Lateralization of Inter-Implant Timing and Level Differences in Children Who Use Bilateral Cochlear Implants

by

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Cochlear implants provide hearing to people who are deaf, by electrically stimulating the auditory nerve. Children with a single cochlear implant suffer deficiencies inherent to unilateral hearing, including inability to locate sounds. A second cochlear implant may improve sound localization, which normally requires interpretation of differences in sound intensity and time of arrival between two ears. Currently, it is unknown whether these cues are available to children who were provided with a second cochlear implant after a period of using one implant alone. We asked whether such children could interpret inter-implant level and timing cues. Results indicated that children using two cochlear implants detected level cues but had difficulty interpreting timing cues. Further, children rarely reported that sounds were perceived to come from the middle. Children receiving bilateral cochlear implants sequentially do not process bilateral auditory cues normally but can use inter-implant level cues to make judgments about where sound is coming from.
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List of Abbreviations

AVCN – anteroventral cochlear nucleus
DCN – dorsal cochlear nucleus
EABR – electrically evoked auditory brainstem response
CI – cochlear implant
CI-1 – first implanted cochlear implant
CI-2 – second implanted cochlear implant
CU – clinical units
IC – inferior colliculus
ILD – inter-implant/aural level difference
ITD – inter-implant/aural timing difference
LL – lateral lemniscus
LLD – dorsal nucleus of the lateral lemniscus
LLV – ventral nucleus of the lateral lemniscus
LSO – lateral superior olive
MSO – medial superior olive
MNTB – medial nucleus of the trapezoid body
SNHL – sensorineural hearing loss
SOC – superior olivary complex
PVCN – posteroventral cochlear nucleus
Chapter 1
Introduction

1.1 Background and Research Questions

We aimed to understand how young children with bilateral cochlear implants interpret inter-implant level and timing difference cues. Specifically, we asked: 1) can children using bilateral cochlear implants perceive changes in trains of electrical pulse stimuli with inter-implant level or timing differences? And 2) can electrophysiological recordings aid in predicting balanced stimuli between children’s two devices?

Cochlear implants are prosthetic devices that directly stimulate the auditory nerve with electrical pulses, and thus provide auditory stimulation to people with severe to profound hearing loss. Cochlear implants allow deaf adults and children to hear and to develop oral speech and language skills. However, the use of only one implant does not allow for access to binaural hearing, which is necessary for sound localization and speech understanding in noisy environments.

Normally, binaural hearing allows listeners to compare small differences in intensity and time of arrival of acoustic signals between ears. These comparisons are important for locating the origin of a sound and for improved speech understanding in noise. For children, binaural hearing is important in every-day situations, allowing them to locate sound sources and to pick out one voice among many. The ability to perform such seemingly simple auditory tasks requires the central auditory system to interpret and compare fine timing and level differences of sounds reaching the two ears.

Many children with severe to profound hearing loss in both ears have been provided with bilateral cochlear implants in the expectation of promoting binaural hearing. However, it is not currently known whether bilateral cochlear implantation is sufficient to restore the precision of the normal binaural auditory system required to make interaural sound comparisons. Previous research has shown improved sound localization in children with bilateral implants compared to unilateral implant users (Litovsky, 2004; Grieco-Calub et al, 2008; Van Deun, 2009b). Others
have shown that adults with two implants can use inter-implant signal level cues to localize sounds, but are less successful at using inter-implant sound timing cues (van Hoesel and Clark, 1997; van Hoesel and Tyler, 2003; van Hoesel, 2004; Litovsky, 2004). To date, no studies have directly investigated the ability of children with bilateral CIs to interpret inter-implant level or timing differences.

In the following sections, I will overview relevant background on the psychoacoustics and physiology of binaural hearing. I will then detail the effects of deafness on the development of the auditory system. Finally, I will give a review of bilateral cochlear implants and detail relevant research into how these devices may lead to the promotion of binaural hearing in people who suffer from profound deafness.

1.2 Binaural Hearing

1.2.1 Psychoacoustics of Binaural Hearing

An acoustic signal from a single sound source will arrive with slightly different acoustic properties to one ear compared to the other. Normal “binaural hearing” takes advantage of these interaural differences, as they provide information about the location of the original sound source in space and facilitate the extraction of a single acoustic source amid a complex auditory environment. The most important interaural differences for binaural hearing are interaural time differences (ITDs) and interaural level differences (ILDs) in the acoustic signal.

ITDs arise as a result of the physical separation of left and right ears; acoustic signals will arrive first at the ear closest to the source and a few microseconds later, will arrive at the second ear (Fig. 1.1(A)). Low frequency sounds are best lateralized by interpreting ITDs because of the loss of phase-locking in the auditory nerve with higher frequency sounds (Macpherson and Middlebrooks 2002). Normal-hearing listeners can recognize timing delays between ears of as small as 10 µs (Akeroyd 2006).
Figure 1.1 Inter-aural timing differences (A): an acoustic signal arrives at the ear closest to the sound source slightly before arriving at the other ear. **Inter-aural level differences** (B): the listener’s head attenuates an acoustic signal, leading to a slight decrease in intensity of signal arriving at the ear further away from the sound source, compared to the other ear.

Inter-aural level differences (ILDs) can best be explained by the head-shadow effect, whereby sounds arrive with greater intensity at the side closest to the source because the head creates a sound “shadow”, attenuating the intensity of the signal (Fig 1.1(B)). ILDs are greatest at high frequencies because at frequencies of less than 500Hz, wavelengths become larger than the diameter of a human listener’s head, canceling out the effects of the head shadow (Macpherson and Middlebrooks 2002; Schnupp and Carr 2009). Normal-hearing adults can be sensitive to ILDs of as low as 0.5 dB (Akeroyd 2006; Harrison 1988).

For people with bilateral hearing loss, bilateral cochlear implants would ideally provide access to both ILD and ITD cues. To do this, the central auditory system would need to process the information provided by each of the bilateral cochlear implants. It is reasonable to assume that similar processes to those involved in the normal auditory system would be required for the comparison of signal inputs from the two ears. The physiology of the normal binaural auditory system is thus discussed below.

### 1.2.2 Physiology of Binaural Hearing

The auditory brainstem is an area of particular interest when considering binaural auditory processing because it is the first site in the auditory pathway to receive innervations from both ears (Harrison 1988). The peripheral auditory system is thus the first site where
binaural processing can occur. A schematic representation of the auditory brainstem is shown in figure 1.2 (A). The auditory nerve (VIII) projects from the cochlea and innervates the cochlear nucleus (CN) (Harrison 1988). The three subdivisions of the CN (the anteroventral (AVCN), posteroventral (PVCN) and dorsal cochlear nuclei (DCN)) each have separate output pathways. The two ventral nuclei (AVCN and PVCN) project to the ipsilateral and contralateral superior olivary complex (SOC), which then projects through the lateral lemniscus to the central nucleus of the inferior colliculus (IC) (Harrison 1988). Neurons in the DCN connect directly to the central nucleus of the contralateral inferior colliculus (Harrison 1988).

Figure 1.2: Anterior view of the auditory brainstem (A) and Auditory Brainstem Response (B) with proposed neural generators. Eighth (Auditory) Nerve (VIII); Cochlear Nucleus (CN); Superior Olivary Complex (SOC); Lateral Lemniscus (LL), dorsal nucleus (LLD) and ventral nucleus (LLV); Inferior Colliculus (IC). Amended from (Hall 1992).

Activity in the auditory brainstem can be visualized non-invasively in animal models and in humans using a far-field evoked potential response referred to as the auditory brainstem response (ABR), which consists of five characteristic peaks (Fig 1.2 (B)). Numerous
investigations into the neural generators of the ABR, including lesion studies, brain pathology analyses, and calculated neural conduction times have led to the following associations: I and II reflect activity along the auditory nerve; III has been associated with activity in the cochlear nucleus; IV and V are attributed to activity in the lateral lemniscus (Hall 1992; Moller et al. 1995; Parkkonen et al. 2009).

The area of the auditory brainstem most relevant to the present paper is the superior olivary complex, as interaural level and timing differences are initially processed here (King et al. 2000) (Fig. 1.3). The SOC is innervated by projections from both the ipsilateral and contralateral ventral cochlear nuclei (AVCN and PVCN), thus allowing for inter-aural comparisons. Two specialized nuclei of the SOC, the lateral superior olive (LSO) and the medial superior olive (MSO) are responsible for encoding ILDs and ITDs, respectively.

Figure 1.3 Schematic representation of relevant structures in the auditory brainstem. Cochlear nucleus: anteroventral cochlear nucleus (AVCN), posteroventral cochlear nucleus (PVCN), dorsal cochlear nucleus (DCN). Superior olivary complex: lateral superior olive (LSO), medial superior olive (MSO), medial nucleus of the trapezoid body (MNTB).

The lateral superior olive (LSO), responsible for processing ILDs, consists of bipolar neurons excited by ipsilateral stimulation and inhibited by contralateral stimulation (Boudreau and Tsuchitani 1968; Moore 2000; Moore and Caspary 1983). The net result of excitatory and inhibitory inputs to each LSO encodes the range of ILDs, which can thus be further processed and interpreted at higher centres of the auditory system.
Interaural time differences are encoded in the medial superior olive (MSO), where bilateral stimuli are processed depending on their relative time of arrival. The exact mechanism for ITD encoding in mammals has recently come under dispute (Grothe 2003; Schnupp and Carr 2009). Classically, ITD processing has been understood according the “delay-line coincidence” model. This model, originally posited by Jeffress (1948), describes a system whereby bipolar neurons in the MSO fire maximally to simultaneous excitatory inputs from both left and right projections (Grothe 2003). Phase-locked activation from the cochlear nuclei is sent down “delay-lines” set up by varying axonal lengths that compensate for external interaural time differences. In this way, activation from both the left and right sides arrive simultaneously to a particular set of neurons in the MSO. Each MSO neuron will respond best to the ITD that corresponds to the “delay-line” innervating that neuron. The Jeffress model has been well documented with respect to avian auditory systems, however, in mammalian systems, Jeffress-type models of ITD encoding have been questioned. More recent models are based on research showing that MSO neurons, in addition to receiving excitatory input from each ear, also receive inhibitory input bilaterally (Grothe 2003). In addition, recent evidence indicates that MSO neurons with similar characteristic frequencies, (the frequency of acoustic stimulation that elicits a maximal response) also have similar best ITDs (Schnupp and Carr 2009). This contradicts the Jeffress model, which predicts that each frequency is represented by a distinct delay line of coincidence detectors. Newer models of ITD encoding in mammals suggest that ITD processing involves comparisons of all four types of inputs to the MSO (ipsilateral excitatory, ipsilateral inhibitory, contralateral excitatory and contralateral inhibitory) (Grothe 2003). Importantly, regardless of the method, encoding of interaural time differences relies on extremely faithful preservation of temporal information in acoustic signals.

The distinct roles of the two major nuclei of the SOC are reflected in their comparative sizes across mammalian species. Across different species, head diameters tend to correlate to MSO size (Moore 2000). This can perhaps be understood by the fact that as head sizes increase, so does the range of ITDs that are available for sound localization (Moore 2000). Therefore, the MSO in humans is nearly twice as large as that of the cat (Moore 2000), whereas the LSO is smaller in humans than cats. The size of the LSO tends to correlate to the range of usable
auditory frequencies, as animals who use echolocation, such as bats, dolphins or porpoises have well-developed LSOs and small or absent MSOs (Boudreau and Tsuchitani 1968; Irving and Harrison 1967; Moore 2000).

