (i.e. 3.33 ms) measured for this electrode.

DISCUSSION

Repeatable responses were recorded for all electrodes tested in this study using either the CI or the ABI (see Tables 2 and 3). Despite the ABI bypasses the auditory nerve, peak latencies of responses recorded for ABI electrodes were not noticeably different from those measured for CI electrodes. It has been shown that the wave V latency of the electrically evoked auditory brainstem response (eABR) recorded in CI users is around 5 ms (e.g. Firszt et al., 2002). These data suggest that it takes approximately 5 ms for electrical stimulus to be transmitted from the auditory nerve to the auditory brainstem. Theoretically, the potential difference in peak latency of responses recorded for the ABI and the CI electrode should be around 5 ms, which is negligible for the cortical auditory evoked potential due to its long latency.

Onset cortical responses recorded for all CI electrodes consist of the P1-N2 complex, which was consistent with previous results in implanted children with CND (He et al., 2012). The Type I onset response was recorded for seven out of the 12 ABI electrodes and the Type II onset response was recorded for the other five ABI electrodes. Overall, the mean ICCs measured for all onset responses ranged from 0.66 to 0.99, which is consistent with results measured in young listeners with normal hearing (e.g. Hensch et al., 2008), elderly listeners (Tremblay et al., 2003), and implanted listeners with CIs (He et al., 2013; Friesen & Tremblay, 2006) or ABIs (He et al., 2016).

Measuring the eACC in Children with CND using CIs or ABIs

The first aim of this study was to evaluate the feasibility of measuring the eACC in children with CND. For all subjects tested in this study, eACCs to temporal gaps were successfully recorded for one or more stimulating electrodes using either the CI or the ABI. There was no association between the presence of the eACC and the response type of the onset response (i.e. Type I vs. Type II). To our knowledge, this is the first study to show that the eACC response can be measured in this patient population using either device.

The eACC evoked using the CI—The eACC recorded for the CI electrodes showed similar morphology (i.e. the P1-N2 complex) to that of the onset response, which is consistent with previously published results (Kim et al., 2009; Brown et al., 2008). For all three subjects (S2, S3 and S5), cortical responses recorded for different CI electrodes showed variations in response amplitude, peak latency and waveform repeatability, which

resulted in varied objective GDTs across CI electrodes. The most notable difference was observed for responses recorded for CI electrodes 7 and 16 in S5 (see Figure 6). It needs to be pointed out that the stimulation level used to evoke responses for electrode 16 and electrode 7 was 198 and 190 clinical units (CUs), respectively. Other stimulating parameters, including durations of pulse phase and interphase gap, were the same. In addition, these results were measured using the same recording parameters in two consecutive sessions scheduled on the same day. Therefore, poor responses recorded for electrode 16 were unlikely caused by an insufficient stimulation level or faulty recording parameters.

In a follow up study, we explored potential neurophysiological factors that might account for inter-electrode variations in cortical responses observed in S2, S3 and S5. One factor of interest was the responsiveness of the electrically evoked auditory nerve fibers near these CI electrodes. In this pilot study, the response input/output (I/O) function and neural refractoriness of the auditory nerve were evaluated using the electrically evoked compound action potential (eCAP). Parameters reflecting the responsiveness of the auditory nerve included the slope of the I/O function and the time for the auditory nerve to recover from the refractoriness induced by a previous electrical pulse (i.e. the masker). Details of procedures used to obtain these measures were reported in He et al. (2017).

Figure 7 shows eCAP results recorded for CI electrode 7 (left column) and electrode 16 (right column) in S5. These results were measured using a biphasic, charge-balanced electrical pulse with a pulse duration of 50 μ s/phase and an interphase gap of 7 μ s. Panels (a) and (b) show eCAP waveforms measured at the C level. eCAP amplitudes and C levels used to evoke these responses are indicated in each panel. Panels (c) and (d) show normalized eCAP amplitudes (re. the eCAP amplitude measured at the C level) plotted as a function of stimulation level (i.e. the I/O function). The slope of the I/O function was estimated using a sigmoidal regression function and is indicated in each panel. Results of our most recent study showed that the I/O function measured in implanted children with CND was best characterized by a sigmoidal instead of a linear regression function (He et al., 2017). Panels (e) and (f) show eCAP amplitudes measured at the C level plotted as a function of the time interval between the masker and the probe pulse used for eCAP recordings (i.e. the refractory recovery function). The absolute and relative refractory recovery time estimated for electrode 7 using a mathematical model with an exponential decay function (e.g. Botros & Psarros, 2010; Fulmer et al., 2011; Morsnowski et al., 2006) was 1.00 and 1.01 ms, respectively. These values are within the range reported for typical CI users (He et al., 2017; Morsnowski et al., 2006; Wiemes et al., 2016). In contrast, the eCAP could only be recorded when the interval between the masker and the probe (i.e. the masker-probe-interval) was 6.51 ms or longer for electrode 16, which indicated prolonged recovery from refractoriness. The absolute and relative refractory recovery time constants could not be estimated for electrode 16 due to insufficient data. Overall, the auditory nerve fibers near electrode 16 showed a smaller eCAP amplitude measured at the C level, a flatter I/O function, and prolonged recovery from refractoriness than those near electrode 7. These results suggest that the electrically stimulated auditory nerve fibers near electrode 16 had worse responsiveness than those near electrode 7. Preliminary results measured in S2 and S3 followed a similar pattern: poorer responsiveness of the auditory nerve fibers near CI electrodes with longer objective GDTs. These pilot data supported the possibility that

