ELSEVIER

Clinical Neurophysiology 118 (2007) 1671–1684

www.elsevier.com/locate/clinph

Auditory brainstem activity and development evoked by apical versus basal cochlear implant electrode stimulation in children

K.A. Gordon [a,c,*], B.C. Papsin [a,c], R.V. Harrison [b,c]

[a] *Cochlear Implant Laboratory, the Hospital for Sick Children, Rm. 6D08, 555 University Avenue, Toronto, Ont., Canada M5G 1X8*
[b] *Auditory Science Laboratory, the Hospital for Sick Children, Toronto, Ont., Canada*
[c] *Department of Otolaryngology-Head and Neck Surgery, University of Toronto, Ont., Canada*

See Editorial, pages 1655–1657

Abstract

Objective: The role of apical versus basal cochlear implant electrode stimulation on central auditory development was examined. We hypothesized that, in children with early onset deafness, auditory development evoked by basal electrode stimulation would differ from that evoked more apically.
Methods: Responses of the auditory nerve and brainstem, evoked by an apical and a basal implant electrode, were measured over the first year of cochlear implant use in 50 children with early onset severe to profound deafness who used hearing aids prior to implantation.
Results: Responses at initial stimulation were of larger amplitude and shorter latency when evoked by the apical electrode. No significant effects of residual hearing or age were found on initial response amplitudes or latencies. With implant use, responses evoked by both electrodes showed decreases in wave and interwave latencies reflecting decreased neural conduction time through the brainstem. Apical versus basal differences persisted with implant experience with one exception; eIII–eV interlatency differences decreased with implant use.
Conclusions: Acute stimulation shows prolongation of basally versus apically evoked auditory nerve and brainstem responses in children with severe to profound deafness. Interwave latencies reflecting neural conduction along the caudal and rostral portions of the brainstem decreased over the first year of implant use. Differences in neural conduction times evoked by apical versus basal electrode stimulation persisted in the caudal but not rostral brainstem.
Significance: Activity-dependent changes of the auditory brainstem occur in response to both apical and basal cochlear implant electrode stimulation.

Keywords: Deafness; Hearing loss; Evoked potentials; Apical; Basal; Cochlea; Hearing aid; Age at implant; Residual hearing; Electrically evoked auditory brainstem response (EABR); Electrically evoked compound action potential of the auditory nerve (ECAP); Neural response telemetry (NRT)

1. Introduction

In the present study, we examined the development of the central auditory pathways as stimulated by an apical versus basal cochlear implant. We hypothesized that there could be poorer neural survival and/or development in the base of the cochlea versus more apical areas which might compromise changes in the auditory brainstem evoked in basal versus apical ends of the cochlear implant array.

Development of the auditory pathways is likely based on both "nature", genetically mediated processes, and "nurture", activity-dependent processes, and either might be disrupted in children with early onset deafness. It is also possible that the effects of deafness might not be uniform along the length of the cochlea. Although the mechanisms are not clear, hearing loss in both children and adults tends to be larger in high rather than lower frequencies. In addition to poor residual hearing in high frequencies, most current hearing aid technologies are not able to provide high

* Corresponding author. Address: Cochlear Implant Laboratory, the Hospital for Sick Children, Rm. 6D08, 555 University Avenue, Toronto, Ont., Canada M5G 1X8. Tel.: +1 416 813 7259.
E-mail address: karen.gordon@utoronto.ca (K.A. Gordon).

1388-2457/$32.00
doi:10.1016/j.clinph.2007.04.030

gain at frequencies beyond 3–4 kHz. Thus, prior to cochlear implantation, children with severe to profound hearing loss are likely to hear low but not high frequency auditory input. This disparity of stimulation along the cochlear nerve could impact the central auditory system and, indeed, temporal bone analyses from humans who had hearing loss show smaller populations of spiral ganglion cells in the cochlear base compared to more apical areas (Nadol, 1997; Zimmermann et al., 1995).

Auditory nerve and brainstem responses in cochlear implant users show effects of electrode location in the cochlea. Responses evoked by cochlear implant electrodes at the apical end of the array show higher wave amplitudes, shorter latencies and lower thresholds than those evoked electrodes at the basal end both in adults (Allum et al., 1990; Firszt et al., 2002; Miller et al., 1993; Shallop et al., 1990) and in children (Gordon et al., 2002, 2004; Thai-Van et al., 2001, 2004). This apical–basal profile of evoked responses appears to depend on the etiology of the deafness; differences in auditory nerve responses evoked by apical versus basal electrodes were found in children with two normal copies of the GJB2 gene whereas no significant differences were found in children with homozygous GJB2 mutations (Propst et al., 2006a). Those results suggested that there were more similarities in the neural populations stimulated by the basal and apical electrodes in children with GJB2 related deafness than in children with deafness of other causes. The differences in neural responses stimulated by electrodes at different implant locations are important to understand if we are to provide optimal stimulation parameters along the entire cochlear implant array for children and adults who use cochlear implants.

Any assessment of responses evoked at different locations along the cochlear implant array must consider the possibility of interaction between the electrodes. Many factors can influence the spread of neural excitation evoked by any single cochlear implant electrode. The first set of factors include those related to the electrical current such as the distance between the electrode and neurons (Araki et al., 1997; Firszt et al., 2002), the mode of stimulation (Bierer and Middlebrooks, 2002, 2004), the geometry of the electrodes and array (Kral et al., 1998), and the presence of fibrous tissue around the electrode array (Araki et al., 1997). The second set of factors relate to potential differences in the neural population (Nadol, 1997) due to such issues as varying survival/development, presence or absence of dendritic fibres (Lai and Dillier, 2000), and differences in axonal length (Miller et al., 1993). Recently, a forward masking paradigm used in recording the electrically evoked compound action potential of the auditory nerve (ECAP) (measured by implant telemetry systems) has been manipulated to define the impact of these factors on the spread of neural excitation at specific electrode locations in human implant users (Cohen et al., 2003; Eisen and Franck, 2005; Hughes and Abbas, 2006). A probe stimulus is delivered from one implant electrode and a masking stimulus from another. The masker-probe response is subtracted from a probe alone evoked response in order to eliminate stimulus artifact. As the distance between the masker electrode and the probe electrode increases, the overlap between the neural response evoked by the stimulus and that evoked by the masker decreases. This diminishing effectiveness of the masker appears as an increase in amplitude of the forward masking response but a decrease in the subtracted (probe alone minus masker-probe) ECAP amplitude. Using this technique at loud levels, the neural activation evoked by monopolar stimulation from one electrode has been shown to encompass 5–8 electrodes in total (in the Nucleus 24 straight array electrode which caused greater spread than the peri-modiolar version) (Hughes and Abbas, 2006). There are 17 electrodes between the apical electrode #20 and the basal #3 electrode in the Nucleus 24 straight array suggesting little potential overlap between the populations of primary auditory neurons excited by each of these two electrodes. Interestingly, two reports suggested that the spread of excitation was similar at different probe electrodes along the array (Cohen et al., 2003; Hughes and Abbas, 2006) and the other reported a narrower spread at basal versus more apical locations (various electrode arrays) (Eisen and Franck, 2005) despite the potential for the basal end of the array to be further away from the modiolus than the apical end. If basal electrodes provide a similar or narrower spread of neural excitation, the smaller response amplitudes and shallower slopes of amplitude growth evoked by the basal versus apical electrode (i.e., in children with non-GJB2 related deafness) (Propst et al., 2006a) are more likely to reflect differences in the neural populations stimulated by these two responses than issues related to current spread.