The relationship between the SOC and children’s head sizes could be an important consideration in the present study, as children do not reach adult head size until the age of 21 years (Ashmead et al. 1991). It has been suggested the normally-developing SOC retains the ability to calibrate ITD sensitivity to changes in head size throughout childhood but that the basic functional structure for processing interaural cues is intact very early in development (Ashmead et al. 1991; Scott et al. 2005). This raises the question of whether bilateral cochlear implantation provides sufficient information for the proper calibration of the SOC in congenitally deaf children.

The advantages of binaural listening in individuals with normal hearing are well known, and include improved sound localization and speech understanding in noise. However, the ability of pediatric bilateral cochlear implant users to interpret ILDs and ITDs is not well understood. Attempting to replicate this complex system using electrical stimulation in a bilaterally deaf auditory system requires consideration of several factors: electrical signals must accurately reproduce important timing and level information, the peripheral auditory system must relay those signals faithfully to the SOC, and the SOC, in turn, must effectively decode the ILD and ITD information from the incoming bilateral signals. Further areas of consideration include higher centres implicated in the coding of auditory space, such as the superior colliculus (King et al. 1998; King et al. 2000; Middlebrooks and Knudsen 1984) and the primary auditory cortex (King et al. 2000). In order to promote binaural processing in children with bilateral cochlear implants, an understanding of the effect of deafness on the development of these important auditory centres is necessary.

1.3 The Deaf Auditory System

Development of normal auditory structures requires activation of the cochlea and the resulting cascade of activity throughout the rest of the auditory system (Friauf and Lohmann 1999; Shepherd and Hardie 2001). Therefore, early loss of activity in the auditory nerve, due to congenital sensorineural hearing loss (SNHL) for example, can result in degeneration and
aberrant development in key structures along the bilateral auditory system (Friauf and Lohmann 1999).

The effects of deprivation on the development of the auditory system have been studied extensively in animal models. Common models for SNHL include ototoxic poisoning, acoustic trauma or genetic mechanisms, all of which lead to the loss of activity in the auditory nerve. Studies using these models have indicated that SNHL can result in degeneration throughout the auditory system (Lee et al. 2001; Moore 2002; Nishiyama et al. 2000; Shepherd and Hardie 2001). At the level of the cochlea, auditory nerve inactivation results in de-myelination of spiral ganglion cells and consequently, loss of activation of the auditory nerve fibers. If experimental deafening occurs before the onset of hearing, the cochlear nucleus undergoes extensive cell death (50-70% of neurons) (Moore 2002; Shepherd and Hardie 2001). Further downstream, cochlear inactivation can lead to atrophic changes (such as reductions of neurons’ soma areas or synaptic densities) in the SOC, the nucleus of the lateral lemniscus and the central nucleus of the inferior colliculus (Nishiyama et al. 2000; Shepherd and Hardie 2001). Imaging studies have shown that, without activity from lower centres of the auditory system, the auditory cortex undergoes cross-modal plasticity, whereby other sensory modalities (particularly vision) take-over areas of the cortex normally specialized for hearing (reviewed in Lee et al. 2001; Lee et al. 2007). Studies using the deaf white cat as a model for congenital deafness have indicated that these animals have decreased spiral ganglion cell density, decreased cell size in the MSO, and decreased number and size of synaptic terminals in the MSO (Schwartz and Higa 1982). As evidenced by the above literature, the auditory system requires input in order to develop properly.
The functional consequences of cochlear inactivation (i.e. hearing loss) can be overcome through the use of a cochlear implant, which provides auditory input to individuals with severe to profound SNHL by directly stimulating the auditory nerve with electrical pulses. Conversion of acoustic into electrical stimulation allows the cochlear implant user to perceive sound. Cochlear implants consist of an external component, including: a microphone, which selectively picks up auditory signals, and a speech processor, which converts the acoustic information into electrical signals (Fig. 1.4). The signals are sent to the transmitting coil, which is held in place on the head by a magnet. The information is then sent to the internal receiver (Fig. 1.5). An electrode array in the cochlea is then activated, stimulating the auditory nerve.
Previous literature has suggested that electrical stimulation delivered from within the cochlea may help to prevent some of the degeneration normally caused by profound SNHL (Leake et al. 2008; Vollmer et al. 2005). For example, in order to diminish cross-modal takeover, children are often provided with cochlear implants as early as possible; so as to best promote speech perception performance (Lee et al. 2007). Moreover, evoked potential studies have shown that the deaf and immature auditory brainstem retains the ability to change in response to prolonged stimulation from a single cochlear implant (Gordon et al. 2003). This ability does not diminish with age at implantation/duration of deafness, suggesting that the auditory brainstem remains plastic in the absence of stimulation during development (Gordon et al. 2003; 2006; Gordon et al. 2008; Thai-Van et al. 2007). Therefore, while congenital deafness results in degeneration and rearrangement along the auditory system, provision of a single cochlear implant may help to prevent further degradation and also results in some degree of
maturation in the auditory brainstem (Gordon et al. 2003; 2006; Gordon et al. 2008; Leake et al. 2008; Lee et al. 2007; Thai-Van et al. 2007; Vollmer et al. 2005).

### 1.4.1 Sequentially provided bilateral cochlear implants

Often children are provided with a second cochlear implant after experiencing a period of unilateral CI use. Currently, the impact of unilateral, electrically-driven auditory development on the organization and function of the binaural auditory system is not well understood. Furthermore, sequential implantation often leads to the use of different device generations between sides, as manufacturers continue to upgrade technologies. Therefore, children provided with two different device generations may experience slightly different types of stimulation between the first and second implanted sides.

Animal models have shown that early-induced unilateral deafness results in reorganization of projections from the CN to the SOC (Kitzes et al. 1995; Shepherd and Hardie 2001) and cell death in the LSO of the inactivated side (Moore 1992). Kitzes et al (1995) have shown that unilateral auditory deprivation results in ectopic projections from the cochlear nucleus to the three main nuclei of the SOC (the medial and lateral nuclei and the medial nucleus of the trapezoid body). Unilateral auditory deprivation has also been shown to result in a decrease in the size and number of neurons in the LSO ipsilateral to the damaged cochlea but not in the contralateral LSO (Moore 1992). These studies indicate that orderly connections in the auditory midbrain require binaural input to develop properly (Friauf and Lohmann 1999; Shepherd and Hardie 2001). Further, this research indicates that unilateral auditory deprivation can change the typically symmetrical order of the binaural auditory system into an asymmetrical, unilaterally-weighted system (Kitzes et al. 1995; Moore 1992).

Research from our group involving electrically-evoked ABRs has indicated that children who had experienced a delay between receiving their first and second implant showed prolonged wave eV latencies on the newly implanted side relative to the first implanted side (Gordon et al. 2008). Moreover, a possible electrophysiological marker of binaural processing, the Binaural Difference (BD), was also observed to be delayed in latency in children with sequential CIs compared to children using simultaneously provided CIs (Gordon et al. 2008). This work...
suggests that sequential implantation may result in some degree of aberrant processing in the auditory brainstem in deaf children with little to no normal acoustic experience.

Results from animal models and electrophysiological evidence from children with bilateral cochlear implants indicate that a period of unilaterally-driven auditory development may result in asymmetry in the auditory brainstem. It is currently unknown how developmental changes driven by unilateral cochlear implantation affects the potential for binaural processing in children with little to no acoustic auditory experience. Potentially, promotion of binaural processing in children with sequentially provided bilateral cochlear implants could be impeded by a period of bilateral deafness, resulting in degeneration of the auditory system, and/or by a subsequent period of unilateral deafness, resulting in aberrant connections and abnormalities in timing of activation in the auditory brainstem.

1.5 Adult Bilateral Cochlear Implant Users

An understanding of the physiology of the binaural auditory system and changes resulting from auditory deprivation sheds light on some challenges that may arise for binaural processing in bilateral cochlear implant users. Binaural processing in adult bilateral cochlear implant users has been investigated directly by several groups who have indicated that in this population, some degree of binaural processing may be accessible through bilateral cochlear implant use.

Several studies have reported that adult bilateral CI users have improved sound localization along the horizontal plane when using two implants as opposed to one (Nopp et al. 2004; Van Hoesel et al. 2002; van Hoesel and Tyler 2003). This improvement has been widely attributed to detection of inter-implant level differences (Grantham et al. 2008; Grantham et al. 2007; Laback et al. 2004; Seeber and Fastl 2008; Senn et al. 2005; Van Hoesel et al. 2002). Indeed, adult bilateral CI users have been reported to have ILD thresholds nearing normal levels. Van Hoesel and Tyler (2003) have shown that adult bilateral CI users can have ILD sensitivities of as little as 0.17dB, as defined in terms of stimulation current, when instructions to the bilateral CI electrodes are delivered directly through a research interface rather than through the two speech processors. Studies which used acoustic stimuli presented to participants’ speech processors have reported ILD sensitivities of as low as 1.4-5.2 dB (Laback et al. 2004) and 0.9-3.3dB (Grantham et al. 2008), in terms of acoustic input levels.
The contribution of inter-implant timing differences to sound localization in adults using bilateral CIs is less clear. The ability to discriminate temporal differences between implants depends greatly on the mode of stimulation, and in particular, on rates of presentation. At rates typically used in speech processors (>400 pulses per second (pps)), adult CI users have greater difficulty interpreting timing differences than when lower stimulation rates are used. Van Hoesel and Tyler (2003) reported ITD sensitivity thresholds of 100µs when pulses were presented at 50 pps in a group of high performing adult bilateral CI users. When pulse presentation rates were increased to 200 pps, ITD thresholds were higher (~200µs) (van Hoesel and Tyler 2003). Others have likewise reported that ITD thresholds increase with increases in stimulus rates (Laback et al. 2004; Long et al. 2003; Van Hoesel et al. 2002; van Hoesel 2004; van Hoesel and Clark 1997). Our group has shown that auditory brain stem response amplitudes in children using cochlear implants deteriorate as the rate of electrical pulse rates increases (Davids et al. 2008). This supports the idea that neural adaptation may occur at this level of the auditory pathways for faster rates of stimulus presentation, perhaps impairing ITD sensitivities. In this context, neural adaptation refers to increased numbers of stimulated spiral ganglion neurons remaining in the refractory period with successive pulse trains (Davids et al. 2008). Due to the greater synchrony of spiral ganglion cell activation with electrical as opposed to acoustic activation, neural adaptation may be a factor for cochlear implantation. Therefore, above a certain threshold of presentation rates, the number of activated neurons may actually decrease, causing electrophysiological responses to deteriorate. Neural adaptation may be an important consideration with respect to the processing of ITDs, as interpreting these cues requires extremely faithful representations of temporal information. Decreases in active spiral ganglion cells with increases in stimulus frequency may result in deficient representation and extraction of important timing information. However, the observer weighting data from (van Hoesel 2008) showed that, for high-rate pulse-trains, ITD information following the onset pulse was reduced immediately, rather than gradually as might be expected from an adaptation process.

Despite decreased sensitivities to ITD cues, some studies (Long et al. 2003; Van Hoesel et al. 2002; van Hoesel 2004; van Hoesel and Tyler 2003) have nonetheless indicated that adults with bilateral cochlear implants can perceive differences in time and especially intensity between
devices. This suggests that some degree of binaural processing is available to adult bilateral cochlear implant users. However, in comparing adult results with those from pediatric populations, one must consider that most adult implant users developed normal bilateral auditory pathways before suffering a loss of hearing later in life. There may be a limit, therefore to the extent to which adult populations can be compared to pediatric cochlear implant users, who often have little to no auditory experience, with thus more limited auditory development, before initial electrical stimulation from cochlear implant electrodes.