differences in recorded cortical responses primarily reflect the intrinsic difference in neural pathways activated by electrical stimuli delivered by different CI electrodes. We are currently verifying this preliminary finding in a large group of children with CND.

The eACC evoked using the ABI—The eACC recorded for the ABI electrodes showed less variation in morphological characteristics across patients and stimulating electrodes than the onset response. It consisted of one single vertex positive peak followed by a trough, which is similar to those observed for the Type I onset response. None of the eACCs demonstrated the multiphasic morphology observed for the Type II onset response. To date, neural generators of the onset or the eACC in ABI users have not been identified. Consequently, underlying neural mechanisms for the observed difference in morphology between these two responses remain unknown. Objective GDTs measured for the ABI showed substantial inter-subject variations (Figure 4). We speculate that these variations may be due to potential differences in electrode pad placement and variations in underlying neurophysiological insults to the auditory system across subjects. This speculation, however, needs further investigation.

Neural Encoding and Auditory Perception of Temporal Gaps

The second aim of this study was to explore the association between neural encoding of, and perceptual sensitivity to temporal gaps in children with CND using CIs or ABIs. In this study, the temporal gap is surrounded by two identical pulse train bursts. Therefore, it can be considered as the within-channel temporal gap (Schneider & Hamstra, 1999).

Only S2 and S5 were able to participate in both behavioral and electrophysiological tests. Their limited data showed inconsistent results in terms of the association between electrophysiological measures of the eACC and perceptual sensitivity to temporal gaps. For one CI and two ABI electrodes with identifiable eACC responses in S5, objective and behavioral GDTs were comparable (see Table 3), which suggests that within-channel temporal gaps presented to these electrodes were encoded in the entire auditory pathway and could be perceived by this subject. These data support the idea that the eACC can be used to objectively evaluate temporal resolution acuity in the central auditory system, which is consistent with previously published studies (e.g. He et al., 2013, 2015b; Lister et al., 2007; Martin et al., 2008).

In contrast, discrepancy between results of behavioral and electrophysiological tests was observed for one CI and two ABI electrodes in S5 and one ABI electrode in S2. Specifically, temporal gaps delivered by these electrodes were perceived by these two subjects, as evidenced by measurable behavioral GDTs. However, these temporal cues did not evoke identifiable eACCs. Interpretation of results recorded for these ABI electrodes is complicated due to the possibility that the eACC was masked by the large broad onset response. Nevertheless, results recorded for CI electrode 16 in S5 showed the discrepancy between neural encoding of and perceptual sensitivity to within-channel temporal gaps. This discrepancy has been previously observed in one child with auditory neuropathy spectrum disorder (ANSO) using acoustic stimulation (S13 in He et al., 2015b). That subject also showed poor neural response and prolonged objective GDT compared with his behavioral

GDT. Underlying neurophysiological mechanisms for the dissociation between neural encoding and auditory perception of within-channel temporal gaps remains unclear. Based on results of some animal studies, it has been proposed that within-channel gap detection is primarily associated with the function of the subcortical auditory structures (Kirby and Middlebrooks, 2012; Rybalko et al., 2010). However, this possibility has not been investigated in any human listeners and is beyond the scope of this study.

Study Limitations

This study has several limitations. One limitation is the small number of subjects who could participate in behavioral GDT measures. This limitation was unexpected given that 1) four subjects were older than five years of age with at least two years of experience with their devices; and 2) a relatively easy procedure (i.e. 2AFC) was adopted for behavioral measures. Behavioral gap detection can be successfully measured in three-year-olds children with normal hearing using a similar procedure (Wightman et al., 1989). Apparently, this is not the case for implanted children with CNL who lack early auditory experience. Due to the limited number of subjects who completed both psychophysical and electrophysiological measures and the inconsistency between results measured using these two procedures, data collected in this study did not provide conclusive evidence to support using the eACC to evaluate temporal resolution in children with CNL. A second limitation is that electrical artifacts contaminated responses recorded in some stimulation conditions. Applying the EEG cap with multiple recording electrodes was unsuccessful due to limited subject compliance. In this study, EEGs were only recorded at five recording electrode locations. Therefore, stimulus artifacts could not be removed or minimized using mathematical modeling techniques (e.g. independent component analysis). Finally, the study aimed to identify an objective tool for evaluating temporal processing in children with CNL using either the ABI or the CI. It was not designed to systematically compare temporal resolution acuity in CNL children with CIs with that measured for CNL children with ABIs. Therefore, results of this study did not provide an answer to the important question of whether the ABI provides better temporal information to the central auditory system than the CI in children with CNL. Further studies are warranted.

