Auditory Development Promoted by Unilateral and Bilateral Cochlear Implant Use

Karen Gordon

Introduction

Auditory development after cochlear implantation in children with early onset deafness is inferred through behavioral improvements in speech perception skills. However, these outcomes can be highly variable and may depend on numerous factors ranging from the delay to implantation, to the child’s IQ, to family structure or even the educational environment (Geers and Brenner 2003; Geers, Brenner and Davidson 2003; Niparko 2007). At the most basic level, the cochlear implant is designed to stimulate activity in the central auditory system, which is anticipated, in children, to lead to development of the auditory pathways.

In this paper we will provide evidence that the auditory system is formed even in the absence of significant activity in children with early onset/congenital deafness, but that the pathways require auditory input to develop. If deprived of activity bilaterally, the auditory thalamus and cortex will likely be driven by non-auditory inputs including those from the visual pathways (Finney, Fine and Dobkins 2001; Finney, Clementz, Hickok and Dobkins 2003; Fine, Finney, Boynton and Dobkins 2005) which could compromise their use for auditory processing post-implantation (Giraud, Price, Graham, Truy and Frackowiak 2001; Lee et al. 2001; Lee et al. 2007). The auditory brainstem has comparatively less competitive influences than the auditory thalamus and cortex and consequently remains virtually unchanged, or “frozen”, during the period of auditory deprivation. We have shown that development in the auditory brainstem can proceed in children with severe-profound sensorineural hearing loss once a cochlear implant is provided. However, this unilateral input may drive development which alters the plasticity of the contralateral pathways. Finally, we will show that stimulation from bilateral cochlear implants can be integrated in the auditory brainstem, but that the patterns of integration can be compromised by a period of unilateral implant use. Our results to date indicate that there may be at least two sensitive periods during auditory development: the first from a delay between onset of deafness in early childhood to cochlear implantation, which compromises thalamo-cortical development with implications for speech-language acquisition, and the second due to a delay between unilateral and bilateral input which may alter development of binaural auditory processing.

Effects of Auditory Deprivation on the Developing Central Auditory Pathways

Neural pathways, including those of the central auditory system, form in the developing fetus prior to the onset of hearing through inherent mechanisms that are likely mediated genetically. Once the cochlea develops and becomes functional, these pathways are available to respond albeit in an immature way. With age, the pathways develop becoming more adult-like; more peripheral portions of the central auditory system appear to have shorter developmental time courses than relatively central portions, which can extend throughout childhood into adolescence. Much of this information has been learned from measuring auditory evoked potentials from different levels of the system in children with normal hearing. These responses change over time, be-
coming more clearly detectable and changing in both latency and amplitude (Eggermont 1985; Eggermont 1988; Ponton, Moore and Eggermont 1996; Sharma, Kraus, McGee and Nicol 1997; Ponton, Eggermont, Khosla, Kwong and Don 2002). Whilst some developmental processes likely occur inherently (through genetic instruction), others require input or experience.

For children with early onset deafness, any development of the auditory pathways prior to the use of an auditory prosthesis occurs in the absence of significant input. Our research focuses on the effects of deafness on the pathways originally intended to carry sound to the brain and on the ability to stimulate these neural connections with a cochlear implant. We focus on discrete areas of the pathways using evoked potential recordings and can compare the responses we find in children using cochlear implants with those recorded in normal hearing children.

A typical cochlear implant, both internal and external components, is shown in figure 1. Electrical pulses are delivered by electrodes, which are implanted along an array into the scala media of the cochlea. As we will discuss, these electrical pulses are highly effective in stimulating the auditory nerve and consequently stimulating the central auditory system.

A typical cochlear implant, both internal and external components, is shown in figure 1. Electrical pulses are delivered by electrodes, which are implanted along an array into the scala media of the cochlea. As we will discuss, these electrical pulses are highly effective in stimulating the auditory nerve and consequently stimulating the central auditory system.

Figure 2 displays evoked responses from the auditory nerve and brainstem evoked by stimulation from a basal implant electrode in a child with early onset deafness. Because the first wave of the electrically evoked auditory brainstem response (EABR) is obscured by artifact, we also measure the electrically evoked compound action potential (ECAP) of the auditory nerve us-
ing the device’s telemetry system to record from an intracochlear implant electrode. The close proximity of the recording electrode to the neurons being activated, and the use of a subtraction paradigm to eliminate stimulus artifact, allows this response to be recorded as previously described (Abbas et al. 1999).

In combination, we can assess interwave latencies between the eN1 of the ECAP and the EABR waves to measure the time of neural conduction along the auditory brainstem in children using cochlear implants. The interwave latencies also allow a comparison between electrically evoked responses in children using implants and acoustically evoked responses in normal hearing individuals. In figure 3, ECAP and EABR wave latencies are compared with published ABR values suggesting similar latency and interwave latencies for the early waves but shorter eIII and eV values compared to the acoustic homologues (III and V, respectively).