1.6 Auditory development in Pediatric Bilateral Cochlear Implant Users

As mentioned above, inter-implant level and timing discriminations have yet to be directly investigated in children who use bilateral CIs. However, a number of studies have investigated behavioural measures of bilateral cochlear implant use including free-field sound localization (the identification of sound sources from one of several speakers) (Galvin et al. 2007; Galvin et al. 2008; Litovsky et al. 2006a; Litovsky et al. 2006b; Litovsky et al. 2004; Van Deun et al. 2009b) and measurements of minimum audible angle (MAA) (the smallest discernable change in the location of a sound that can be consistently measured) (Grieco-Calub et al. 2008; Litovsky et al. 2006a; Litovsky et al. 2006b). These studies have shown that many children with bilateral cochlear implants are better at identifying sound sources using two CIs rather than a single CI (Galvin et al. 2008; Grieco-Calub et al. 2008). Grieco-Calub and colleagues (2008) reported that five of ten children with bilateral cochlear implants could correctly identify the direction of sound sources for sounds placed 70° or less away from midline. Of this group, 3 children’s performances were similar to those of their normally hearing peers, who could correctly localize sound sources of as small as 10-20°. None of the 8 participants who used only one cochlear implant could correctly localize sound sources even at the maximum angle tested (70°). Litovsky (2006a) similarly showed that 9 out of 13 pediatric bilateral implant users had minimum audible angles less than 40° and of these, 8 could distinguish angles smaller than 20°. Two of six children using one implant and one hearing aid had MAAs similar to the bilateral implant users, but the remaining children in this group performed much worse than the
average child with bilateral implants. Using a left-versus-right localization task (with speakers placed at 90° to the right and left of the child), Galvin and colleagues (2008) reported that seven of nine children who received their second implant before the age of 4 performed significantly above chance when using both as opposed to only one implant. None of the participants in that study performed above chance when using only one implant on their more experienced side (Galvin et al. 2008).

The above research groups have shown that children with bilateral implants have the ability to identify differences in sound sources (Galvin et al. 2008; Grieco-Calub et al. 2008; Litovsky et al. 2006a; Litovsky et al. 2006b; Litovsky et al. 2004). However, despite observed improvements over unilateral performance, many bilaterally implanted children were not able to localize sounds in space as accurately as their peers with normal hearing. Further, Galvin and colleagues (Galvin et al. 2007) reported that children who received their second CI after 4 years of age did not show any improvement using both implants over unilateral conditions on tests of sound localization after 6-13 months of bilateral experience. Litovsky (Litovsky et al. 2006a; Litovsky et al. 2006b; Litovsky et al. 2004) also report high degrees of variability within groups of implanted children, which could not always be attributed to duration of deafness or length of bilateral implant use. In order to better predict and promote improved outcomes with bilateral cochlear implants, further research is needed to gain understanding into what factors determine localization abilities in these children.

Observed improvements in sound localization and decreased minimum audible angle thresholds may not be strictly a result of binaural processing in these children. Rather, it is possible that these outcomes could simply be explained by adding a second source of auditory information. For example, children using bilateral implants may be able to attend to the ear with the best SNR (which often corresponds to the position of the sound source of interest). This type of judgment likely provides some benefits for bilateral CI users but is not necessarily an indication of binaural processing. Performance of implanted children in localization tasks may be more fully understood by investigating binaural cues, ILDs and ITDs, directly, as this would allow for control of signal to noise differences. The ability to interpret ITDs, for example, would be an indication that binaural processing was taking place, as this relies on comparing input from
two sources. The present study therefore attempted to define sensitivities to ILDs and ITDs in children who use two cochlear implants.

Children who have been provided with a second cochlear implant after a period of unilateral implant use present a unique population, as they have experienced auditory deprivation in two-stages. First, children experienced a period of bilateral deafness which was followed by a period of unilateral cochlear implant use before they finally received their second device. As such, children provided with bilateral cochlear implants sequentially present an opportunity to observe the effects of bilateral and subsequently, unilateral deafness on the binaural auditory system. The present thesis therefore focuses on a group of children who have received their cochlear implants sequentially.

1.7 Summary

The ability to interpret ILDs and ITDs, known as sound lateralization, could be compromised in pediatric bilateral CI users for a number of reasons. First, many children, including the participants in the present study, received their second implant after a period of bilateral congenital deafness and subsequent unilateral implant use. It is possible that a period of unilaterally-driven development of the auditory system alters the ability of the pathways to process binaural stimuli (Gordon et al. 2008). Second, electrical, as opposed to acoustic, stimulation of the auditory system may not provide sufficient information for binaural processing. Finally, sequential implantation tends to result in the use of two different device generations, which could mean that the two auditory pathways are being stimulated in different ways, perhaps hindering binaural comparisons.

The present study measured the abilities of children who received a second CI after a period of unilateral CI use to lateralize pulses with ILDs or ITDs. Stimuli were balanced using electrically evoked brainstem responses and were presented directly to the participant’s cochlear implant, bypassing the speech processors. A group of children with no history of hearing loss also participated in this study and were asked to lateralize clicks presented with ILDs or ITDs.
Chapter 2
Methods

This study involved electrophysiological recordings and behavioural measures. In the following chapter, we outline participant demographics, protocols for collecting electrophysiological and behavioural responses and our methods of analysis.

This study was conducted under approval by the Research Ethics Board at the Hospital for Sick Children, Toronto, Canada.

2.1 Participants

Twenty-eight children, 19 with bilateral cochlear implants (CI group) and 9 normally hearing (NH group) participated in this study. CI users were recruited from the Cochlear Implant Program at the Hospital for Sick Children in Toronto, Canada.

Demographic information for the participants with cochlear implants is provided in Table 2.1. All children in the CI group had been provided with bilateral CIs sequentially; they received their first implant (CI-1) at 2.1±1.0 years of age and were provided with a second CI (CI-2) after 4.9±2.8 years of unilateral implant use. All had normal cochlear morphology, as judged by high resolution computed tomography and magnetic resonance imaging of the temporal bones. Three children in the CI group had a period of usable residual hearing (aided or unaided thresholds <40 dB HL) before onset of bilateral deafness (CI-N, CI-Q and CI-R). These 3 children were diagnosed with profound binaural hearing loss at age 2.1, 2.7 and 1.6 years, respectively and were provided with their first implant 0.3, 0.2 and 0.3 years later. As shown in Table 2.1, their etiologies of deafness were unknown (CI-N), mutations in GJB-2 (CI-Q) and Meningitis (CI-R). The remaining children in the CI group were profoundly deaf from birth, and had no significant auditory experience in either ear before receiving their first implant.
<table>
<thead>
<tr>
<th>Child</th>
<th>Onset of HL (age (yrs))</th>
<th>Etiology</th>
<th>Age (yrs)</th>
<th>Binaural Experience (yrs)</th>
<th>CI-1</th>
<th>CI-2</th>
<th>Interimplant delay (yrs) (CI-1 – CI-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Congenital connexin 26</td>
<td></td>
<td>12.3</td>
<td>13.6</td>
<td>2.7</td>
<td>4.0</td>
<td>Right 24M 9.6 24CS 5.9</td>
</tr>
<tr>
<td>B</td>
<td>Congenital Usher’s</td>
<td></td>
<td>11.3</td>
<td>12.4</td>
<td>1.0</td>
<td>2.0</td>
<td>Right 24M 10.3 24RE 8.3</td>
</tr>
<tr>
<td>C</td>
<td>Congenital connexin 26</td>
<td></td>
<td>5.4</td>
<td>6.4</td>
<td>0.6</td>
<td>1.5</td>
<td>Right 24CS 4.9 24RE 3.8</td>
</tr>
<tr>
<td>D</td>
<td>Congenital connexin 26</td>
<td></td>
<td>13.2</td>
<td>13.0</td>
<td>0.7</td>
<td>0.6</td>
<td>Left 24M 12.4 24RE 9.3</td>
</tr>
<tr>
<td>E</td>
<td>Congenital unknown</td>
<td></td>
<td>5.5</td>
<td>6.9</td>
<td>1.0</td>
<td>2.4</td>
<td>Right 24CS 4.5 24RE 3.6</td>
</tr>
<tr>
<td>F</td>
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<td></td>
<td>5.2</td>
<td>6.2</td>
<td>0.7</td>
<td>1.7</td>
<td>Left 24CA 4.5 24RE 3.0</td>
</tr>
<tr>
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<td></td>
<td>6.2</td>
<td>7.2</td>
<td>0.6</td>
<td>1.6</td>
<td>Left 24CS 5.6 24RE 3.3</td>
</tr>
<tr>
<td>H</td>
<td>Congenital waardenburg type2</td>
<td></td>
<td>4.5</td>
<td>5.7</td>
<td>1.9</td>
<td>3.1</td>
<td>Right 24CA 2.6 24RE 0.7</td>
</tr>
<tr>
<td>I</td>
<td>Congenital connexin 26</td>
<td></td>
<td>6.0</td>
<td>7.2</td>
<td>0.8</td>
<td>2.1</td>
<td>Right 24CS 5.2 24RE 3.3</td>
</tr>
<tr>
<td>J</td>
<td>Congenital connexin 26</td>
<td></td>
<td>5.0</td>
<td>6.4</td>
<td>0.5</td>
<td>1.9</td>
<td>Right 24CS 4.5 24RE 2.6</td>
</tr>
<tr>
<td>K</td>
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<td>8.3</td>
<td>2.7</td>
<td>4.5</td>
<td>Right 24CS 3.72 24CA 3.0</td>
</tr>
<tr>
<td>L</td>
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<td></td>
<td>10.9</td>
<td>12.1</td>
<td>0.9</td>
<td>2.1</td>
<td>Right 24M 10.0 24RE 7.8</td>
</tr>
<tr>
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<td>Congenital unknown</td>
<td></td>
<td>12.3</td>
<td>12.2</td>
<td>1.4</td>
<td>1.3</td>
<td>Right 24CS 10.9 24RE 6.3</td>
</tr>
<tr>
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<td>Progressive (2.1)</td>
<td>unknown</td>
<td>4.4</td>
<td>5.7</td>
<td>1.1</td>
<td>2.3</td>
<td>Right 24RE 3.3 24RE 0.9</td>
</tr>
<tr>
<td>O</td>
<td>Congenital connexin 26</td>
<td></td>
<td>9.6</td>
<td>11.0</td>
<td>2.6</td>
<td>4.1</td>
<td>Right 24M 7.0 24CA 5.3</td>
</tr>
<tr>
<td>P</td>
<td>Congenital Usher’s</td>
<td></td>
<td>7.5</td>
<td>8.6</td>
<td>1.0</td>
<td>2.1</td>
<td>Right 24CS 6.5 24RE 5.5</td>
</tr>
<tr>
<td>Q</td>
<td>Progressive (2.7)</td>
<td>connexin 26</td>
<td>8.4</td>
<td>9.4</td>
<td>0.4</td>
<td>1.4</td>
<td>Right 24CS 8.0 24RE 5.1</td>
</tr>
<tr>
<td>R</td>
<td>Sudden (1.6) meningitis</td>
<td></td>
<td>13.6</td>
<td>13.7</td>
<td>0.7</td>
<td>0.7</td>
<td>Right 24M 13.0 24RE 11.1</td>
</tr>
<tr>
<td>S</td>
<td>Congenital connexin 26</td>
<td></td>
<td>6.8</td>
<td>7.9</td>
<td>0.9</td>
<td>2.1</td>
<td>Right 24CS 5.9 24RE 3.8</td>
</tr>
</tbody>
</table>

*Maximum stimulus levels for child CI-Q were different between sides in order to evoke measureable EABR waveforms from both CI-1 and CI-2.

