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Longitudinal Changes in Electrically Evoked Auditory Event-Related Potentials (eERPs) in Children with Auditory Brainstem Implants: Preliminary Results Recorded over Three Years

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Abstract

Objective—This preliminary study aimed 1) to assess longitudinal changes in electrically evoked auditory event-related potentials (eERPs) in children with auditory brainstem implants (ABIs); and 2) to explore whether these changes could be accounted for by maturation in the central auditory system of these patients.

Design—Study participants included five children (S1-S5) with an auditory brainstem implant (ABI) in the affected ear. The stimulus was a train of electrical pulses delivered to individual ABI electrodes via a research interface. For each subject, the eERP was repeatedly measured in multiple test sessions scheduled over up to 41 months after initial device activation. Longitudinal changes in eERPs recorded for each ABI electrode were evaluated using intra-class correlation tests for each subject.

Results—eERPs recorded in S1 showed notable morphological changes for five ABI electrodes over 41 months. In parallel, signs or symptoms of non-auditory stimulation elicited by these electrodes were observed or reported at 41 months. eERPs could not be observed in S2 after nine months of ABI use but were recorded at 12 months after initial stimulation. Repeatable eERPs were recorded in S3 in the first nine months. However, these responses were either absent or

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showed remarkable morphological changes at 30 months. Longitudinal changes in eERP waveform morphology recorded in S4 and S5 were also observed.

Conclusions—eERP responses in children with ABIs could change over a long period of time. Maturation of the central auditory system could not fully account for these observed changes. Children with ABIs need to be closely monitored for potential changes in auditory perception and unfavorable non-auditory sensations. Neuroimaging correlates are needed to better understand the emergence of non-auditory stimulation over time in these children.

Keywords

auditory brainstem implant; cochlear nerve deficiency; auditory event-related potential; longitudinal change

INTRODUCTION

The auditory brainstem implant (ABI) was developed by William F. House and William Hitselberger in the House Ear Institute (e.g. Hitselberger et al., 1984). It was initially designed to restore hearing for patients with neurofibromatosis type II (NF2). The first ABI surgery was performed in an adult NF2 patient in 1979 (Hitselberger et al., 1984).

The ABI bypasses the cochlea and the auditory nerve, and directly stimulates the cochlear nucleus (CN) in the auditory brainstem. Electrical stimuli delivered by the ABI are encoded by the CN and transmitted to the higher auditory neural structures to elicit auditory perception. In patients with NF2, reported ABI benefits include increased awareness of environmental sounds and access to auditory pattern and stress cues, which facilitates lip reading (e.g. Lenarz et al., 2001, 2002; Nevision et al., 2002; Otto et al., 2002). Only a few patients with NF2 achieved open-set speech perception with the ABI (Colletti & Shannon, 2005). The ABI has been used in non-tumor, hearing-impaired adults and children who had contraindications to cochlear implantation since 2000 (e.g. Colletti et al., 2000, 2001, 2002; Puram et al., 2016; Wilkinson et al., 2017). Non-tumor adult ABI users typically show better auditory capabilities than patients with NF2 (e.g. Colletti & Shannon, 2005; Colletti et al., 2009). The ABI provides auditory perception in most pediatric patients (Colletti et al., 2014; Colletti & Shannon, 2005; Puram et al., 2016; Sennaroğlu et al., 2011; Sennaroğlu & Sennaroğlu, 2013; Wilkinson et al., 2017). In some children, it also supports speech and language development and improves cognitive functions, including selective visual/spatial attention and multisensory reasoning (Colletti, 2007; Colletti et al., 2014; Colletti & Shannon, 2005; Sennaroğlu et al., 2011; Sennaroğlu & Sennaroğlu, 2013). However, despite better ABI outcomes observed in non-tumor patients compared to those reported in patients with NF2, the amount of ABI benefit varies substantially among individual users (e.g. Otto et al., 2002; Colletti et al., 2009; Colletti et al., 2014; Colletti & Shannon, 2005; Puram et al., 2016; Sennaroğlu et al., 2011; Wilkinson et al., 2017).