Differences in the neural population stimulated by a basal versus apical electrode in the cochlear implant could affect development after implantation. In previous studies, we have investigated auditory brainstem activity in children with prelingual onset of deafness (Gordon et al., 2006); electrophysiological responses were evoked using a cochlear implant electrode at the basal end of the array. While neural conduction time, measured as interwave latencies, was not correlated with a period of auditory deprivation, this duration decreased with implant use. The interwave latency between the most prominent waves of the electrically evoked auditory brainstem response (EABR), waves eIII and eV, decreased significantly with implant use suggesting an improvement in neural conduction between the generator of eIII and that of eV, both of which are likely to be located in the rostral rather than caudal portion of the brainstem (Gordon et al., 2006). Similar changes have been shown in the auditory brainstem responses of normal hearing infants and children (Salamy, 1984) and are thought to reflect myelination and/or improved synaptic efficacy with age (Eggermont, 1988). These changes largely occur over the first year of life (Ponton et al., 1996); we similarly found that latency changes promoted by implant use in children were largely

complete within the first year of implant use (Gordon et al., 2006) although recent data suggest a slightly longer time course of change (Thai-Van et al., 2007). Thai-Van and colleagues have confirmed our EABR findings and have also shown that a period of normal auditory development prior to deafness results in shorter wave eV latencies at initial stages of implant use and more limited decreases in eV latency with implant use compared to children with early onset deafness (Thai-Van et al., 2007). We showed that the degree of EABR latency change was not dependent upon the age of the children (Gordon et al., 2003, 2006) and this has been confirmed (Thai-Van et al., 2007). All children in our study had pre-lingual hearing loss which meant that their age at time of device activation was essentially equivalent to their duration of deafness. These data suggested that neural connections in the brainstem during the period of deafness remain static or that neural degeneration at this level of the brainstem is too limited to be detected in evoked potentials recorded using either cochlear implant or surface recording electrodes. In addition, the results indicated that the duration of deprivation does not significantly impact developmental plasticity promoted by implant use.

In the present study, we asked if the pattern of auditory brainstem response evoked by a basal implant electrode at initial cochlear implant activation and over a period of implant use differs from that evoked by a more apical electrode.

2. Methods

2.1. Subjects

Fifty children (34 male, 16 female) participated in this study. All had early onset of hearing loss and were implanted unilaterally at 5.4 ± 4.0 years of age with Nucleus 24 devices (40 N24M and 10 N24RCS devices) at the Hospital for Sick Children in Toronto, Canada. Most were implanted in the right ear ($n = 47$) reflecting a preference for this ear at this centre. All but one had full electrode array insertions. As shown in Fig. 1, measurable residual hearing (thresholds defined by a behavioral response) was, on average, in the severe to profound hearing loss range. Fig. 1 also presents the percentage of thresholds which could be measured within the intensity limits of the audiometric equipment. Measurable residual hearing was most often observed in the low frequencies. Thresholds in the higher frequencies were commonly beyond the limits of the audiometric equipment (110–120 dB for 250–4000 and 100–105 for 6000 and 8000 Hz). For the purposes of regression analyses (discussed below), thresholds at 250, 500, and 1000 Hz were averaged to give an estimate of residual hearing. In order to include all children in the analyses, thresholds >120 dB HL were assigned a value of 130. Of the 50 children, 46 were fitted with hearing aids by 2 years of age (mean = 1.3, SD = 0.7 years). The other four children were diagnosed at older ages and were fitted with aids by 4 years of age (mean = 3.7, SD = 0.9 years). All children were in therapy programs prior to implantation which emphasized audition and hearing aid use.

2.2. Evoked potential recordings

Electrically evoked compound action potentials of the auditory nerve (ECAP) and electrically evoked brainstem responses (EABR) were recorded in all children repeatedly over the first year of implant use. No sedation was used. The EABR was collected within the first week of device activation, typically on the day of device activation, and after 2, 6, and 12 months of implant use. The ECAP was recorded within the first week of device activation, typically on the day after initial device activation, and after 1 and 6 months of implant use. Responses were recorded at both an apical implant electrode (#20) and a basal electrode (#3) in a random presentation order. The N24M array is 24 mm long with 22 active and 10 non-active support platinum electrodes located at 0.75-mm intervals. The N24 RCS is pre-curved and the intervals between electrodes are tapered from larger intervals in the base to smaller at the apical end. Once fully inserted, the electrode array typically extends to within or just beyond the first basal turn of the cochlea. Single biphasic pulses were delivered at 11 Hz at comfortably loud levels. Initial stimulation levels were within 90% of maximum presentation levels at later stages of device use. It has been previously reported that ECAP and EABR thresholds do not significantly change with implant use (Gordon et al., 2004) and that latency measures made at the upper portion of the dynamic range, as was used in this study, do not change significantly with intensity level (Abbas and Brown, 1988; Firszt et al., 2002; Gordon et al., 2003). Moreover, changes in latency with duration of implant use were shown to occur both when stimulation is provided at slightly changing comfortably loud levels and when stimulus intensity is held constant over time (Gordon et al., 2006).

ECAP recordings were made using the Nucleus Neural Response Telemetry software (version 2.04). This system uses a subtraction method described in detail previously (Abbas et al., 1999) in which one electrode delivers electrical pulses at 80 pulses per second and a neighbouring electrode (at a slightly more apical location) records the evoked response. EABRs were recorded using a Neuro-Scan system with SynAmps amplifier. Surface recording electrodes were placed on the centre-midline of the head (Cz) and referenced to the ipsilateral earlobe with a ground at a fronto-midline position (Fpz). The recording electrodes passed through an analogue filter (fc = 32 kHz) which reduced the frequency modulated signal sent by the transmitting coil of the external equipment to the internal receiver-stimulator. Signals were sampled at 20 kHz and amplified by a gain of 5000. Frequencies outside the range of 10–3000 Hz were filtered out and signals of ±30 to

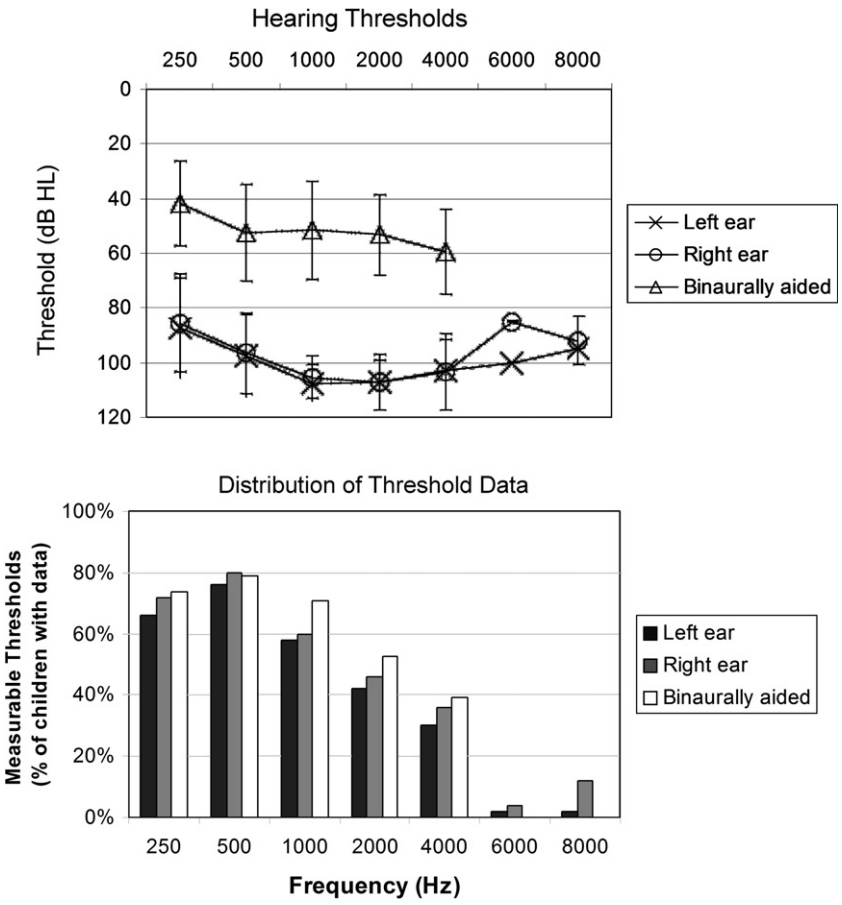

Fig. 1. Mean (SD) hearing thresholds measured within the limits of the audiometric equipment are plotted by frequency for the left and right ears and in binaural hearing aid condition. The distribution of measured thresholds is plotted showing that, of the children with audiometric data available, hearing in the low frequencies was measurable in most children but was often beyond audiometric equipment limits in the high frequencies (4000–8000 Hz).

40 μV were rejected. Typically 300 acceptable sweeps occurring at −5 to 80 ms relative to stimulus onset were averaged.