**Table 2.1 Participant Demographics** Demographic information is provided for each participant in the CI group, including: onset and etiology of hearing loss; age and binaural experience at 1st and 2nd visits; age at activation of first and second cochlear implants; time period between receiving first and second cochlear implants.
The participants in the CI group were all Nucleus 24 device users, with varying combinations of system generations (M, CS, CA and 24RE), as described in detail in Table 2.1. The Nucleus 24M consists of a straight array of electrode bands whereas the Nucleus 24CS, 24CA and 24RE generations are systems with pre-curved arrays (Cohen et al. 2003). The pre-curved devices are designed to and sit anatomically closer to the modiolus than the straight-array devices (Cohen et al. 2003). The pre-curved devices also contain 22 half-banded platinum electrodes, which are thought to reduce the current required to achieve similar levels of loudness as compared to the fully banded electrodes in the straight array (Cohen et al. 2003; Patrick et al. 2006). The 24M, CS and CA devices use slightly different conversions between clinically used Current Units (CU) and current µA than does the N24RE, leading to some differences in µA delivered by the same CU. For example, 200 CU presented by 24M, CS and CA devices is approximately equal to 574.4 µA (pulse width = 25 µs), whereas 200 CU delivered from a CI24RE device is slightly higher (648.1µA). Current clinical techniques employ CU for programming cochlear implants, rather than µA, therefore the present study determined stimulus intensities using CU in order to reflect the clinical environment, despite differences in current conversion.

All but one child (CI-N) were bilaterally implanted with 2 different generations of electrode arrays. CI-N used a 24RE in both ears. In 15 participants, the second implant was a 24RE. Importantly, the types of devices used by the children (CI-2) were moderately correlated with the duration of bilateral use at time of testing during the first and second visits (Spearman correlation, Visit 1: ρ=0.64; p<0.005; Visit 2: ρ=0.63; p<0.005), because new devices became available over time. The oldest generation of device used by the children in the present study was the Nucleus 24M, followed in chronological order by the 24CS, 24CA and finally, the 24RE. Therefore, children with long periods of bilateral use received earlier device generations on both sides compared to children who received their second CI more recently.

All children in the CI group completed the study protocol over the course of two visits. During the first visit, electrically-evoked auditory brain stem responses (EABRs) were recorded in order to objectively match the amplitude of auditory responses evoked by the left and right CIs. During the second visit, the children performed a behavioural lateralization task, using
stimulus levels identified from brain stem recordings for the ITD task. At the first visit, children ranged in age from 4.4-13.6 years with a mean of 8.1±3.2 years, as detailed in Table 2.1. Ages at the second visit ranged from 5.7-13.7 years with a mean of 9.1±2.1 years.

The 9 participants in the normally hearing (NH) group ranged in age from 5-13.5 years (mean 9.9±2.9 years) and there was no significant difference between the age of the NH group compared to the CI group \( t(26) = -0.619, p = 0.54 \). Audiometric thresholds were screened at 30 dB HL. All 9 children in the NH group completed the behavioural task.

### 2.2 Stimuli for Electrophysiological and Behavioural Tests

Careful consideration was given to matching inputs between left and right implants in the present study for intensity and place of stimulation. Currently, however, there is no known method for accurately balancing these parameters in children, as subjective reports can be unreliable. With respect to place of stimulation, apical electrode no. 18 was chosen on both sides for all children. An apical electrode was preferred over more basal electrodes because evoked potential responses from the brainstem and cochlear nerve are greater in amplitude and hearing thresholds are lower when evoked from the apical as opposed to basal end of the cochlea (Gordin et al. 2009; Gordon et al. 2007a; Propst et al. 2006). The same electrode in each implant (i.e. electrode no. 18) was chosen in the absence of any reliable method to match pitch between the two electrode arrays in these children. This setup was also consistent with the fact that frequencies allocated to electrode no. 18 were the same for both implants and that these parameters formed the children’s only bilateral hearing experience.

With respect to matching intensities between implants, unilaterally evoked auditory brainstem responses (EABRs) were recorded over a range of stimulus levels. Our objectives in doing this were twofold. First, we aimed to identify intensities delivered to left and right implants separately which evoked the most similar wave eV amplitudes. This was considered to be an indication of stimuli evoking the same magnitude of response in the auditory brain stem. Our second objective in recording EABRs was to compare eV amplitudes with behavioural responses to inter-implant level differences at equivalent intensities. In order to assess these correlations, the same range of stimulus intensities used to complete EABR recordings were also used for the behavioural ILD task (detailed below). The study protocol was thus conducted over
the course of two visits. First, EABRs were recorded, then children returned 1.0±0.5 yrs later for a second visit, during which behavioural responses were evaluated. One child (CI-D) completed the behavioural task during her first visit and the electrophysiological recordings were done two months later. For this child, stimulus intensities were determined using electrophysiological recordings collected during a previous and independent study.

Stimuli for evoking EABRs were single biphasic electrical pulses (25μs/phase) delivered at a frequency of 11 pulses per second (pps) from electrode no.18. Stimulation parameters were programmed and delivered through a SPEAR processor and custom software (The Hearing CRC, Melbourne, Australia). Current intensities were customized for each implanted child. Children identified the loudest levels which remained comfortable to listen to on each side. The lower of these two values was defined as the maximum stimulation level for that child and the same set of five intensities (CU) was provided from each CI (with the exception of one child, CI-Q, as detailed below). EABRs were evoked by five unilaterally presented stimulus intensities, ranging over 20 clinical units (CU) and decreasing in steps of 5 CU. The stimulus intensities defined for each child are detailed in Table 2.2. As indicated above, conversion of µA into clinically used current units differs slightly between the 24M, CS and CA and 24 RE devices. For this reason, Table 2.2 describes intensities in CU, µA and in dB as defined by the following formula:

\[
\text{Decibel (dB)} = 20 \log (A/B)
\]

Where \(A\) = current for CI-1 or CI-2 (µA)

\[B = 100\mu\text{A}\]

CU values were converted to µA using the correct current conversion algorithm for each device.
Table 2.2 Stimulus intensities for children in the cochlear implant group: CI2 and CI1 columns detail unilaterally presented stimuli for electrophysiological recordings in CU, µA and dB(re:100uA). The columns labeled ILD detail the corresponding inter-implant level differences in CU and in dB.
Stimuli used for behavioural testing consisted of electrical pulses delivered by the same apical electrode (no. 18) (in the CI group) or 80 µs broadband clicks presented through insert earphones (in the NH group) at 11 pulses per second for 500 ms. For the CI group, the same stimulus equipment used to evoke the EABR was used for the behavioural studies. In the NH group, click trains (24 bit with 192 kHz sampling rate) were delivered through insert earphones at 11 per second. Stimuli were programmed and delivered via MathWorks Matlab 7.3.1 (R2006b) (Natick, MA) using a Creative Sound Blaster Audigy2 ZS (Notebook version) soundcard (Milpitas, CA) and Microsoft DirectX 9cAPI software (Redmond, WA).

2.3 Electrophysiological Recordings

Evoked responses were recorded by the NeuroScan 4.3 system with a Synamps I amplifier. Surface electrodes were used for recording; the non-inverting electrode was placed at Cz (center mid-line) and referenced to electrodes placed on each earlobe (A1-left and A2-right) in two separate bipolar recording channels (Cz-A1 and Cz-A2). A ground electrode was placed on the forehead. Responses were sampled at 20 kHz, a gain of 5000 was used and recordings were filtered on-line (10–3000 Hz, 12 dB/octave). A minimum of two visually replicable recordings were obtained at each stimulus intensity. Sweeps containing responses greater than ±30-40 µV were rejected from the average. During recording, children sat quietly and watched a movie. Their CI microphones were inactive during stimulus presentation and recording meaning that they had no access to any environmental sounds. Movie captions were provided when requested. Depending on the age and comfort level of the children, they either sat by themselves or on a parent’s lap.

2.4 Behavioural Lateralization Task

Children in the NH and CI groups participated in a behavioural lateralization task. Each child listened to stimuli presented unilaterally or bilaterally and were instructed to indicate verbally or by pointing, whether sounds were perceived as coming from the left side, right side, middle of the head or both sides simultaneously.
A short training period was carried out with the children in the CI group before testing, using unilateral stimuli. Four to five random presentations of CI-1- and CI-2-only stimuli were provided. Children were encouraged when they gave responses which corresponded to the side of stimulation. Training was not necessary for the children in the NH group, as all children showed an understanding of the task at the onset of testing. During testing, if children were unsure of which side to indicate, they were encouraged to give their “best guess”.

<table>
<thead>
<tr>
<th>Unilateral Presentations</th>
<th>Cochlear Implant (CI) group</th>
<th>Normal Hearing (NH) group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intensity (CU)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CI-2</td>
<td>CI-1</td>
</tr>
<tr>
<td>CI-1</td>
<td>0</td>
<td>220</td>
</tr>
<tr>
<td>CI-2</td>
<td>220</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Inter-implant Level Differences</th>
<th>Intensity (CU)</th>
<th>Interaural Level Differences</th>
<th>Intensity (dB SPL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI-2</td>
<td>CI-1</td>
<td>Left</td>
</tr>
<tr>
<td>+20</td>
<td>220</td>
<td>200</td>
<td>70</td>
</tr>
<tr>
<td>+10</td>
<td>215</td>
<td>205</td>
<td>65</td>
</tr>
<tr>
<td>0</td>
<td>210</td>
<td>210</td>
<td>60</td>
</tr>
<tr>
<td>-10</td>
<td>205</td>
<td>215</td>
<td>55</td>
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<tr>
<td>-20</td>
<td>200</td>
<td>220</td>
<td>50</td>
</tr>
<tr>
<td>-30*</td>
<td>195</td>
<td>225</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Inter-implant Timing Differences</th>
<th>Time delays (μs)</th>
<th>Interaural Timing Differences</th>
<th>Time delays (μs)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CI-2</td>
<td>CI-1</td>
<td>Left</td>
</tr>
<tr>
<td>+2000</td>
<td>0</td>
<td>2000</td>
<td>0</td>
</tr>
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<td>+1000</td>
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<td>0</td>
<td>400</td>
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</tr>
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</tr>
<tr>
<td>-2000</td>
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<td>2000</td>
</tr>
</tbody>
</table>

* -30 CU ILD was added to the lateralization protocol for 5 of the 19 children in the CI group.

Table 2.3 Stimulus conditions presented to CI and NH groups during the behavioural lateralization task. Each stimulus condition was presented six times. Unilateral, ILD and ITD presentations were presented randomly within one block.

In the CI group, as indicated above, the range of current intensities varied among children because each child had unique maximum comfort levels. Table 2.3 provides an example of the full set of stimuli presented in one behavioural session for a child in the CI group, and a child in
the NH group. For each CI child’s individual stimulus intensities, please see Table 2.2. In the CI group, unilateral stimuli were presented at each child’s maximum intensity. Bilaterally delivered stimuli were presented with inter-implant/inter-aural time or level differences (ITD and ILD, respectively). Bilateral electrical pulses or clicks were presented simultaneously for all ILDs. ILDs were presented at 0, ±10 and ±20 current units for the CI group (CU) or dB for the NH group (where + indicates higher intensities to CI-2 or left ear for NH listeners and – indicates higher intensities to CI-1 or right ear for NH listeners and 0 ILD indicates equal CU delivered to both sides). In 5 children (CI C, CI D, CI E, CI G and CI J), an additional ILD condition of -30 CU difference was added to the protocol. All delivered ILD pairs in the CI group matched intensities used for electrophysiological recordings. Note that, although ILDs are indicated in both CU and in dB in Table 2.2, stimulus intensities were determined using CU at the time of testing. Conversion from CU into dB was done offline, using the formula detailed above. In the NH group a range of 20 dB SPL (50 to 70 dB SPL in 5 dB steps) was presented to each ear, as indicated in Table 2.3.