Inner ear malformations occur in approximately 20% of patients with congenital sensorineural hearing loss (Sennaroğlu, 2010). Cochlear implantation is not feasible in patients with complete labyrinthine aplasia (i.e. Michel aplasia), cochlear aplasia, cochlear nerve aplasia or cochlear aperture aplasia (Sennaroğlu et al., 2011). Anatomical and

histopathological characteristics of these malformations have been described in detail by Sennaroğlu (2016). Currently, the ABI is the only treatment option to provide auditory perception for children with these severe inner ear malformations. There is a standing debate over whether the cochlear implant (CI) or the ABI is a better treatment option for children with small (hypoplastic) auditory nerves. In one recent study, Colletti et al. (2014) reported that the ABI provided better speech and language outcomes for children with hypoplastic auditory nerves than the CI, and concluded that the ABI might be the preferable device for these patients.

Due to the lack of other treatment options for children who have contradictions to cochlear implantation, several medical centers around the world began to implant the ABI in non-tumor pediatric candidates. In August of 2012, the U.S. Food & Drug Administration (FDA) approved a clinical trial, entitled “*An Early Feasibility Study of the Safety and Efficacy of the Nucleus 24 Auditory Brainstem Implant in Children with Cochlear or Cochlear Nerve Disorder Not Resulting from Neurofibromatosis Type II*”, to be conducted at University of North Carolina at Chapel Hill. Study participants included four children with cochlear nerve deficiency (CND) and one child with Michel aplasia. In this study, CND refers to conditions where the cochlear nerve is either absent (i.e. cochlear nerve aplasia) or smaller than normal (i.e. cochlear nerve hypoplasia) (Buchman et al., 2006). Details of the ABI surgeries and progress in auditory and speech and language development within the first three years of ABI use are reported in a companion study (Teagle et al., submitted for publication). In this preliminary study, we focused on longitudinal findings in electrophysiological results in these five children.

Auditory cortices of children are highly plastic and mature over time with adequate auditory input (Eggermont, 2008). Electrical stimuli delivered by the CI can at least partially restore the arrested auditory neural maturation in pre-lingually deaf children (Ponton et al., 1996). Maturation changes in the auditory pathway result in increased conduction velocity and faster synaptic transmission, which leads to reduced peak latency of the electrically evoked auditory event-related potential (eERP). The eERP is a neural response generated in the central auditory system that can be recorded from surface electrodes placed on the scalp. The presence of an eERP indicates that electrical stimulation has been transmitted to and encoded by the central nervous system (Martin et al., 2008). In normal-hearing infants and young children, the acoustically-evoked ERP is dominated by a large positive peak (P1) with a latency of approximately 100 ms, followed by a broad negativity (N2). In pre-lingual deaf children with CIs, the eERPs show prolonged peak latency compared to responses recorded in normal hearing children (e.g. Gordon et al., 2005; Ponton et al., 1996; Sharma et al., 2005; Sharma & Dorman, 2006). The delay in peak latency is reflective of the duration of hearing deprivation prior to the CI (Ponton et al., 1996) and tends to decrease as listening experience with the CI increases due to auditory development promoted by electrical stimulation (e.g. Gordon et al., 2005; Ponton et al., 1996; Sharma et al., 2002, 2005; Sharma & Dorman, 2006). For children who were implanted at seven years of age or younger, P1 latency could fall within age-appropriate limits after approximately six to nine months of CI use (Sharma et al., 2002; Silva et al., 2017). However, for patients with a long duration of hearing deprivation, P1 latency could be prolonged even after years of CI experience (e.g. Ponton et al., 1996; Sharma et al., 2002). With adequate auditory input, the eERP could

show age-dependent morphological changes due to maturation of the central auditory system (Goron et al., 2005; Ponton et al., 1996; Sharma et al., 2005; Sharma & Dorman, 2006). The eERP recorded in a mature auditory system consists of three response peaks occurring in sequence between 50 and 300 ms after stimulus onset: P1, N1 and P2.

The feasibility of measuring the eERP in children with ABIs has been established in our previous studies (He et al., 2015, 2016). Unlike the well-described P1-N2 complex for children with normal hearing and CIs, eERP recorded in children with ABIs show two types of waveform morphology. The Type I response is dominated by a vertex positive peak followed by a trough occurring within a time window of 40 to 250 ms after stimulus onset. The Type II response consists of multiple positive and negative peaks within the first 500 ms after stimulus onset. In addition, substantial inter-subject variations in peak amplitude and latency are observed for both types of responses.