CONCLUSIONS

The eACC could be recorded in children with CNL using either CIs or ABIs. GDTs measured using either the ABI or the CI varied across subjects and stimulating electrodes. Objective and behavioral GDTs appeared to be comparable when results of both electrophysiological measures of the eACC and behavioral measure of GDT could be obtained. However, temporal gaps delivered by some ABI and CI electrodes could be perceived by these listeners without evoking an identifiable eACC.

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Figure 1.

Responses including both the onset and the eACC recorded for one ABI electrode in all five subjects. Each panel shows results recorded in one subject. Grey and black dashed lines represent replications and the averaged responses of all replications recorded for each stimulation condition, respectively. The vertical dashed line represents the time point when the first 400 ms of stimulation ended. The rectangle indicates the time window for the eACC response. Vertex positive peaks of the onset and the eACC response are indicated using filled and open triangles, respectively.

Figure 2.

Responses with only robust onset responses recorded for ABI electrode 21 in S2 and ABI electrodes 9 and 12 in S5. Grey dashed lines represent replications recorded for each stimulation condition. Black lines represent the averaged responses of all replications recorded for the same stimulation condition. The vertical dashed line represents the time point when the first 400 ms of stimulation ended.

Figure 3.

Electrically evoked neural responses evoked by electrical stimulation of one CI electrode in S2, S3 and S5. Grey dashed lines represent replications recorded for each stimulation condition. Black lines represent the averaged responses of all replications recorded for the same stimulation condition. The vertical dashed line represents the time point when the first 400 ms of stimulation ended. The rectangle indicates the time window for the eACC response. Vertex positive peaks of the onset and the eACC response are indicated using filled and open triangles, respectively.

Figure 4. Objective GDTs in millisecond (ms) measured for electrodes of ABIs (filled triangles) and CIs (open triangles) in all subjects.

Figure 5.
Means and errors of behavioral GDTs measured for ABI (filled circle) and CI (open circle) electrodes in S5.

Figure 6.

Neural response recorded for CI electrodes 7 and 16 in S5. Grey dashed lines represent replications recorded for each stimulation condition. Black lines represent the averaged responses of all replications recorded for the same stimulation condition. The vertical dashed line represents the time point when the first 400 ms of stimulation ended. The rectangle indicates the time window for the eACC response. Vertex positive peaks of the onset and the eACC response are indicated using filled and open triangles, respectively.

Figure 7. eCAP responses recorded at the C level (upper panels), the I/O functions (middle panels) and the refractory recovery functions (lower panels) measure for electrodes 7 (left column) and 16 (right column) in S5.

Table 1

Demographic information and most recently measured speech perception scores of subjects who participated in this study.

Subject Number	Gender	Etiology	Device	Implant Age (yrs)	Test Age (yrs)	Ear	Electrodes Tested	Pulse Duration (μs/phase)	Speech Perception score (%)
S1	M	CHARGE syndrome	ABI	3.3	6.2	L	14, 21	100–150	ESP-S: 70% pattern, 62% word, 50% monosyllabic, 41% spondee
S2	F	Unknown	ABI	5.5	7.2	R	18, 21	100	ESP-S: 46% pattern, 29% word, 8% monosyllabic, 8% spondee
			CI (24RE)		7.2	L	12, 19, 15, 21	88	ESP-S: 66% pattern, 33% word, 8% monosyllabic, 8% spondee
S3	F	Unknown	ABI	2.2	3.8	R	17, 19	150	CNT
			CI (24RE)	2.2	3.8	L	12, 15	88	CNT
S4	M	CHARGE syndrome	ABI	3.47	5.84	R	3, 5	150	ESP-S: 33% pattern, 16% word, 12% monosyllabic, 8% spondee
S5	F	Unknown	ABI	6.08	8.20	R	5, 7, 9, 12	200–300	MLNT: 80% Common phrases: 60%
			CI (24RE)	2.10	8.20	L	7, 16	75	MLNT: 53% Common phrases: 30%

ABI: Auditory Brainstem Implant; CI: Cochlear Implant; 24RE: Cochlear Nucleus Freedom; ESP-S: Standard Early Speech Perception Test; MLNT: Multisyllabic Lexical Neighborhood Test

Table 2

Response type, latency and amplitude of onset responses recorded at different electrodes of auditory brainstem implants and cochlear implants.