Timing differences between sides of 0, ±400, ±1000, and ±2000 µs leading from the left and from right sides were presented, as detailed in Table 2.3. Positive ITDs denote bilateral input leading in CI-2 or left ear for NH listeners, negative values denote bilateral input leading in CI-1 or right ear for NH listeners and 0 ITD indicates stimuli arriving to both CIs or ears at the same time. For participants in the CI group, ITDs were presented at the pair of current levels evoking the smallest eV amplitude difference for that child as defined using EABR recordings. For children in the NH group, ITDs were delivered at 60 dB SPL in both ears. The rationale for providing inter-aural/implant timing differences beyond the physiological range (±2000 µs) was based on the desire to describe listeners’ lateralization of stimuli within (400µs), at (1000µs) and beyond (2000µs) naturally occurring ITD ranges.

As illustrated in Table 2.3, a total of 13-14 different unilateral and bilateral stimuli were presented and each was repeated 6 times. A total of 78-84 trials were presented randomly in one block. The behavioural task took a maximum of 20 minutes to complete per child. Some children found this more challenging than others, but all eventually completed the task.
2.5 Analysis of Electrophysiological Recordings

EABR recorded waveforms were visually analyzed for wave eV amplitude peaks at latency ranges defined previously (Gordon et al. 2006) using Matlab 6.5.2. A time window of 2 to 10 ms was used for visual inspection of waveforms. Amplitude was measured as the difference from the positive peak to the following trough. The total sweeps from all replicable recordings were averaged together.

As indicated above, brainstem responses were recorded as a method for matching the amplitudes of auditory responses evoked by each CI. Figure 2.1(A) demonstrates typical EABR recorded responses evoked in one child (CI-A) by the first (CI-1) (grey) and second (CI-2) (black) CIs individually at 5 decreasing intensities (225-205 CU). Figure 2.1(B) shows measured eV amplitudes from the recorded waveforms. For the purposes of inter-implant comparisons, stimulus intensities are shown along the x-axis from left to right in descending order for CI-2 stimuli and in ascending order for CI-1 stimuli.

![Figure 2.1](image)

**Figure 2.1** Unilaterally evoked EABR waveforms from a representative child (CI-A) at 5 decreasing stimulus intensities (A). Wave eV amplitudes, measured from peak to following trough, are shown (B) with CI-1 intensities increasing from left to right, and CI-2 intensities decreasing from left to right.

Dashed lines represent measured response amplitudes evoked by CI-1 (grey) and CI-2 (black). The best fit linear regression lines are represented by the thick solid lines. The point at which
regression lines intersect was defined as the child’s “minimum amplitude difference point”, and this is highlighted by a vertical line (Figure 2.1(B)). Thus, as shown in Figure 2.1(B), the minimum amplitude difference point for child CI-A occurred when delivered stimulus intensities were of near equal CU.

Minimum amplitude difference points were identified for each child in the CI group (mean±sd -12±11 CU, -1.62±2.01 dB) and the corresponding stimulation levels were used during the subsequent behavioural lateralization task for ITD presentations. This was possible to do using the same 20 CU range in both ears in all but one child (CI-Q). For this child, clear EABRs were only evoked by stimulation from CI-2 using a maximum stimulus level of 170 CU from both implants, as shown in Figure 2.2(A). Therefore, an additional visit was scheduled and a second EABR recording was made, this time offsetting intensity ranges delivered to either ear. During this visit, EABRs were re-recorded using a maximum stimulus level of 180 CU to CI-2 and 220 CU to CI-1, stimulus intensities for this visit are indicated in Table 2.2. As shown in Figure 2.2(B), this yielded clear EABR waveforms evoked by each side.

Figure 2.2 EABR waveforms recorded from child CI-Q recorded during her first (A) and second (B) visits. In the second visit, different stimulus intensities were delivered to each implant in order to evoke measurable responses from both sides.
2.6 Analysis of Behavioural Data

The percentage of each type of report (CI-1, CI-2, Middle or Both) was calculated for each child at all stimulus conditions. These values are represented graphically using “circle plots”, as seen in the bottom rows of Figure 3.2 (CI A - CI O). In these figures, the percentages of each child’s responses are conveyed by the size of circles relative to a circle 5 mm in diameter. Thus, 100% was depicted by a circle of 5 mm diameter and, for example, 50% by a circle with a diameter of 2.5 mm. Responses greater than 65% represented a lateralization-percentage that was significantly above chance (25%). Along the x-axis of each circle plot figure depicting are inter-implant level (ILD) or inter-implant timing (ITD) differences and two unilateral only presentations (CI-1 and CI-2). Children’s responses to unilateral-only presentations were used as a measure of how well the task was understood. Four children whose responses to one or both unilateral presentations were less than 65% accurate (CI-P, CI-Q, CI-R and CI-S) were excluded from analyses. These children’s electrophysiological and behavioural responses to ILDs are shown in Figure 3.4.

One objective in recording behavioural responses to ILDs was to determine for each child where bilateral stimuli were perceived to be balanced in terms of level. In normally hearing listeners, one would expect balanced bilateral inputs to be perceived to come from the middle of the head; however, early observations revealed that few children in the CI group reported sounds as coming from the middle. Therefore, cumulative Gaussian fits to the data, describing percent responses toward the first-implanted ear, were determined using a maximum likelihood criterion. Subsequently 50% thresholds reflecting equally likely lateralization responses towards CI-1 and CI-2 were calculated using a bootstrap procedure (Foster, D. H. and Bischof, W. F. 1991). For the purposes of this calculation, ILDs were expressed using dB. These curves are represented in grey and are superimposed over the behavioural “circle plots” in figure 3.2 (bottom rows). Therefore, in lieu of using middle responses as an indication of bilaterally balanced inputs, 50% thresholds indicate the ILD equally likely to elicit either a CI-1 or CI-2 response from the child. This point was called the point of equal probability and is indicated on the circle graphs in figure 3.2 (bottom rows) by a vertical yellow line.
Chapter 3  
Results

3.1 Electrically Evoked Responses from the Auditory Brainstem

EABRs were recorded for five stimulus intensities delivered to CI-1 and CI-2 individually. The range of delivered CU was the same for both implants in all but one child (CI-Q). Mean eV amplitudes evoked from CI-1 ranged from (mean±sd) 0.43±0.29µV to 1.19±0.40µV, while CI-2 evoked responses ranged from 0.71±0.30µV to 1.51±0.45µV. These amplitudes were consistent with previous EABR data evoked by stimulus levels in the middle to upper portion of the dynamic range of current intensity (Gordon et al. 2007a). Amplitude growths with increasing stimulus intensity for CI-1 and CI-2 are plotted in Figure 3.1. The mean slope of wave eV amplitude growth was similar for both implants.

![Figure 3.1](image)

**Figure 3.1** Mean wave eV amplitudes evoked from CI-2 (solid line) and CI-1 (dashed line). Y-axis plots absolute eV amplitude increases relative to each side’s minimum amplitude. X-axis plots intensity increases in CU relative to the minimum intensity delivered to each child individually.
3.2 Inter-implant Level Differences

Electrophysiological and behavioural results from each child in the CI group are shown in Figure 3.2. Line-graphs depict wave eV amplitudes from unilaterally-evoked responses at five stimulus intensities (Figure 3.2, top rows). Response amplitudes evoked by the first implant (CI-1) are represented in red and those evoked by the second (CI-2) are shown in blue. Best fit linear regression lines are shown for each side. The minimum amplitude difference point, where regression lines intersect, is designated by a vertical yellow line.

Figure 3.2 (bottom rows) also includes “circle plots” for each child, detailing behavioural lateralization of ILD-only stimulus presentations. A scale is provided in the bottom right corner of the Figure 3.2, with examples of the size of circles representing 100%, 83%, 67%, 50%, 33% and 17%.

Regression lines based on CI-1 lateralization responses are depicted with grey lines superimposed over the circle plots (bottom rows). Vertical yellow lines in bottom rows designate points of equal probability, where the regression lines reached 0.5. Points of equal probability were not defined for 2 children in Figure 4 (CI-N and CI-O), because a clear shift from CI-2 to CI-1 could not be defined. In these cases, the dominance of responses shifted from CI-2 to “both” before shifting to CI-1. Mean points of equal probability for the remaining children were 1.9±2.2 dB greater towards CI-1.

For 13 children in the CI group, we defined both a minimum amplitude difference and a point of equal probability. These two values represented the electrophysiological- and behaviourally-defined intensity matches, respectively, between CI-1 and CI-2 for each child. Inspection of Figure 3.2 reveals that, for many children, minimum amplitude difference points and minimum percent lateralized values occurred at equal or near-equal intensity pairs. This observed match between the two measures is more closely considered below in Figures 3.5 and 3.6. Figure 3.2 also highlights that many children indicated that they heard bilateral stimuli more frequently on the side of CI-2 and that EABR wave eV amplitudes were often larger at similar intensity levels when evoked by CI-2 compared to CI-1. Consequently, dominance shifts were more often defined at ILDs in which CI-1 current level was greater than CI-2 current level.
Figure 3.2 Measured eV amplitudes evoked by the second cochlear implant (CI-2) (blue) and the first cochlear implant (CI-1) (red) are shown for individual children in the CI group at 5 different intensities measured in dB (re: 100 µA) (top figures). Vertical yellow lines in the top figures indicate the minimum amplitude difference, where eV amplitudes regression lines intersect. Circle plots (bottom figures) show the percentage of times each response (CI-2, Middle, CI-1, Both) was given for each ILD and unilateral condition. Yellow lines in the bottom row figures indicate points of equal probability (response probability = 0.5).

Differences in current level requirements between sides were found to be particularly noticeable in children who used one 24RE device. Specifically, EABRs evoked by a 24RE were observed to require lower current levels than other devices to generate the same amplitude of response in the same child. The difference in CU between implants needed to evoke the most similar wave eV amplitudes was significantly greater for children using one 24RE (-13.33±11.13 CU) compared to that of the other children (2.50±5.00 CU) (t(17)= -2.728; p<0.05). When intensities were expressed in dB (re: 100 µA) rather than CU, these differences were still significantly different. Children with one 24RE device required 2.2±2.8 dB greater current in CI-1 than CI-2 to evoke similar wave eV amplitudes whereas the difference in current was 0.5±1.2dB towards CI-2 in the remaining children (t(17)= -2.826; p<0.05). Related analyses showed that the current differences required to evoke similar EABR wave eV amplitudes could not be explained by the use of straight versus curved electrode arrays (CU: t(17)=0.27, p>0.05 or dB: t(17)=0.147; p>0.05). Differences in dB evoking similar wave eV amplitudes did not show a significant correlation to duration of unilateral CI use (R^2= -0.242; p=0.318) but did show a moderate correlation to duration of bilateral use (R^2=0.451; p=0.05). Importantly, the duration of bilateral implant use was also correlated to the generations of devices used (R^2=0.44; p<0.005). Similarly, the effects of duration of unilateral implant use could not be separated from issues related to the types of CI devices used. Children who used one 24RE and one 24M/CS/CA tended to experience longer periods of unilateral CI use (60.3±15.7% of their lives) than children using bilateral 24REs or no 24RE (42.5±14.8% of their lives) (t(17)= 2.025; p=0.06).

Mean behavioural responses to inter-aural level differences (ILD) from children in the normally hearing (NH) group are shown in Figure 3.3(a – left side). Solid circles represent mean responses from all NH children, while outlined circles represent the ±95% confidence intervals. As demonstrated in this figure, the percentages of left, right and middle responses changed significantly with changes in ILDs (F(12)=27.20; p<0.005). Children in the NH group
consistently identified the side receiving the greater stimulus intensity. Thus, sounds presented 20 dB louder to the left side (+20 ILD) were perceived to come from the left (mean±sd 87.0±16.2%). A smaller level difference between ears (+10 ILD) resulted in a reduced percentage of “Left” reports (48.1±24.2%) and increased “Middle” reports (+10 ILD: 42.6±26.5% vs +20 ILD: 9.2±14.7%). When there was no level difference between ears (0 ILD), the NH group frequently chose the “Middle” position (74.1±30.2%). Sounds with greater intensities delivered to the right side led to increased reports that sounds were perceived from that side (50.0±25.0% at -10 dB and 68.5±32.7% at -20 dB).