**Initial Auditory Activity: Effects of Bilateral Auditory Deprivation**

We are particularly interested in the responses obtained immediately following cochlear implant activation because they: a) confirm that neural pathways are present, can be stimulated by the implanted device and are organized in an expected way; b) provide a measure of the effects of deafness on the auditory pathways; and c) are a baseline for any changes realized with ongoing cochlear implant use. ECAP and EABR wave latencies and amplitudes evoked by a basal electrode at initial device activation are shown in figure 4. Of the 50 children included in this study cohort, 47 (94%) had clear EABRs at initial activation (in two children a large myogenic response was recorded, possibly obscuring a present EABR and, in one child, EABRs were recorded at later time points in response to stimulation with wider pulse widths). As shown in figure 3, no significant relationship between wave latencies, maximum amplitudes or the slope of amplitude growth (with increasing intensity) were found with respect to age at testing. Given that these children all had early onset (typically congenital) deafness, their age at this time was equivalent to their duration of bilateral deafness. The lack of significant change of latency or amplitude values with respect to this time period suggests that: a) developmental changes in the auditory nerve and brainstem do not occur in the absence of significant input; and b) if degenerative changes occur during this period, they are not large enough to be detected by the evoked potential measures.

The “frozen” state of the auditory nerve and brainstem prior to implantation is not mirrored in more central areas of the auditory system. We assessed thalamocortical activity at device activation in awake children by recording electrically evoked middle latency responses (EMLR). A sample response is shown in figure 5.
Estingly, we found that children older than 8 years of age (who also experienced eight years of deafness) were more likely to show detectable EMLRs (> 60% present) than children younger than this (< 40% present) at initial implant use. This suggests that, unlike the auditory brainstem, the thalamo-cortical pathways undergo change during the period of deafness. We do not yet fully understand what changes are occurring, but both normal and/or abnormal developmental processes could be involved. Because there is no significant auditory input to drive these changes, these could be processes that are activity-independent (perhaps genetically mediated) or processes driven by non-auditory input. The latter argument is supported by evidence that the auditory cortex undergoes reorganization during the period of deafness, which is driven by non-auditory activity including input from the visual and somato-sensory systems (Finney et al. 2001; Finney et al. 2003; Fine et al. 2005) and that the auditory cortex can be reorganized by experimentally connecting retinal neurons (from the visual system) to the central auditory system (von Melchner, Pallas and Sur 2000).

Donald Hebb’s notion of neural development might help to explain why non-auditory inputs stimulate the auditory cortex after many years of bilateral deafness, as well as why there is relatively little change occurring in the auditory brainstem during this period of auditory deprivation. It is known that abundant connections between neurons are made during development, but that only some of these connections survive (Huttenlocher and Dabholkar 1997). Hebb explained this phenomenon by proposing that those connections which provide coordinated signaling resulting in successful activation of the target neuron would be strengthened, while the other, less successful inputs would be eliminated (Hebb 1949). Because cortical neurons receive connections from multi-sensory neural pathways, it is possible that those inputs carrying auditory information are dormant in bilateral deafness and therefore eliminated or weakened, whereas non-auditory inputs are more successful and thus are abnormally strengthened in traditionally auditory dominant areas of the cortex. In contrast, neurons in the auditory brainstem receive the majority of their inputs from the left and right ears. Without significant input from either side, we hypothesize that these neurons are left virtually without input and thus do not show any change as measured by evoked potentials during the period of bilateral auditory deprivation. We further hypothesize that a period of unilateral auditory input will drive connections from the stimulated side at the expense of those from the unstimulated side.

In the following sections, effects of unilateral stimulation from a single cochlear implant on the central auditory system will be addressed. Further discussion will then focus on how chronic unilateral stimulation during development might impact contralaterally evoked responses after bilateral cochlear implantation.

**Changes with Unilateral Cochlear Implant Stimulation**

Our studies have examined development promoted by unilateral cochlear implant use by following a large cohort of children with early onset deafness over the first year of implant use. A typical example of repeated ECAP and EABR recordings evoked by an apical and basal cochlear implant electrode is shown in figure 6; wave latencies appear to decrease with implant use. This is confirmed by the group data shown in figure 7; significant decreases in both wave and interwave latencies were found. Decreasing EABR wave and interwave latencies reflect increasingly rapid neural conduction through the auditory brainstem with ongoing cochlear implant use. Similarly, the acoustically evoked Auditory Brainstem Responses (ABR) undergoes latency decreases over the first year of life in normal hearing infants (Beiser, Himelfarb, Gold and Shanon 1985; Ponton, Eggermont, Coupland and Winkelaar 1992; Jiang 1995; Ponton et al. 1996). These changes have been explained by increased myelination and improved synaptic efficiency through processes such as that proposed by Hebb (Eggermont 1985; Eggermont 1988). Synaptic changes alone might explain the evoked potential find-
ings in both the developing ABR in normal hearing children (Ponton et al. 1996) and the EABR in pediatric cochlear implant users. The developmental time course for the EABR eIII-eV interwave latency in children with early onset deafness was calculated to span over the first year of implant use, meaning that the unilaterally electrically stimulated auditory brainstem should be approaching maturation around the first year anniversary of device activation.

We have also examined changes in the EMLR over time. As plotted in figure 8, the ability to detect the EMLR increased dramatically over the first six months of implant use in children implanted at ages < 8 years, whereas less change was observed in children implanted at least 8 years of age. However, the more restricted change over this period in the oldest group of children might be associated with the increased ability to detect this response at initial stimulation. A similar

Figure 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. This figure appears in (Gordon et al. 2007b) on page 1679.

Figure 7. Mean wave latency and inter-latency data during the duration of implant use. Error bars indicate ±1SE. Repeated measures ANOVA performed on complete datasets indicate a significant decrease in wave latency for waves eN1, eIII, and eV. Significant decreases in interwave latency were found for eN1-eIII reflecting neural conduction time in the lower brain stem, and eIII-eV reflecting neural conduction time in the upper brain stem. These figures appear in (Gordon et al. 2003) on pages 492 and 493.
finding has been reported by Sharma and colleagues who found that late latency cortical responses in children implanted “late” had shorter wave latencies compared to children implanted at younger ages and changed relatively little compared to the younger group (Sharma, Dorman and Kral 2005). As discussed above, it is possible that the auditory thalamo-cortex, as assessed by EMLR and late latency responses, changes either through activity-independent mechanisms or undergoes abnormal development promoted by non-auditory input during extended periods of bilateral auditory deprivation in childhood. In either case, normal auditory development might not be reestablished after cochlear implantation. Ponton and Eggermont have suggested that children using cochlear implants might never develop normal adult-like cortical responses (Ponton and Eggermont 2001; Ponton 2006), which in turn would reflect persistent differences in the electrically driven auditory cortex. This will only be completely resolved as we follow children implanted at young ages/short durations of deafness into adulthood.

Studies examining behavioral responses in children using unilateral cochlear implant show that there are many factors which contribute to post-implant outcomes, including speech perception abilities, speech and language acquisition, and reading. Age at implantation appears to be one of these predictors in children with early onset deafness, and this supports the idea that bilateral auditory deprivation in early years of life compromises a sensitive period in auditory development. Based on our previous and current work, we suggest that there may be more than one sensitive period in auditory development. In the following section, we will examine the possibility that a sensitive period for bilateral input is present in the developing auditory system.

**Effects of Unilateral Cochlear Implant Stimulation on Contralaterally Evoked Responses after Bilateral Cochlear Implantation**

Recently we have been conducting studies asking if a period of unilateral implant use compromises development of the contralateral auditory pathways. This has particular implications for children who receive a second cochlear implant a number of years following implantation of the first ear. We hypothesized that the auditory brainstem would be most plastic during the period of auditory brainstem development as measured by changes in the EABR. We therefore examined plasticity in the contralaterally stimulated auditory brainstem in children who had over two years of unilateral implant use (and likely a mature auditory brainstem as measured by EABR); children who had less than one year of unilateral use prior (EABR still undergoing change); and children with no unilateral implant experience prior to bilateral implantation. In children using bilateral cochlear implants, we have measured the EABR evoked...
Auditory Development Promoted by Unilateral and Bilateral Cochlear Implant Use

57

by the cochlear implant on the right and on the left sides, as well as by bilateral cochlear implant stimulation. Responses recorded from the first day of bilateral device activation are shown in figure 9 for Child A who received both cochlear implants in the same surgery (simultaneous implantation) and Child B who received a second implant in the left ear five years after the implantation of the right ear (sequential implantation after a long delay between implants). Responses evoked by the right implant are shown in black and the left in gray. While there are no clear differences between responses evoked by either implant in Child A, wave latencies in Child B’s newly activated left implant are prolonged compared to those evoked by the experienced right side. Predicted binaural responses, the sum of the left and right responses, are shown for two recording channels by the dashed line, and the measured binaurally evoked response is shown by a solid line. The difference

Figure 10. Mean latencies (±1SE) of wave eV and interwave eIII-eV latencies evoked in the left ear at initial device activation were not significantly different in each bilateral implant group than age-matched unilateral users at the same stage of implant use (p > 0.05). Response latencies in the right ear are not significantly different from the left in the simultaneous group (n = 9) (p > 0.05), slightly shorter in the short delay group (n = 15) (p > 0.05), and significantly shorter in the long delay group (n = 15) (p < 0.05). This figure appears in (Gordon et al. 2007a) on page 615.

Figure 11. Wave eV is indicated and appears prolonged in the less experienced left ear in the child on the right. Both children had used their bilateral implants for 3 months. Responses were evoked by the right implant, the left implant and binaurally. The binaural difference response is present in each recording channel for each child. In the bottom left panel, mean wave eV latencies evoked by the left implant are plotted relative to the right evoked eV latency for four groups of children at three separate time intervals. Children initially implanted at under 3 years of age had either long (> 2 years), short (6–12 months) or no inter-stage delays and a small group (n=4) of children initially implanted at over 3 years of age had long inter-stage intervals. Left evoked eV was prolonged in all groups of children other than the simultaneous group. This difference decreased over time (but was still present in the two groups with long delays) and resolved by 9 months in the group with a short inter-stage interval. At the bottom right, the mean latency of the binaural difference response is plotted relative to the right evoked eV latency. The same trend is shown; the difference response remains prolonged in children with long inter-stage intervals but is resolved at the 9-month time point in children with short delays. This figure appears in (Papsin and Gordon, in press).
between the measured and predicted binaural response is displayed for two recording channels. This calculated response, termed the binaural difference (BD) wave, in Children A and B can be seen for responses evoked by the apical but not the basal implant electrode.

Figure 10 displays the mean wave eV latency data for either ear in a group of children with long delays (> 2 years); short delays (6–12 months); and no delays between implantation of the first and second ears, as recorded at initial device activation. The right ear was the ear first implanted in all children. Mean latencies for a group of age-matched unilateral cochlear implant users recorded at initial device stimulation are also plotted. Response latencies evoked by the right experienced ear are significantly shorter in the children with long and short delays between implants, relative to their newly implanted left ears and responses evoked at the first unilateral stimulation in the age-matched unilateral group. These responses were recorded over the first year of bilateral implant use in all groups of children. As plotted in figure 11, the prolongation of wave eV latencies evoked in the naïve relative to the more experienced ear was: a) not found in children with simultaneous implants at any time point; and b) decreased in children with short but not long delays between implants. In both groups of children with long delays (children initially implanted > 3 or < 3 years of age), there appears to be little change over time in the degree to which responses from the naïve ear lagged behind the experienced ear in latency. In this figure, the latency of the BD response is also plotted relative to the wave eV latency of the experienced ear. In children with short delays, the BD at 9–12 months of bilateral implant use appears to have decreased to latencies (relative to wave eV latency evoked in the ear first implanted), which were similar to those found in the children receiving simultaneous bilateral cochlear implants, whereas the BD in children with long delays appears to remain prolonged (relative to eV evoked by the first implant). Thus, a period of unilateral implant use, which extends beyond the time course of electrically evoked auditory brainstem response maturation, appears to alter the developmental potential of the contralaterally stimulated pathways. Moreover, the ability of the contralateral pathway to integrate with the connections stimulated by the first implanted side might also be compromised. Based on these data, we suggest that in addition to sensitive periods missed during a period of bilateral deprivation in childhood, there may be a sensitive period for bilateral stimulation that is missed during an extended period of solely unilateral auditory input. Whereas the former may have implications for speech and language acquisition, the latter is more likely to affect binaural processes.

Summary and Conclusions

Our data suggest that experience has a major role in shaping the developing central auditory system. Although the pathways form without significant input, they become refined based on the input they receive. We hypothesize that there is very little input to the auditory brainstem during the period of bilateral deafness in childhood, which leaves the auditory brainstem immature and virtually unchanged. In contrast, the thalamo-cortical pathways of the auditory system may be subject to reorganization by non-auditory inputs that have connections to these areas. Our further work, based on this Hebbian view of neural development, showed that the introduction of unilateral stimulation from a cochlear implant promoted development of the auditory brainstem regardless of the duration of deafness, but that changes in the thalamo-cortical areas were dependent upon the child’s age/duration of deafness. Although these findings indicated a positive role of chronic stimulation by a cochlear implant, the unilateral input over several years was found to alter the potential for developmental change in the contralaterally stimulated brainstem pathways following sequential bilateral cochlear implantation and for expected timing of binaural integration as measured by the binaural difference response. This suggests a benefit of simultaneous bilateral implantation or sequential implantation after a short inter-implant interval. We therefore propose that there are at least two sensitive periods in auditory development; the first depends on auditory input, having implications for development of speech-language, and the second depends on bilateral input, which has implications for development of binaural processing.

References