2.3. Data analyses

One person identified ECAP and EABR wave peaks guided by expected latencies and measured peak latencies and wave amplitudes (from wave peak to following trough). A subset of EABR waveforms was measured by a second marker who was blinded to earlier determinations and all identifying information. Good agreements for eIII and eV wave latencies and amplitudes were found between markers as reported previously (Gordon et al., 2003). Statistical analyses were completed using SPSS 13.0 software. Linear regression analyses were used to assess: (1) effects of stimulus intensity and electrode location on wave amplitudes and (2) possible relationships between wave latencies and amplitudes and either age at implant or residual hearing. Two way repeated measures ANOVAs were used to test the effects of electrode location and duration of implant use on wave latencies and interwave latencies. Paired *t*-tests were used for post hoc analyses and to compare amplitudes at initial stimulation and after 1 year of implant use; Bonferroni adjustments are indicated.

3. Results

3.1. Initial responses

ECAP and EABR waveforms were recorded in all 50 children beginning at the initial device activation. A typical set of waveforms evoked by an apical and a basal implant electrode in a child implanted at 3 years of age are shown in Fig. 2. Responses evoked by apical electrodes appear at earlier latencies and are larger in amplitude than responses evoked by basal electrodes. In Fig. 3, initial wave eV amplitudes are shown as a function of stimulus intensity for both apical and basal electrodes. Stimulus intensity is plotted in dB (re: 100 μA) and, because thresholds are higher for basal versus apical evoked responses (Gordon et al., 2004), intensity was normalized to the visual threshold for each response in each child. Fig. 3 shows a slightly steeper amplitude growth curve for apically evoked responses and this was confirmed by a linear regression analysis ($R = 0.58$) which indicated significant effects of stimulus level ($p < 0.001$) and electrode ($p < 0.05$). Maximum amplitude responses for each child were used for further analyses. As shown in Table 1, the group of children had shorter latencies and higher amplitude nerve and brainstem responses when evoked by an apical versus basal electrode.

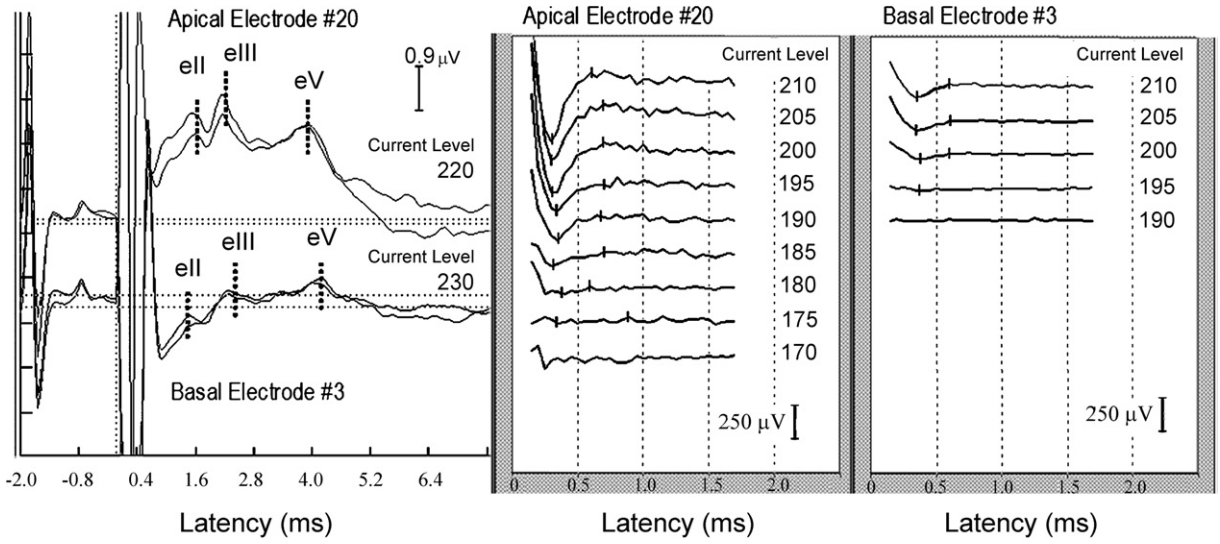

Fig. 2. The left panel shows typical EABRs elicited by stimulation corresponding to a comfortably loud level from a child with congenital hearing loss aged 3 years at initial stimulation; two responses evoked by an apical implant electrode are shown above two responses evoked by basal electrode stimulation. The middle and right panels show typical ECAPs recorded from the same child at a comfortably loud level and at decreasing stimulus intensities; responses evoked by an apical electrode are shown in the middle panel and responses evoked by a basal electrode are shown in the right panel.

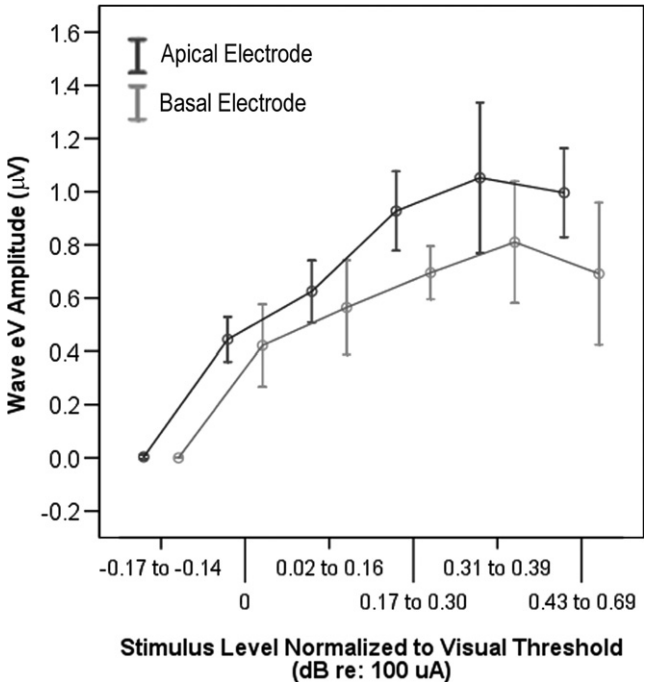

Fig. 3. Mean (±1SE) wave eV amplitude obtained at initial stimulation in 50 children is plotted with respect to intensity (dB re:100 μV). Intensity is normalized to visual response thresholds; negative intensities are below visual threshold, 0 dB is equal to visual threshold and positive values are suprathreshold measures. Amplitude growth appears slightly steeper when evoked by the apical versus basal implant electrode.

Amplitude differences between apically and basally evoked responses were found for all waves and latency differences were found for all wave latencies (bar eII) and all interwave latencies (bar eII–eIII).

It is possible that acoustic stimulation prior to cochlear implant use could influence electrically evoked neural responses. If true, there would be a relationship between the degree of hearing loss and response latencies and/or amplitudes. This analysis is shown in Fig. 4a and b in which wave and interwave latencies and wave amplitudes are plotted against averaged hearing thresholds at 250, 500, and 1000 Hz. There were no significant correlations between hearing thresholds and either response latencies or amplitudes as indicated in Table 4. The trend toward significant increases in eIII–eV latencies with higher hearing thresholds ($p = 0.09$) suggests very small changes; the 95% confidence intervals of the regression slope indicate changes $\leqslant 0.006$ ms.

It is also possible that initial responses are related to the age at implantation. Fig. 5a and b display scatterplots of wave and interwave latencies and wave amplitudes against age at activation. The regression lines are included. As detailed in Table 4, there were no significant relationships found between the latency or amplitude measures and age at implantation. The 95% confidence intervals of the regression lines for latency showed no overlap with the 95% confidence intervals for wave and interwave latencies which significantly changed over time. Confidence intervals for amplitudes also suggested that the trends of eV to increase with age (basal eV: $p = 0.09$ and apical eV: $p = 0.12$) were very small (<0.07 μV). Thus, any effects of degree of residual hearing or age at implantation prior to implantation in areas stimulated by cochlear implant electrodes were smaller than the effects of implant use (to be discussed in the next section below).