Figure 3.3 Mean behavioural reports from the normal hearing (NH) and cochlear implant (CI) groups in response to interaural or inter-implant level differences (ILDs). For responses from children with cochlear implants, mean values are represented in clinical units (CU) (a) and in dB (b). In Figure 3.3(A) the sizes of the solid circles represent the percentage of times each response was given. Outlined circles represent ±95% confidence intervals. On average, children with normal hearing indicated “middle” percepts when ILD=0 dB whereas children using CIs rarely indicated “middle” in response to the ILD step sizes provided. The group of children using CIs responded more frequently to the side of the second CI (CI-2) until ILDs were weighted toward to the first CI (CI-1).
Mean responses to ILD presentations from the CI group are shown in Figure 3.3 (A – right side) in the form of a circle plot. This figure represents how children’s responses change with respect to changes in ILD measured in CU. Significant changes in side of lateralization responses (to CI-1 or to CI-2) were observed in response to changes in ILD presentations (F(18)=23.22; p<0.005). The frequency of CI-2 reports decreased with decreases in intensity to that side (80.5±23.5% for +20 ILD vs 34.4±28.2% for -20 ILD), and the percentage of reports that the stimuli lateralized to CI-1 increased as current level in CI-1 increased for each child (9.4±11% for +20 ILD vs 48.9±25.6% for -20 ILD). However, the profiles of response changes with ILDs were noticeably different from the normally hearing group in 3 ways. First, the NH group reported that sounds presented at 0 ILD were heard as coming from the middle but the CI group reported 0 CU ILD sound perception from the middle significantly less frequently (NH: 74.1±30.2% versus CI: 4.4±9.9%) (t(22)=11.23; p<0.005). Second, unlike the NH group, there was no significant effect of ILD on the frequency of the CI group’s Middle response (F(4)=0.69; p=0.76). Third, children in the CI group occasionally reported that ILD presentations were perceived to come from both sides, while no child in the NH group gave this response. There was no significant change in “both” responses with change in ILD in the CI group ((4)=1.55; p=0.20).

Mean behavioural responses to ILDs from both groups are represented in the format of a line graph in Figure 3.3(B). For the purposes of this figure, CUs delivered to the children in the CI group were converted to dB. Since the stimuli delivered to each child differed across the CI group, mean responses were grouped into 6 categories, according to the ILD delivered as expressed in dB: 4.8 to 3.1 dB, 3.1 to 1.4 dB, 1.4 to -0.3 dB, -0.3 to -2.0 dB, -2.0 to -3.7 dB, and -3.7 to -5.4 dB. As shown in Figure 3.3(A), mean responses from the CI group are most similar when greater intensities are delivered to CI-1 than CI-2. Conversion of CU into dB, as shown in Figure 3.3(B) highlights that the bias towards CI-2 remains when differences in current conversion between device generations are taken into account.
3.2.1 Outliers in the CI Group

Four children in the CI group were excluded from data shown in Figure 3.2 and from statistical analyses. The exclusion criterion was <65% accuracy to unilaterally presented stimuli, indicating that the child may have not understood the task. The electrophysiological and behavioural results from these 4 children are shown in Figure 3.4. Amplitudes of wave eV evoked by unilaterally presented electrical pulses in these children decreased with stimulus intensity. Also, larger amplitudes were evoked by CI-2 than CI-1 stimulation at the same CU levels in 3 of the 4 children (CI-P, CI-R and CI-S). Note that stimulus intensities for CI-Q were different between implants. This was due to large differences in stimulation levels needed to evoke similar wave eV amplitudes as shown in Figure 2.2 and described in the Methods section above.

![Figure 3.4](image_url)

Figure 3.4 Measured eV amplitudes (top), and behavioural response circle plots (bottom) are shown for 4 children in the CI group who were excluded from mean analyses. The exclusion criterion was less than 65% accuracy to stimuli delivered unilaterally from the first or second cochlear implant (CI1 or CI2, respectively).
3.3 The Relationship between Electrophysiological Responses and ILD Lateralization in Children Using CIs

We asked whether matching amplitudes of the EABRs minimized lateralization to either CI. Figures 3.5 and 3.6 demonstrate the degree to which ILD behavioural lateralization reports corresponded to auditory brain stem response amplitudes evoked using the same electrical stimuli.

Figure 3.5 plots the behavioural CI-2 minus CI-1 response percentages from each child at all ILDs versus the difference in eV amplitudes evoked by either implant \([(\text{CI}-1(\text{uV}))-(\text{CI}-2(\text{uV}))]\) at equivalent intensities. This figure shows that large percent lateralized values corresponded to large differences in wave eV amplitude between sides. Conversely, at levels where differences in wave eV amplitudes were small or nil, the percent lateralized was also small. The relationship between these measures was \(R^2 = 0.51\), \(p<0.005\).

![Figure 3.5](image)

**Figure 3.5** Lateralization percentage measures are plotted against wave eV amplitude difference between CI-2 and CI-1 evoked responses at all inter-implant level difference (ILD) conditions. Lateralization percentage is calculated as the difference between responses (% of total) to the side of the second versus first cochlear implant (CI-2-CI-1) for each child.

We determined the stimuli which evoked the minimum EABR wave eV amplitude difference and the points of equal probability from behavioural responses for each child in the CI group. These points are indicated for each child in Figure 3.2 (top and bottom rows, respectively) with vertical yellow lines. Differences between points of equal probability and minimum
amplitude difference values were calculated for each child and are expressed in Figure 3.6. In this figure, a negative value indicates electrophysiological measures predict a larger difference than the behavioural measures. As shown in this figure, one child (CI-M) had differences of between -4.0 and -6.0 dB between the two measures. In this case, the electrophysiological measure predicted a much greater difference (-4.8 dB) than the behavioural measure (0.4 dB). Of the remaining children, differences between measures fell into three categories: 2.0 to 3.9 dB (n=2), 0.0 to 1.9 (n=5) and -2.0 to -0.1 (n=5). Response profiles from CI-N and CI-O were excluded because a point of equal probability could not be defined for these two children, as described above.

Figure 3.6 Balanced inter-implant levels were predicted using the regression of behavioural measures (equal probability=0.5) and the minimum wave eV amplitude difference from electrophysiological measures. Differences between these two measures are shown for children in the CI group. Negative values indicate electrophysiological responses predicted greater differences than behavioural responses. In 10 of 13 children, the two measures were in agreement (5 with agreements of between -2.0 and -0.1 dB and 5 between 0 and 2.0 dB). Three children had larger differences between the two measures (- 4.0 dB in 1 child and between 2.1 and 4.0 dB in 2 children).
3.4 Inter-Implant Timing Differences

![Figure 3.7](image)

Figure 3.7 Individual behavioural reports from children with cochlear implants in response to presentations of changing inter-implant timing differences (ITDs). The sizes of the solid circles represent the percentage of times out of 6 presentations that each response was given. Only children 2 showed any trend toward perception of changing ITDs (CI F and CI M).

Lateralization tasks included stimuli with interaural and inter-implant timing differences (ITDs). Individual responses to ITDs from children in the cochlear implant group are shown in Figure 3.7. This figure, when compared with individual responses to ILDs in Figure 3.2, highlights that in general, children with cochlear implants had more difficulty lateralizing presentations with ITDs than with ILDs. Only two children (CI F and CI M) had response profiles that indicated stimuli were perceived to come from the leading side. The remaining
children responded inconsistently. As with ILDs, children rarely reported that sounds were perceived to come from the middle, occasionally reported that sounds were heard from both sides simultaneously, and often reported that sounds were perceived to come from CI-2 than CI-1.

Figure 3.8 Mean behavioural reports from normal hearing (NH) and cochlear implant (CI) groups in response to inter-implant timing differences (ITDs). The sizes of the solid circles (A) represent the percentage of times each response was given. Outlined circles represent ±95% confidence intervals. Children in the NH group showed a clear shift from left to middle to right as ITDs changed from left leading to no ITD to right leading. No significant changes in responses were found in children using CIs with change in ITDs.

Mean data from normal hearing children plotted in Figure 3.8 (A and B) indicate that all non-0 µs ITD presentations were most often lateralized towards the leading side. “Left” responses were greater for left-leading stimuli (ITD: mean±sd; +2000: 87.0±26.0%; +1000: 90.7±16.9%; +400: 81.5±21.2%) than for right-leading stimuli (-2000: 3.7±7.3%; -1000: 5.5±11.8%; -400: 13.0±21.7%). Likewise, “right” responses were greater for right-leading stimuli (-2000: 88.9±16.7%; -1000: 94.4±11.8%; -400: 79.6±28.6%) than for left-leading stimuli.
(+2000: 9.2±18.8%; +1000: 5.6±16.6%; +400: 9.2±12.1). Changes in responses with ITDs were statistically significant \((F(12)=37.16; p<0.005)\). Children in the NH group consistently indicated that bilateral stimuli of equal intensity presented at 0 µs ITD (simultaneously) were perceived to come from the middle (74.1±30.2%).

Figure 3.8 (A and B) displays mean responses from the CI group to pulse trains presented with inter-implant timing differences and shows a very slight decrease in frequency of CI-2 responses as stimuli changed from CI-2 leading to CI-1 leading (+2000: 63±31.5% vs. -2000: 43.3±33.8%). This decrease was not statistically significant \((F(6)=1.95; \ p=0.81)\). CI-1 reports did not change significantly across ITDs (+2000: 23.3±30.7 vs -2000: 28.3±27.8) \((F(6)=1.1; \ p=0.36)\). As illustrated in this figure, children showed a significant preference towards the second implanted side and all ITD conditions generated a higher percentage of CI-2 responses than CI-1 responses \((F(1)=15.31; \ p=0.002)\). Notably, the frequency of “Middle” reports did change significantly across ITDs \((F(6)=4.201, \ p=0.001)\). This significance can be attributed to an increase in the percentage of “middle” responses at -2000 ITD (-1000 ITD: 6.7±20.9% vs -2000 ITD: 16.7±20.9%). Nonetheless, the children in the CI group reported sounds were perceived from the “middle” significantly less frequently than the children in the NH group \((F(6)=34.4, \ p<0.005)\).
Chapter 4
Discussion

As expected, the children with normal hearing who participated in the present study were able to lateralize clicks presented with interaural level or timing cues without difficulty. Many of the children using CIs were able to detect changes in level differences between electrical pulses delivered simultaneously from bilateral CIs but could not accurately perceive changes in inter-implant timing cues. Further, lateralization abilities of children using CIs based on inter-implant level cues differed significantly from lateralization in their normally hearing peers. Children in the CI group rarely perceived sounds to come from the middle of the head and occasionally perceived sounds to come from both sides simultaneously. These findings suggest that children using bilateral CIs after a period of unilateral CI use rely, at least in part, on monaural cues for processing of inter-implant level cues to localize sounds. Differences from normal lateralization abilities could relate to effects of bilateral auditory deprivation, auditory development driven by electrical and unilateral stimulation and/or possible mismatches in pitch and level of stimulation provided by two different CI devices. We discuss these possibilities in detail in sections 4.5 and 4.6 below. Behavioural responses from the children in the CI group were correlated with electrically evoked auditory brainstem response amplitudes. We suggest that this electrophysiological response may be a useful objective measure for balancing intensities between implants for patients whose subjective reports may be unreliable. We address this possibility in section 4.7 below. Finally, we suggest future investigations that may arise as a result of the present study in section 4.8.