Subject number	Device	Type I response				Type II Response													
		Electrode number	Latency (ms SD)		Amplitude (µV SD)	Electrode number	Latency (ms SD)				Amplitude (µV SD)								
			Positive	Trough			1 st Peak	1 st Trough	2 nd Peak	2 nd Trough	3 rd Peak	3 rd Trough	1 st Peak	2 nd Peak	3 rd Peak				
S1	ABI	14	125.5 (46.05)	309.5 (57.42)	5.66 (2.71)														
		21	92.40 (54.80)	176.80 (39.94)	1.70 (0.87)														
S2	ABI					18	59.17 (10.94)	131.50 (7.61)	220.33 (3.39)	273.17 (3.76)					3.06 (0.62)	12.64 (2.66)			
						21	130.71 (8.81)	228.86 (8.15)	296.14 (7.82)	403.29 (2.36)	483.00 (7.46)	569.86 (10.22)	35.63 (7.21)	22.26 (2.60)	8.01 (1.52)				
	CI	12	124.25 (4.27)	182.00 (2.71)	5.29 (1.36)														
		15	121.29 (2.37)	175.43 (2.38)	4.29 (0.82)														
		19	132.00 (3.32)	199.57 (8.00)	5.37 (1.50)														
		21	117.80 (3.56)	209.00 (56.16)	3.58 (0.75)														
S3	ABI					17	27.00 (19.01)	125.86 (6.28)	207.57 (6.50)	274.14 (9.91)	374.14 (8.53)	447.71 (12.41)	13.46 (1.21)	9.71 (2.42)	7.46 (2.00)				
	CI	12	129.57 (11.67)	211.86 (8.93)	4.25 (0.79)														
		15	124.14 (30.01)	199.71 (20.69)	1.97 (1.02)														
S4	ABI	3	57.63 (13.08)	181.75 (37.51)	3.35 (0.63)														
		5	71.43 (11.99)	165.00 (19.35)	3.50 (0.53)														
S5		5	88.60 (3.36)	201.00 (19.42)	3.80 (1.16)														
		7	63.71 (17.26)	193.29 (24.37)	4.70 (0.35)														
	ABI					9	188 (2.53)	250.67 (4.84)	318.67 (2.07)	374.00 (6.07)	457.33 (9.00)	558.00 (14.48)	43.69 (7.64)	9.04 (0.81)	9.29 (2.00)				

Table 3

Amplitude and latency of eACCs and GDTs measured for different electrodes of auditory brainstem implants and cochlear implants.

Subject number	Device	Electrode number	eACC		GDTs	
			Latency (ms SD)			
			Positive	Trough	Amplitude(μ V SD)	Objective GDT (ms) Behavioral GDT (ms)
S1	ABI	14	646.67 (7.64)	735.67 (43.02)	3.59 (0.36)	64
		21	491.75 (24.74)	611.75 (19.19)	2.23 (0.73)	8
S2	ABI	18	518.60 (20.80)	607.20 (48.03)	5.25 (2.09)	8
		21*	NR			CNM 15.13
	CI	12	516.00 (21.00)	586.67 (11.02)	7.76 (4.20)	8
		15	511.00 (21.20)	590.17 (10.70)	4.92 (1.39)	4
		19	553.5 (7.78)	622.5 (21.92)	5.14 (0.31)	32
		21	507.00 (16.27)	588.75 (3.77)	5.78 (0.92)	8
S3	ABI	17	507.00 (13.86)	632.17 (14.50)	14.20 (2.52)	4
		19	626.33 (43.18)	691.83 (92.29)	2.79 (0.97)	4
	CI	12	528.67 (31.80)	686.33 (25.70)	8.62 (2.39)	4
		15	524.5 (41.72)	623 (67.88)	5.23 (0.83)	64
S4	ABI	3	641.00 (82.16)	731.67 (81.94)	4.03 (0.43)	64
		5	502.00 (28.00)	652.50 (26.50)	6.17 (0.34)	64
S5	ABI	5	500.52 (13.44)	618.50 (17.68)	3.04 (1.29)	32 33.73
		7	504.60 (36.04)	653.20 (31.81)	3.94 (0.89)	8 11.07
		9*	NR			CNM 9.20

Subject number	Device	Electrode number	eACC			GDT's	
			Latency (ms SD)			Objective GDT (ms)	Behavioral GDT (ms)
			Positive	Trough	Amplitude(μV SD)		
CI		12*	NR		CNM	10.13	
		7	537.33 (15.11)	628.00 (33.18)	2.75 (1.22)	2.00	3.13
		16	NR		CNM	3.33	

eACC: electrically evoked auditory change complex.

GDT: gap detection threshold.

NR: no response.

CNM: cannot be measured.