3.2. Changes with implant use

Fig. 6 displays a complete set of waveforms recorded from a child who was 3 years of age at the time of implant activation. ECAPs are shown in the top panel and EABRs in the bottom panel. Responses evoked by apical electrodes have noticeably shorter latencies than those evoked by the

Table 1
Descriptive and statistical data from paired *t*-test analyses of responses evoked by apical versus basal cochlear implant electrodes at initial device activation

		Basal		Apical					
	N	Mean	SD	Mean	SD	*t*	df	Sig.	
Latencies (ms)									
eN1	40	0.35	0.058	0.32	0.050	2.18	39	0.035	*
eII	31	1.46	0.30	1.45	0.28	0.54	30	0.59	
eIII	45	2.39	0.15	2.25	0.18	6.90	44	<0.00001	***
eV	47	4.42	0.28	4.19	0.28	10.31	46	<0.00001	***
eN1–eII	24	1.12	0.17	1.15	0.14	−1.28	23	0.21	
eII–eIII	31	0.92	0.28	0.79	0.26	5.32	30	<0.00001	***
eN1–eIII	38	2.03	0.16	1.90	0.14	5.47	37	<0.00001	***
eIII–eV	44	2.00	0.17	1.90	0.14	3.71	43	0.0006	**
Amplitudes (μV)									
eN1	40	173.7	147.7	272.5	205.5	4.61	41	<0.00001	***
eIII	45	0.35	0.17	0.66	0.30	7.86	44	<0.00001	***
eV	47	0.81	0.42	1.18	0.56	4.47	46	<0.00001	***

* Significant at 0.05 which does not meet significance for Bonferroni adjustment for 8 repeated tests ($p < 0.004$).
** Significant at $p < 0.001$.
*** Significant at $p < 0.00001$.

basal electrode. Decreasing latencies with implant use can also be seen. Wave and interwave latencies were measured in all responses and assessed for effects of electrode and duration of implant use in two way repeated measures ANOVAs; the details of the statistical analyses are provided in Tables 2 and 3. Mean (±1SE) data from complete datasets included in repeated measures ANOVAs are plotted in Fig. 7 and display significant decreases in wave and interwave latencies over the first year of implant use for responses evoked by a basal as well as by an apical electrode. The exception is the interwave eII–eIII which does not significantly change in response to either apical or basal electrode stimulation.

Differences between responses evoked by apical and basal electrodes persist over time. When evoked by the basal implant electrode, latencies remain prolonged over the first year of implant use. Also shown in Fig. 7, the interpeak latencies eN1–eIII and eII–eIII of basally evoked responses remain longer than those evoked by apical electrode stimulation during this period. However, the interpeak interval, eIII–eV, has a different pattern; the initial difference between responses evoked at either end of the implanted array ($t(43) = 3.7$, $p < 0.001$) decreases with implant use becoming non-significant ($t(41) = 1.28$, $p > 0.05$) by 2 months of implant experience. Fig. 8 shows the same analysis of wave eV amplitude growth as shown in Fig. 3 but for data collected at 6 or 12 months of implant use. When normalized for threshold, amplitude growth is steeper when evoked by the apical electrode and this was confirmed by linear regression analysis ($R = 0.71$, stimulus intensity: $p < 0.0001$; electrode: ($p < 0.0001$).

4. Discussion

Evoked potential recordings, used in the present study, measure electrical fields produced by the synchronous activity of a single group or groups of neurons. The wave peaks in the acoustically evoked Auditory Brainstem Response (ABR) arise from the ascending pathways of the auditory nerve (waves I and II) to the cochlear nucleus (wave III) through the superior olivary complex to the lateral lemniscus which innervates the inferior colliculus (waves IV and V) (Moller and Jannetta, 1982a,b; Ponton et al., 1996). Although the ABR does not reflect activity from all connections in the auditory brainstem, it does provide a picture of neural activity which is propagated from generators in the caudal brainstem to more central generators in the rostral portion of the brainstem. The interpeak latencies reflect neural conduction time between the generators of the first peak to the generators of the second; this is a general measure of many time constants including those associated with axonal conduction and synaptic transmission. Wave amplitudes are measures of the strength of the electrical field produced by synchronous neural responses at the recording electrode. Increasing wave amplitudes reflect an increase in the number of neurons which respond in synchrony to the stimulus (Simmons and Smith, 1983). Decreasing ABR interwave latencies with age reflect developmental changes in myelination and/or synaptic efficacy in the auditory brainstem (Ponton et al., 1996). The interwave latencies of the electrically evoked ABR (EABR) are comparable to the acoustic click evoked response in children using cochlear implants (Gordon et al., 2006). However, early interwave latencies, eN1–eII and eII–eIII, show unique patterns of change in response to implant use as compared to normal developmental changes of homologous interwaves I–II and II–III (Gordon et al., 2006) as well as unique time constants of change. Differences in the degree of change in early versus later interpeak latencies suggest different mechanisms affecting rostral versus caudal areas of the auditory brainstem with ongoing cochlear implant use. In the present

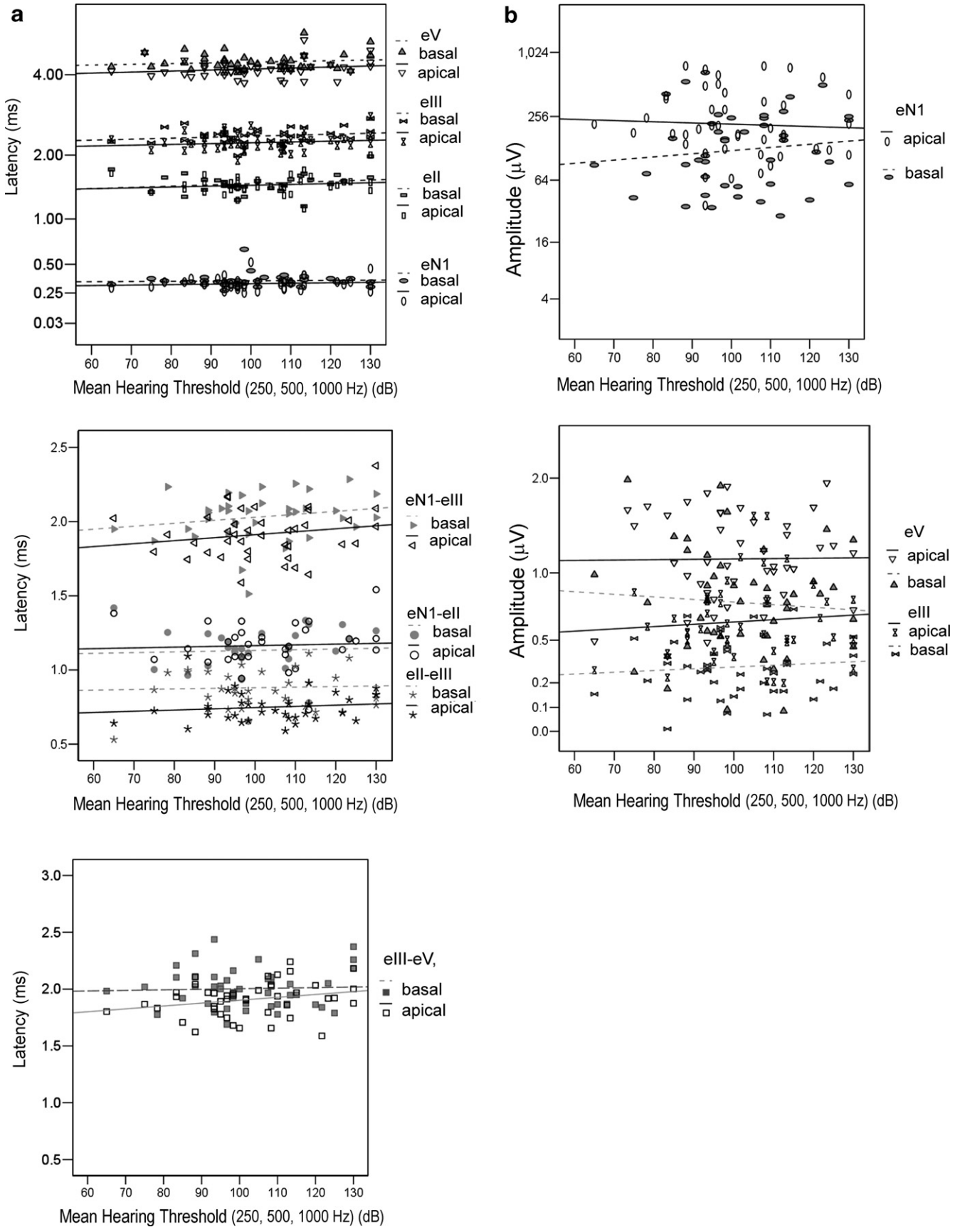

Fig. 4. (a) Wave and interwave latencies at initial activation and (b) wave amplitudes are plotted against the mean low frequency hearing thresholds in the implanted ear. Logarithmic scales are used to display wave latencies and wave amplitudes (y-axis) but not wave inter-wave latencies. No significant relationships were found ($p > 0.05$).

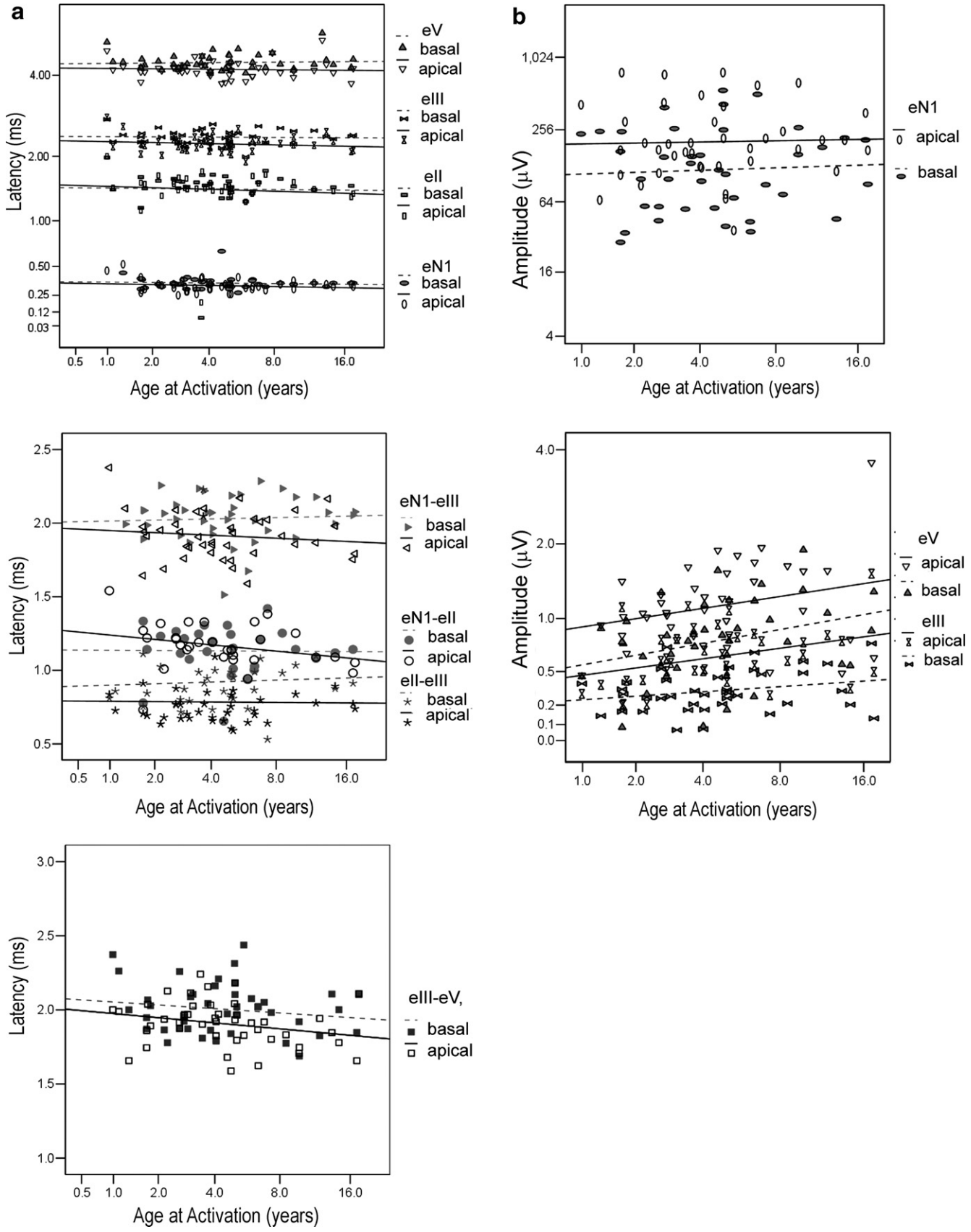

Fig. 5. (a) Wave and interwave latencies at initial activation and (b) wave amplitudes are plotted against age at this test time. Logarithmic scales are used for display purposes only for wave latencies and amplitudes (y-axis) but not interwave latencies. No significant relationships were found ($p > 0.05$).

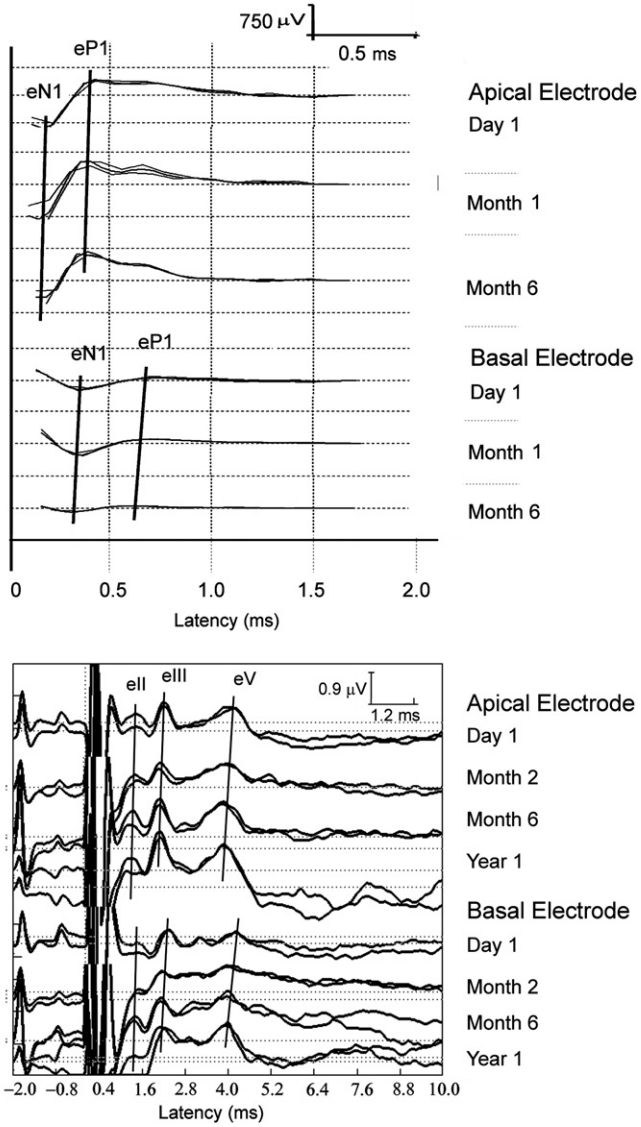

Fig. 6. Measures completed over the first year of implant use in a child with pre-lingual deafness implanted at 3 years of age. The electrically evoked compound action potential is shown in the top panel and the electrically evoked auditory brainstem response in the panel below. Responses evoked by apical electrodes have noticeably shorter latencies than those evoked by basal electrodes. Decreasing latencies with implant use can also be seen.

study, the ECAP and the EABR were used to measure and compare auditory nerve and brainstem activity evoked by stimulation from the apical and basal ends of the cochlear implant array in children with severe to profound hearing loss.

4.1. Measures at initial cochlear implant activation

Results from the present study indicate significant differences between auditory nerve and brainstem activity evoked in basal versus more apical regions of the cochlea at initial device activation. Similar results have been reported in adult implant users (Allum et al., 1990; Firszt et al., 2002; Miller et al., 1993; Shallop et al., 1990), however, these studies did not extend their findings of effects on wave latencies and amplitudes to interwave latencies or effects of duration of implant use. We have shown here that stimulation from an apical versus basal cochlear implant electrode evokes responses with larger amplitudes, steeper amplitude growth with stimulus intensity, and more rapid neural conduction beyond the primary auditory nerve (differences were found in all latencies and interwave latencies except eN1 and eN1–eII). These differences provide evidence that the neurons activated by the basal electrode may have neural response properties which differ somewhat from those activated by the apical electrode. The functional implications of these differences are not known; in particular, the latency differences are small (~0.10 to 0.20 ms) in the context of more central and behavioral responses.

Recent evidence suggests that apical–basal differences in auditory nerve responses are linked to the etiology of prelingual hearing loss (Propst et al., 2006a). In that study, we found that children with GJB2 mutations show similar amplitudes and slope of amplitude growth in responses evoked at apical and basal ends of the cochlea. In children whose non-syndromic hearing loss was not caused by this mutation, apically evoked responses were higher in amplitude than basally evoked responses, had steeper slopes of amplitude growth, and lower stapedius reflex thresholds. Given that the incidence of homozygous GJB2 mutations in our own implant population is approximately 20% (Propst et al., 2006a,b), we expected and found that apical–basal differences in the EABR were consistent with differences in ECAP responses in children without GJB2 mutations.

Differences in responses evoked at either end of the implanted array might also be due to activity-dependent mechanisms. Indeed, children with better residual hearing often have better speech perception abilities prior to implantation and achieve better outcomes after implantation than their peers with poorer hearing (Cowan et al., 1997; Dettman et al., 2004; Dowell et al., 2004; Gordon et al., 2001; van Dijk et al., 1999) and children who had late onset of deafness show decreased latencies relative to their peers who were deaf from an early age (Thai-Van et al., 2007). Yet, the present results suggest that the extent to which poor residual hearing can promote auditory brainstem development is limited in areas which can be stimulated by a cochlear implant. If even minimal residual hearing was able to drive development in these areas, one would expect that electrically evoked brainstem responses in children implanted at older ages, who had longer durations of hearing aid use, would have shorter latencies than in younger children. Moreover, better residual hearing should theoretically promote larger changes than more limited hearing. It is also possible that effects would be clearer in responses evoked by an apical versus basal electrode array given the potential for more apical areas to receive acoustic input through hearing aid use relative to more

Table 2
Results of repeated measures ANOVA on wave latencies: effects of duration of implant use and electrode location (apical versus basal)

Wave	*N*	*F*	df	*p*-value
Effect of duration of implant use				
eV	33	37.7	3,30	<0.0001
eIII	30	14.9	3,27	<0.0001
eII	13	4.6	3,10	<0.05
eN1	21	3.8	2,19	<0.05
Effect of electrode location				
eV	33	82.3	1,32	<0.0001
eIII	30	65.7	1,29	<0.0001
eII	13	1.2	1,12	0.29
eN1	21	11.6	1,20	<0.005
Interaction of duration and electrode effects				
eV	33	3.2	3,30	<0.05
eIII	30	1.1	3,27	0.36
eII	13	2.1	3,10	0.17
eN1	21	0.4	2,19	0.70

Table 3
Results of repeated measures ANOVA on interwave latencies: effects of duration of implant use and electrode location (apical versus basal)

Wave	*N*	*F*	df	*p*-value
Effect of duration of implant use				
eIII–eV	30	31.8	3,27	<0.0001
eN1–eIII	17	9.1	2,15	<0.005
eII–eIII	13	0.1	3,10	0.94
eN1–eII	8	8.9	2,6	<0.05
Effect of electrode location				
eIII–eV	30	3.8	1,29	0.06
eN1–eIII	17	24.8	1,16	<0.0001
eII–eIII	13	29.0	1,12	<0.0001
eN1–eII	8	0.4	1,7	0.57
Interaction of duration and electrode effects				
eIII–eV	30	2.3	3,27	0.10
eN1–eIII	17	2.8	2,15	0.27
eII–eIII	13	4.7	3,10	<0.05
eN1–eII	8	7.7	2,6	<0.05

basal areas. Our results presented in Figs. 4 and 5 show that these scenarios were not the case or that changes were too small to be measured by electrically evoked potentials (as compared with the statistically significant changes found with continuing implant use). Even the trend toward increased eIII–eV latency (apically evoked) with higher hearing thresholds suggested very small changes as shown in Table 4 (95% confidence interval for slope was 0.000–0.006 ms). However, it is interesting that this trend for very small changes was found in the apical rather than basal evoked responses. Thai-Van and colleagues (2007) have recently confirmed the lack of significant effect of age at implantation on wave eV latencies in children and the importance of a period of normal hearing prior to deafness.

Apical–basal differences in evoked potential responses need to be considered when using such measures to predict behavioral measures of threshold and comfort levels in device programming (Gordon et al., 2004; Thai-Van et al., 2001). However, it remains unclear to what extent these differences impact on functional outcomes of implant use particularly as the differences may change over time (Gordon et al., 2004; Thai-Van et al., 2001; and Gordon et al., present study).

4.2. Effects of implant use

It is clear that the effectiveness of a cochlear implant relies on adequate survival of the primary auditory neurons and on the integrity of the pathways to carry the input to cortical regions necessary for hearing. We hypothesized that the integrity of the pathways at the time of implantation will impact evoked potential stimulation patterns and perhaps the developmental plasticity of the central auditory system. Results from the present study show that while some apical–basal differences in evoked responses persist with implant use (wave eV amplitude and eN1–eIII, eII–eIII interwave latency) others do not (eIII–eV latency).

Consistent stimulation from either end of the implanted array did promote developmental plasticity of the auditory brainstem, as shown in Figs. 6 and 7, by decreasing wave and interwave latencies. We originally reported the changes evoked by the basal implant electrode (Gordon et al., 2003, 2006) and Thai-Van and colleagues (2007) have recently confirmed that significant decreases in wave eV occur over two years of implant use (both apical and basal evoked changes were shown). The same types of latency changes have been shown to occur in normal hearing children over the first two years of life and have been attributed to increased myelination and improved synaptic efficacy (Eggermont, 1988). Our present results indicate that differences in responses evoked by apical versus basal electrodes at initial stimulation continue to be present with ongoing implant use; these differences remain in early but not later latency waves.

4.2.1. Changes in caudal brainstem

It appears that eN1–eIII interwave latency differences between responses evoked by apical and basal electrodes are due to differences in eII–eIII which persist over the first year of implant use. Of note, no significant changes in eII–eIII with implant use were found. This suggests a limited role of stimulation to improve conduction of action potentials along the pathways connecting the generators of waves eII and eIII particularly when compared to the clear changes in eIII–eV (reflecting neural conduction times in more rostral areas).

The unique characteristics of the eII–eIII interval, namely the resistance to change with implant use and the apical to basal gradient in latency, highlight that the impacts of electrical stimulation on the auditory brainstem remain somewhat unclear. In a previous publication (Gordon et al., 2006), we questioned which population of neurons give rise to wave eIII. While eN1–eII is similar in latency to I–II of the acoustic click evoked response, representing neural conduction along the auditory nerve

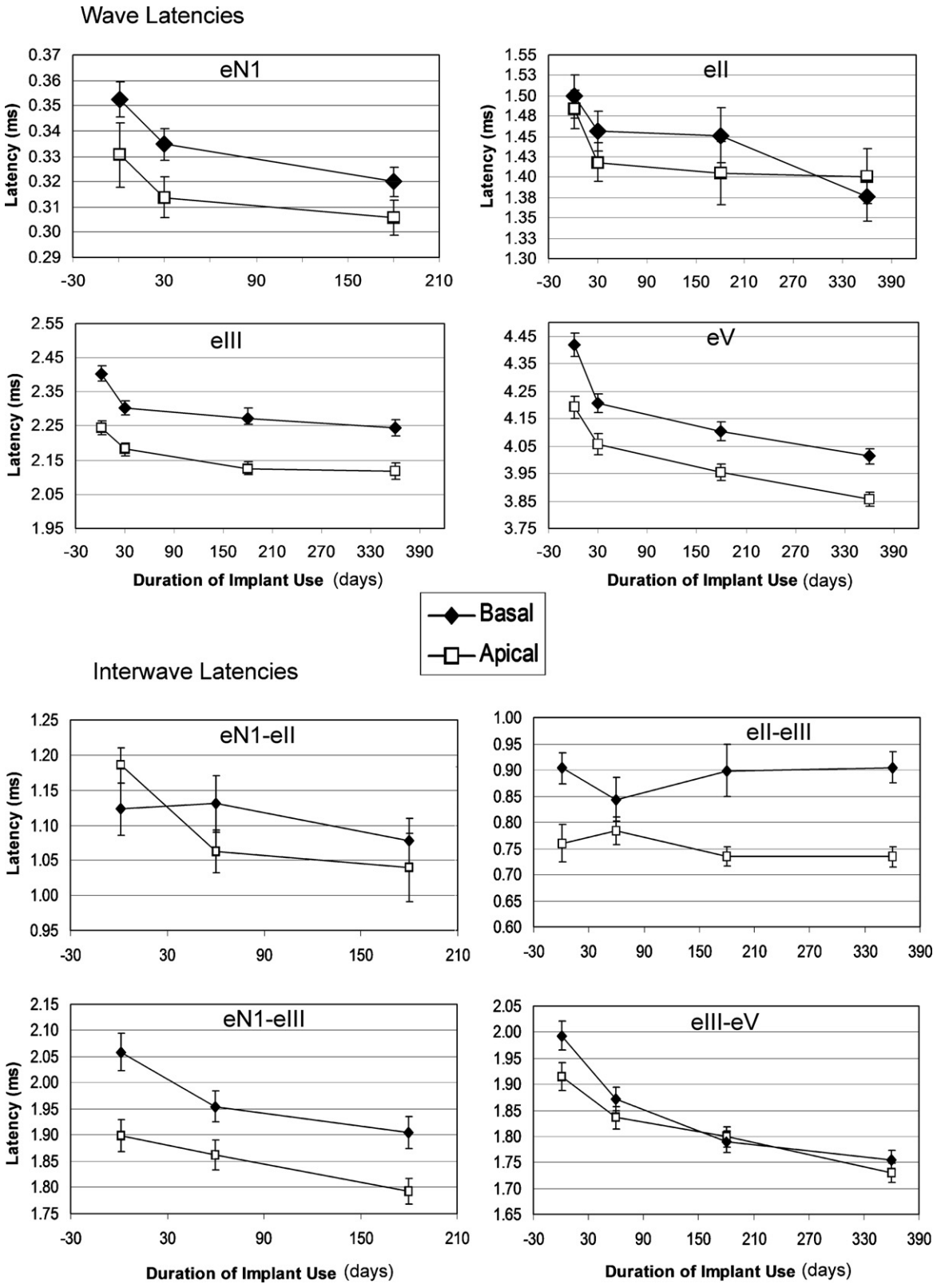

Fig. 7. Mean (±1SE) wave and interwave latencies evoked by an apical and basal implant electrode over the first year of implant use. Significant decreases were shown for responses evoked by both electrodes for all latencies bar eII–eIII as detailed in Tables 2 and 3.

(Moller, 1994), eII–eIII appears to be slightly shorter than the normal II–III (Gordon et al., 2006). Moreover, the lack of significant change in eII–eIII with ongoing cochlear implant use is curious given that II–III shows considerable change over the first year of life in normally hearing infants (Ponton et al., 1996).

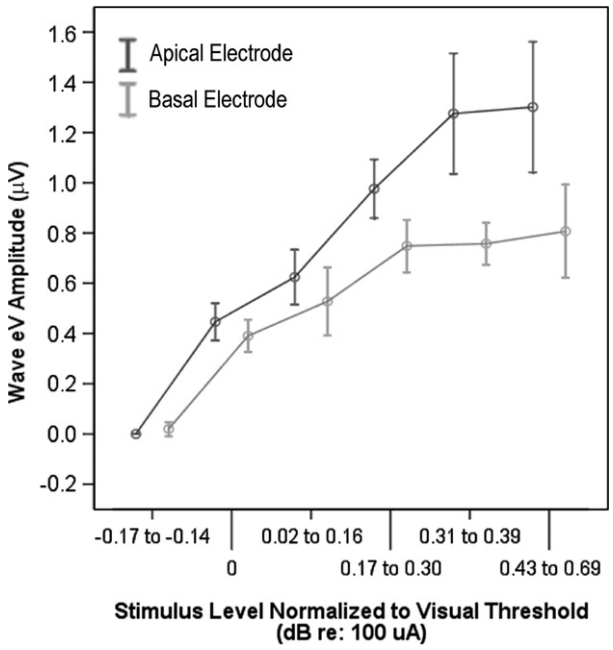

Fig. 8. Mean (±1SE) wave eV amplitude obtained after 6 or 12 months of implant use in 50 children is shown with respect to stimulus intensity (dB re:100 μV) normalized to visual threshold. The amplitude growth appears steeper when evoked by an apical versus basal implant electrode.

4.2.2. Changes in rostral brainstem

We have previously shown that the most prominent changes in brainstem neural conduction time with implant use occur in the rostral portion (Gordon et al., 2006). Results of the present study suggest that decreases in interwave latencies occur in response to stimulation from either an apical or a basal cochlear implant electrode in children with pre-lingual deafness. Yet, there are subtle differences between connections stimulated by an apical and those by a basal cochlear implant electrode. At initial stimulation, prolonged neural conduction in response to basal versus apical electrode stimulation is shown by longer eIII–eV interwave latency. Changes over the first 2 months of implant use occurred more rapidly in responses evoked by a basal rather than the apical implant electrode such that basal eIII–eV interwave latencies "catch up" with those evoked more apically. Thereafter, it appears that both apical and basal electrode stimulation promote similar rates of change in the rostral brainstem as measured by decreasing eIII–eV latencies.

Evoked potential measures suggest that cochlear implant use has unique effects on the rostral auditory brainstem as compared to more caudal areas. First, cochlear implant use in children promotes normal-like rates of change in neural conduction time in this area of

Table 4
Results of linear regression between EABR measures and either age at implantation or residual hearing (defined as the average of hearing thresholds at 250, 500, and 1000 Hz)

	Effects of age at activation Latency (ms)				Effects of residual hearing Latency (ms)				Effects of implant use Latency (ms)	
	95% CI		*R*-value	df	95% CI		*R*-value	df	95% CI of change	
Basal										
eN1	−0.005	0.003	0.068	1,41	−0.001	0.001	0.045	1,40	0.009	0.040
eIII	−0.011	0.012	0.015	1,43	−0.001	0.005	0.217	1,42	0.070	0.180
eV	−0.013	0.280	0.108	1,45	−0.003	0.008	0.144	1,44	0.320	0.460
eN1−eIII	−0.009	0.015	0.082	1,38	−0.001	0.005	0.189	1,37	0.031	0.237
eIII–eV	−0.019	0.007	0.137	1,42	−0.003	0.004	0.043	1,42	0.180	0.290
Apical										
eN1	−0.005	0.003	0.073	1,40	−0.001	0.002	0.116	1,39	0.004	0.420
eIII	−0.017	0.009	0.092	1,44	−0.002	0.005	0.150	1,43	0.090	0.170
eV	−0.022	0.020	0.009	1,46	−0.002	0.009	0.186	1,45	0.270	0.410
eN1–eIII	−0.015	0.010	0.070	1,39	−0.001	0.005	0.188	1,38	0.090	0.170
eIII–eV	−0.020	0.002	0.248	1,43	0.000	0.006	0.251	1,43	0.150	0.230

	Amplitude (μV)				Amplitude (μV)			
	95% CI		*R*-value	df	95% CI		*R*-value	df
Basal								
eN1	−11.52	10.946	0.008	1,42	−2.337	3.813	0.075	1,41
eIII	−0.005	0.021	0.188	1,43	−0.003	0.004	0.086	1,42
eV	−0.004	0.055	0.249	1,45	−0.011	0.005	0.106	1,44
Apical								
eN1	−18.349	12.907	0.053	1,43	−4.6	3.976	0.023	1,42
eIII	−0.008	0.037	0.194	1,44	−0.004	0.008	0.093	1,43
eV	−0.008	0.071	0.228	1,46	−0.011	0.011	0.012	1,45

Confidence intervals of the effects of implant use are from post hoc comparisons (with Bonferonni adjustments) of repeated measures ANOVAs detailed in Tables 1–3.

the central auditory system as opposed to the very rapid and small degree of change which occurs in more peripheral areas (Gordon et al., 2006). Second, there is no difference in neural conduction time, measured by eIII–eV, in responses evoked by an apical versus basal implant electrode after 2 months of consistent implant use. In contrast, conduction times in more peripheral areas of the pathway remain prolonged when evoked by a basal electrode and change little with implant use. Thus, it appears that the rostral brainstem retains a greater potential for plasticity than the more peripheral portions of the pathway.

In conclusion, brainstem responses evoked by acute stimulation from electrodes at either end of the implanted array are marked by differences in wave amplitude and latency and are not significantly affected by either degree of residual hearing or age at implantation. On the other hand, chronic cochlear implant use promotes: (1) significant decreases in interwave latencies reflecting shortening neural conduction times along the brainstem in responses evoked by an apical and basal implant electrode; (2) similar neural conduction times in responses evoked by apical versus basal implant electrodes in the rostral, but not caudal, portion of the brainstem. This suggests a considerable and unique impact of apical versus basal cochlear implant electrodes on auditory brainstem development in children with severe to profound hearing loss.

Acknowledgement

Funding for this project was provided by the Canadian Institutes of Health Research.

References

Abbas PJ, Brown CJ. Electrically evoked brainstem potentials in cochlear implant patients with multi-electrode stimulation. Hear Res 1988;36(2–3):153–62.

Abbas PJ, Brown CJ, Shallop JK, Firszt JB, Hughes ML, Hong SH, et al. Summary of results using the nucleus CI24M implant to record the electrically evoked compound action potential. Ear Hear 1999;20(1):45–59.

Allum JH, Shallop JK, Hotz M, Pfaltz CR. Characteristics of electrically evoked 'auditory' brainstem responses elicited with the nucleus 22-electrode intracochlear implant. Scand Audiol 1990;19(4):263–7.

Araki S, Kawano A, Seldon HL, Clark GM. Intracochlear factors affect the auditory brainstem response to intracochlear electrical stimulation in the cat. Adv Otorhinolaryngol 1997;52:39–42.

Bierer JA, Middlebrooks JC. Auditory cortical images of cochlear-implant stimuli: dependence on electrode configuration. J Neurophysiol 2002;87(1):478–92.

Bierer JA, Middlebrooks JC. Cortical responses to cochlear implant stimulation: channel interactions. J Assoc Res Otolaryngol 2004;5(1):32–48.

Cohen LT, Richardson LM, Saunders E, Cowan RS. Spatial spread of neural excitation in cochlear implant recipients: comparison of improved ECAP method and psychophysical forward masking. Hear Res 2003;179(1–2):72–87.

Cowan RS, DelDot J, Barker EJ, Sarant JZ, Pegg P, Dettman S, et al. Speech perception results for children with implants with different levels of preoperative residual hearing. Am J Otol 1997;18(Suppl. 6):S125–6.

Dettman SJ, D'Costa WA, Dowell RC, Winton EJ, Hill KL, Williams SS. Cochlear implants for children with significant residual hearing. Arch Otolaryngol Head Neck Surg 2004;130(5):612–8.

Dowell RC, Hollow R, Winton E. Outcomes for cochlear implant users with significant residual hearing: implications for selection criteria in children. Arch Otolaryngol Head Neck Surg 2004;130(5):575–81.

Eggermont JJ. On the rate of maturation of sensory evoked potentials. Electroencephalogr Clin Neurophysiol 1988;70(4):293–305.

Eisen MD, Franck KH. Electrode interaction in pediatric cochlear implant subjects. J Assoc Res Otolaryngol 2005;6(2):160–70.

Firszt JB, Chambers RD, Kraus Reeder RM. Neurophysiology of cochlear implant users I: effects of stimulus current level and electrode site on the electrical ABR, MLR, and N1-P2 response. Ear Hear 2002;23(6):502–15.

Gordon KA, Ebinger KA, Gilden JE, Shapiro WH. Neural response telemetry in 12- to 24-month-old children. Ann Otol Rhinol Laryngol Suppl 2002;189:42–8.

Gordon KA, Papsin BC, Harrison RV. Activity-dependent developmental plasticity of the auditory brainstem in children who use cochlear implants. Ear Hear 2003;24(6):485–500.

Gordon KA, Papsin BC, Harrison RV. Toward a battery of behavioral and objective measures to achieve optimal cochlear implant stimulation levels in children. Ear Hear 2004;25:447–63.

Gordon KA, Papsin BC, Harrison RV. An evoked potential study of the developmental time course of the auditory nerve and brainstem in children using cochlear implants. Audiol Neurootol 2006;11(1):7–23.

Gordon KA, Twitchell KA, Papsin BC, Harrison RV. Effect of residual hearing prior to cochlear implantation on speech perception in children. J Otolaryngol 2001;30(4):216–23.

Hughes ML, Abbas PJ. Electrophysiologic channel interaction, electrode pitch ranking, and behavioral threshold in straight versus perimodiolar cochlear implant electrode arrays. J Acoust Soc Am 2006;119(3):1538–47.

Kral A, Hartmann R, Mortazavi D, Klinke R. Spatial resolution of cochlear implants: the electrical field and excitation of auditory afferents. Hear Res 1998;121(1–2):11–28.

Lai WK, Dillier N. A simple two-component model of the electrically evoked compound action potential in the human cochlea [In Process Citation]. Audiol Neurootol 2000;5(6):333–45.

Miller CA, Abbas PJ, Brown CJ. Electrically evoked auditory brainstem response to stimulation of different sites in the cochlea. Hear Res 1993;66(2):130–42.

Moller AR. Neural generators of auditory evoked potentials. In: Jacobson JT, editor. Principles and applications in auditory evoked potentials. Boston: Allyn and Bacon; 1994. p. 23–46.

Moller AR, Jannetta PJ. Auditory evoked potentials recorded intracranially from the brain stem in man. Exp Neurol 1982a;78(1):144–57.

Moller AR, Jannetta PJ. Evoked potentials from the inferior colliculus in man. Electroencephalogr Clin Neurophysiol 1982b;53(6):612–20.

Nadol Jr JB. Patterns of neural degeneration in the human cochlea and auditory nerve: implications for cochlear implantation. Otolaryngol Head Neck Surg 1997;117(3 Pt. 1):220–8.

Ponton C, Moore JK, Eggermont JJ. Auditory brain stem response generation by parallel pathways: differential maturation of axonal conduction time and synaptic transmission. Ear Hear 1996;17(5):402–10.

Propst EJ, Papsin BC, Stockley TL, Harrison RV, Gordon KA. Auditory responses in cochlear implant users with and without GJB2 deafness. Laryngoscope 2006a;116(2):317–27.

Propst EJ, Stockley TL, Gordon KA, Harrison RV, Papsin BC. Ethnicity and mutations in GJB2 (connexin 26) and GJB6 (connexin 30) in a multi-cultural Canadian paediatric Cochlear Implant Program. Int J Pediatr Otorhinolaryngol 2006b;70(3):435–44.

Salamy A. Maturation of the auditory brainstem response from birth through early childhood. J Clin Neurophysiol 1984;1(3):293–329.

Shallop JK, Beiter AL, Goin DW, Mischke RE. Electrically evoked auditory brain stem responses (EABR) and middle latency responses

(EMLR) obtained from patients with the nucleus multichannel cochlear implant. Ear Hear 1990;11(1):5–15.

Simmons FB, Smith L. Estimating nerve survival by electrical ABR. Ann NY Acad Sci 1983;405:422–3.

Thai-Van H, Chanal JM, Coudert C, Veuillet E, Truy E, Collet L. Relationship between NRT measurements and behavioral levels in children with the Nucleus 24 cochlear implant may change over time: preliminary report. Int J Pediatr Otorhinolaryngol 2001;58(2):153–62.

Thai-Van H, Cozma S, Boutitie F, Disant F, Truy E, Collet L. The pattern of auditory brainstem response wave V maturation in cochlear-implanted children. Clin Neurophysiol 2007;118(3):676–89.

Thai-Van H, Truy E, Charasse B, Boutitie F, Chanal JM, Cochard N, et al. Modeling the relationship between psychophysical perception and electrically evoked compound action potential threshold in young cochlear implant recipients: clinical implications for implant fitting. Clin Neurophysiol 2004;115(12):2811–24.

van Dijk JE, van Olphen AF, Langereis MC, Mens LH, Brokx JP, Smoorenburg GF. Predictors of cochlear implant performance. Audiology 1999;38(2):109–16.

Zimmermann CE, Burgess BJ, Nadol Jr JB. Patterns of degeneration in the human cochlear nerve. Hear Res 1995;90(1–2):192–201.