4.1 Results from children with normal hearing

The participants in the present study with normal hearing were able to consistently identify the leading side for clicks presented with interaural timing differences and the side with greater intensity for clicks with interaural level differences. Mean data from the normally hearing group is shown in figures 3.3 (ILD) and 3.8 (ITD). Figure 3.3 highlights that as intensities toward the left side decreased children indicated “left” less frequently and “middle” more
frequently. Likewise, as intensities towards the right side increased, children’s responses toward that side increased. Children’s responses to timing differences between sides were even more consistent. Figure 3.8 shows that in the normally hearing group, mean responses were lateralized toward the leading side more than 75% of the time for all stimulus conditions with ITDs greater than 0.

Previous studies have investigated the ability of children with normal hearing to interpret difference cues between ears. Van Deun (Van Deun et al. 2009c) reported that, at 5 years of age, children with normal hearing can correctly identify the leading side when ITDs are as small as 20 μsec. The authors highlight that children’s performance was significantly poorer than that of adults, possibly indicating effects of cognitive and attention differences and/or immature myelination along the auditory brainstem (Van Deun et al. 2009c). Nonetheless, the children in the present study were asked to lateralize ITDs of much greater magnitude (±400, 1000, 2000 μs). Few studies have directly investigated the minimum ILDs children with normal hearing can perceive, however previous research has shown that children reach adult localization abilities by approximately 5 years of age, with minimum audible angles of at small as 2° (Litovsky 1997). Thus, minimum ILD lateralization in normally hearing children is likely near-adult levels (0.5dB HL) (Akeroyd 2006) by 5 years of age. Consistent with this, we found that children with normal hearing had little difficulty completing our lateralization task.

4.2 Children with bilateral cochlear implants can detect changes in inter-implant level differences

We show that children with bilateral cochlear implants can detect changes in inter-implant level differences. Figure 3.2 highlights that many children shifted their responses from CI-2 to CI-1 as intensities delivered to CI-2 were decreased. Mean responses from this group, as shown in figure 3.3, changed significantly with changes in ILDs. These findings indicate that these children are likely able to make use of naturally-occurring level differences for sound localization. Importantly, the children in the present study who used cochlear implants often required a short training period, while the children with normal hearing did not. This suggests
that, while interpreting ILDs was possible in the CI group, this task did not come as naturally to them as it did to their normally hearing peers.

One limitation of the present study, made clear by children’s responses to ILDs, was that the forced-choice, four alternative task may have obscured the finer points of the children’s responses. We chose to limit children to only four possible responses (Left, Right, Middle or Both) in order to make the task accessible to younger children. In future studies, a scaled response, allowing children to indicate degrees of lateralization, could provide more information as to how children with bilateral implants perceive two inputs. For example, if children’s responses shift gradually from left to right with small changes in ILDs, true binaural processing may be occurring. Alternatively, if children’s response profiles resemble those generated in the present study, it would suggest that lateralization of ILDs is based heavily on monaural comparisons between sides in these children.

While children in the CI group were able to lateralize pulses with inter-implant level differences, we observed that responses differed significantly from the NH group. Children with bilateral cochlear implants rarely indicated that sounds were perceived to come from the middle, and occasionally indicated sounds were perceived from both sides simultaneously. These outcomes are further discussed in section 4.4. A final difference observed in the responses from the children with cochlear implants was that balanced stimulation was often achieved at intensities weighted towards the first implanted side. This outcome is likely a result of device differences between sides, and is considered in section 4.5.3.

### 4.3 Children have difficulty lateralizing bilateral CI stimulation using inter-implant timing cues

Most children in the CI group were unable to lateralize pulses with ITDs, while the NH group performed this task without difficulty, suggesting that binaural processing is at least partially disrupted in the CI group. Considering that ITDs are generally the dominant cue for sound localization in normal hearing individuals (Seeber and Fastl 2008), this finding may indicate that children receiving bilateral CIs sequentially after a significant period of unilateral CI use (mean±sd = 4.9±2.8 years) have some difficulties localizing sound under everyday circumstances.
listening conditions. We suggest that children’s poor performance interpreting ITDs could relate to a combination of factors, including; electrical as opposed to acoustic stimulation, unilaterally-driven auditory development, and insufficient matching of left and right cochlear implants with respect to place of stimulation. Previous research involving adult bilateral CI users and animal models helps to shed light on the former possibility.

Poorer abilities using ITDs than ILDs observed in the CI group is consistent with previous literature involving adult bilateral cochlear implant users (Grantham et al. 2008; Grantham et al. 2007; Laback et al. 2004; Seeber and Fastl 2008; van Hoesel and Tyler 2003). These studies demonstrated that bilateral CI users were less sensitive to ITDs, than they were to ILDs, regardless of the stimulus parameters. Grantham and colleagues (2007) showed that in adult bilateral CI users, low-pass filtering a 1kHz free-field sound resulted in greater errors than when the sound was high-pass filtered. In other words, removing the high-frequency component of a 1kHz free-field sound resulted in greater localization errors than when the high-frequency sounds were included. As free-field ILD discrimination normally relies on high frequency sounds, this suggests a reliance on ILD cues as opposed to ITDs in everyday listening conditions for CI users. Likewise, research that has used direct stimulation of participants’ CIs, as opposed to free-field localization, revealed ITD thresholds of up to an order of magnitude greater than their normally hearing counterparts (Lawson et al. 1998; van Hoesel 2004). Many have suggested, therefore, that ITDs contribute minimally to sound localization in bilateral CI users under everyday listening conditions (Grantham et al. 2007).

Previous research indicates a deficit in adult bilateral CI users’ abilities to interpret ITDs, however, inter-implant timing cues can nonetheless be perceived by these listeners, albeit at higher than normal thresholds. Indeed, several groups have shown that ITD sensitivities in adults tend to improve when stimuli are presented at slower rates (Majdak et al. 2006; van Hoesel 2007; van Hoesel and Tyler 2003). Van Hoesel and Tyler (2003) reported ITD sensitivities in the range of 100-150μs when pulses are presented at stimulus rates of 200 per second or less. The same group later indicated that at rates of 100pps, ITDs could contribute substantially to lateralization performance (van Hoesel 2007). However, in the present study, ITDs were presented at extremely low rates of 11 pps. According to previous research, presentation rates this slow would
allow for ITD sensitivities of at least 100μs in adult listeners, which was not observed in the children who participated in the present study.

Further research using animal models confirms that electrical as opposed to acoustic stimulation may lead to abnormal sensitivity to ITDs but does not necessarily diminish it entirely. Bilateral electrical pulses have been used to study ITD-sensitive neurons in the inferior colliculus (IC) of acutely deafened cats (Smith and Delgutte 2008; 2007), and in the dorsal nucleus of the lateral leminiscus (DNLL) in normal hearing gerbils (Reference Note 2). Findings indicate that brainstem neurons are sensitive to ITDs presented at slow rates by bilateral electrical pulses presented but that these responses are marked by differences from normal responses to acoustic stimuli. As was seen in adult CI users, sensitivity to ITDs decreases as the rates of electrical pulse presentation increases (Smith and Delgutte 2007).

The above cited studies highlight that one factor contributing to decreased ITD sensitivity in bilateral CI users may be electrical as opposed to acoustic stimulation. Several studies have shown that changes in the rates of presentation affect ITD sensitivities in adult users (Majdak et al. 2006; van Hoesel 2007; van Hoesel and Tyler 2003) and in animal models (Smith and Delgutte 2008; 2007). Higher rates of presentation may result in neural adaptation at the level of the brainstem, which is where binaural processing first occurs (Smith and Delgutte 2007). This premise is supported by electrophysiological research from our group which has shown that brainstem response amplitudes decrease with increased presentation rates (Davids et al, 2008).

The present study has shown that children with sequentially provided bilateral cochlear implants have little to no ITD sensitivity even at low rates of presentation, unlike previous studies which have shown some degree of sensitivity in adult CI users or animal models of bilateral cochlear implantation. This apparent difference indicates that electrical as opposed to acoustic stimulation cannot by itself account for the observed inability of children to interpret ITDs. A recent study which investigated ITD sensitivities in the IC of congenitally deaf white cats (Reference Note 1) indicated that the numbers of ITD-sensitive neurons are reduced in cats with bilateral congenital deafness compared to acutely deafened animals. This suggests a further complication to ITD processing caused by the lack of normal bilateral auditory experience in development, which could also be the case in our group of children who had little to no auditory
experience prior to receiving a cochlear implant. The effect of congenital deafness on the development of binaural auditory processing is addressed below in section 4.6. A final complication which may have contributed to this finding is the difficulties in matching left and right cochlear implants for place of stimulation along the cochlea. This issue is addressed below in section 4.5.

4.4 Children using bilateral CIs rarely perceived presentations to come from the “middle”

Children using bilateral CIs after a period of unilateral CI use seldom reported that bilateral stimulation was perceived as coming from the “middle” and occasionally indicated that bilateral input was coming from “both” sides. Both “middle” and “both” responses were inconsistent and, across the group, these responses did not significantly change with changes in stimulus presentation (ILD or ITD). No child in the NH group reported that sounds were perceived from both sides simultaneously, despite the fact that both groups of children were instructed before testing began that “both” was an appropriate response. Children in the NH group did not describe sounds as coming from both sides simultaneously even when ITDs of 2000μs were presented, in spite of this signal being greater than physiologically relevant values (Furst et al. 1985).

The lack of middle responses is a new finding and can be attributed to the protocol used in the present study. Previous research has typically measured just noticeable differences (JNDs) for ILDs and ITDs or percent accuracy in free-field sound localization tasks. In these tasks, participants are typically not asked to describe the perceived locations of near-equal inter-implant stimuli. A recent study has shown, however, that children using bilateral CIs make significantly larger errors in tasks of sound localization accuracy than normal hearing children and some have difficulties identifying when sounds are coming from the front (Van Deun et al. 2009b).

The absence of a perceived “middle” and abnormal “both” responses in our group of bilateral CI users may suggest that these children fail to hear a normally fused auditory image upon bilateral CI stimulation. If so, the lack of fused image may be due to differences in auditory
development relating to sequential implantation. Alternatively, it is possible that a fused image was not elicited because of imprecision in balancing intensity and place of stimuli between implants. These two possibilities are addressed below in sections 4.5.3 and 4.5.2 respectively.

A further possibility in explaining the lack of middle responses in our group of CI users could be related to their clinical experiences. The children with cochlear implants who participated in our study have routine visits with an audiologist to ensure that the cochlear implants are optimally programmed. In this clinical setting, children’s implants are programmed one at a time, and thus children may have developed the habit of expressing their hearing in terms of left and right sides alone rather than the combined perception of both implants. Future research involving children who received two cochlear implants in a single surgery or who had significant periods of auditory experience before suffering from hearing loss would be helpful in determining how clinical experience effects children’s ability to describe auditory perception.

4.5 Limitations of electrical bilateral stimulation for binaural processing

Bilateral electrical pulses are processed in the auditory brainstem but may cause different responses than would acoustic stimulation (Reference Note 2). Mismatches in pitch or place of stimulation between the two CIs or unbalanced current levels could add to difficulties processing bilateral electrical stimulation.

4.5.1 Mismatches in pitch or place of electrical stimulation

Unlike previous research in adults using bilateral CIs (Majdak et al. 2006; van Hoesel 2007; van Hoesel and Tyler 2003), subjective matching for place of stimulation was not possible in our CI group. Rather, the same electrode (no. 18) was chosen for stimulation from both CIs. To do otherwise would have provided stimulation patterns which were abnormal for the children, as their speech processors were programmed to represent the same frequency bands at equal electrode numbers, under normal listening conditions. However, it could be argued that there were pitch mismatches between the two implants which could have disrupted meaningful binaural processing. Indeed, lateralization of interaural timing differences suffers when different frequencies of sound are delivered to each ear in normally hearing listeners (Henning 1974;
Nuetzel and Hafter 1976). On the other hand, matching the place of stimulation in the two cochleae may not be as challenging to do with electrical stimuli compared to bilaterally presented acoustic input perhaps due to the wide spread of electrical current (Long et al. 2003; Van Deun et al. 2009a; van Hoesel 2004). In adult bilateral implant users, mismatches in place of stimulation of 7-8 electrode bands between the two cochleae diminishes ITD sensitivity but does not eliminate it entirely (van Hoesel 2004). It is unlikely that all 19 children who participated in the present study had such large differences in place of stimulation for electrode no. 18. In sum, the lack of subjective inter-implant electrode matching in the present study is likely not enough to account for the inability of children in this group to interpret ITDs or to perceive bilateral input as coming from the middle.