Theoretically, electrical stimuli delivered by the ABI could also promote cortical auditory maturation in pre-lingual deaf children, which could be documented by the eERP. However, due to the limited number of pediatric ABI recipients, this possibility has not been previously investigated. In this preliminary study, we examined eERPs that were repeatedly measured in five children with up to 41 months of listening experience with the ABI. The goals of this study were 1) to assess if the eERPs recorded in pediatric ABI users would show longitudinal change; and 2) to explore whether maturation in the central auditory system could account for changes in eERPs in these patients.

METHODS

Data were collected in at least two test sessions. The time interval between test sessions ranged from one to 35 months. In each session, prior to electrophysiological recordings, the maximum comfortable level (C level) was estimated for each ABI electrode using the procedure described in detail in our previous article (He et al., 2016). Briefly, an ascending and bracketing method was used. The stimulus was directly presented to individual electrodes through a speech processor. The initial stimulus level was very low and then was gradually increased. C level was determined based on responses obtained using conditioned play audiometry or a loudness scaling task. Study participants were asked to report any discomfort caused by electrical stimulation using sign language or Cued Speech. In addition, they were monitored for visible signs of non-auditory stimulation.

Study Participants

Study participants included five children with prelingual deafness (S1 – S5) ranging in age between 4.1 and 7.5 years (mean: 6.0 years; SD: 1.3 years) at the time of the most recent test session. All study participants were diagnosed with CNL by an experienced neurotologist (C.A.B) based on results of Magnetic Resonance Imaging (MRI) using the same diagnostic criteria as those described previously (Adunka et al., 2006; Buchman et al., 2006; Roche et al., 2010). For each study participant, the CNL diagnosis in the ABI side was confirmed by intra-operative observation of anatomical status of the cochlear nerve. All study participants were unilaterally implanted with a Cochlear Nucleus 24M ABI and had at least one month

of ABI use prior to participating in this study. All participants developed reliable behavioral responses to electrical stimulation of the ABI over time.

Prior to enrollment in the study, S1 was unilaterally implanted with a CI in the test side. S5 was unilaterally implanted with a CI in the contralateral side of the ABI. These two subjects did not wear their CIs prior to the clinical trial due to lack of sound awareness or intolerance. For S1, the CI in the test side was removed to place the ABI. For S5, the contralateral CI was reprogrammed and reintroduced after six months of ABI use. S4 used bilateral CIs consistently prior to ABI surgery, but had plateaued in progress with speech production and auditory discrimination skills after four years of intensive therapy. S2 and S3 did not use any amplification devices prior to the ABI.

Detailed demographic information of study participants is listed in Table 1. Also shown are the numbers of active electrodes and electrical pulse phase durations used in their programming maps, their most recent averaged hearing thresholds with the ABI for 500, 1000 and 2000 Hz, and the duration of ABI use at the time they were tested in this study. The biomedical institutional review board (IRB) of The University of North Carolina at Chapel Hill approved this study (IRB study # 12-1737). Written informed consent was obtained from all study participants and/or their legal guardians prior to participation. All study participants were paid for their participation.

Stimulus

The stimulus was a train of biphasic, charge-balanced electrical pulses with a pulse rate of 250 pulses per second (pps) per channel presented in monopolar-coupled stimulation mode (MP1+2). For S1 and S3–S5, the duration of the stimulus was 100 milliseconds (ms) with an inter-stimulus interval of 800 ms. For S2, the duration of the stimulus was 400 ms with an inter-stimulus interval of 1400 ms. The stimulus was created using custom-designed software incorporating Nucleus Implant Communicator (NIC) programming routines. The ABI speech processor was bypassed. The stimulus was delivered to individual ABI electrodes at the C level using a research interface. Stimulating electrode and pulse phase duration were selected based on speech processor programming maps of individual study participants.

Electrodes Tested

For S1, S2, and S3, all active electrodes included in their speech processor programs were tested in this study. Three additional electrodes (i.e. electrodes 17, 19, and 22) were used in the speech processor program of S4 but were not tested in any test sessions due to time constraints. For S5, the speech processor program included three additional electrodes (i.e. electrodes 6, 7 and 9). Unfortunately, these three electrodes were only tested once for eERP recordings. Responses recorded for these electrodes have been reported in He et al. (2016). These three electrodes were not repeatedly tested in any other sessions due to time constraints.

Electrophysiological Measures

Study participants were tested in a single-walled sound booth. They were seated in a comfortable chair or on a caregiver's lap and watched a silent movie with closed captioning. Breaks were provided as needed. Each recording session took approximately 1.5 – 2 hours.

Electroencephalographic (EEG) activity was recorded using a Neuroscan system (version 4.4) and a SynAmp² amplifier (Compumedics, Charlotte, NC). Disposable, sterile Ag-AgCl surface electrodes were used to record the EEG. Responses were differentially recorded between electrodes positioned on the high forehead (F_z , active) and the contralateral mastoid ($A_{1/2}$, reference). A ground electrode was placed on the low forehead (Fpz). Eye-blink activity was monitored using a pair of recording electrodes placed superior and inferior to the eye, contralateral to the ABI. Electrode impedances were maintained below 5000 Ohms with an inter-electrode impedance difference of less than 2000 Ohms. The recording window included a 100 ms pre-stimulus baseline and a 700 ms peri/post-stimulus time. The EEG was sampled at 1000 Hz, amplified with a gain of 10, based line corrected, and analog filtered online between 0.1–100 Hz (12 dB/octave roll-off) prior to averaging. Responses exceeding $\pm 120 \mu V$ were rejected from averaging. After artifact rejection, the remaining artifact-free sweeps were averaged and at least three averaged responses (replications) of the 100 sweeps were recorded for each stimulating electrode in every subject. These replications were digitally filtered between 1–30 Hz (12 dB/octave) offline. Replications recorded for the same stimulating electrode in the same test session were averaged together and the averaged response was used for data analysis.

Data Analysis

Instead of focusing on specific response components, this study evaluated the entire eERP response since it has richer information than individual peaks. In addition, changes in overall eERP morphology might carry important information. The intra-class correlation test was used to evaluate test-retest reliability of eERPs measured across test sessions. This statistical test takes both amplitude and latency differences into account and has been used successfully for the same purpose in several previously published studies (Friesen & Tremblay, 2006; He et al., 2013; He et al., 2016; Tremblay et al., 2003). Therefore, it is an appropriate statistical analysis test for this study. For S3-S5, Wilcoxon Signed-rank tests were used to compare intra-class correlation coefficients (ICCs) calculated for responses measured between two test sessions.

RESULTS

There was no change in the pulse phase duration over time for all electrodes tested in S1, S4 and S5, and electrodes 2–5 tested in S3. However, changes in pulse phase duration were made for all electrodes tested in S2 and electrodes 6–8 tested in S3. Specifically, the pulse phase duration decreased from 400 to 300 μs for electrodes tested in S2. Phase duration gradually increased from 150 to 300 μs for electrodes 6–8 tested in S3. For all except two electrodes (electrode 16 in S1 and S5), current levels (in clinical units) increased over time regardless whether the pulse phase duration changed or not. For electrode 16 in S1 and S5, current levels decreased by seven and five clinical units over time. Due to inter- and intra-

subject variations in pulse phase duration, stimulation levels were calculated using units of electrical charge per phase (nC).

Results of eERP measures are reported individually for each study participant due to substantial inter-subject variations in observed patterns. For all figures included in this article, each trace represents an averaged response of at least 300 artifact-free sweeps. Electrodes used to evoke these responses are labelled for recorded traces. ICCs are listed to the right of recorded responses. ICCs of 0.4 or lower suggest poor response repeatability (Cicchetti, 1994) and are indicated with asterisks. This study focused on evaluating morphological changes in overall eERP responses instead of any specific response component. Therefore, response peaks were not labelled.

Figure 1 shows responses recorded in S1 at six months (black lines) and 41 months (red lines) after initial stimulation. Stimulation levels used at 41 months were higher than those used at six months for all electrodes except for electrode 16. The C level measured for electrode 16 at 41 months was 15.41 nC lower than that measured at six months. Responses recorded for electrodes 18–19 and 21–22 demonstrate good repeatability over 35 months of ABI use, as evidenced by the robust ICCs (Cicchetti, 1994). There was no report or visible sign of non-auditory stimulation when these electrodes were activated in both test sessions. In contrast, poor repeatability and low ICCs were observed for responses recorded for electrodes 13–17. Repeatable responses cannot be identified for traces recorded for electrodes 13 and 15–16 at 41 months. Stimulating electrodes 14 and 17 at C levels at 41 months evoked strong and notable contraction of ipsilateral sternocleidomastoid muscle (SCM). In addition, S1 reported discomfort when electrode 13 was activated and facial twitching was observed when electrodes 15 and 16 were activated at stimulation levels slightly higher than those used for electrophysiological recordings at 41 months. Caregivers had noted signs of non-auditory stimulation at around 36 months in the form of muscle twitching around the neck and face when the child wore the speech processor in natural environments. However, these symptoms could not always be replicated during the clinical visit. Due to the child's inability to report on the sensation, changes were made to current levels on specific electrodes based on visually observed responses at the time of device programming. In general, tolerance for and acceptance of device use did not appear to be hindered by these non-auditory stimulations.

Figure 2 shows results recorded in S2 at nine months (blue dashed lines), 12 months (black lines) and 34 months (red lines) after ABI activation. Due to high stimulation levels required by this participant, contaminations of electrical artifact are observed around 0 and 400 ms in these responses. Traces recorded at nine and 12 months were evoked using the same stimulating parameters (e.g. pulse phase duration, current level, coupling mode, etc.). No repeatable response was recorded for any ABI electrodes at nine months. It should be pointed out that measuring eERPs were attempted at one and six months after initial stimulation in addition to results shown in Figure 2. No repeatable responses were recorded in these test sessions. Consistent with these electrophysiological findings, S2 did not show any reliable behavioral responses to electrical stimulation of the ABI for the first nine months. Responses were recorded for electrodes 19–21 at 12 months and for electrodes 18 and 21–22 at 34 months. Reliable behavioral responses were also observed in the audiologic

appointment at 18 months. Stimulation level used to test electrode 20 at 34 months was 56.61 nC lower than that used at 12 months, which might account for the lack of response at 34 months and the small calculated ICC for this electrode.

Figure 3 shows responses recorded in S3 at six months (blue dashed lines), nine months (black lines) and 30 months (red lines). Responses recorded for electrodes 3–5 were evoked using the same stimulation parameters in all test sessions. For electrodes 2 and 6–7, higher stimulation levels were used at 30 months than at six and nine months. For S3, responses recorded at six and nine months show good repeatability, as evidenced by the robust ICCs listed in the first column to the right of these traces. eERPs recorded in both sessions at all ABI electrodes were dominated by a vertex positive peak followed by a trough. In contrast, traces recorded at 30 months are remarkably different from those recorded in the first two test sessions. Repeatability responses cannot be identified for traces recorded for electrodes 2 and 5. Responses recorded for electrodes 3 and 4 demonstrate reversed polarities. The eERP recorded at electrode 7 showed the most noticeable change. Specifically, additional positive and negative peaks were observed for response recorded at 30 months. More importantly, response recorded at 30 months had a peak-to-peak amplitude of 54.5 μ V, which was more than one magnitude larger than that measured for responses recorded at 6 and 9 months (around 2.6 μ V). Consequently, ICCs calculated for results measured at nine and 34 months were significantly smaller than those calculated for responses recorded in the first two test sessions, as evidenced by result of Wilcoxon signed-rank test ($p < 0.05$). There were no visible signs or complaints of discomfort caused by the non-auditory stimulation for electrodes 2–7 in any test sessions. At 16 months, S3 reported discomfort when electrode 8 was stimulated during the clinical appointment. Therefore, this electrode was deactivated and not tested at 30 months. Limited expressive language skills may have prevented him from making this information known before, and from providing more explicit information.

Figure 4 shows responses recorded in S4 at two months (blue dashed lines), three months (black lines) and 32 months (red lines). Traces recorded for electrodes 13, 18 and 21 were elicited using the same stimulating parameters. For all other electrodes, stimulation levels used at 32 months were higher than those used at three months. ICCs calculated for responses recorded at two and three months, and responses recorded at three and 32 months are listed to the right of these traces. Overall, repeatability of recorded response decreased over time. ICCs calculated for responses recorded at two and three months were significantly higher than those calculated at three and 32 months, as evidenced by the result of the Wilcoxon signed-rank test ($p < 0.05$). No visible sign of non-auditory stimulation was observed in any test sessions. S4 never reported any discomfort for all of the electrodes tested.

Figure 5 shows results recorded in S5 at one month (blue dashed lines), three months (black lines) and 24 months (red lines). Stimulation levels used at one month and three months were the same for all electrodes. Stimulation levels used at 24 months were higher than those used in the first two test sessions for all electrodes except for electrode 16. The stimulation level used for electrode 16 at 24 months was 4.9 nC lower than those used in previous test sessions. Overall, responses recorded across test sessions showed good repeatability. Results of Wilcoxon signed-rank test showed that there was no significant

difference in ICCs calculated for response measured in the first and the last two test sessions ($p=0.34$). There was no visible sign or complain of discomfort caused by non-auditory stimulation for all electrodes tested in any test session.

DISCUSSION

Our results showed that eERPs recorded in children with ABIs could change over time. These changes demonstrated substantial inter-subject variations. Factors accounting for these changes are not entirely clear. Results of this study provide some evidence to support the hypothesis that some changes in eERPs observed in this study might be due to auditory maturation. The strongest piece of evidence is the emergence of the eERP in S2 over time (Figure 2). For this patient, eERPs were not observed for the first nine months of ABI use but measured at 12 months. It should be pointed out that these traces were evoked using the same stimulating parameters (e.g. pulse phase duration, current level, coupling mode, etc.). Therefore, the emergence of the eERP at 12 months could not be accounted for by these extrinsic factors. In addition, reliable behavioral responses were only observed after the presence of the eERP in this subject. These results supported the possibility that electrical stimulation provided by the ABI might partially restore the arrested auditory maturation in this patient. However, auditory maturation would not change auditory perception to non-auditory sensation for electrical stimulation delivered to the same ABI electrode, as observed for electrodes 13–17 in S1 (Figure 1). In addition, the disappearance of eERPs over time (e.g. results measured for electrodes 2 and 5 in S3) could not be accounted for by auditory development at all. Therefore, maturation in the central auditory system could not fully account for observed longitudinal changes in eERPs.

Another potential factor accounting for poor response repeatability observed in some participants is the change in stimulation level over time. eERPs in CI and ABI users showed decreased peak latency and increased peak amplitude as stimulation level increased (He et al., 2016; Visram et al., 2015). However, either reduced or absent responses were recorded at increased stimulation levels in several study participants (e.g. results recorded for electrodes 13, 15 and 17 in S1 and electrode 2 in S4). Therefore, it is unlikely that observed changes in eERPs are primarily caused by changes in stimulation level.

Finally, we speculated that electrode migration might be another factor to be considered. For the 24M ABI, T-shape and square multifilament polyester (PET) meshes are used to stabilize electrode position and minimize the possibility of electrodes migrating out of the lateral recess of the fourth ventricle. Even though long-term stability of electrode position has been reported for most adult ABI users (Otto et al., 2002; Otto et al., 2012; Shannon et al., 1993), electrode migration has also been observed in a few cases (Otto et al., 2002; Shannon et al., 1993). In pediatric ABI users, part of the PET mesh needs to be cut in order to fit the relative small space of the lateral recess. In addition, unlike relatively stable brain and skull sizes in adults, children show increased brain sizes and cranial capacities within the first 10 years of life (Dekaban et al., 1978; Gordon et al., 1995). Both processes could potentially affect the electrode stability. Furthermore, S1 showed newly developed SCM contractions in the ipsilateral side when electrodes 14 and 17 were stimulated at 41 months. Shannon et al. (1997) showed that it would require current levels of 1500 – 5000 μA for 200 μs /phase

biphasic pulses to stimulate the non-auditory brainstem nuclei, including cranial nerve XI that innervates the SCM, if the electrode pad is located in the lateral recess. For biphasic pulses with shorter phase durations, it is reasonable to expect that higher current levels may be required to create sufficient current spread to activate these non-auditory brainstem nuclei. For S1, the pulse phase duration used for electrode 14 and 17 was 150 μ s. Current levels used for electrodes 14 and 17 in all test sessions ranged between 610.4 and 762.8 μ A, which is much lower than that estimated by Shannon et al. (1997). Therefore, it is unlikely that the activation of cranial nerve XI was caused by the current spread. For this participant, his initial electrode placement in the lateral recess was confirmed by the result of a postoperative high-resolution computed tomography (CT). Therefore, results measured in S1 provide indirect evidence to support the possibility of electrode migration. Nevertheless, even though electrode migration could reasonably explain part of our results, this explanation is speculative due to the lack of imaging results and only limited, reliable behavioral responses measured in these study participants.

Results recorded in S2 are exciting and promising. This participant has Michel aplasia, which is the most severe form of inner ear malformation and is believed to result from arrested development of the otic placode at the third week of gestation (Jackler et al., 1987). Currently, the ABI is the only treatment option to enable auditory perception for patients with Michel aplasia since they do not have cochleae or auditory nerves. However, it remains unknown whether these patients can achieve benefit from the ABI due to the uncertainty of normal growth or function of their central auditory neural structures. Our results clearly show that patients with Michel aplasia can benefit from the ABI for at least environmental sound awareness.

Study Limitations

This study has several limitations. One limitation is the relatively small number of subjects tested in this study. In the United States, the ABI has only been approved to be implanted in non-tumor children as an investigational device in FDA-approved clinical trials since 2012. Therefore, the number of children with ABIs that can be enrolled in this longitudinal study is limited. Due to the small sample size and the heterogeneity of recorded results, the underlying mechanism for long-term eERP changes remains unclear.

Another limitation is that subjects tested in this study could only provide limited reliable behavioral responses due to their young age and lack of sufficient speech and language skills. In addition, we also found that speech perception assessment materials chosen (Infant Toddler Meaningful Auditory Integration Scale and CID Early Speech Perception Test battery) were not sensitive enough to the slow and small changes that occurred over time in this unique patient population. This lack of appropriate speech perception assessment materials became evident as the study progressed. Speech perception test results measured for each subject and limitations of speech perception assessment materials are reported in the companion study (Teagle et al., submitted for publication). Due to limited information of auditory perception obtained in these five subjects, the behavioral significance of observed changes in eERPs remains unknown.

Due to these limitations, the results from this preliminary study are descriptive and exploratory in nature. Further study is warranted in order to understand the underlying mechanism and behavioral significance of these long-term eERP changes in children with ABIs.

CONCLUSIONS

eERP responses in children with ABIs could change over a long period of time. These changes could not be fully accounted for by auditory cortical maturation. Other factors, including changes in stimulation level and possible electrode migration, might also partially account for observed changes. Children with ABIs need to be closely monitored for potential changes in auditory perception and unfavorable non-auditory sensations. Further studies combining behavioral and electrophysiological measures and neuroimaging techniques are warranted in order to identify neurophysiological mechanisms underlying long-term change in eERPs in children with ABIs.

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Figure 1.

Responses recorded in S1 at six and 41 months post initial stimulation. ICCs calculated for responses recorded in these two test sessions are listed to the right of these traces. Asterisks indicate ICCs of 0.4 or lower.

Figure 2.

Responses recorded in S2 in three test sessions. ICCs calculated for responses recorded in the last two test sessions are listed to the right of these traces. Asterisks indicate ICCs of 0.4 or lower.

Figure 3.

Responses recorded in S3 at six, nine and 30 months. The first column of ICCs is results calculated for responses recorded at six and nine months. The second column of ICCs is results calculated for responses recorded at nine and 30 months. Asterisks indicate ICCs of 0.4 or lower.

Figure 4.

Responses recorded in S4 at two, three and 32 months. The first column of ICCs is results calculated for responses recorded at two and three months. The second column of ICCs is results calculated for responses recorded at three and 32 months. Asterisks indicate ICCs of 0.4 or lower.

Figure 5.

Responses recorded in S5 at one, two and 24 months. The first column of ICCs is results calculated for responses recorded at one and two months. The second column of ICCs is results calculated for responses recorded at two and 24 months. Asterisks indicate ICCs of 0.4 or lower.

Table 1

Demographic information of subjects who participated in this study.

Subject Number	Gender	Etiology	Implant Age (yrs)	Ear	Hearing age with the ABI (yrs)	Number of active electrodes	Pulse duration (μs/phase)	3-Frequency hearing thresholds average (dB HL)	Duration of ABI use at the time of eERP recordings (months)
S1	M	CHARGE syndrome	3.3	L	3.5	9	100–150	30	6 and 41
S2	F	Michel Aplasia	2.5	L	3	4	300	48	1, 6, 9, 12 and 34
S3	M	Unknown	3.5	R	2.5	6	150–300	32	2, 3 and 32
S4	F	Unknown	5.5	R	2	15	100	23	6, 9 and 30
S5	F	Unknown	2.2	R	2	6	150	35	1, 3 and 24

ABI: Auditory brainstem implant

eERP: Electrically evoked auditory event-related potential