4.5.2 Unbalanced Current Levels

It is possible that intensity matching between implants was not precise enough to generate a “middle” response. As ILD increments were provided in steps of 10 CU, perceptually matched intensities could have fallen somewhere between these parameters for children using CIs. It should be noted, however, that clinical methods for determining minimum and maximum CI stimulation levels typically employ step intensities of 5-10 CU and rarely attempt to balance levels provided bilaterally. Given that we didn’t by chance provide stimulation which fell into this “balanced sweetspot” in any one of our participants, more specific efforts to find balanced inter-implant levels would be necessary. In order to more directly address the question of fusion of bilaterally presented sound in children with two CIs, a comparison of the lateralization abilities of sequentially and non-sequentially implanted children is required and an ILD task with smaller increments would be valuable.

4.5.3 Mismatched CI devices

Response patterns from many participants indicated that binaural stimuli lateralized to the second implanted side (CI-2) more frequently than to the first (CI-1). Similarly, measured eV amplitudes were often greater when evoked by CI-2 than CI-1 at similar stimulus intensities. The higher sensitivity to CI-2 evoked responses over CI-1 in the same range of intensities can
perhaps be explained by the use of different device generations between sides as a result of sequential implantation.

Advances in CI technology have led to several changes in the way electrical pulses are delivered, any of which could result in stimulating the two auditory nerves in slightly different ways. The participants of the present study used combinations of Nucleus 24M, 24CS, 24CA and 24RE devices. Only one child (CI-N) used the same device generation in both sides (24RE). Electrophysiological responses from this child show closely matched eV amplitudes at equal stimulus intensities and, behaviourally, CI-N reported that for ILD between +10 and -10 pulses were perceived to come from “Both” sides more often than from CI-1 or CI-2. Thus CI-1 and CI-2 intensities were perceived to be similar when the current levels were within 10 CUs of one another, suggesting an inter-implant match in level at near-equal CU.

In the remaining 18 children, potential differences in device generations include, but are not limited to: the use of half-banded electrodes, which directs stimulation towards the spiral ganglion cells in the modiolus; the use of straight versus curved electrodes; and methods of current conversion. Correlating discrepancies in responses evoked by each device to differences in device generations was complicated by the variety of device combinations used within the CI group and the feasibility of measuring important variables such as the distance of the electrode array from the modiolus. However, analyses did indicate that children who used one 24RE device had significantly larger mismatches between their EABR responses evoked by CI-1 and CI-2. Effects of device differences were observed despite the fact that all children in the present study used devices from the same manufacturer. Previous work from our lab has shown that ECAP thresholds evoked from 24RE generations are lower than those from other devices (Gordin et al. 2009). This supports the idea that 24RE devices may require lower levels of stimulation than earlier generations to generate the same perception. Similar differences in responses were not observed for children who used a combination of curved versus straight electrodes. Some correlations between duration of bilateral and unilateral implant use and mismatches in EABR amplitudes were observed, however these observations cannot be meaningfully delineated from the effects of device differences.
4.6 The potential role of auditory experience for binaural processing

A major difference between the children in our CI group and adult CI users is that the adults studied often had developed hearing loss after many years of acoustic auditory experience. The children in the present study experienced little to no auditory development before receiving their first CI and then were subject to unilaterally driven auditory development prior to receiving a second implant. The auditory experience of the children in this group raises two important questions: 1) is bilateral electrical stimulation sufficient for the development of normal binaural processes? and 2) does a period of unilaterally-driven auditory development hinder the development of normal binaural processes?

The durations of unilateral and bilateral implant use and/or acoustic experience prior to implantation may have affected the children’s abilities to interpret inter-implant level and timing cues. Congenitally deaf white cats retain neurons capable of processing binaural cues both in the brainstem and cortex (Reference Note 1; (Kral et al. 2009) but these neurons are fewer in number and demonstrate some abnormal response properties to electrical stimulation. In our study cohort, 3 children had some degree of auditory exposure prior to receiving their first CI (CI-N, CI-Q and CI-R). However, these children did not show any better sensitivity to ILD or ITD cues than the other 16 children in the CI group. In fact, CI-Q and CI-R were excluded from analysis, as they did not respond with >65% accuracy to unilaterally-presented pulse trains. Therefore, despite having had some history of acoustic experience, CI-Q and CI-R found the lateralization task difficult. Previous research has indicated that, in children, acoustic experience (through the use of hearing aids) prior to receiving CIs resulted in improved localization performance later on for bilateral CI users (Van Deun et al. 2009b). Unfortunately, similar conclusions cannot be made based on the present research, possibly due to the small numbers of children who had useable residual hearing prior to bilateral CI use. Further investigations involving children with varying durations of acoustic experience are required.

It is also possible that unilateral CI use, although effective for auditory development (Gordon et al. 2003; 2007a; 2005; 2006; Ponton et al. 1996; Sharma and Dorman 2006; Svirsky et al. 2004), may not be sufficient for normal development of neural centers necessary for comparing binaural hearing cues. EABR responses from children receiving bilateral CIs
sequentially have been shown to have delayed eV latencies when evoked from CI-2 relative to CI-1 (Gordon et al. 2008). Moreover, a possible electrophysiological marker of binaural processing, the Binaural Difference (BD), was also observed to be delayed in latency in children with sequential CIs compared to children using simultaneously provided CIs (Gordon et al. 2008). This work suggests that sequential implantation may result in some degree of aberrant processing in the auditory brainstem in deaf children with little to no normal acoustic experience. The significant difficulties children with CIs have in perceiving changes in bilateral level and timing cues may thus be related to deficits in the auditory brainstem pathways after electrically and unilaterally evoked auditory development. This should be examined further in children who receive bilateral CIs simultaneously and after shorter periods of unilateral CI use.

The children in the CI group experienced variable lengths of unilateral implant use (0.7 - 11.1 years; mean±sd=4.9±2.8) and bilateral implant use (0.7 - 4.5 years; mean±sd=2.2±1.1) at completion of the behavioural lateralization task. Unfortunately, findings such as the lack of ITD lateralization and the lack of perceived “middle” were observed in all children, regardless of unilateral CI use or length of bilateral CI use. This consistency made it difficult to assess the effects of duration of unilateral or bilateral implant use. In addition, these variables are significantly associated with the types of devices used; children with the longest periods of bilateral implant use were also the children who did not use a 24RE on either side. However, it is possible that more sensitive binaural processing abilities may develop after longer bilateral CI use in these children, particularly considering the percentage of their lifetimes spent with unilateral (57±17%) versus bilateral auditory exposure (32±18%). A longitudinal study in children with different combinations of device generations would be useful to delineate these effects.

4.7 Using electrophysiology to balance inter-implant stimulation in children

Wave eV amplitudes of electrically evoked auditory brain stem responses (EABRs) were significantly correlated with behavioural lateralization of ILDs in our CI group suggesting that these measures could provide a tool to match inter-implant current levels. As shown in Figure
3.1, amplitude growth functions of wave eV were similar between the two CIs on average but this would be important to verify for individual children if this tool were to be useful. Individual results indicated that, as the wave eV amplitudes evoked by CI-2 versus CI-1 became increasingly different, bilaterally presented stimuli were increasingly lateralized. Moreover, the lateralization occurred in the direction of the side with the larger amplitude response. The use of EABRs may thus be helpful to match inter-implant intensities in children who cannot reliably indicate which implant sounds louder than the other. We suggest that this behavioural task is difficult for children who have no prior bilateral hearing experience. Providing children with “balanced” bilateral stimuli might help to develop appropriate sound localization or lateralization abilities.

4.8 Future directions

The present study raises several questions. In the short term, we aim to repeat our protocol in a group of children who received two cochlear implants simultaneously (in one surgery). This line of inquiry will help to elucidate the effect of sequential implantation, and the associated period of unilateral implant use, on the observed lack of “middle” response and children’s difficulty interpreting ITDs. A second group of interest is children with later-onset hearing loss who received bilateral cochlear implants simultaneously. Observations from this group may shed light on the effect of normal acoustic experience, as opposed to bilateral deafness followed by cochlear implantation, on the development of binaural auditory processing.

The present work also highlights that balancing bilateral cochlear implant stimulation for place and intensity may be an important consideration in attempting to promote binaural hearing in CI users. We observed that children’s second implanted devices required less intensity compared to the first to generate the same magnitude of response. This likely reflected device differences resulting from generational advances in cochlear implant technologies. In addition, we were unable to ask children to subjectively match the place of stimulation used between sides, so equal electrodes (no.18) were chosen to reflect clinical procedures. However, mismatches in place of stimulation may arise for a number of reasons, including different device insertion depths, or differences in neuronal survival between sides. It is possible that careful programming of bilateral input to children’s bilateral devices might promote better use of ILDs.
and ITDs. Importantly, however, these issues are not routinely taken into consideration in the clinical programming of children’s devices. In the long term, we suggest that future research be directed towards devising clinically useful methods for balancing intensity (across dynamic ranges) and place (along the electrode array) of electrical stimulation. Some tools in this endeavor include electrophysiological responses (including EABR and the electrically evoked compound action potential, which measures responses from the auditory nerve) and the electrically evoked stapedius reflex threshold (a measure of upper dynamic range stimuli). A final tool which we aim to investigate is the electrophysiologically generated Binaural Difference (BD), which has been proposed to reflect binaural processing of ILDs and ITDs (Furst et al. 1995, Furst et al. 1990, Hausler and Levine 1980). The BD has been measured in pediatric and adult bilateral implant users (Gordon et al. 2007b; Gordon et al. 2008; Pelizzone et al. 1990), however it has yet to be conclusively linked to binaural processing in CI users. Future research from our group aims to compare BD waveforms with behavioural lateralization responses in order to clarify its clinical and scientific relevance.
Chapter 5
Conclusions

The results from the present study demonstrate that children using bilateral CIs after a period of unilateral CI use can recognize ILDs. Thus, these children have the potential to make use of naturally-occurring ILDs in order to successfully localize sounds in every-day listening situations. However, the children using bilateral CIs in this study were unable to lateralize bilateral stimuli presented with ITDs and rarely indicated that bilateral input was coming from the center. These findings indicate that, while bilateral implantation likely allows for some degree of bilateral comparisons, binaural processing is hindered in these children. This may be the result of bilateral deafness, unilaterally driven auditory development and/or electrical stimulation of the auditory system including complications relating to unmatched CI devices. It is possible that considerably greater attention to matching of level and pitch between the implants would yield better perception of both ILD and ITD cues and increase responses of centered responses. If so, this would be an important consideration in clinical programming of bilateral CIs in children in which current intensities are typically manipulated in steps similar to those used in the present study (ie. 5-10 CU). Perhaps such measures would help these children to perceive bilateral input as a fused image. Objective measures such as comparisons between unilaterally evoked EABR wave eV amplitudes may help to balance inter-implant levels. Further work is needed to determine whether an optimum place of bilateral electrical stimulation is required in children and how to measure it. We must also examine whether bilateral perception as well as ITD and ILD discrimination improves in these children after longer periods of bilateral CI use.
References


Reference Notes:
