In the name of God

Improvement of binaural hearing in long sequential bilateral cochlear implantation

by

Parvaneh Abbasalipour Kabirrah

A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Medical Science
University of Toronto

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The University of Toronto
2013

Providing children with bilateral cochlear implants after many years of unilateral hearing leads to asymmetric hearing and a persistent mismatch in auditory development in the central auditory pathways. These abnormalities were evident when we compared auditory evoked responses from each of the two ears at the level of brainstem, cortex, loudness perception, and identifying binaural cues.

We asked whether the asymmetry in auditory development could be resolved by asking the children to wear the second device alone for periods of time during the day (aural patching).

Even though children did adhere to aural patching, they did not do it for the requested amount of time. Furthermore, changes occurred at the level of the brainstem and cortex which were not related to the aural patching regimen, suggesting that the aural patching cannot reverse the abnormal plasticity produced by several years of unilateral hearing with the first cochlear implant.
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List of Abbreviations

ABR- Auditory brainstem response
AEP- Auditory evoked potential
ANOVA- Analysis of variance
AVCN- Antero ventral cochlear nucleus
BAHA- Bone anchored hearing aid
BATOD- British Association of Teachers of the Deaf
CAEP- Cortical evoked potential
CI- Cochlear implant
CI1- First implant
CI2- Second implant
CN- Cochlear nucleus
CNS- Central nervous system
CROS- Contra routing of the signal
CU- Current unit
DSP- Digital signal processing
DR- Dynamic range
EABR- Electrically evoked auditory brainstem response
EACR- Electrically evoked auditory cortical response
ECAP- Electrically evoked compound action potential
EEG- Electroencephalography
ESRT- Electrically evoked stapedius reflex
FM- Frequency modulate
fMRI- Functional magnetic resonance imaging
FS- Facial stimulation
GABA- Gamma aminobutyric acid
IC- Inferior colliculus
IC- Integrated circuit
IHC- Inner hair cell
ILD- Inter-aural (-implant) level difference
ITD- Inter-aural (-implant) timing difference
kΩ- Kilo Ohm, a unit for impedance measurement
LDL- Loudness discomfort level
LL- Lateral lemniscus
LSO- Lateral superior olive
LNTB- Lateral nucleus of trapezoid body
MC- Maximum compliance
MNTB- Medial nucleus of trapezoid body
MSO- Medial superior olive
MP- Monopolar
MCL- Most comfortable level
NF2- Neurofibromatosis type 2
NR- No response
PEDIG- Pediatric Eye Disease Investigator Group
SNR- Signal to noise ratio
SOC- Superior olivary complex
T-level- Threshold level
VEP- Visual evoked potential
VRA- Visual reinforcement audiometry
UCL- Uncomfortable level
Chapter 1

Introduction

1.1. Background and research questions

The aim of the present study is to determine whether the development of the binaural auditory pathways can be restored in children with bilateral cochlear implants (CIs) after long durations of unilateral hearing, while using the second implant alone for periods of time during the day (aural patching). We asked the following questions:

1- Will asymmetry in auditory development and function, produced by unilateral CI use, be reduced by providing a second implant in the other ear?

2- Can this be done more efficiently by removing the first implant and wearing the second one alone for a few hours per day (aural patching)?

Neonatal hearing screening nowadays detects a high prevalence of sensorineural hearing loss among newborns (1 to 2:1000 births) (Martines F. et al., 2013). The invention of multichannel CI provides an incredible opportunity for those with profound deafness to achieve normal speech perception skill (Graham J., et al., 2009). Recent studies have shown that children with bilateral CIs who receive both implants simultaneously or within a short delay between both implants will have additional benefits compared to their peers who receive two implants after long delays. Symmetrical development of the auditory brainstem pathway (Gordon et al., 2008), normal-like patterns of auditory cortical activity (Gordon et al., 2010), and higher scores on tests of speech perception in noise (Chadha et al., 2011) are strong indicators for standardizing bilateral CIs in children as an intervention for bilateral sensorineural deafness (Papsin & Gordon, 2008). In order to provide the benefits of bilateral CIs, the second device needs to be implanted at early ages.
Since the delayed implantation would unlikely activate the degenerated auditory neural fibers efficiently (Graham J., et al., 2009), and restricts the potential benefits of bilateral CIs in children who are congenitally deaf in both ears.

1.2. Consequences of bilateral hearing loss in children

Most of the participants in the present study were diagnosed with bilateral hearing loss early in childhood, and were recommended to use appropriate hearing prosthesis (hearing aid or CI).

The importance of early detection of hearing loss has been well documented in many studies. Hearing impairments have different symptoms each of which causes physiological abnormalities and affects conduction of sound waves towards the central auditory pathway. The most common symptom of this abnormality is elevated hearing thresholds and reduced speech discrimination skills. This might be attributed to disorders of the conducting pathway from external ear to the cochlea, which causes conductive hearing loss, or pathologies in cochlea and/or the auditory nerve. This type of impairment is called a sensory neural hearing loss.

Whatever may be the cause of the hearing loss (conductive or sensorineural pathologies), their outcomes are devastating and result in decreased exposure to sound. In turn, this impacts the normal development of the auditory pathway (Shepherd & Hardie, 2001). The earlier the age of onset of the hearing loss, the more impairment occurs in this pathway. There is a strong link between hearing ability and speech and language acquisition. Permanent childhood hearing losses are known to have detrimental effects on the development of speech and language skills. Given that language is acquired during a sensitive period, the absence of appropriate inputs during this period resulted from hearing deprivation, negatively impacts on the language-related
neural pathways (Pimperton & Kennedy, 2012). For those children, alternative approaches, such as sign language, can be used for communication. A recent study in Sweden showed that preschool children with more severe hearing handicaps were more dependent on sign language and had more difficulties with word pronunciation, compared with those children who had a lesser degree of hearing loss (Borg et al., 2007). Similarly, deaf students with partial speech coding ability tended to combine oral speech with signs language to communicate and read, rather than using speech alone (Marschark & Mayer, 1998). Language (either spoken or non-spoken form) requires appropriate memory function. Deaf and normal hearing people have comparable memory capacity, so a deficit in language acquisition in hearing impaired children is not related to the small memory capacity. However, the sign codes which play an important role in communication among the deaf individuals require greater cognitive resources than spoken language which results in less encoding information into a limited capacity, and consequently, greater difficulty in later recalling the information (Marschark & Mayer, 1998).

In humans, the auditory and visual sensory systems are closely integrated. Auditory deprivation results in compensatory plasticity in the central nervous system and increases visual cognition (Bavelier et al., 2006). Deaf children though, are easily confused by peripheral visual distractors. This can be due to modifications in the central visual pathways towards enhanced peripheral vision in these individuals. This has been confirmed with brain imaging studies (Bavelier et al., 2006). fMRI data indicated that even though anatomical visual areas were similar in deaf and in normal hearing listeners, the primary auditory cortex responded extensively to moving visual stimuli in the group of children who were deaf. This might be a consequence of using sign language. In turn, this might drive greater abnormal asymmetrical activity in the right hemisphere rather than the left (Fine et al., 2005). The primary auditory cortex in this hemisphere
as well as the inferior parietal cortex is normally involved in discrimination of moving sounds (Ducommun et al., 2002).

Poor educational performance in hearing impaired children is most often attributed to the lack of hearing feedback (Verhaert et al., 2008). The British Association of Teachers of the Deaf (BATOD) survey in England indicated that hearing impairments had a negative impact on children’s academic achievements and approximately 50% of students dropped out of educational system after finishing the high school (Davis et al., 1997).

One of the most prominent necessities in todays’ society is having a successful literacy skill. Children with hearing loss do not have the same literacy skills as do their hearing peers. Reading is not joyful and pleasure for them. It may be due to their inability to comprehend the author’s purpose and to match their knowledge with the text to fluently read the words and phrases. This lack of literacy skill limits deaf children’s ability to understand the final conclusion (Luckner & Handley, 2008). Hearing impairments in children are often accompanied by a remarkable reduction in reading performance at any age cohort between 8 to 17 years old. At the age of high school graduation, reading skill drops as low as fourth-grade level for adolescents with hearing loss (Qi & Mithchell, 2012). Similarly, writing proficiency is impacted by phonological awareness, limited vocabulary, disability in using patterns of language, fewer cohesive markers, and grammatical difficulties in hearing impaired individuals. Since the hearing impaired children are not able to find relationship among words and cannot find historical origin of the words, it is not surprising that they are poor speller (Geers & Hayes, 2011).

Solving mathematical problems is also negatively influenced by hearing loss in deaf and hard of hearing students. Their average performance in mathematics falls below that of their hearing
peers and their ability unlikely exceeds grade six when they are at the last grade of high school (Qi & Mithchell, 2012).

Regression in performance in educational settings among deaf children might be related to deficits (less than normal performances) in memory function (Alloway et al., 2009). In this respect, several weak points have been identified in deaf children’s *working (short term) memory*. They have great difficulties recalling the orders of digits, words, signs, and pictures (*deficit in sequential memory*). This affects the children’s ability to comprehend sentences with similar and redundant items (*deficit in memory load*) (Hamilton, 2011). Therefore, the speed of processing and comprehending signed or written information is reduced (*deficit in processing speed*) (Hamilton, 2011). This is reflected by low academic achievements and low scores in math, reading, and written language in children with hearing loss (Braden, 1990). Children who are deaf typically require auditory or visual communication to be presented at a low rate, in order to process the input and avoid overloading their memory capacity (Hamilton, 2011). As was mentioned previously, deaf children have a strong peripheral visual cognition (Bavelier et al., 2006). Therefore, they tend to ignore attention-dependent activities in the educational environments (*deficit in attention*) (Hamilton, 2011). On the other hand, children with hearing impairments have several positive memory functions. They have similar or even better performance than normal hearing people in recalling sequential items regardless of their order (*free recall*), recalling items while they are presented in a visual sequence with shapes and colors (*visuospatial recall*), creating and manipulating a visual image (*Imagery*), and using signs and speech codes simultaneously (*dual encoding*) (Hamilton, 2011).

Learning disability as a consequence of hearing loss has been documented in several studies. It impacts children’s ability to achieve new skills and understand complex concepts. Adaptation
with social conditions is also affected by this impairment (Devine & Taggart, 2008). As the severity of this condition increases, the dependency of the child to the parents or caregivers becomes higher. In normally developing individuals, as children grow and mature, their dependency to their parents decreases and adulthood attitudes form. In handicapped individuals in turn, the care-based behaviors do not limited to childhood and are often long-lasting (Myklebust, 1960). Special needs in social situations such as school, peer relations, work areas, and among family members results an emotional pressure and stress to people with learning disability such as deaf children (Myklebust, 1960).

Given that approximately 90% of hearing impaired children are born into hearing families and their parents know very little or no information about appropriate behaviors with their handicapped child, their interaction in the hearing community is highly affected (Hindley 1997). They might have hyperactivity, disobedience, high level of dependency and short attention (Hindley 1997). Deaf preschool children do not play in groups as much as their normal hearing peers, and rather often play alone (Hindley 1997). Interestingly, medical treatment of those with temporary hearing loss improved these socially impaired behaviors (Hughes & Wright, 1988). Therefore, lack of parental information about an appropriate communication method with hearing impaired child would be represented in the society.

Edgar Arnold Doll (1940) was an American psychologist that defined the term social maturity as “the ability to care for one-self and to assist with the care of the others” (Myklebust 1960). More than a half century ago deaf individuals indicated 20% less social maturity score than normal people. They had difficulties in self-help (e.g. to be able to feed and dress oneself), self-direction (e.g. going out on his/her own), and care of others (Bradway, 1938; Myklebust 1960). However, nowadays, early diagnosis of the hearing disorders and appropriate interventions such as hearing
aids and cochlear implantation, along with integration into the mainstream schools instead of isolated deaf schools has increased interactions between normal and hearing impaired individuals. Approximately all hearing parents have signing skill and are able to communicate with their deaf child/ren (Hindley 1997). Furthermore, new designs of classrooms provide more benefit for hearing impaired children to develop their speech and language skills (Moog & Geers, 2010; Thoutenhoofd, 2006).

1.3. **Binaural hearing**

In the present study we attempted to improve binaural hearing in children with bilateral CIs who experienced a long duration of unilateral deafness. The second implant however, does not provide them this ability.

Normal binaural hearing allows the listeners to hear sounds louder using both ears together (binaural loudness summation), to recognize speech amongst environmental noise (squelch effect), and to localize sounds in the horizontal plane (inter aural timing and level differences) (Bess & Tharpe, 1986; Wieselberg & Iorio, 2012). These components will be discussed later with more details.

1.3.1. **Binaural loudness summation**

Binaural summation has been documented by Flecher & Munson in 1933 as early as 80 years ago (Irwin, 1965). The most common definition for this phenomenon is increasing the loudness of the auditory stimuli (either pure tone or speech) once they are heard from both ears rather than one side. This excessive level reaches to 3 to10 dB (Figure 1.1) in normal hearing individuals, while the greater numbers are attributed to supra-threshold levels (Hawkins et al., 1987; Bess &
Hence, this small change in hearing threshold allows speech perception abilities to increase by as much as 18% (Bess & Tharpe, 1986). Other studies specified that in order to have a complete summation (i.e. doubled loudness binaurally vs monaurally) the signal has to be presented in a narrow bandwidth, with similar phases to both ears, and with equal hearing sensitivity in both ears (Lawrence, 1986).

Hawkins and his colleagues (1987) in an attempt to assess the influence of the input levels on loudness summation determined three sound levels including “LDL” or loudness discomfort level, “MCL-A” or soft but comfortable, and “MCL-B” or loud but comfortable. By presenting binaural stimuli at these three conditions, they noticed that binaural summation decreased at higher levels in normal hearing individuals (Figure 1.2). However, perception of loudness was not reduced for patients with high frequency hearing loss. They also found that at the levels at

![Figure 1.1 Improvement of hearing threshold with binaural hearing vs. monaural hearing. Figure courtesy of Bess and Tharpe, 1986.](image)
which the sounds were uncomfortably loud, there was no significant changes between binaural and monaural loudness.

Figure 1.2 Binaural loudness summation at three conditions (MCL-A, MCL-B, and LDL) for normal hearing and hearing impaired individuals. Figure courtesy of Hawkins et al., 1987.

Hawkins and his colleagues (1987) noticed that high frequency sensorineural hearing loss did not impact binaural summation, unless the hearing loss in both ears was symmetrical. Thus, this should be taken into consideration when two separate hearing aids are fitted to these patients. Indeed, over amplification as a result of binaural loudness summation is a reason for refusing a second hearing aid in bilateral hearing loss (Kobler et al., 2010). By contrast, patients with asymmetric hearing impairments might miss this binaural hearing advantage. However, they would perform better once loudness between two hearing aids is balanced (Hawkins et al., 1987). Therefore, binaural amplification is highly recommended to individuals who have bilateral hearing loss. The only exception for this prescription is when performance on speech perception tests reveals that fitting a second hearing aid causes further distortion of sounds (Kobler et al., 2010).
1.3.2. Squelch effect

Listening to speech in a room full of noise and trying to focus to the conversation is virtually impossible (cocktail party effect). However, normal hearing listeners are able to communicate in these environments by raising their voices, ignoring noise coming from one ear and selectively attending to the conversation at right hand. This phenomenon is referred to as the *squelch effect* or *release from masking* (Bess & Tharpe, 1986). To be made more intelligible, the target message should be presented from right side (Bolia et al., 2001), while the interfering signal should be delivered from the opposite direction (left side) (Bolia et al., 2001; Bess & Tharpe, 1986). It is proposed that more selective attention to speech occurs once the sounds with higher preference are presented from one hemifield and those with lower preference are delivered from the other hemifield (Bolia et al., 2001). An appropriate explanation for this phenomenon could be a hemispheric preference for speech signals. Neuroimaging studies indicated that language is processed in the left hemisphere (Tzourio et al., 1998). Fitting children who have bilateral hearing loss with monaural amplification causes both the target signal and the noise to be delivered to the one side only. In these cases, spatial differentiation between speech and noise decreases and speech intelligibility, in turn, is reduced.

1.3.3. Sound localization

Spatial hearing conception is defined based on comparing the auditory inputs between two ears. This enables the listener to locate the sources of sound in the space. The ability to localize sound is critical not only for understanding speech in challenging listening environments, but also for safety purposes. Several acoustic features contribute to this processing at the horizontal plane including: inter-aural level differences (ILDs), and inter-aural timing differences (ITDs), which
will be discussed in more details. These internal components are relied by bilateral hearing and in turn, monaural hearing restricts this ability for listeners.

Sound vibrates air molecules and changes the static air pressure. It clusters them at some points in the space (condensation) and gets them farther apart at other place (rarefaction). The distance between each condensation (or rarefaction) is the *wavelength* of sound. It can also be defined as the distance between each two adjacent peaks (Yost, 2000, Chapter 3). Sound waves with high frequency (i.e. higher repetition rate per second) have shorter wavelengths than those with low frequency. In cases where the wavelengths are shorter than the head diameter (high frequency sounds) and sound source are not locate exactly in front (Figure 1.3), the head and pinna act as a barrier against the sound and attenuate the amplitude of the sound. The sound’s energy in turn, decreases when it reaches to the farther ear and the sound is perceived with lower level than the near ear. This means that there is a reverse relationship between ILD and the frequency of sounds (Grothe et al., 2010; Altschuler et al., 1991, Chapter 8) with major effect for frequencies above 1600 Hz in adults. The head shadow effect thus, appropriately explains this phenomenon and allows identification of ILDs (Altschuler et al., 1991, Chapter 8).

![Figure 1.3](image-url) Sound localization cues. Figure courtesy of Grothe et al., 2010
Individuals with unilateral hearing may not have considerable problems hearing sounds from the impaired side only if it is presented in a quiet environment and is delivered at an appropriate level to be identified after dampening by the head shadow effect. High frequency components of speech establish approximately 60% of speech intelligibility. Given that the phenomenon of head shadow most often affects high frequencies, it is not surprising to know that unilateral hearing loss decreases the ability of speech comprehension (Bess & Tharpe, 1986).

While the ability to understand ILDs is represented at frequencies above 1600 Hz, distinguishing ITD components is critical in lower frequencies (in adults) (Altschuler et al., 1991, Chapter 8). Inter aural timing differences arise from the time that the sound travels around the head to reach to the far ear. Even though this delay was measured for normal hearing listeners to be as small as 10µsec (Akeroyd, 2006), various values with a minimum of 100µsec were reported for CI users when pulses were presented at a rate of 50 pulse per second (van Hoesel & Tyler, 2003). At higher pulse rate ITDs’ thresholds increased in CI users (van Hoesel & Tyler, 2003).

Neural mechanism of binaural hearing starts at the level of the cochlea, where mechanical energy transduces to an electrical potential at the synapses between inner hair cells (IHCs) and cochlear nerve. The electrical pulses are then transmitted to the cochlear nucleus (CN). Anteroventral cochlear nucleus (AVCN) contains three types of cells including: bushy cells, stellate cells, and granule cells. The first projections from CN arise towards superior olivary complex (SOC) where it has been denoted as the primary location for binaural processing. It includes three principal nuclei: lateral SOC (LSO), medial SOC (MSO), and medial nucleus of terapezoid body (MNTB) (Altschuler et al., 1991, Chapter 1).
Bushy cells, as shown in Figures 1.4a and 1.4b, send excitatory outputs towards MNTB. It seems that they have the largest axons in the CN and make the largest synaptic structures in the central nervous system (CNS) named the Cylex of Held. The major inputs of MNTB come from contralateral CN. The neurons in MNTB are glycinergetic and inhibitory. They send their outputs most often to ipsilateral LSO and ipsi- and contralateral MSO (Altschuler et al., 1991, Chapter 1). Meanwhile, LSO receives some excitatory inputs from ipsilateral CN, together with inhibitory projections from contralateral MNTB. This makes the LSO as a well-displaced structure for detecting ILDs (Altschuler et al., 1991, Chapters 1 & 8; Grothe et al., 2010). The ability of LSO to detect level differences is based on the speed of transducing the inputs from CN to the contralateral LSO. The distance between MNTB to contralateral LSO is more than ipsilateral LSO (approximately 7 mm). But the speed of conducting the inputs is higher at this long pathway than the shorter rout (57 m/sec vs 21 m/sec). Consequently, the inhibitory inputs from the contralateral ear and the excitatory inputs from the ipsilateral ear reach the LSOs almost simultaneously when no ITD exists (Altschuler et al., 1991, Chapter 8).

The tonotopic organization of MSO is tuned for low frequencies from lower at the dorsal part to higher frequencies located at the ventral part (Altschuler et al., 1991, Chapter 1). The main role of MSO is to detect the inter-aural timing and phase differences; since it receives outputs from both ipsilateral and contralateral CN, the out of phase signals inhibit MSO by GABAergic neurons (Altschuler et al., 1991, Chapter 1). Figures 1.4c and 1.4d show that MSO also receives excitatory inputs by glutamergic transmission (Grothe et al., 2010). These projections arise only during developmental processes at the onset of hearing (Grothe et al., 2010, Altschuler et al., 1991, Chapter 1). Distribution of the auditory signals to both ipsilateral and contralateral nuclei
makes the SOC an important location for integration of binaural information (Grothe et al., 2010; Altschuler et al., 1991, Chapter 1).

ITD sensitivity is related not only to the MSO neurons but is also attributed to the action potential of the proximal auditory nerve synapsing at the base of the IHCs of the cochlea. Stimulus waveforms change IHC membrane potentials. This is represented with a phase-locked action potential in the nerve. Interestingly, the precision of this temporal interaction decreases at the higher frequencies (Grothe et al., 2010).
1.4. Cochlear implantation

Cochlear implantation provides the ability of hearing for children with severe to profound hearing loss. CIs stimulate the auditory nerve directly with electrical pulses. This prosthetic
device, shown in Figure 1.5 consists of an internal and external component. The internal component includes a hermetically packaged receiver-stimulator integrated circuit (IC) and an electrode array which bypasses the malfunction of cochlear IHC; while the external part consists of a transmitting coil and an analog speech processor with a digital signal processing (DSP) hardware to transfer the hearing information to the implanted device (An et al., 2007).

**Figure 1.5** The basic components of cochlear implant. Internal part consists of receiver and electrode array; external part includes transmitting coil and speech processor. Figure courtesy of EJ Propst. http://www.sickkids.ca/CochlearImplant/Information-for-Parents

The electrode array is placed inside the cochlea after securing the receiver in the bone beneath the skin. The implant remains unstimulated for four weeks when the speech processor is activated for the first time. In this process, acoustic sounds are transduced as electrical pulses and transmitted to the internal receiver. The newly established auditory input then travels within the cochlea through the intracochlear electrode array and stimulates the residual auditory nerves based on tonotopically organized basilar membrane. Hair cells located in the basal part of the
basilar membrane are activated by high frequency stimuli whereas, the more apical turns of the cochlea are elicited by low frequencies (Rauschecker & Shannon, 2002). CI therefore, bypasses the abnormal function of the cochlea, and its benefit for the lesions beyond the cochlea, such as neurofibromatosis type 2 (NF2) is reduced (Rauschecker & Shannon, 2002).

Studies on assessing the use of electrical stimuli to hear date back to more than two centuries by Alessandro Volta, and he heard a sound like boiling of a viscid liquid (Brackmann 1976). However, the first clinical experiment was reported in the middle of the 20th century by Djourno and Eyries using a single-channel implant (Spelman 1999). The reason for this long delay between the first report of Volta on hearing the electrical sound and actual clinical trial might be due to unpleasant sound which was produced by primarily electrical stimuli (Brackmann 1976).

Number of research on cochlear implants was increased in the 1930s after discovering the role of the cochlea for transducing acoustic input into electrical energy. Investigators realized that they could provide artificial hearing by delivering the electrical stimuli directly to the auditory nerve for those with hearing deprivation (Brackmann 1976). In order to produce such simulation, it is necessary that the hearing prosthesis mimics the normal function of the cochlea in terms of place pitch mechanism, so that the efferent neural system can convey the information based on tonotopic organization. The first recipient of this technology was able to hear environmental noise and recognize a few words with lipreading (Brackmann 1976). Further efforts were made to develop the electrodes structure and to provide sufficient information for speech perception with multichannel stimulation.

The efficacy of the CI depends on the types of damage to the cochlear structures including mechanical, chemical, thermal, and electrolytic injuries. Insertion of an external device in deaf cats increased the risk of mechanical trauma to the remaining cochlear structures such as organ
of Corti, hair cells, ganglion cells and auditory nerves (Simmons, 1967). Since the function of the remaining auditory nerves depend in part on the supporting cells of the organ of Corti, protecting of the integrity of this structure is very important. For this reason, the scala tympani was selected as the best placement for the electrode array (Brackmann 1976). Chemical injuries as the second risk factor have been minimized by using resistant materials to corrosion and alkalis, such as platinum, iridium, and titanium (Brackmann 1976). Figure 1.6 shows a cross sectional view of the electrode array and shows the materials that were used for each part of the array (Clark G, 2003). Another type of potential damage is increasing the temperature of the neural tissue by delivering direct electrical energy to the neural fibers. However, using low currents (<200 µA) for stimulation can maintain the safe environmental temperatures. Such low current consumption also reduces the electrolytic hazards. Furthermore, the small surface of the electrodes prevents the risk of electrolysis (Brackmann 1976).

Figure 1.6 The electrode array cross section. Stylet uses in pre-curved electrode arrays and is removed during the insertion of the electrode array to bend the array closer to the modiolus. Figure courtesy of Clark (2003).
Tonotopic organization of primary auditory cortex (A1) is also affected by auditory amplification. Following cochlear ablation, neural plasticity occurs from the codal to the rostral part of the central auditory pathway. While this reorganization changes the difference limen for frequency, fitting an individual with a hearing aid or a CI leads to secondary- or rehabilitation plasticity. This recovery of the tonotopic map is age-dependent. Younger individuals achieve more benefits from hearing amplifications. Recordings of evoked potential from the scalp of adult CI users also revealed that three months of chronic electrical stimulation yields to tonotopic re-organization in the cortical regions of the auditory cortex, which mimics that of normal-hearing listeners (Thai-Van et al., 2010).

1.4.1. Bilateral vs. unilateral amplification

Most professionals in the past believed that unilateral hearing loss does not comprise a serious problem and individuals with only one good ear are able to communicate normally. Since the affected children had presumably normal language acquisition, unilateral hearing loss was rarely detected at early onset unless the child had a medical problem. Such difficulty in detecting the impairment imposed a name of silent handicap for those children suffering from unilateral hearing loss (Lieu, 2004; Bess & Tharpe, 1986).

On the other hand, studies on oralism of children who experienced unilateral hearing loss at early ages reported an average of 5 months delay in expressing the first two-word phrases, even though the first one-word utterances occurred at the same age as that of their normal hearing peers. Children with unilateral hearing loss have a limited vocabulary and are more dependent on lipreading (Lieu, 2004). These listeners might experience more challenges in their communications when sounds are presented from their impaired side. It is not surprising to know
that in the presence of competing noise, additional difficulty occurs. Therefore, the listeners might experience annoyance, confusion, embarrassment, helplessness (Bess & Tharpe, 1986), and insecurity (Wieselberg & Iorio, 2012), which might lead to social isolation.

Various educational progress of school-age children with unilateral hearing loss have been reported with a range from small problems (Klee & Davis-Dansky, 1986) to serious challenges (Peckham & Sheridan, 1976). The major reason for this variation might be due to variability in individual aptitudes, available facilities and accessories at school, and teacher and family supports. In turn, children with hearing loss tend to have lower IQ and lower scores on verbal academic tests compared to their normal hearing peers (Culbertson & Gilbert, 1986; Lieu, 2004). Repeating the grade (22-35%) (Culbertson & Gilbert, 1986; Lieu, 2004), and assistive services requirements at school (12-41%) (Oyler et al., 1988; Lieu, 2004) also increase the vulnerability of these children in educational environments.

Fitting only one ear with a hearing aid or cochlear prosthesis deprives individuals with bilateral hearing loss from interactions between both central auditory pathways and causes an internal discrepancy. In such case they would require a high signal to noise ratio (SNR) to be able to participate effectively in oral communications. Reasonably, the listeners do not have any experience of stereo sound and tinnitus suppression (Wieselberg & Iorio, 2012). These consequences tend to be more serious when the hearing loss is sensorineural in nature rather than conductive. The impairment in the former remains stable for a longer duration and is less likely to be offset by amplification (Silman et al, 1984). Adverse effects of unilateral hearing loss also attributes to side of the handicap. Given that the left hemisphere is dominant for language processing in the majority of people, unilateral deafness on the right side might lead to more adverse consequences, and resulted in poorer performance (Lieu, 2004).
For the above reasons, audiologists have mandated universal hearing screening for newborns to identify minor hearing deficits at birth (Lieu, 2004). This then allows for early identification and in turn, allows clinicians begin the necessary medical and audiological interventions at very early ages. Audiologists have attempted to restore hearing impairments with state of the art technologies such as the CROS hearing aids (contra routing of the signal) (Johnson, 1975), FM systems (Kenworthy et al., 1990), bone anchored hearing aid (BAHA) (Snik et al., 2004), and cochlear implants (Hassepass et al., 2013).

The early attempts in 1960s for restoring hearing in deaf patients were limited to only one ear (Spelman, 1999). Yet there was no unanimous agreement on efficacy of multichannel versus single channel devices. Years later in 1983 when the former was supported with more clinical trials, another question was raised. The number of electrodes which provided speech perception abilities without lipreading remained as the main argument among investigators (Spelman, 1999). Shannon in 1995 indicated that speech information can be extracted by normal hearing listeners with as few as three channels when stimuli were presented in quiet environments. However, similar performance required more number of intracochlear electrodes in a noisy background (Spelman, 1999).

Even though unilateral CIs allow individuals to hear in quiet, hearing in the presence of background noise is particularly difficult for them. Since the deaf side is blocked, users are deprived from sufficient auditory information in noisy environment. Indeed all benefits of binaural hearing are restricted by single side deafness. Given the benefit of bilateral hearing in sound localization, it is not surprising to know that monaural stimulation hinders this skill. Localizing sound sources in space is particularly important for language acquisition. Learning speech and language skills in childhood is not limited to a specific time and place. Speech
perception would be reduced with competitive noise when both signal types are heard in only one ear. In fact, monaural hearing restricts benefit of spatial localization which is important not only for improvement of communication skills, but also for protection against danger such as crossing the streets (Brown & Balkany, 2007).

Vestibular dysfunction after CI has been critiqued by several studies (Brey et al., 1995). However, detailed evaluations indicated that the instability after CI does not last more than a week and this restoration occurs with the same rate even in bilateral cochlear implantation (Papsin & Gordon, 2008).

One of the major goals of binaural amplification with hearing aids or CIs is improvement of speech recognition under various listening conditions. Given the benefits of binaural hearing, which has been mentioned earlier, communication with unilaterally fitted devices requires better SNRs relative hearing with two devices (Brown & Balkany, 2007). However, bilateral hearing increases sound localization accuracy, and thereby improves speech intelligibility in noise comparing to the unilateral hearing (Asp et al., 2012).

1.4.2. Concerns regarding sequential bilateral cochlear implantation

Early exposure to auditory stimuli with CI drives neural plasticity along the CNS and establishes the ability of processing the inputs for the auditory pathway (Kral & Tillein, 2006). CIs are adequate substitution for bypassing damaged cochlear structure and restore deprived functions in the auditory system (Ryugo et al., 2005). In fact, CIs have been shown to facilitate language acquisition, if they are provided no later than sensitive periods (Gordon et al., 2003; Kral & Tillein, 2006). During this time, high rates of myelination and more effective synaptic changes occur (Gordon et al., 2007a). Studies on congenitally deaf cats indicated that synaptic vesicles in
CN are smaller compare to hearing animals. Furthermore, pre- and postsynaptic areas were larger in deaf cats than normal hearing groups. Interestingly, long term sound stimulation with CI restores these morphological features (Kral & Tillein, 2006) suggesting that the developmental process of central auditory pathway is activity dependent (Gordon et al., 2006). Although the auditory stimuli increase axonal myelination and synaptic efficiency, it seems that these changes occur more often at early exposure to the sounds. The amount of the neural reorganization at the older ages depends on the time of the intervention during the developmental age (Harrison et al., 2005).

Unilateral auditory stimuli in bilateral deaf individuals drive dominant changes at the level of the brainstem ipsilateral to the implant. In turn, the maturation of the pathway on the opposite side is restricted and an asymmetrical plasticity in the pathway is formed (Gordon et al., 2007a). These changes are demonstrated by increasing the excitatory activity from CN to ipsilateral inferior colliculus (IC) and increasing the inhibitory projections from CN to contralateral IC (Gordon et al., 2007a). Therefore, when sound stimuli are delivered to the unimplanted ear after a long delay from the first side, different neural processing is represented.

Electrophysiological studies of auditory brainstem potentials have shown sufficient evidence of this asymmetrical development in the central auditory pathways when implantation of the second ear is delayed. Auditory brainstem responses (ABRs) that are elicited by electrical pulses are typically comprised of three major peaks which are labeled as wave eII, eIII, and eV (Gordon et al., 2006) (Figure 1.7); each of which are generated from ongoing electrical activity in different regions of the brainstem. Intracranial portion of the auditory nerve generates peak II (Burkard et al., 2007, Chapter 16), whereas, near field recordings indicated that peak III comes from the output of nerve fibers at CN (Burkard et al., 2007, Chapter 16). Wave V is the later response that
is generated by the lateral lemniscus where it is terminated in the contralateral IC (Burkard et al., 2007, Chapter 16).

![EABR wave peaks](image)

**Figure 1.7** EABR wave peaks. Figure courtesy of Gordon et al (2006).

Neural conduction in the auditory brainstem matures during the first year of life (Gordon et al., 2003). This maturation can also be observed in deaf children who received two CIs at the same time (simultaneously) or within a short inter-implant delay (sequentially) (Gordon et al., 2007a, Gordon et al., 2008). Interestingly, electrical and acoustical hearing provide similar plastic changes in the auditory brainstem, and this maturity occurs via an activity-dependent process (Thai-Van H., et al. 2007).

However, asymmetrical plasticity and mismatched timing of activity in the auditory pathways caused by several years of unilateral hearing is unlikely restored even by chronic auditory stimuli over the long term (Gordon et al., 2007a). **Figure 1.8** indicates an example of prolonged eV latency of EABR that was recorded from a congenitally deaf child who received a CI in the unimplanted ear several years after hearing unilaterally with the first CI only. As shown in this Figure, eV latency, which represents activity in the rostral portion of the brainstem is faster in the more experienced ear (right ear) compares to the second-implanted naïve side (left ear). It is
worth noting that this timing difference in neural conduction between the two sides of the brainstem pathways persists even after chronic implant use for 30 months (Gordon et al., 2007a). This suggests abnormal neural conduction in the naïve brainstem.

Figure 1.8 Auditory brainstem potentials from an apical electrode in a child with bilateral CI with 30 months follow up. This child received the first implant on the right ear before age 3 years, and >2 years later was implanted on the left side. Dashed lines show the eV latency which is prolonged on the left side. Wave eV of the naïve ear was not overlapped on the response of the experienced side. Figure courtesy of Gordon et al, 2007a.

Unilateral cochlear implantation impacts not only on the auditory brainstem but also higher levels of the CNS. In 1967 Portmann and his colleague succeeded in recording cochlear evoked activity using a non-surgical approach with one inserted electrode. Now, however, these potentials can be recorded using multiple recording sites (≥32) on the surface of scalp (Burkard et al., 2007, Chapter 1). Typically, late auditory evoked potentials (AEP) are characterized by P$_1$-N$_1$-P$_2$-N$_2$ each of which has different rates of maturation (Ponton et al., 2002). Figure 1.9 shows AEP morphology across age recorded by electrode Cz on the middle of the head of a normal hearing individual. Even though P$_2$ is a late recorded peak, it is the fastest component to mature
among the other peaks (Ponton et al., 2002; Burkard et al., 2007, Chapter 18). This early large positive peak reflects the massive synaptic density in the auditory cortex (Jiwani et al., 2013). The maturation includes changes in morphology, latency, and amplitude. While, P_2 has a mature adult-like latency at around age 2, P_1 development completes only after age 16-18 (Burkard et al., 2007, Chapter 18; Jiwani et al., 2013).

![Figure 1.9 AEP morphology across age recorded by electrode Cz. Figure courtesy of Burkart et al., 2007](image)

Since the maturation of AEP is activity-dependent, auditory deprivation changes the maturational process of AEP (Burkart et al., 2007, Chapter 18). These changes can be assessed by latency and morphology of the waveforms (Sharma et al., 2009; Ponton & Eggermont, 2001). Figure 1.10 compares the waveforms of a normal child with responses recorded from a CI user across age.
Figure 1.10 AEP waveforms in a normal hearing individual with an age-matched CI user. The vertical lines show the adult latency values of P₁, N₁, and P₂. Figure courtesy of Ponton & Eggermont, 2001

The most obvious difference between the two series of the above waveforms is the absence of peak N₁ in the CI user, resulting in a large dominant positive peak. This large positive peak might be a combination of two positive peaks (P₁ and P₂). N₁ represents maturation of superficial cortical layers in normal hearing adolescence and these layers play an important role in inter-hemispheric connections. These cortico-cortical connections are critical for development of several complex auditory skills such as speech perception in noise. Since this negative peak emerges after a decade of hearing experience, it seems that auditory activity improves the developmental process of the cortical area (Jiwani et al., 2013). AEP morphology in CI users matches that of normal hearing children who had similar time-in-sound (Burkart et al., 2007, Chapter 18) as long as CI is provided at early ages in childhood (<3.5 years) (Sharma et al., 2009). In cases of delayed implantation, N₁ does not reach the normal-like appearance and consequent to its absence, P₁ would not be recorded with normal latency and amplitude (Burkart et al., 2007, Chapter 18). These findings along with better speech and language acquisition at
younger ages (Geers, 2006), suggests the presence of a sensitive period for central auditory development (Sharma et al., 2009). To the best of our knowledge no published study has evaluated the late cortical responses in long sequential bilateral cochlear implantation.

As the duration of unilateral hearing increases, more changes in cortical activity occur compared to those children who received both implants in the same surgery. Stimulation from the new implant in sequentially cochlear implanted users, results in different activity regions in the cortical area relative to normal hearing listeners. Figure 1.11 compares the cortical lateralization in response to right (CI1) and left (CI2) stimuli of a normal hearing listener with CI users who had a long inter-implant delay, short inter-implant delay, simultaneous bilateral implantation, and unilateral implantation (Gordon et al., 2013). Anatomophysiological evidences (Demanez & Demanez, 2003; Moore, 1987) and clinical experiences (Gordon et al., 2010, Gordon et al., 2013) indicated that sounds coming from either ear normally activates the contralateral hemisphere more than the ipsilateral side. However, as shown in Figure 1.11, children who had longer inter-implant delay had greater than normal lateralization towards the contralateral stimuli. Meanwhile, CI2 stimulation was lateralized toward ipsilateral hemisphere.

Figure 1.11 Average percent of cortical lateralization in response to right (CI1) and left (CI2) stimuli. Figure courtesy of Gordon et al, 2013.
Generally, there are two time points in bilateral cochlear implantation. One concerns the delay between the detection of the hearing loss and the intervention with CI. The second relates to the inter-implant interval. While the former affects speech and language acquisition, the latter impacts on binaural processing (Papsin & Gordon, 2008).

Sound localization ability is one of the benefits of binaural processing. Localizing sounds can only be done by accessibility ILD and ITD cues. Although bilateral CIs provide auditory inputs from both sides for deaf children, interpretation of these cues might be impacted by introducing a delay between implantation of both ears. This has been shown by previous studies in our lab and the results are shown in Figure 1.12 (Salloum et al., 2010). Comparison of lateralization abilities between children who received two implants sequentially and those who had normal hearing indicated that implant users could reliably identify inter-implant level cues. However, they never reported that they could hear the sound in the middle of the head as do their normal hearing peers. Instead, most often they heard the sound as coming from both sides, which was a rare response among the normal hearing peers. Furthermore, CI users were unable to identify inter-implant timing differences, despite chronic use of both implants, and their responses were most often lateralized towards the naïve ear.
Figure 1.12 Mean responses to the auditory signals with A) ILDs in normal hearing children, B) ILDs in CI users C) ITDs in normal hearing children, and D) ITDs in CI users. Red lines indicate the responses that were lateralized towards the right ear/CI1, blue lines indicate the responses lateralized towards left ear/CI2, green lines indicate the responses that were lateralized to middle of the head, and black lines indicate the reports of hearing the sound from both ears. Zero on the x-axis denotes the levels that were perceived as balanced in bilateral presentation. Negative values represent the values that were lateralized toward the right ear/CI1, and positive values show the signals that were lateralized towards the left ear/CI2. Figure courtesy of Salloum et al, 2010.

Adverse effects of long term unilateral hearing is identified in speech perception in noise by children who received their implants sequentially. Chadha and his colleagues (2011) in an experiment found that these children have weaker performance with separation of speech from noise, compared to those who were implanted simultaneously in both ears. These results suggest that the shorter the delay in receiving the second implant, the more benefit of binaural hearing (e.g. speech perception in noise) is achieved (Gordon & Papsin, 2009).
1.5. Treatment for unilateral deprivation

About 80% of corticospinal tracts (CST) in human are decussated and three hemisphere connectors including corpus callosum and anterior and posterior commissures provide these crossing pathways. One important finding in anatomical studies indicated that the crossed CSTs are dominant from left hemisphere to the right side (Vulliemoz et al., 2005) and the majority of the crossing fibers are attributed to the neural fibers that mediate spatial information and provide a feeling of 3D body (Shinbrot & Young, 2008). Optic chiasm is an example of crossing of the visual fibers, whereas, the pons is the location of crossing of auditory fibers (Shinbrot & Young, 2008). Crossing the fibers integrates the information that was received by the two eyes and the two ears, and provides binocular and binaural fusion, respectively. Therefore, we decided to compare these two sensory systems when unilateral deprivation derives mismatches in the central neural pathways and leaves asymmetrical neural plasticity.

Decussation of motor neurons provides a compensational benefit for the muscles in case of unilateral injury. Clinical observations indicated that the damaged function of these muscles such as in the upper face, that are innervated bilaterally, can be recovered in part by ipsilateral corticospinal projections (Vulliemoz et al., 2005). Nevertheless, the available information indicates that spontaneous recovery in injured adults does not reach the same amount as an immature CNS and its robustness require additional treatments (Raineteau et al., 1999), since crossing axons navigate the contralateral destination only during the developmental age. But the reality that a well-developed strategy might reconnect the crossing fibers in adulthood is unclear (Shinbrot & Young, 2008).
1.5.1. Amblyopia: Definition, Etiology, and History

The term Amblyopia (one lazy eye) describes a unilateral deprivation in visual acuity without any pathological signs in the eye ball (Barrett et al., 2004; Astle et al., 2011a, Astle et al., 2011b). It is the most common visual abnormality among children and usually appears unilaterally (Tacagni et al., 2007). There is a range of severity of amblyopia from mild deficits to blindness (Mitchell, 2008). The prevalence of amblyopia has been documented between 0.3% in Nigeria (Megbelayin, 2012) to 5.9% in Nepal (Karki, 2006). While Australia has 1.9% of chance of visual loss (Pai et al., 2012), this number rises to 3% among UK population (Astle et al, 2011a) and 1 to 4% of United States people (Doshi & Rodriguez, 2007). This instability of the prevalence relates to the population, study design and method.

Amblyopia rarely occurs as an isolated condition (Barrett et al., 2004) and is most often associated with anisometropia and strabismus (Astle et al., 2011a; Barrett et al., 2004), where the first shows better prognosis for treatment than the other type, even though, it is undetectable before eye screening for registration at school (Menon et al., 2008). It is not clear whether strabismic amblyopia or anisometric amblyopia is more prevalent (Astle et al., 2011a). Strabismus is a misalignment of visual axes at which the affected eye turns towards or outwards from the midline, while anisometropia is a general definition for unequal refractive power of two eyes. In this condition one eye might be myopia (near sight) and the other one might be hyperopia (far sight) (Barrett et al., 2004).

Two models have been assumed for the etiology of amblyopia (Figure 1.13). The classical model suggests that amblyopia is a concurrent result of anisometropia and strabismus. However, a newly defined mechanism conflicts with the former. Studies on animals and humans have
introduced the possibility that a different relationship exists between these disorders. In this pattern amblyopia can be either the primary or the secondary to the other two visual deficits (Barrett et al., 2004).

Figure 1.13 Two assumptions for etiology of Amblyopia. Figure courtesy of Barrett et al., 2004

Amblyopia is originally a Greek word. It is made up to two roots: *ambly* =dull, and *ops* =vision and was used for the first time in 480 BC by Hippocrates (an ancient Greek physician). He applied a combined pharmacy with natural resources for the treatment including oil, vinegar, water, wine, and minerals. Concurrently, onion and fresh vegetables were recommended as part of the food regimen. High prevalence of blindness among Arab people was a strong motivation for regional physicians to find an appropriate treatment. Thabit ibn Qurrah (836-901), who was living in Turkey at the time, was known as the first physician who introduced the occlusion therapy for strabismus. Over the next years other treatments were suggested, such as using hoods with holes for eyes (Figure 1.14). This method came from the idea that the muscle of the abnormal eye was not strong enough to keep it in the midline and these masks encourage the strabismic eye to look straight. Some surgical methods also were developed to cut the nerve
which innervated the stronger muscle in order to restore the balance between the muscles of the two eyes. Unsuccessful outcomes and arguments against the efficiency of these methods regained the occlusion strategy in 1743 by a French ophthalmologist (Georg-Louis Leclerc).

![Figure 1.14 Wooden hoods were used as a treatment in 1583. Figure courtesy of Loudon and Simonsz, 2005.](image)

Invention of ophthalmoscope at 1850 and examining the retina demonstrated that the structure of most amblyopic eyes is healthy (Loudon & Simonsz, 2005).

Born (1899) who was a member of the Ophthalmological Society of the United Kingdom suggested that atropine can be an effective therapy for mild amblyopia. He also found that as the ratio of the age at the visual ablation relative to the age at the beginning of the treatment increases, the prevalence of the therapy improves. This proposal strengthens the idea of congenital origin of strabismus (Loudon and Simonsz, 2005).

Subsequently, other treatments were suggested such as eyeball massage (1904), diet of wine and veal (1914), Mastisolverband (1927), children’s spectacles (1929), surgically suturing the eyelids (1932), Pleoptophor (1936), self-adhesive material onto the inside of the glasses (1953), Visuskop (1956), Hypnosis (1958), red filter on the spectacle frame (1963), occluding the stronger eye along with using inverted prism in front of the amblyopic eye (1966), and blue filter
(1998). However, the majority of these treatments were abandoned. Low rates of improvement in visual acuity, prolonged duration of the treatments, and the cosmetic situations were considered as the main reasons for this variable history (Loudon & Simonsz, 2005). Currently numerous studies all over the world are emphasizing on the efficacy of the two main treatments: occlusion (with patching), penalization (with atropine).

1.5.2. Neural basis and treatment of amblyopia

Before 1960s nothing was known about the neurogenesis of amblyopia from when Nobel Prize-winners, Hubel and Wiesel conducted several researches on cats and monkeys to present the first insights into neural basis of amblyopia (Barrett et al., 2004). Through a series of studies on monocular deprivation by amblyopia they realized for the first time that the main abnormality was localized in the primary visual cortex (Hubel & Wiesel, 1959). Although some studies believed that the primary deficit for this may be found in the ganglion cell layers in retina (Hess, 2001), the current consensus is that the striate (visual) cortex is the main affected region in amblyopic eye (Barrett et al., 2004). This unanimous consideration is supported by more attention to the results of Hubel’s study on monkey where he indicated that terminals of afferent axons of the geniculate nuclei in layer IV dramatically changed in amblyopic eye (Hubel et al., 1977). Further studies suggest that these changes are followed by abnormal cortical function (Barrett et al., 2004). Moreover, the balance between excitatory and inhibitory connections in strabismic amblyopia is altered (Lowel & Singer, 1992). Therefore, interocular summation is reduced and interocular inhibition is promoted (Webber & Wood, 2005). Furthermore, newer technologies using functional magnetic resonance imaging (fMRI) and localizing the reduced activity of the occipital lobe in amblyopic eye relative to the normal side (Barrett et al., 2004) confirmed the cortical origin of amblyopia. Figure 1.15 compares the activity driven by visual
stimuli in the occipital lobe of the normal eye (Figure 1.15a) with amblyopic eye (Figure 1.15b).

![Image](image.png)

**Figure 1.15** Activity of the occipital lobe recorded by fMRI when an observer looking at the visual stimuli with normal eye (a) and with amblyopic eye (b). Figure courtesy of Barrett et al., 2004.

The ability of temporal processing of spatial frequency is considerably reduced in amblyopic eye, and this deficit is more common in high frequencies (Levi & Harwerth, 1978). Generally, the visual nervous system analyzes different information that it receives from the visual world through spatial frequency context. According to the spatial frequency model, the visual system would be able to analyze the number of cycles of light-dark patches in various visual stimuli. These stimuli might be different in terms of width (narrow or broad), color (light or dark), and direction (vertically or horizontally). **Figure 1.16** shows examples of different visual spatial frequencies in a same horizontal space. **Figure 1.16a** has double the special frequency of the **Figure 1.16b** (Watson & Breedlove, 2012).
Each spatial frequency conducts different information about an image. Low spatial frequency is critical for a rapid recognition of an object which derives a reliable guess about the context frame. However, high spatial frequency represents more detailed information about the edge of an image. **Figure 1.17** compares an original image (middle) with low frequency filtered (left) and high frequency filtered (right) (Bar, 2004).

**Figure 1.16** Comparison of A) high spatial frequency and B) low spatial frequency context. Figure courtesy of Watson and Breedlove, 2012.
As a result of deficiency in temporal processing of high frequencies (Levi & Harwerth, 1978), the amblyopic eye would experience blurry vision and subsequently would interpret the target object based on the estimations and previous experiences rather than the real image (Figure 1.18) (Bar, 2004).

![Input](image1)
![Low spatial frequency filtered](image2)
![Possible identities of the highlighted object](image3)

**Figure 1.18** Estimation of a target object in amblyopic eye. An amblyopic eye has difficulty in spatial resolution, especially in high frequencies. Therefore, the target object would be estimated based on the general frame and previous experiences. Figure courtesy of Bar, 2004.

### 1.5.3. Eye patching concerns

Several conventional treatments depend on the coexistence of impairments with amblyopia (strabismus or anisometropia) are recommended including correcting refractive errors, surgical correction of strabismus, and occlusion of the good eye (Astle et al., 2011a). Among these therapies the last method (patching) is the focus of the present study and is simulated for our participants. Temporary occluding the dominant eye forces the amblyopic eye to capture the images and to transfer the inputs to the target cortical region in order to strengthen the weaker pathways and establishing binocular vision (Webber & Wood, 2005).

There are several concerns in occlusion therapy to be notified such as the most appropriate age for efficiency of this strategy and neural plasticity beyond the sensitive period of development, optimum regimen, split versus continuous patching, and patients’ adherence for the patching.
1.5.3.1. The most appropriate age for effective eye patching and treatment beyond the sensitive period

Development of many sensory systems is restricted within a sensitive period (Pandipati & Schoppa, 2012; Greenough et al., 1987) during which experience manipulates the system anatomically and physiologically (Greenough et al., 1987). Indeed, effectiveness of the treatments in neurophysiological deficits depends on both diagnostic and treatment age (Greenough et al., 1987). Visual acuity improves in the first 6 to 7 months after birth, and binocular fusion begins at 4 months of age (Stager et al., 1990). Given that this development occurs after birth and normally projections from the two eyes compete for the connections at the cortices, any blockage against transferring the inputs from one eye within the developmental age, leads to asymmetrically organization at the CNS. If this deprivation is removed after the sensitive period has passed, the normal binocular function cannot be restored (Stager et al., 1990).

The American Academy of Ophthalmology Preferred Practice Pattern for amblyopia recommends that amblyopia in children must be treated before age 10 (Wu & Hunter, 2006). When amblyogenic conditions are detected before age five years, the prevalence of clinical amblyopia reduces to only two percent suggesting the importance of early screening and treatment of amblyopia before school age (Webber, 2007). Since the upper age of the treatment of amblyopia has not been well recognized, several studies have investigated the effects of eye patching in older children. Visual acuity was improved in about 80% of children between 10-16 years old who had full-time patching along with near visual activities such as coloring and crafts (Erdem et al., 2011). Other studies believe that the neural plasticity in older aged children is based on perceptual learning concept which describes activity-dependent improvements in
performance during a sensory task (Polat et al., 2009; Astle et al., 2011a; Astle et al., 2011b). Perceptual learning is a newly introduced concept that improves the plasticity of visual mechanisms at early cortical stages, such as V1 (Polat et al., 2009). But the degree of the improvement relates to the duration of the training task and the size of the initial deficit; i.e. more deficiency needs further intervention to be an effective therapy (Astle et al., 2011a). Investigations on amblyopic adults indicated that performance in some visual tasks is recovered considerably after training for ten days with duration of 90 minutes with complex and broadband stimuli (Astle et al., 2011b). A question about the preference of eye patching against perceptual learning might be raised. One study compared these two methods and showed that similar improvement in visual acuity would be achieved by either of the methods only if the duration of occlusion is doubled (Chen et al., 2008). In a newly published report dichoptic training suppressed negative effects of amblyopia in adults and restored binocular visual function (Li et al., 2013).

1.5.3.2. Optimum regimen of eye patching

It seems that the success of occlusion therapy in amblyopia with patching the stronger eye depends on the number of hours that eye is patched. The Pediatric Eye Disease Investigator Group (PEDIG) indicated that in moderate amblyopia, a regimen more than 2 hours per day would not have extra benefit (Quinn et al., 2004). However, in severe visual deficit 6 hours of occlusion provided maximum improvement in visual acuity compared to full time patching. The frequency of the treatment was another ambiguous issue among the studies. The researchers in PEDIG conducted studies that addressed the question, and they mentioned that the benefits of weekend treatment for moderate amblyopia were not less than daily performance (Wu & Hunter, 2006). No relation was found between age and required eye patching in children who were
between 3 to 7 years of age and had similar visual acuity (Repka et al., 2005). **Figure 1.19** Shows the changes in visual acuity of an amblyopic eye relative to dose rate (hours/day) suggesting that dose rate greater than 2 hours/day for children between 3 to 8 years of age did not have significant impact on visual acuity (Stewart et al., 2004).

**Figure 1.19** Improvement in visual acuity of amblyopic eye as a function of patching dose rate. Figure courtesy of Stewart et al., 2004.

Visual acuity in amblyopic children with an age of less than 8 years achieved 80% improvement after at least 1.5 month of continuous occlusion. More weeks of treatment (up to 3 months) compromises further improvements (Stewart et al., 2004). However, older children (between 8 to 20 years old) required 3.7 months to achieve the best visual acuity (Menon et al., 2008).
1.5.3.3. **Split versus continuous patching**

A study compared two methods of eye patching in an attempt to assess whether split occlusion has similar effects than continuous patching in children younger than 11 years old. The authors concluded that the binocular vision improves with both methods significantly and children had better compliance with the split method (Sachdeva et al., 2013).

1.5.3.4. **Patients’ adherence for the patching**

When eye patching is prescribed for children it is important to remember that the actual performance is unlikely equal to the recommended schedule (Webber, 2007). So monitoring the compliance of the patients with the treatment enables clinicians to evaluate the effectiveness of the occlusion therapy. One study demonstrated an average performance of 2.8 hours for six hours prescribed patching while children younger than four years old had better function of patching compare to those who were older than six years of age (Stewart et al., 2004). The compliance of this method can be influenced by physical, visual, social, and psychological issues (Wu & Hunter, 2006; Webber, 2007). Patients’ ages and parental understanding of the condition and treatment as well as financial situations were also mentioned as significant impacts on the compliance (Webber, 2007). Most parents and children older than 8 years of age refuse to follow the treatment for cosmetic and psychological reasons (Menon et al., 2008). Therefore, patching therapy is recommended for older children who have enough motivation to follow the treatment (Webber, 2007).
Chapter 2
Methods

This chapter describes participants’ ages, devices, etiologies of hearing loss, and the methods that were used for each evaluation, including: brainstem responses, cortical responses, behavioral evaluations, aural patching performance, and patients’ satisfaction questionnaire.

2.1. Participants

Forty five children with bilateral CIs were recruited for this study and randomly assigned numbers from 1 to 45 (Table 2.1). All children had used a unilateral CI for >2 years before receiving a second implant (CI2) in their contralateral ear. Children received their first implant (CI1) at an average age of 3.2±2.2 years (mean±SD) and experienced a period of unilateral hearing for an average of 9.4±3.0 years, before receiving a second implant. All but three participants received two 24-channel CI devices (Cochlear Corporation). A long inter-implant delay increased the likelihood of receiving a different CI device generation (24M, 24CA, 24RECA, and CI513) on the other side (Table 2.1). Three children were implanted with one 22-channel intracochlear device in one ear. Another three children received the same device type (Nucleus 24RE) bilaterally and experienced shorter inter-implant delay (5.1±1.0 years) than the other 42 children (9.6±2.8 years).

The etiology of deafness was unknown for 22 children (Table 2.1). However, among the 23 children with known etiologies, most had a GJB-2 mutation (n=12) with resulting deficiencies in the gap junction protein Connexin 26. Meningitis at early age (n=2) and hyperbilirubinemia (n=2) were also known to be causes of deafness in a small number of the participants. KID
syndrome, CMV, and ototoxicity were other rare etiologies (n=1 for each) for children with prelingual hearing loss. Of the three children who had progressive hearing loss, one had deterioration in hearing sensitivity from moderately severe at age 1.8 years to profound deafness at age 2.1 years. She experienced 12 months of bilateral acoustic hearing with a conventional hearing aid before receiving her first CI at 3 years of age, at which point she discontinued hearing aid use. The second child had asymmetric hearing sensitivity with profound to moderate hearing loss (rising audiogram) in the better ear which declined to profound hearing loss at age 7.1 years. He was fitted with bimodal devices (CI in one side and a conventional hearing aid on the other side) for 5 years before receiving the second implant at age 11.8 years. The third child wore a pair of conventional hearing aids for four years before receiving his first CI. However, due to symmetrical hearing loss, the second ear could not be aided and he did not use his hearing aid for the opposite ear after cochlear implantation. Computerized tomography scan revealed normal cochlear structure in all children.

Children in this study were asked to remove their first devices for certain time periods each day, following activation of their second implants. These children established aural patching group. The devices were removed for either 2-4 hours (n=17) or 8 hours (n=21) per day. Data collected from the patching group was then compared to data from the control group, in which children were asked to wear both devices for the entire duration of each day (n=7). Furthermore, all children have been involved in rehabilitation program during which they were asked to use only their new implant.

Aural patching performance was monitored with three methods: parents’ reports on pre-printed papers (Figure 2.1), which showed the duration and frequency of patching and the children’s activity during the patching, telephone interviews, and e-mail. The children were encouraged to
do auditory activities during the aural patching, such as conversation, listening to music, reading aloud, etc.

<table>
<thead>
<tr>
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<th>Etiology</th>
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<th>CI2</th>
<th>Inter-implant delay/ bimodal hearing (yrs)</th>
<th>Recommended aural patching regimen (hours/day)</th>
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2.2. Measurements

Auditory processing was evaluated over nine months, beginning immediately after activation of the second implant (day1). Children and parents were given information about the aim of the study and the expected duration of aural patching (0, 2-4, 8 hours per day). They were also provided with a printed timetable defining times they were expected to be in the lab to complete the measurements. Measurements were completed within six sessions and each test was repeated at least two times (Table 2.2). During the first session, baseline measurements of bilateral hearing were taken, while subsequent measurements were expected to indicate whether aural patching had any influence.

<table>
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<th>Week1</th>
<th>Month1</th>
<th>Month3</th>
<th>Month6</th>
<th>Month9</th>
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<td>Loudness growth function</td>
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</table>

Table 2.2 Visits were scheduled according to the above test timetable. Measurements were completed at specified times in the schedule.
All auditory stimuli were delivered through an apical electrode (#20), which corresponds to low pitch sounds. During all measurements and recordings, the children’s speech processors were removed and the stimuli were presented directly to their implants through a research speech processor (SPEAR) (Hearing CRC, Melbourne, Australia).

2.2.1. Electrically evoked auditory brainstem response (EABR)

Auditory brainstem potentials were evoked unilaterally by delivering the electrical pulses directly to the implants on the day following activation of CI2 (day1). The recording of the EABR in day1 was completed for two main purposes: 1) providing a baseline measurement of brainstem responses at the beginning of bilateral hearing experience, and 2) determining bilaterally balanced levels with amplitude-matched responses.

EABR data was collected with a Neuroscan system (NSI, Virginia, USA, version 4.3) and Synamp I (AC/DC) amplifier. In this setup, unilateral brainstem responses were recorded via a surface electrode placed on the middle of the head (Cz) and referenced to an electrode on the ipsilateral earlobe (Cz/A1 for left ear, Cz/A2 for right ear). Electrical biphasic pulses were delivered at 11 Hz using a SPEAR processor. A minimum of 300 sweeps were recorded and averaged for each trial. Individual sweeps with amplitudes beyond ±30 µV were rejected. In cases where the number of rejected sweeps was unusually high, the range of accepted sweeps was increased to ±40 µV. A bandpass filter between 10 and 3000 Hz was used and the responses were averaged in a time window of -5 to 80 ms. Children were awake during the recording and watched a silent movie with closed captioning.

**Figure 2.2a** shows a series of EABRs for CI1 and CI2 (CI-39) as an example and three typical peaks of EABR (eII, eIII, and eV) evoked by CI1 (grey lines) and CI2 (black lines). The
amplitude of these peaks increases as a function of stimulus intensity. Wave eV amplitude was matched in this series of recordings, because it has the largest peak of the EABR and is the most persistent peak in the recordings with different levels. The amplitude of eV was measured as the difference between the peak of eV and the following trough.

Stimuli were first delivered to CI1 from sub-threshold level (160 current unit (CU) in the example Figure) and increased by 10 current units (CUs) until a clear response was recorded (210 CU in the example Figure). In cases where a myogenic response (Cushing et al., 2009) or sign of discomfort was observed, the input level was decreased by 5 CU; CU is a manufacture defined scale for current value, which can be converted to decibels, as described in previous reports (Salloum et al., 2010; Gordon et al., 2012a). In the present study, the CU values were used for data analysis.

The same procedure of EABR recording was followed in CI2 until the eV amplitude of the responses from both sides matched visually. Figure 2.2b depicts changes in EABR amplitude with increasing input levels. The levels that provided matched eV amplitudes (dashed line) are indicated by arrows in this figure. Figure 2.2a-right compares the latency of the two amplitude-matched responses. Even though the amplitudes are similar when evoked from either side, differences in latency of eV peaks between the two implants suggest that neural conduction is faster when stimulation is provided by the first implanted ear than the naïve side. Dashed lines indicate wave eV recorded at each CU.
Figure 2.2 A) CI1 responses (grey lines) and CI2 responses (black lines) of auditory brainstem that were recorded immediately after activation of the second implant. Latency of amplitude-matched responses is compared in the right graph. B) The amplitude of the responses increased relative to the intensity at both sides. The two arrows shows the responses that were matched based on the amplitude.

In order to address the second question of the study and determine the impact of aural patching, EABRs were recorded again after 9 months (10.5±2.1 months) with the levels that established similar amplitudes at day1. Figure 2.3 indicates the responses of the same child from Figure 2.1 at month9.
Figure 2.3 A) EABRs of CI1 (grey lines) and CI2 (black lines) at month9. Right graphs compare the latencies of the two responses. B) The amplitudes of the responses remained consistent with the same input levels.

In this example as shown in the Figure 2.3a-right, the amplitudes of both responses (CI1 and CI2) remained similar and the gap between the eV latencies shortened. Figure 2.3.b shows the similarity of the amplitudes of CI1 and CI2. In the next chapter, further comparisons will be made between wave eV latencies and amplitudes at the two test times.

2.2.2. Auditory evoked cortical responses

Basic information with respect to auditory evoked cortical potentials was provided after one week of bilateral hearing experience and the recordings were subsequently repeated three times, i.e., at month1, month3, and month6 or month9. This part of the study was completed in about one hour during which the children were fitted with an electroencephalography (EEG) cap
containing 64 electrodes. The cap was connected to a Neuroscan system (NSI, Virginia, USA, version 4.3) and Synamp II (AC/DC) amplifier. Conducting gel was used for reducing the impedance between electrodes and scalp surface to less than 10 kΩ. Stimulus and recording parameters are detailed in Table 2.3 and Table 2.4, respectively. These trains evoked cortical responses at 10 CU lower than the levels that provided eV amplitude-matched in EABR recordings. For each recording at least two replicable on-line averaged waveforms were collected. A minimum of 200 sweeps were accepted before the recordings stopped.

| Table 2.3 Stimulus parameters for evoking cortical responses via 64-channel EEG system |
|---------------------------------|-------------------------------|
| Stimulus type                   | Biphasic monopolar            |
| Rate/sec(Hz)                    | 1                             |
| N. of pulses/train              | 9                             |
| Rate/train                      | 250                           |
| Duration(ms)                    | 36                            |
| Pulse width(μs/phase)           | 25                            |
| Inter stimulus interval(ms)     | 964                           |

| Table 2.4 Recording parameters in auditory evoked cortical potentials via 64-channel EEG system |
|---------------------------------|---------------------------------|
| Time window (ms):               |                                |
| Start                           | End                            |
| -200                            | 800                            |
| Amplifier setting:              |                                |
| Low pass filter (Hz)            | 100                            |
| High pass filter (Hz)           | 0.15                           |
| Artifact rejection:             |                                |
| Start (ms)                      | End (ms)                       |
| 100                             | 800                            |
| Min (μs)                        | Max (μs)                       |
| -100                            | 100                            |
| Baseline correction:            |                                |
| Start(ms)                       | End(ms)                        |
| -50                             | 0                              |
Children’s external devices were replaced with a SPEAR’s transmitting coil and the stimuli were delivered unilaterally. Children watched a silent subtitled movie during the recordings. An example of auditory evoked cortical responses collected by 64-electrodes is shown in Figure 2.4. In this example, the stimuli were presented from the left implant (CI2) and Cz response is shown in a box. The top of the Figure shows recordings from the anterior portion of the scalp and the bottom of the Figures indicates the posterior portion of the scalp.

Figure 2.4 Auditory evoked cortical potentials from 64-electrodes in response to the left ear stimuli (CI2). The top of the figure indicates the responses from anterior portion of the scalp, while those of the bottom of the figure correspond to the responses of posterior portion of the scalp. The responses from electrode Cz (shown in a box) will be assessed in the future analysis.

Further assessments in the present study have been focused on the recordings from the electrode Cz, where maximal potential is seen. The reference electrode was placed on the right earlobe. Frequency-modulated (FM) waves, used by the CI transmitting coil to transfer the electrical
information, influence the responses. To minimize this interference, an analog low pass filter with a frequency cutoff of 32 kHz is used.

2.2.3. Behavioral evaluations

Asymmetric function of the auditory pathways due to unilateral hearing deprivation in children who had one cochlear implant for several years before receiving the second implant causes abnormal function in identifying binaural cues (Salloum et al., 2010). In the present study, basic information was acquired from the children’s ability to understand the binaural cues. This information was obtained at 1.3±0.8 months post-activation of the second implant. During this visit, the children completed two behavioral tasks: lateralization of bilateral auditory stimuli by different inter-implant level differences (ILDs) and loudness growth measurements. We also included stimuli with different inter-implant timing differences (ITDs) in the lateralization task. The measurements were repeated at month9 to determine the influence of aural patching.

2.2.3.1. Behavioral lateralization

Children completed the behavioral lateralization task two times. Month1 data provided a baseline of the participants’ ability in lateralizing ILDs and ITDs, and month9 findings assessed the influence of aural patching on this ability. We hypothesized that the currents levels evoking similar EABR eV amplitudes from each ear would provide equal loudness. Therefore, these levels were defined initially as ILD=0. However, in a few participants, as will be discussed later, the levels were adjusted based on behavioral judgments rather than electrophysiological measures.
The task included a presentation block with different ILD and ITD conditions. Tables 2.5 and 2.6 illustrate the conditions for one child (CI-26). The block contained 5 bilateral presentations for ILDs (ILD=20, 10, 0, -10, -20) and 6 bilateral presentations for ITDs (ITD=2000, 1000, 400, -400, -1000, -2000 µs). Negative values denote stimulus conditions that were weighted towards CI1 whereas positive values denote conditions at which the stimulus was weighted towards CI2.

The presentation block was presented 6 times for each child. In short term training trials with unilateral stimuli the children were encouraged to listen to at least three pulses and within a 4-choice task (right side, left side, both sides, or middle of the head), indicated which side the sound was coming from. The unilateral stimuli were used to verify the reliability of the responses. It was assumed that children who responded with ≤50% accuracy to the unilateral presentations did not understand the task and their results were excluded from averaging. Each child completed 78 random trials in approximately 30 minutes.

<table>
<thead>
<tr>
<th>Table 2.5</th>
<th>A typical presentation block in lateralization task (ILD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral presentations</strong></td>
<td>Inter-implant level differences (ILD)</td>
</tr>
<tr>
<td>Implant</td>
<td>CI2</td>
</tr>
<tr>
<td>CI2</td>
<td>220</td>
</tr>
<tr>
<td>CI1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 2.6</th>
<th>A typical presentation block in lateralization task (ITD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bilateral presentations</strong></td>
<td>Inter-implant timing differences (ITD)</td>
</tr>
<tr>
<td>Implant</td>
<td>CI2</td>
</tr>
<tr>
<td>CI2</td>
<td>220</td>
</tr>
<tr>
<td>CI1</td>
<td>0</td>
</tr>
</tbody>
</table>
As mentioned previously, in 10 children, EABR data was not used to determine ILD=0, because clear brainstem responses were not recorded for CI1 and/or CI2. The main reasons for unsuccessful recordings in these children were non-auditory reactions such as myogenic responses and large baseline drifts in the recordings, which made it difficult to accurately measure EABR amplitudes. Alternatively, bilaterally balanced inputs were defined based on behavioral measurements. For this purpose, bilateral inputs were first delivered at equally comfortable CUs and the child was asked to indicate where s/he heard the sound. If the response was towards CI2, the level was increased in CI1 and decreased in CI2 by 5 CU until responses shifted toward CI1 and vice versa. The last levels presented before the response shifted were defined as ILD=0. The data from these children was analyzed separately from the data of the 35 children whose brainstem responses were used to determine ILD=0 at month1.

In the repeated test at month9, consistent levels were used in behavioral lateralization for the majority of children. However, for 12 random participants whose EABR data was used to complete this task at month1, a new balanced level was defined based on their behavioral judgments at month9. The rational for this modification was to allow for a comparison between the two methods (EABR and behavioral) for estimation of the levels at which the bilateral sounds were perceived as balanced for the same children. Therefore, the lateralization task data at month9 was analyzed for three groups (i.e., EABR/EABR, EABR/Behavioral, and Behavioral/Behavioral) based on the method used for estimation of the balanced level at the two test times.
2.2.3.2. Loudness growth perception

Loudness perception of electrical pulses was assessed across the dynamic range (DR) of hearing of each ear independently. In this assessment, the DR was defined as the difference between the behavioral hearing threshold (T-level) and the electrically evoked stapedius reflex threshold (ESRT).

Figure 2.5 indicates the four steps that were followed to obtain the two extremes of the DR for each child. The assessment began randomly from either ear. The electrically-evoked compound action potential (ECAP) of the auditory nerve was recorded (Figure 2.5a) and used to predict T-level values. ECAP thresholds are typically loud enough to be heard by the children (Hughes et al., 2000; Gordon et al., 2002; Potts et al., 2007), and it is therefore expected that T-levels be obtained at lower inputs than ECAP thresholds. Custom Sound EP software version 3.2 (The HEARing CRC Melbourne, Australia) was used for this recording and the pulses were delivered through electrode #20. The responses were recorded from electrode #22, which locates slightly more apical. Morphology of the responses was optimized using various gains and delays to reject the noise from the recordings (Abbas et al., 1999). A pulse width of 25μs and probe rate of 80 Hz were used for all of the children. Stimulus artifacts were excluded from the evoked potentials using the subtraction method (forward-masking paradigm) (Brown et al., 1990). The stimuli were delivered over a range of CU. ECAP recordings started from 30 CU less than the hearing threshold and intensity was increased in 10 CU steps. The recording was stopped whenever any evidence of discomfort was observed in the children. The ECAP threshold (as shown in a box in Figure 2.5a) was defined as the minimum CU that generated an initial negative peak followed by a positive peak. Negative peaks were recorded between 0.3 to 0.5 msec post stimulus onset (Brown et al., 1990).
Figure 2.5 Loudness perception of input levels within a dynamic range (DR) between minimum audible level (T-level) and electrically evoked stapedius reflex (ESRT) was determined in a 4 step procedure: A) electrically evoked compound action potential (ECAP) was recorded by increasing the input levels by 10 CU. The threshold (boxed) was determined where a negative peak was detected on the baseline. B) The stimulus presentation was initiated from ECAP threshold to find T-level and the levels were decreased by 10 CU. The child raised his/her hand in response to the audible sounds. T-level was defined as the lower level of the DR. C) The stimuli were increased from the ECAP threshold until the ESR was visualized on the baseline with 3 small peaks (boxed) to form the upper limit of the DR. D) The derived DR then was divided into 20% steps and made a presentation block for loudness perception task.

Minimum hearing levels (T-levels) (Figure 2.5b) defined the lower extreme of each child’s DR and were determined using a descending bracketing method. That is, the stimulus levels were presented at the ECAP threshold and the children were asked to raise their hands in response to audible sounds. The levels were then decreased by 10 CU each time the stimulus was correctly detected until the sound was no longer heard. They were then increased by 5 CU until a response
was re-elicited. Similar rates and pulse widths to those used in the ECAP recordings were utilized in this measurement. The T-level was defined as the lowest CU level at which the child identified the presence of the stimulus ≥75% of the time.

Previous reports have shown that the stapedius reflex can be used as an objective indicator of the highest comfortable input level for CI users (Hodges et al., 1999). In the current study, the stapedius reflex threshold (ESRT) (Figure 2.5c) defined the upper limit of the DR and was measured with a tympanometer (Madsen, Zodiac 901 Bridge). For this purpose, the probe tip of the tympanometer was placed in the ear canal of the test ear, ipsilateral to the test implant. Three monopolar (MP1+2) electrical pulse trains of 36 ms (250 pulse per second) were delivered at a rate of 1 Hz via electrode #20. Starting at ECAP threshold, the stimuli were increased by 10 CU until three clear peaks (time-locked with the pulses) emerged on the baseline (enclosed in the box in Figure 2.5c). We were able to record ESRs in only a few children (CI1: n=3, 10%; CI2: n=6, 20%). In lieu of the ESR, other indicators were used to define the upper extreme of the DR including: eye blinking that was time-locked to the stimulus presentation, complaining about uncomfortable levels, and reaching the maximum compliance of the electrode. The upper limit of the DR was set 5 CU below the levels of these indications.

The derived hearing DR was divided into 20% steps (Figure 2.5d) to create a block of stimulus presentations for loudness judgments. The levels included 0% (T-level), 20%, 40%, 60%, 80%, and 100% (either ESRT or substituted indicators) of the DR. Furthermore, a control level of 20% below the T-level was included in the presentation block. The block was repeated four times in random order. That is, 28 stimuli were delivered to each implant for a total of 56 loudness judgments. Participants completed the task in 30-40 minutes.
Children indicated their judgment of the loudness of each stimulus using an unmarked printed scale on a white paper. The scale, as shown in Figure 2.6, was a 20 cm length triangle with three short black vertical lines at 5, 10, and 15 cm to show 25%, 50%, and 75% of the line length, respectively. Children were trained to listen to the stimuli, which were repeated three times, and to score their estimation of the loudness by marking a small vertical line on the horizontal scale. The children were told that the narrowest end of the triangle represented the softest sound they could hear, while the widest end represented the loudest sound that they heard. Each judgment was performed on a new printed scale. In turn, the distance (cm) between the children’s mark and the tip of the scale was measured and expressed as a percentage of the entire length of the scale.

![Figure 2.6](image)

**Figure 2.6** Continuous scale for loudness measurement from soft in the left to loud in the right. The scale is a 20cm triangle of which 25%, 50% and 75% of the horizontal length was marked by small vertical lines.

### 2.2.4. Satisfaction questionnaire

Patients’ satisfaction of aural patching was assessed at the last test session (month9) with a pre-printed questionnaire. It contained 10 questions, six of which were quantitative questions, and parents responded to them by marking a continuous scale (Figure 2.7). The questions were as follows:
1) How do you feel to ask your child to do the aural patching?
2) How do you feel to write the reports of the aural patching?
3) How do you feel about your child’s ability to understand speech while using only the new implant?
4) How does your child feel about his/her ability to understand speech while he/she using only the new implant?
5) How do you feel about the number of requested hours for aural patching?
6) How do you feel about staying in the cochlear implant laboratory to do the tests?

While the tip of the scale denoted the *very dissatisfied* condition with 0% value, the wider end of the scale indicated *very satisfied* with 100% value. Three short vertical lines from the tip to the wider end showed *somewhat dissatisfied* or 25%, *neither satisfied nor dissatisfied* or 50%, and *somewhat satisfied* or 75%, respectively. The distance between the parents’ mark and the tip of the scale were measured and converted as percentage.

**Figure 2.7** Continuous scale used in satisfaction questionnaire. Parents were asked to score their satisfaction of the aural patching plan by marking the scale. The tip of the scale had a value of 0%, while the wider end revealed 100% pleasure of the plan.

The seventh question included multiple choice answers and asked for the reason(s) why the child(ren) did not have enough levels of motivation to follow the aural patching. The following items were mentioned as examples for the parents:
- The child was tired after school
- The child did not seem to like the plan
- The child complained about not understanding speech with the new implant
- The child felt stressed when taking the first implant off
- You were worried that your child would not understand speech with the new implant.
- You were too busy to remember to remove the first implant
- You were not confident that this plan would be helpful
- There were difficulties in the hardware or software of the new implant

The parents could add any extra information, whenever necessary.

Question eight asked whether the aural patching was followed most often by the parents or the children.

Question nine asked whether the child was implementing the aural patching most often at home, at school, or at both places.

The last question tried to indicate whether the aural patching was performed most often during the silence or along with an auditory task.
Chapter 3

Results

The first part of this study addressed this question: “Will asymmetry in auditory development and function, produced by unilateral cochlear implant (CI) use, be reduced by providing another implant in the contralateral ear?” We hypothesized that unilateral implant use causes an asymmetry in the auditory pathway that persists with bilateral implant use. We investigated this hypothesis by comparing the function of the two ears via several measurements, including auditory brainstem responses, cortical responses, identifying inter-implant level differences (ILDs), identifying inter-implant timing differences (ITDs), and loudness growth function, each of which will be explained separately.

The second part of the study addressed this question: “Can the asymmetry in auditory development be reduced more efficiently by removing the first implant and wearing the second one alone for periods in a day (aural patching)? We hypothesized that using the second CI alone will improve:

1) development of auditory brainstem and cortical pathways from that ear.

2) detection of binaural timing cues.

3) symmetry of loudness between the two ears.

Investigation of the above hypotheses was completed by comparing the results of the measurements between the two test times during which the children were asked to implement aural patching.
This chapter will first discuss aural patching adherence. Subsequently, it will provide baseline information of every function of the auditory pathway post-activation of second implant and discuss about the findings of the same functions after aural patching. Finally, all changes in outcomes will be assessed with respect to aural patching (Table 3.1).

3.1. Aural patching adherence

Aural patching performance was documented by the children and their parents. They were occasionally interviewed by phone calls to be reminded for doing the plan and writing the reports. Of 38 children initially were decided to participate as patching group, 34 children followed the instructions, the patching data of 2 children were not accessible (CI-32, CI-45); one of the remaining two, was not willing to do the plan and used both implants all day (CI-44) and the other one used the new device less than a month (CI-16). As shown in Figure 3.1 there is a high correlation (R=0.695; p<0.0001) between the duration and the frequency of the aural patching (0 hours/day: n=8; 2-4 and 8 hours/day: n=34).
Figure 3.1 The relation between the duration and the frequency of aural patching in 42 children (including control group).

As it is obvious in the distribution bar graphs and shown in Table 3.1, the average documented duration of aural patching was approximately 2 hours per day with frequency of 4 days per week. This is independent of the requested hours for aural patching.

<table>
<thead>
<tr>
<th>Requested duration of patching (hours/day)</th>
<th>Number of children</th>
<th>Performed duration (mean±SD)</th>
<th>Performed frequency (mean±SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2-4</td>
<td>13</td>
<td>2.1±1.7</td>
<td>4.3±2.3</td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td>2.1±2.0</td>
<td>4.3±2.4</td>
</tr>
</tbody>
</table>
The number of weeks that was mentioned in the patching reports varied between 4 to 51 weeks. To determine the children’s compliance with the patching within the period of study we calculated the average duration and frequency of aural patching per week. Figure 3.2 shows that the average duration of aural patching was consistent over time. However, the number of days of aural patching per week decreases gradually. While in the first three months the frequency of adherence was 3.6±0.9 days per week, this frequency decreased to 2.7±0.7 days per week, following week 12 (p=0.003, r= -0.4).

Figure 3.2 Average ±SD of aural patching adherence over time. A) duration of aural patching over time, B) Frequency of aural patching over time
As shown in Figure 3.3, age of the children at receiving the second implant did not have negative impact on the aural patching performance (duration: $p=0.2$; frequency: $p=0.9$). Although the older children had better compliance with the schedule, no significant difference was found between performance of older and younger children.

![Figure 3.3 Relationship between children’s age at the time of CI2 surgery (n=42) with aural patching duration (top panel), and frequency (bottom panel)](image)

### 3.2. Asymmetric EABR between the two ears

EABRs were recorded for 45 children at day1 and the test was repeated at month9, during which the children were asked to participate in aural patching plan. We aimed to monitor the function
of the brainstem and to determine whether removing the first device and using only the naïve ear to hear could strengthen the pathways from the deprived ear established by unilateral cochlear implant use. This was conducted with parallel studies to compare the eV amplitude and latency between the two sides, as well as two test times. Thirty five children completed this assessment at month9, from which three children had a CI22 in one ear, whose the implant artifact interfered with the EABR responses, and their data was not used for averaging. One child’s implant stopped working (CI-25) at month6 and one child (CI-16) was not willing to use her second implant at early months post-activation. The remaining 8 children left the study at different test times.

A comparison between the grand average wave eVs ±1SE that were matched in amplitude is shown in Figure 3.4a for control group (left panel) and for patching group (right panel). Since one aim of evoking the auditory brainstem potentials was detecting the levels at which the responses of both sides provide similar amplitudes, it is not surprising to find that the bar graphs had the same height in both test times in control group (mean±1SE, CI1\textsubscript{day1}: 1.02±0.27µV; CI2\textsubscript{day1}: 0.99±0.13µV; CI1\textsubscript{month9}: 0.98±0.26 µV; CI2\textsubscript{month9}: 0.93±0.1µV; F(1,5)= 0.08, p=0.8 ). Comparing the amplitudes between CI1 and CI2 responses in patching group also showed similar result, and no significant difference was found between the two test times (mean±1SE, CI1\textsubscript{day1}: 1.09±0.1µV; CI2\textsubscript{day1}: 1.16±0.08µV; CI1\textsubscript{month9}: 1.12±0.12 µV; CI2\textsubscript{month9}: 1.14±0.09µV; F(1,25)= 0.4, p=0.5).

There was a slight difference in eV amplitude between the responses of the two ears. The difference was calculated (CI1\textsubscript{amp}-CI2\textsubscript{amp}) for day1 and month9 and averaged. The result along with individual values was plotted in Figure 3.4b for control group (left panel) and patching group (right panel). As shown in this Figure, the variability in eV amplitude between CI1 and
CI2 did not influence the average values. Paired sample t-test confirmed that the mean difference eV amplitude between CI1 and CI2 at day1 in control group was not significantly different from the mean difference at month9 (mean±SD, CI1\textsubscript{day1}: 0.04±0.1 µV, CI2\textsubscript{day1}: 0.06±0.1 µV; t(5)=−0.276, p=0.8). Similar result was found in the patching group (mean±SD, CI1\textsubscript{day1}: -0.05±0.5 µV, CI2\textsubscript{day1}: 0.03±0.4 µV; t(24)=−0.831, p=0.4).

**Figure 3.4** A) Bar graphs compare the eV amplitudes recorded by CI1 and CI2 at two test times. Grey bars correspond to the findings by CI1 versus black bars which attribute to the findings by CI2. B) eV amplitude difference (CI1-CI2). Unfilled symbols show the individual values at day 1 and month9 tests and filled circles show the mean±1SE of group of children. Data of control group are shown in the left panels, and data of patching group are shown in the right panels.
A second comparison was made, in parallel, between the average eV latencies of CI1 and CI2 that was evoked immediately after activation of the second device and that which was evoked after periods of aural patching. As mentioned in chapter 2, eV amplitude-matched EABRs were recorded earlier, when evoked by CI1 relative to CI2, on the first day of activation of the second implant in all of children.

An independent sample t-test was used to compare the eV latency of the two devices at each test time, separately. **Figure 3.5a** shows the results of this comparison in the control group, and **Figure 3.5b** illustrates the findings in the patching group. Latency of CI1 remained consistent at the two test times in the control group (day1: 3.7±0.2 ms; month9: 3.7±0.1 ms; t(5)=0.0001; p=1), and in the patching group (day1: 3.6±0.03 ms; month9: 3.6±0.04 ms; t(25)=0.23; p=0.8). This pattern was expected, since the experienced brainstem evoked by CI1 has already matured. Therefore, we normalized the changes in CI2-evoked EABRs relative to the first device responses. Repeated measure ANOVA indicated significant difference between CI1 and CI2 responses in day1 and month9 in control group (F(1,5)=0.283, p=0.05). Similar result was also shown in the patching group (F(1,25)=13.808, p=0.001). Bonferroni adjustment was used for multiple comparisons.

**Table 3.2** compares the findings between the two test times. The data from month9 in this Table shows that, irrespective of aural patching, the average gap between latencies of eV evoked by CI1 and CI2 at month9, was persistent and was statistically significant.
Figure 3.5 Comparison of the average of eV latency between devices and between two test times in A) control group, and B) aural patching group.

<table>
<thead>
<tr>
<th>Time</th>
<th>Device</th>
<th>eV latency (Mean±1SE)</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Lower bound</td>
<td>Upper bound</td>
</tr>
<tr>
<td>Day1</td>
<td>CI1</td>
<td>3.61±0.03</td>
<td>3.548</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>3.84±0.04</td>
<td>3.759</td>
</tr>
<tr>
<td>Month9</td>
<td>CI1</td>
<td>3.61±0.04</td>
<td>3.531</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>3.73±0.04</td>
<td>3.644</td>
</tr>
</tbody>
</table>

Wave eV latency difference of the CI2-evoked response between day1 and month9 is indicative of CI2-evoked brainstem development. Using the following formula we calculated the CI2-evoked brainstem changes:

\[(eV_{CI2_{day1}})-(eV_{CI2_{month9}}) = (CI2-evoked brainstem changes)\]

We then determined the relationship between these changes with aural patching adherence, inter-implant delay, and etiology of hearing loss.
Although EABR eV latency evoked by CI2 in 16 of 32 children (50%) of patients improved after 9 months (52% of aural patching group and 40% of control group), Fischer exact test indicated that there was no statistically significant difference between the two groups in term of changes in eV latency (df=1, \( p=0.3 \)). Furthermore, bivariate correlation analyses did not provide evidence of a statistically significant relationship between CI2 brainstem changes and duration of aural patching (\( p=0.6 \)) (Figure 3.6a). A similar result was found when the relationship between the CI2-evoked brainstem changes and the frequency of aural patching was assessed (\( p=0.5 \)) (Figure 3.6b).

![Figure 3.6](image)

**Figure 3.6** A) Relationship between CI2-evoked brainstem changes within 9 months and duration of aural patching, and B) frequency of aural patching.

Given the expanded range of inter-implant delays of participants, i.e., 4.1 to 13.7 years (mean±SD= 9.1±3.0 years), it seemed reasonable to assess the relationship between the change in CI2-evoked brainstem response and the inter-implant delays. As shown in Figure 3.7, no relationship was found between these parameters, suggesting that even lower durations of unilateral hearing in this study group did not elicit greater changes in the brainstem responses than higher durations (\( p>0.05 \)).
Etiology of hearing loss was an additional parameter that might affect the brainstem responses. Two etiologies of hearing loss had higher prevalence among the others including unknown etiologies (n=15) and genetic-related hearing loss (n=9). As shown in Figure 3.8, the average data reveals that changes in CI2-evoked responses among children with GJB2 mutations were greater (0.14±0.2 ms) than other etiologies. However, this difference did not meet the criteria of significance (p>0.05), suggesting that development of CI2-evoked brainstem activity in children after 9 months of bilateral implant use occurred independent of the reason for their hearing deficit.

**Figure 3.7** Relationship between CI2-evoked brainstem changes (within 9 months) and the inter-implant delay.
3.3. Comparisons between cortical potentials evoked by monaural auditory electrical stimuli

We asked whether several years of unilateral deafness affected cortical evoked potentials (CAEP), and if so, whether this could be modified by aural patching. The study was performed at 4 time points for each child. However, the rate of participation was different at every test time, including: week 1 (n=42), month1 (n=27), month3 (n=33), and month6 (n=22). Those who missed their month6 appointment completed the task at month9 (n=13). Week1 recordings provided a baseline of the cortical activity over the unilateral hearing periods. Further recordings were completed to answer our second question in terms of aural patching effects on the asymmetric auditory pathway. Figure 3.9 shows a series of typical 64 channel EEG recording in one child (CI-26) in patching group at the four time points at which the stimuli were delivered unilaterally. In these series of waveforms the recordings of the 64 sensors on the scalp were overlaid and only the response from the vertex electrode (Cz) was highlighted. Further investigations will be focused on findings from the Cz electrode.

Figure 3.8 Comparison of eV latency changes in CI2-evoked responses across different etiologies of deafness.
Figure 3.9 A typical 64 channel EEG evoked responses to the electrical auditory stimuli within first 6 months of bilateral hearing experience. The left series shows the responses when the auditory stimuli were presented to the experienced ear. Two positive peaks are shown which were split by one negative peak. The right series shows the responses when the auditory stimuli were presented to naïve ear. These responses began with one dominant negative peak followed by a large positive peak.
An overview of the responses to the monaural stimuli at week1 indicated that the CAEP evoked by CI2 was highly affected by the several years of unilateral exposure to sound. This was revealed by the morphological difference between the responses evoked by CI1 versus CI2 in all children. The former was characterized by two dominant positive peaks which were split by a negative peak. The amplitude of the positive peaks, as shown in our newly published data (Jiwani et al. 2013), is activity-dependent and its maturity corresponds to the time-in-sound. Conversely, the CI2-evoked responses were initiated with a large negative peak followed by a dominant positive one. This morphology remained stable in our control group (n=8) within the follow up schedule. The responses of the patching group were also found with similar morphology. However, in a small number of participants in the patching group (n=4), this response changed morphologically. That is, the negative peak response was substituted for a positive one within the first 3 months of bilateral hearing experience.

Grand averages of group cortical waveforms at every four test times in response to CI1 and CI2 stimuli were compared in control group (Figure 3.10a) and in the patching group (Figure 3.10b). There was some missing data in these calculations. Number of children were absent at the test time. Non-replicated responses were also excluded from the averaging. Overall, the average graphs for week1 contain responses of 27 children (64.3% of the recordings), for month1 those of 20 children (74.1% of the recordings), for month3 those of 27 children (81.8% of the recordings), and for month6/9 those of 33 children (94.3% of the recordings). The amplitude of grand average responses within a time window of 50 to 300 ms was plotted at each time point. CI1-evoked responses included two positive peaks (P_{ci1}) emerging at 75.9±3 ms and 154.7±12.2 ms (mean±1SE), respectively, which were split by a negative peak (N_{ci1}) at 98.3±4.7 ms; whereas, the first positive peak was not represented in CI2-evoked responses. In these cases it was
initiated by a dominant negative peak ($N_{ci2}$) which was recorded at $101\pm9.9$ ms followed by a large positive peak ($P_{ci2}$) at $165\pm18.4$ ms.

**Figure 3.10** Grand average of CI-evoked responses (grey lines) and CI2-evoked responses (black lines) from the Cz electrode within the time window of 50-300 ms at four time points in A) control group (total n=8), and B) aural patching group (total n= 37). The area difference between the CI1- and CI2-evoked responses is shown by vertical lines at each time point.
Figure 3.11 Grand average of CI1- and CI2-evoked responses of 4 children of aural patching group whose morphology of CI2-evoked responses changed at month3.

The morphology of the average responses to unilateral stimuli (CI1 with grey lines and CI2 with black lines in Figure 3.10) was consistent over time. However, as shown in Figure 3.11 the CI2-evoked responses of 4 children (CI-13, CI-36, CI-39, and CI-40) changed at month3 and a new early positive peak was appeared at 77.7±5.1 ms (mean±1SE) followed by a negative peak at 104±4.7 ms). The average duration of unilateral hearing in these children ±SD was 6.5±0.5 years. They received their second implant at age 8.1±1.1 years of age. All were in the aural patching group, in which the duration of the patching was 2.3±1.03 hours/day with a frequency of 3.8±1.7 days/week. These double positive peaks remained consistent at month6 recording.
Demographic information of the above children is shown in Table 3.3. All of these children had improvement in their eV latency at month9.

<table>
<thead>
<tr>
<th>Children</th>
<th>Etiology</th>
<th>Age at CI2 (yrs)</th>
<th>Duration of unilateral hearing (hrs/day)</th>
<th>Patching duration (days/week)</th>
<th>Changes in eV latency of CI2 (ms) (day1-month9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI-13</td>
<td>Unknown</td>
<td>8.2</td>
<td>6.1</td>
<td>3.6</td>
<td>0.1</td>
</tr>
<tr>
<td>CI-36</td>
<td>Unknown</td>
<td>9.6</td>
<td>7.1</td>
<td>2.5</td>
<td>0.2</td>
</tr>
<tr>
<td>CI-39</td>
<td>Connexin 26</td>
<td>6.8</td>
<td>6.1</td>
<td>1.1</td>
<td>0.2</td>
</tr>
<tr>
<td>CI-40</td>
<td>Unknown</td>
<td>7.8</td>
<td>2.1</td>
<td>2.1</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>Mean±SD</strong></td>
<td></td>
<td>8.1±1.2</td>
<td>6.6±0.6</td>
<td>2.32±1.03</td>
<td>3.8±1.7</td>
</tr>
</tbody>
</table>

In a subsequent experiment to compare the responses from both sides, the area difference between the grand average of CI1-evoked responses and CI2-evoked responses was calculated within a time window between 50 to 300 ms. In order to do this, after calculating the absolute difference between the two side responses, the following formula was used:

\[
\text{Total area difference} = (\text{SUM (amplitude}_{50}: \text{amplitude}_{300}))*2
\]

This is shown by vertical lines between the waveforms of CI1 and CI2 in Figure 3.10b. Repeated measure ANOVA compared these values across the four time recordings among the children who completed all measurements and had replicated responses in cortical recordings (n=9). The analysis of variance revealed that test time impacted significantly on the area difference between CI1-evoked response and CI2-evoked response (F(2.090,16.716)=6.239, \(p=0.009\)). As shown in Table 3.4, the area difference between CI1- and CI2-evoked responses significantly decreased at month3, and the following recordings slightly changed the gap between the waveforms.
<table>
<thead>
<tr>
<th>Test time</th>
<th>Test time</th>
<th>Total area difference (mean±SE)</th>
<th>p-value</th>
<th>95% confidence interval for difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>w1&lt;sup&gt;1&lt;/sup&gt;</td>
<td>m1</td>
<td>1112.2±445.3</td>
<td>0.2</td>
<td>(Lower bound: -437; Upper bound: 2661.5)</td>
</tr>
<tr>
<td></td>
<td>m3</td>
<td>1350.2±383.1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.05</td>
<td>(Lower bound: 17.5; Upper bound: 2682.9)</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>1262.5±410.7</td>
<td>0.1</td>
<td>(Lower bound: -166.2; Upper bound: 2691.2)</td>
</tr>
<tr>
<td>m1&lt;sup&gt;2&lt;/sup&gt;</td>
<td>w1</td>
<td>-1112.2±445.3</td>
<td>0.2</td>
<td>(Lower bound: -2661.5; Upper bound: 437)</td>
</tr>
<tr>
<td></td>
<td>m3</td>
<td>238±319.20</td>
<td>1</td>
<td>(Lower bound: -872.5; Upper bound: 1348.5)</td>
</tr>
<tr>
<td></td>
<td>m6</td>
<td>150.2±356.4</td>
<td>1</td>
<td>(Lower bound: -1082.5; Upper bound: 1390.1)</td>
</tr>
<tr>
<td>m3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>w1</td>
<td>-1350.2±383.1&lt;sup&gt;*&lt;/sup&gt;</td>
<td>0.05</td>
<td>(Lower bound: -2682.9; Upper bound: 17.5)</td>
</tr>
<tr>
<td></td>
<td>m3</td>
<td>-238±319.20</td>
<td>1</td>
<td>(Lower bound: -1348.5; Upper bound: 872.5)</td>
</tr>
<tr>
<td></td>
<td>m6</td>
<td>-87.7±131.2</td>
<td>1</td>
<td>(Lower bound: -544.2; Upper bound: 368.7)</td>
</tr>
<tr>
<td>m6&lt;sup&gt;4&lt;/sup&gt;</td>
<td>w1</td>
<td>-1262.5±410.7</td>
<td>0.1</td>
<td>(Lower bound: -2691.2; Upper bound: 166.2)</td>
</tr>
<tr>
<td></td>
<td>m1</td>
<td>-150.2±356.4</td>
<td>1</td>
<td>(Lower bound: -1390.1; Upper bound: 1089.5)</td>
</tr>
<tr>
<td></td>
<td>m3</td>
<td>87.73±131.2</td>
<td>1</td>
<td>(Lower bound: -368.7; Upper bound: 544.2)</td>
</tr>
</tbody>
</table>

Table 3.4 Repeated measure ANOVA of total area difference (n=9)

Table 3.3 Repeated measure ANOVA compared the total area difference of cortical responses of children who completed the whole measurements (n=9). Maximum change occurred 3 months after using both devices together. 1: Week1 test time, 2: Month1 test time, 3: Month3 test time, 4: Month6 test time. *: Statistically significant

Meanwhile, in order to use all available data, the area difference between the two device responses was compared between every two test times and the trend is shown in Figure 3.12. A paired sample t-test (Table 3.5) indicated that the gap between CI1- and CI2-evoked responses at week1 decreases significantly at the first month of bilateral hearing (week1: 3573.2863±410.2 µVms; month1: 2130.7281±289.8µVms; t(14)=5, p<0.0001). In this series of analyses, α=0.0008 was defined as significant changes. This trend continued until month3, at which the distance between the responses was minimized (month1: 2174.8352±289.8µVms; month3: 1614.2911±177.9µVms; t(14)=2.19, p=0.05), but not considerably different, relative to the first month. The waveforms of the two sides remained distant at month6 (month3: 1575.0644±122.0µVms; month6: 1659.0±124.0µVms; t(21)=0.9, p=0.4). Meanwhile, maximum changes were seen at month3 relative to week1 (week1: 2892.2160±297.0µVms; month3: 1659.0263±113.1µVms; t(19)=5.7, p<0.0001).
Figure 3.12 Comparison of the area difference between CI1- and CI2-evoked responses at 4 test times. Although the gap between the graphs decreased over time, they did not overlap at month 6.

Table 3.5 Paired sample t-test compares the area difference between each pair of test times

<table>
<thead>
<tr>
<th>Test time</th>
<th>Total area difference (mean±SD)</th>
<th>number</th>
<th>t</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>w1</td>
<td>3573.3,1588.7</td>
<td>15</td>
<td>5</td>
<td>14</td>
<td>0.0001*</td>
</tr>
<tr>
<td>m1</td>
<td>2130.7,1122.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w1</td>
<td>2892.2,1328.1</td>
<td>20</td>
<td>5.7</td>
<td>19</td>
<td>0.0001*</td>
</tr>
<tr>
<td>m3</td>
<td>1,659,505.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>w1</td>
<td>2635.9,1188.5</td>
<td>20</td>
<td>4.1</td>
<td>19</td>
<td>0.001</td>
</tr>
<tr>
<td>m6</td>
<td>1647.5,644.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m1</td>
<td>2174.8,1122.3</td>
<td>15</td>
<td>2.2</td>
<td>14</td>
<td>0.05</td>
</tr>
<tr>
<td>m3</td>
<td>1614.3,688.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m1</td>
<td>19,341,028.80</td>
<td>13</td>
<td>0.934</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>m6</td>
<td>1633.3,575</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>m3</td>
<td>1576.1,572</td>
<td>22</td>
<td>-0.896</td>
<td>21</td>
<td>0.4</td>
</tr>
<tr>
<td>m6</td>
<td>1,659,581.50</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

We mainly aimed to determine the impact of aural patching on the auditory evoked cortical responses. Significant changes in total area difference were evident from the first month of the
measurements. Figure 3.13 illustrates the correlation between the total area difference and duration, as well as frequency of aural patching. In this analysis, total area difference between week1/month1 (top panel), week1/month3 (middle panel), and week1/month6 (bottom panel) are shown.

Figure 3.13 Correlation between total area difference and duration and frequency of aural patching. Top panel shows the changes from week1 to month1, middle panel shows the changes from week1 to month3, and bottom panel shows the changes from week1 to month6.
Although the changes in total area difference from week 1 to the following test times were significant, no significant relationship was found between these changes and aural patching performance ($p>0.05$).

In order to determine whether decreasing the area difference between the two device responses related to CI1- or CI2-evoked responses, the Nci-Pci amplitudes in CI2-evoked responses were compared over time. Repeated measurement ANOVA (Table 3.6) indicated that the CI2-evoked amplitudes changed significantly over time ($F(2.24,17.89)=7.909, p=0.003$). The data shows that CI2-evoked amplitude damped dramatically at the third cortical recording (month 3) ($p=0.03$), but at the subsequent test time (month 6), this value did not change significantly ($p=1$). These results suggest that although the morphology of the responses in the naïve ear remained consistent in the majority of children, hearing experience with the new implant drives changes in the cortical regions.

<table>
<thead>
<tr>
<th>Test time1</th>
<th>Test time2</th>
<th>Average difference (test time1-test time 2) (Mean±SE)</th>
<th>p-value</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>W1</td>
<td>M1</td>
<td>9.04±3.3</td>
<td>0.1</td>
<td>-2.377</td>
<td>20.451</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>9.40±2.5</td>
<td>0.03*</td>
<td>0.669</td>
<td>18.126</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>12.8±3.5</td>
<td>0.04*</td>
<td>0.798</td>
<td>24.874</td>
</tr>
<tr>
<td>M1</td>
<td>W1</td>
<td>-9.03±3.28</td>
<td>0.1</td>
<td>-20.451</td>
<td>2.377</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>0.36±2.4</td>
<td>1.000</td>
<td>-7.979</td>
<td>8.700</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>3.80±2.1</td>
<td>0.7</td>
<td>-3.651</td>
<td>11.249</td>
</tr>
<tr>
<td>M3</td>
<td>W1</td>
<td>-9.40±2.5</td>
<td>0.03*</td>
<td>-18.126</td>
<td>-0.669</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>-0.36±2.4</td>
<td>1.000</td>
<td>-8.700</td>
<td>7.979</td>
</tr>
<tr>
<td></td>
<td>M6</td>
<td>3.44±2.5</td>
<td>1.000</td>
<td>-5.290</td>
<td>12.167</td>
</tr>
<tr>
<td>M6</td>
<td>W1</td>
<td>-12.84±3.4</td>
<td>0.04*</td>
<td>-24.874</td>
<td>-0.798</td>
</tr>
<tr>
<td></td>
<td>M1</td>
<td>-3.80±2.1</td>
<td>0.7</td>
<td>-11.249</td>
<td>3.651</td>
</tr>
<tr>
<td></td>
<td>M3</td>
<td>-3.44±2.5</td>
<td>1.000</td>
<td>-12.167</td>
<td>5.290</td>
</tr>
</tbody>
</table>

Table 3.5 Repeated measure ANOVA compares the amplitude of CI2-evoked cortical responses. Significant changes begin 3 months after activation of the second implant.
The average ±SD of Nci-Pci amplitude at every 4 test times is plotted and compared in **Figure 3.14**. Significant differences between the results from week 1 and month 3 responses, as well as week 1 and month 6 responses, are shown by asterisks.

![Changes in CI2 amplitude over time (n=9)](image)

**Figure 3.14** Mean±SD of amplitude of CI2-evoked cortical responses at four test times. Significant changes begin at month 3.

All 9 children who had a complete cortical recording were in the aural patching group. The CI2-evoked amplitude of all but one child (CI-19) (88.9%) damped at the third month. Nonetheless, correlation bivariate analysis did not show a significant relationship between CI2-evoked amplitude changes and aural patching duration ($p=0.3$) (**Figure 3.15a**), and aural patching frequency ($p=0.2$) (**Figure 3.15b**). The amplitude of responses of the child (CI-19), which did not follow similar changes as the other children, decreased at the following recording (month 13).
3.4. Lateralization of binaural cues

In order to address the first question of the present study and understand how binaural cues are used by sequential bilateral CI users, a behavioral lateralization task was conducted within the first month of binaural hearing experience. The evaluations were then repeated at month9 to determine the influence of aural patching on children’s ability to understand the binaural cues.

3.4.1. Inter-implant level difference (ILD)

As was mentioned previously in the methods section, bilateral balanced levels were obtained by recording EABRs immediately after activation of the naïve implant. It was assumed that the levels at which similar eV amplitudes were recorded from both sides are perceived as balanced.

The behavioral lateralization task was completed for 39 children at month1. Three children were absent at the test time, and the other three had an incompatible implant with the test equipment in
one ear (CI22). Figure 3.16a shows a typical response of a child (CI-26) with reliable responses to the lateralization task. Red lines indicate the responses weighted toward CI1 and blue lines represent those weighted toward CI2. Figure 3.16a depicts a typical response of a child who accurately detected unilateral stimuli. The plot clearly indicates that the child successfully identified changes in ILDs; as the input became weighted toward either side (CI1 or CI2), the response proportion increased in that side.

Conversely, Figure 3.16b illustrates inaccurate responses (<50%) of another child (CI-10) to the stimuli presented unilaterally. This indicates that the child may not have understood the task. Such a failure to understand the task was the reason for exclusion of the data of 9 children from
averaging (CI-10, CI-15, CI-20, CI-21, CI-23, CI-24, CI-33, CI-35, and CI-41). Demographic data of these children are shown in Table 3.7.

<table>
<thead>
<tr>
<th>Children</th>
<th>Etiology of hearing loss</th>
<th>Age at CI2</th>
<th>Unilateral hearing with CI1</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI-10</td>
<td>Unknown</td>
<td>7.7</td>
<td>5.1</td>
</tr>
<tr>
<td>CI-15</td>
<td>Unknown</td>
<td>8.7</td>
<td>7.2</td>
</tr>
<tr>
<td>CI-20</td>
<td>Unknown</td>
<td>14</td>
<td>11.5</td>
</tr>
<tr>
<td>CI-21</td>
<td>Unknown</td>
<td>7.3</td>
<td>6.3</td>
</tr>
<tr>
<td>CI-23</td>
<td>Unknown</td>
<td>12.7</td>
<td>8.9</td>
</tr>
<tr>
<td>CI-24</td>
<td>Unknown</td>
<td>11.4</td>
<td>8.8</td>
</tr>
<tr>
<td>CI-33</td>
<td>Meningitis</td>
<td>8.3</td>
<td>7.6</td>
</tr>
<tr>
<td>CI-35</td>
<td>Connexin 26</td>
<td>9.8</td>
<td>8</td>
</tr>
<tr>
<td>CI-41</td>
<td>KID syndrome</td>
<td>10.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>10±2.3</td>
<td>8.1±1.8</td>
</tr>
</tbody>
</table>

Given the low rates of middle and both responses among the 4 choices in the lateralization task, they were excluded from the averaging and only right and left responses were used for this assessment. Further analyses were performed by plotting cumulative Gaussian curves using a bootstrap procedure to describe the response probability toward CI1, regardless of its side (right/left). Each plot was obtained using SPSS, version 20 for each individual. As has been discussed elsewhere (Salloum et al., 2010; Gordon et al., 2012b), the point of 50% on the Gaussian curve was considered to represent equally balanced levels in the bilateral presentations (i.e. there was an equal probability of the child responding left or right). Distribution of the equal probability was then assessed to find the corresponding ILD levels at which balance occurred.

Equal response probability (50% response rate) was assessed by plotting a cumulative Gaussian curve for each child, as shown in Figures 3.16c and 3.16d. It was expected that as the ILDs shifted from the most positive (CI2-weighted) to the most negative (CI1-weighted) amounts, the
CI1 response probability would increase from 0 to 1. In this regard, 0.5 on the y-axis indicates equal response probability at which the bilateral stimuli are heard as balanced (i.e. not weighted to either ear). The dashed line on the Gaussian curve (Figures 3.16c) shows that equal probability of left and right responses occurred at negative ILDs (ILD= -6.1); i.e. the child needed higher CI1 input levels than those of CI2 to perceive the bilateral inputs as balanced. In fact, the levels that were assumed to be bilaterally balanced were CI1-weighted (in bilateral presentation).

The plot for the unsuccessful children in the task was recorded as a roughly flat line (Figure3.16d) at which no changes were shown in the response probability with respect to the changes in ILDs. This was the second exclusion criteria for 8 children in averaging data (CI-3, CI-6, CI-8, CI-14, CI-22, CI-25, CI-36, and CI-39). Therefore, the data of total 17 children were not used for averaging.

As mentioned previously, bilaterally balanced levels (ILD=0) between ears were determined primarily using the “eV amplitude matching method”, but also using the “behavioral judgments method” in those for whom electrophysiological responses were not available. Figure 3.17a shows the mean values of the responses (EABR approach: n=13; Behavioral approach: n=9) and Figure 3.17b indicates CI1 response probabilities collected with these methods at month1.
Figure 3.17 Lateralization task and determining the balanced level with “eV amplitude match method” (on left) and “behavioral method” (on right). A) Mean changes in CI1 and CI2 levels in a stimulus presentation block for lateralization task. Red line shows mean of CI1-weighted responses. Blue line shows mean of CI2-weighted responses. Unilateral stimuli (shaded columns) were included for verification of reliability of the responses and were excluded from further analysis. B) Response probability toward CI1 was plotted with Gaussian curve. 0.5 indicates the responses which were not weighted to either side. Individual responses are represented by grey lines and the averaged point (mean±SD) is shown by a black dot.

Cumulative Gaussian curves also were plotted for each individual (Figure 3.17b). Grey lines indicate the responses with significant changes across ILDs, while orange lines show the responses that did not change significantly across the ILDs. The average ILD at which an equal probability of left and right responses occurred is depicted by a black filled circle and is highlighted via dashed lines for both methods. These lines show that equal probability of left and right responses occurred at a negative value when the balanced level was estimated by EABR measurement (ILD= -5.5±9.9); i.e. the children needed higher CU for CI1 than CI2 to judge the bilateral inputs as balanced. In fact, the levels that were assumed to be bilaterally balanced
(based on EABR data), were CI1-weighted (in bilateral presentation). In the alternative behavioral judgment method, equal numbers of responses were given at ILD = 0.07±5.6, suggesting that children are able to establish accurate balanced levels behaviorally when EABR data is not available.

Upon statistical comparison of the values from both methods, there was no significant difference between the two procedures in terms of the levels that were estimated to be balanced ($p=0.2$).

In order to address the second question of the study and to determine whether aural patching improved the identification of ILDs and ITDs, the lateralization task was scheduled to be repeated at month9. Out of 45 total participants, 42 children had compatible implants (CI24) with this task. Twelve children were absent at the last test time, and 30 completed this part of the study at month13.6±18.2. Similar exclusion criteria as month1 defined the outliers. Accordingly, 6 children’s data were excluded from averaging: 4 did not understand the task and the responses of the other 2 had no significant changes across ILDs. As mentioned previously, children were initially (at month1) divided into two groups in terms of estimation method of the balanced level. For one group, these levels were set based on eV amplitude match, while for the other group, these levels were set based on behavioral judgment. A previous published study (Gordon et al., 2003) indicated that as the time-in-sound increases, wave eV is recorded earlier and its amplitude significantly increases. In order to determine whether the amplitude growth impacts bilateral balanced level, we divided the first group of children in this part of the study into two new subgroups, randomly at the follow-up study. While the first subgroup (n=10) were presented with similar levels as were used at month1 (defined as EABR/EABR), in the second subgroup (n=12), the bilateral stimuli were balanced behaviorally (defined as EABR/Behavioral). There
were also 9 children at month1 whose balanced level was estimated behaviorally (defined as Behavioral/Behavioral). In “EABR/EABR” group, one child (CI-36) did not have accurate responses to the unilateral presentations, and the responses of another child (CI-10) did not change significantly across ILDs. The data of these two children were excluded from averaging. In the “EABR/Behavioral” group, two children (CI-15, CI-20) had inaccurate responses to the monaural electrical pulses. The “Behavioral/Behavioral” group excluded two outliers, one of which did not understand the task (CI-33) and the responses of the other one (CI-40) did not change significantly across ILDs.

**Figure 3.18a** shows the mean (±1SE) responses of these three groups of children to the pulse stimuli across ILDs. The left and right graphs show the responses of children who were presented with similar sound levels as month1, through eV amplitude matching and behaviorally judgment, respectively. The middle graph depicts the responses of the group of children whose balanced level was established behaviorally at month9. **Figure 3.18b** illustrates the cumulative Gaussian curve for each group of children.
Figure 3.18 A) Mean±SE of the responses across ILDs at month9. Left and right graphs show the responses of children for whom similar sound levels as month1 were used for each ear to complete this test. The middle graph depicts the responses of children whom the balanced level were again estimated at month9 behaviorally. They were already (month1) presented with stimuli that provided matched eV amplitudes. B) Cumulative Gaussian curves for each individual were plotted for each group. Black data points on the plots show the Mean±SD of 50% CI1 response probability. Dashed lines indicate the ILDs at which the balanced levels occurred.

Even though 6 children, whose data were not used at month1, were absent at month9, the number of children who successfully conducted the test increased at month9 (successful: 56.4% at month1; 80.6% at month9), and only 6 children were excluded from this analysis (outliers: 43.6% at month1 vs. 19.4% at month9). Table 3.8 compares the levels at which the sound was perceived as balanced at the two test times. An unpaired t-test indicated that similar balanced levels were achieved by both methods. This finding was consistent at the two test times (month1: $p=0.15$; month9: $p=0.65$).
We also compared the results of each method between the two test times with paired t-tests. Irrespective of the method that was used for defining the balanced level, there was no significant difference between the two test times ($p>0.05$). Table 3.8 shows the details of the analysis.

<table>
<thead>
<tr>
<th>Table 3.8</th>
<th>Comparison between the measured balanced levels based on two estimation methods at two test times (month1 and month9). The average values were determined based on cumulative Gaussian curves.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test time</td>
<td>Balanced level estimation method (month1/month9)</td>
</tr>
<tr>
<td></td>
<td>EABR/EABR</td>
</tr>
<tr>
<td></td>
<td>ILD Mean±SD (n)</td>
</tr>
<tr>
<td>Month1</td>
<td>-5.50±9.99 (13)</td>
</tr>
<tr>
<td>Month9</td>
<td>-5.84±12.43 (8)</td>
</tr>
<tr>
<td>Paired t-test</td>
<td>t(3)=0.42, $p=0.7$</td>
</tr>
</tbody>
</table>

CI1-weighted responses across ILDs were compared between two test times. Table 3.9 shows the details of paired t-test analyses at each ILD. Since a significant difference was not found between the mean CI1 response probability of children who had initially behavioral estimated balanced level and those who were newly added to this group at every ILD ($p>0.05$), the data of the total behavioral group was used for the next comparison. As shown in Table 3.9, mean of CI1 responses to each ILD remained consistent at the two test times ($p>0.05$). This result was similar for the two approaches for estimation of balanced levels.
### Table 3.9 Comparison of CI1 response probability (%) across different ILDs at two test times for both balanced level estimation methods

<table>
<thead>
<tr>
<th>Balanced level estimation method</th>
<th>Test time</th>
<th>Mean±SE CI1 responses (%) across Inter-implant level differences (ILDs)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>20 ((n))</td>
<td>10 ((n))</td>
<td>0 ((n))</td>
<td>-10 ((n))</td>
<td>-20 ((n))</td>
</tr>
<tr>
<td>EABR/EABR</td>
<td>Month1</td>
<td>0±0 ((4))</td>
<td>0±0 ((4))</td>
<td>8.25±8.25 ((4))</td>
<td>54±10.46 ((4))</td>
<td>83.25 ±16.75 ((4))</td>
</tr>
<tr>
<td></td>
<td>Month9</td>
<td>0±0 ((6))</td>
<td>4.25±3.80 ((5))</td>
<td>0±0 ((6))</td>
<td>46±14.18 ((5))</td>
<td>80±8.85 ((6))</td>
</tr>
<tr>
<td></td>
<td>Paired t-test</td>
<td>0</td>
<td>t(3)= -1, (p=0.4)</td>
<td>t(3)=1, (p=0.4)</td>
<td>t(3)=0.3, (p=0.8)</td>
<td>t(3)=0.0001, (p=1)</td>
</tr>
<tr>
<td>EABR/Behavioral</td>
<td>Month1</td>
<td>6.25±4.36 ((8))</td>
<td>20.88±8.19 ((8))</td>
<td>30.25±12.49 ((8))</td>
<td>64.13±11.46 ((8))</td>
<td>77.88±7.83 ((8))</td>
</tr>
<tr>
<td></td>
<td>Month9</td>
<td>12.5±8.18 ((8))</td>
<td>15.3±5.80 ((10))</td>
<td>53±8.13 ((9))</td>
<td>81.6±9.48 ((10))</td>
<td>89.5±6.26 ((8))</td>
</tr>
<tr>
<td></td>
<td>Paired t-test</td>
<td>t(5)= -1.35, (p=0.2)</td>
<td>t(7)=0.56, (p=0.6)</td>
<td>t(6)= -2.26, (p=0.06)</td>
<td>t(7)=2.1, (p=0.07)</td>
<td>t(5)= -1.31, (p=0.2)</td>
</tr>
<tr>
<td>Behavioral/Behavioral</td>
<td>Month1</td>
<td>3.75±3.75 ((8))</td>
<td>19.5±7.60 ((8))</td>
<td>45.88±12.47 ((8))</td>
<td>79.63±5.04 ((8))</td>
<td>93.38±4.51 ((8))</td>
</tr>
<tr>
<td></td>
<td>Month9</td>
<td>0±0 ((7))</td>
<td>21.57±9.99 ((7))</td>
<td>35.71±12.93 ((7))</td>
<td>64.29±11.48 ((7))</td>
<td>92.86±4.61 ((7))</td>
</tr>
<tr>
<td></td>
<td>Paired t-test</td>
<td>t(6)=1, (p=0.4)</td>
<td>t(6)= -0.33, (p=0.8)</td>
<td>t(6)=0.31, (p=0.8)</td>
<td>t(6)=1.65, (p=0.2)</td>
<td>t(6)= -0.14, (p=0.9)</td>
</tr>
</tbody>
</table>
3.4.2. Inter-implant timing difference (ITD)

Each presentation block of the lateralization task included stimuli with both ILDs and ITDs. Therefore, the results of ITD lateralization will be explained similar to those of ILD lateralization. Figure 3.19 shows the average responses of children to the stimuli with different inter-implant timing differences measured at month1. The average responses of children whose bilateral balanced levels were estimated by matching eV amplitudes are shown in Figure 3.19a-left, and the data of children whose balanced levels were determined according to the behavioral judgments are shown in Figure 3.19a-right. Mean ±1SE of CI1 responses to the stimuli across ITDs indicated that irrespective of the method of estimation the balanced level, none of the children realized changes in ITDs from the most positive (CI2-weighted) to the most negative (CI1-wighted) values at the first month of bilateral hearing experience (CI1 response probability (eV amplitude matching group) +2000: 15.8±8.8% versus -2000: 14.2±7.0%; (behavioral judgment group) +2000: 44±10.5% versus -2000: 59.6±6.4%). Cumulative Gaussian curves (Figure 3.19b) also show steady rate of weighted responses toward one side across ITDs. This finding was independent of the method that was used for estimation of the balanced levels. Interestingly, comparison of the Gaussian curves between the two methods indicated that CI2 responses were more prevalent than CI1 responses when the balanced levels were set based on EABR findings. However, participants of the other group tended to point to the sides more often by chance (i.e.: +2000: CI1: 44±10.5%, CI2: 56±10.5; +1000: CI1: 51.1±7.9%, CI2: 48.9±7.9; +400: CI1: 45.3±8.2%, CI2: 54.7±8.2; -2000: CI1: 59.6±6.4%, CI2: 40.4±6.4%; -1000: CI1: 48.4±9.1%, CI2: 51.6±9.1%; -400: CI1: 44.9±13.4%, CI2: 55.1±13.4%). This might be due to using larger step sizes in EABR recordings for assessment of the bilateral balanced levels compared to the behavioral judgments, thereby leading to a less accurate estimation in the former approach.
A) Mean±SE responses in ITD lateralization at month1 for children whose balanced levels were estimated based on eV amplitude matching (left graphs), and for children whose balanced levels were estimated based on behavioral judgment (right graphs). B) Cumulative Gaussian curves for the same two groups show CI1 response probability across ITDs.

ITD lateralization task was repeated at month9 to assess the impacts of binaural hearing and aural patching on ability of understanding this binaural cue. As mentioned in ILD results, a new subgroup was delineated from the EABR group at month9 in terms of estimation of bilateral balanced levels. In this newly established subgroup, inter-implant timing differences were provided for the levels at which perceived bilaterally balanced according to behavioral judgments. Figure 3.20a depicts Mean±1SE of responses weighted to either side (CI1 or CI2) across ITDs for EABR/EABR group (left plot), for EABR/Behavioral group (middle plot), and for Behavioral/Behavioral group (right plot). At this test time the children were offered only two choices (right vs. left) for lateralization of the sounds.
The responses accumulated on the side of CI2 in the first group (n=8) (+2000: 81.13±9.18%;
+1000: 75±8.92%; +400: 79.13±9.36%; 0: 64.43±15.69%; -400: 75.13±10.87%; -1000: 70.88±9.34%; -
2000: 72.88±9.96%). This result was roughly repeated for Behavioral/Behavioral group (n=7)
(+2000: 72.17±13.25%; +1000: 57.14±10.10%; +400:54.71±14.30%; 0: 64.63±11.98%; -400:
45.14±13.84%; -1000: 52.57±9.23%; -2000: 45.29±8.77%). The newly established balanced level at
month9 (EABR/Behavioral group) (n=10) also did not change the principal result and the ability
to understanding the inter-implant timing difference still remained unsuccessful.

**Figure 3.20** A) Mean±1SE responses in ITD lateralization at month9 for children whose balanced levels were
estimated based on eV amplitude matching (left graphs), for children whose balanced levels were estimated based
on behavioral judgment (right graphs), and for children who estimated their balanced level behaviorally at month9
(middle graphs). (B) Cumulative Gaussian curves for the same three groups show CI1 response probability across
ITDs.
Figure 3.20b shows the individual cumulative Gaussian curve for all three groups with grey lines, suggesting an inability to understanding the ITDs. However, the data of two children (EABR/Behavioral: CI-13; Behavioral/Behavioral: CI-34) in the behaviorally balanced groups are shown via orange lines. Although the number of CI1-weighted responses in these children changed as the stimuli led toward CI1, this change was not statistically significant (CI-13: p=0.06; CI-34: p=0.09). Both children were in the aural patching group; the first one (CI-13) followed the patching instructions with duration of 3.6 hours/day and a frequency of 4 days/week. Her bilateral profound hearing loss was diagnosed 4 months after birth and the etiology of deafness was unknown. She received her first implant at age 2.1 years old and 6.1 years later was implanted in the opposite ear. She used one pair of conventional hearing aid for less than a year prior her candidacy for cochlear implantation. Parents of the second child (CI-34) reported a good compliance of aural patching with duration of 4 hours/day and frequency of 6-7 days/week (not documented). She was a full term baby at her birthday who suffered from hyperbilirubiniemia. Her hearing deficit was diagnosed at age 2.3 years old with moderate steeply sloping to profound hearing loss bilaterally. She used hearing aid before receiving the first implant for about 5 years. The second implant for the other ear was provided sequentially with 4 years inter-implant delay.

Two purple lines in the cumulative Gaussian curves of the Behavioral/Behavioral group in Figure 3.20b show the findings for other 2 children (CI-42, CI-44) who were successfully identified ITDs. Interestingly, one of these two children (CI-42) participated as control group and was not asked to participate in aural patching. He used both implants all the time over the 9 months duration of the study. He was born as a premature baby with hyperbilirubinemia, low birth weight and mild cerebral pulsy. He was diagnosed with a severe to profound bilateral
sensorineural hearing loss 7 months after birth. But hearing aid trial indicated sufficient evidences of development in speech and language. Therefore, his cochlear implantation was postponed to about 7 years later. He wore his first implant for 4.2 consecutive years before receiving the second implant for the opposite ear.

The second child (CI-44) however, was in the aural patching group and was asked to wear only his new implant for a duration of 8 hours/day. However, he was not willing to follow the plan and instead, wore both implants together. His hearing impairment was diagnosed one year after birth. Responses of visual reinforcement audiometry (VRA) indicated a moderate to moderately-severe hearing loss in at least the better ear leading to prescription of one pair of hearing aids. However, due to deterioration of his hearing performance and his dependency to sign supports rather than oral communication, eventually he met candidacy criteria for cochlear implantation at age 6.5 years. He experienced unilateral hearing for 6 years before receiving another implant on the second ear. It seems that acoustic hearing experience prior to electrical stimulation via CI device provides a positive foundation for identifying ITDs.

In cumulative Gaussian curve, \( p < 0.05 \) indicates the ability to understand the ITD. **Figure 3.21** illustrates the relation between the \( p \)-value with aural patching duration (left panels) and frequency (right panels). The values of the children’s data with orange and purple Guassian curves are shown with the same color codes in the following data points. There are some other small \( p \)-values that were not highlighted in this Figure. These children had more responses toward CI2 rather than CI1 in negative ITDs.
Figure 3.21 Regression linear between p-values cumulative Gaussian curve and aural patching performance. Left panels related to the duration of aural patching, while, right panels related to the frequency of aural patching.

3.5. Loudness growth perception

As mentioned in chapter 2, loudness growth was assessed across hearing DR at month1. Lower and upper limits of the DR were defined based on T-level and ESRT, respectively, each of which was measured at both ears. Forty three children completed this part of the study at month1
(month 1.33±0.75), of which, one child (CI-33) did not have accurate responses to the behavioral tasks and his data were excluded from averaging. ECAP was not recorded clearly in a few children (n=4) while 3 participants did not have compatible implants (CI22) with ECAP software in one ear. We tried to record ESRT ipsilateral to the implants. However, this response could only be evoked in a limited number of children (n=15). Instead, other indications such as facial stimulation (FS), maximum compliance (MC), and uncomfortable loudness (UCL) were substituted and the sound level was decreased by 5 CU from these indications to determine the upper limit of the DR. For nine children even the maximum available level (239 CU for CI22 and 255 CU for CI24) was comfortable. Table 3.10 compares the results of these measurements between CI1 and CI2. The data of shaded cells were used to define the DR.

<table>
<thead>
<tr>
<th>Implant</th>
<th>ECAP$^1$ (n)$^9$</th>
<th>T-level (n)</th>
<th>Total indications$^2$ (n)</th>
<th>ESRT$^3$ (n)/(%)</th>
<th>FS$^4$ (n)/(%)</th>
<th>MC$^5$ (n)/(%)</th>
<th>UCL$^6$ (n)/(%)</th>
<th>NR$^7$ (n)/(%)</th>
<th>DR$^8$ (upper extreme - lower extreme) (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI1</td>
<td>186.14±19.25 (35)</td>
<td>165.52±20.43 (42)</td>
<td>235.22±14 (41)</td>
<td>220±18.03 (3)(7.3)</td>
<td>232.5±16.96 (6)(14.6)</td>
<td>240±15 (3)(7.3)</td>
<td>211.58±11.19 (21)(51.2)</td>
<td>248±9.74 (0)(19.5)</td>
<td>69±20.21 (41)</td>
</tr>
<tr>
<td>CI2</td>
<td>158.05±17.42 (41)</td>
<td>145.67±15.03 (42)</td>
<td>220.4±17.39 (42)</td>
<td>211±14.79 (12)(28.6)</td>
<td>200±17.32 (4)(9.5)</td>
<td>226.25±7.5 (5)(11.9)</td>
<td>227.25±14.37 (20)(47.6)</td>
<td>235 (1)(2.4)</td>
<td>74.8±22.67 (42)</td>
</tr>
<tr>
<td>P-value</td>
<td>0.0001*</td>
<td>0.0001*</td>
<td>0.0001*</td>
<td>0.393</td>
<td>0.02*</td>
<td>0.042*</td>
<td>0.302</td>
<td>0.52</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Table 3.10 Mean±SD components of hearing DR measured via CI1 and CI2 at month1. The DR was measured by subtracting the values of shaded cell in the Table.
1- ECAP: electrically evoked compound action potential
2-Total indications: all indications used as upper limit of dynamic range
3- ESRT: electrically evoked stapedius reflex
4- FS: facial stimulation
5- MC: maximum compliance
6- UCL: uncomfortable loudness
7- NR: no response
8- DR: dynamic range
9- n: number of ears
* statistically significant
Among the children whose ECAP was not recorded, the etiology of hearing loss was unknown (n=3) and genetic mutation (n=1). The average age of these participants was 14.7±3.5 years old and they had reliable responses in behavioral threshold evaluation. As shown in Table 3.10, FS and MC among the alternative indications for upper limit of the DR were significantly different between the two ears, i.e. facial nerve tended to be stimulated with lower levels in the newly implanted side compare to the experienced ear (p<0.05). Meanwhile, the second implant reached the maximum compliance or saturation level earlier than the first implant (p=0.05). These situations might limit the functional levels needed for contraction of the stapedius muscle. Nevertheless, the rate of evoked reflex via CI2 was more than that of CI1 (12 vs. 3). Given a significant difference between the lower extreme of the DR (F(1,82)=25.731, p=0.0001) and the upper extreme (total indications) of the DR (F(1,81)=18.102, p=0.0001) between CI1 and CI2, the derived DR was not statistically different (F(1,81)=1.516, p=0.22).

Figure 3.22a shows the mean loudness growth perception (±1SE) by CI1 and CI2 over the defined DR. This Figure includes the average responses of 41 children at month1 and shows that the sound is heard louder by CI2 versus CI1 across the DR.
Figure 3.22 A) Mean±1SE loudness growth by CI1 (grey line) and CI2 (black line) over the DR at month1 measured for 41 children. B) Comparison the slope of loudness growth at low % of the DR and high % of the DR between CI1 and CI2. There is a statistically significant difference between CI1 and CI2 in terms of loudness growth at low % of the DR.

Table 3.11 indicates the details that were calculated with repeated measure ANOVA to show the changes of loudness perception by CI1 and CI2 across the DR. The values indicate that the children perceived increasing input levels at both sides (CI1: F(6,240)=266.842, p=0.0001; CI2: F(6,240)=369.48, p=0.0001).
### Table 3.11 Repeated measure ANOVA compares loudness perception of each step of DR between CI1 and CI2 at month1 (n=41)

<table>
<thead>
<tr>
<th>Input level (% of DR)</th>
<th>CI</th>
<th>Loudness perception (% of visual scale) (Mean±SD)</th>
<th>p-value</th>
<th>95% Confidential interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower bound</td>
</tr>
<tr>
<td>-20</td>
<td>CI1</td>
<td>0.56±0.99</td>
<td>0.64</td>
<td>0.24</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>0.71±1.90</td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>0</td>
<td>CI1</td>
<td>4.82±4.75</td>
<td>0.17</td>
<td>3.33</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>6.40±5.59</td>
<td></td>
<td>4.64</td>
</tr>
<tr>
<td>20</td>
<td>CI1</td>
<td>12.78±7.08</td>
<td>0.17</td>
<td>10.54</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>15.17±8.61</td>
<td></td>
<td>12.45</td>
</tr>
<tr>
<td>40</td>
<td>CI1</td>
<td>20.19±10.0</td>
<td>0.0001*</td>
<td>17.03</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>30.46±11.89</td>
<td></td>
<td>26.71</td>
</tr>
<tr>
<td>60</td>
<td>CI1</td>
<td>32.97±15.25</td>
<td>0.0001*</td>
<td>28.16</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>48.50±16.42</td>
<td></td>
<td>43.32</td>
</tr>
<tr>
<td>80</td>
<td>CI1</td>
<td>53.59±18.04</td>
<td>0.02*</td>
<td>47.89</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>63.29±17.86</td>
<td></td>
<td>57.66</td>
</tr>
<tr>
<td>100</td>
<td>CI1</td>
<td>69.27±18.29</td>
<td>0.1</td>
<td>63.50</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>75.89±17.21</td>
<td></td>
<td>70.46</td>
</tr>
</tbody>
</table>

Comparison the values of loudness at each test point between the two implants indicated that there is a significant separation at 40% of the DR between CI1 and CI2 ($p=0.0001$) continued at 60% ($p=0.0001$), and decreased towards the higher levels (80%: $p=0.02$, 100%: $p=0.1$). This result indicated that there is not a consistent and linear growth of loudness across the DR. Given that our previous analysis (Table 3.11) showed that there was not a significant difference between the hearing DR of right and left ears, the different perception of the loudness between the two sides might be related to the slope of the loudness growth. In order to address this hypothesis, and with respect to the significant separation of loudness perception between the two sides at 40% of DR, we divided the DR of each individual into two parts including lower percentage of the DR between 0% and 40%, and higher percentage of the DR between 40% and 100% (as shown with vertical dashed lines in Figure 3.22). A trend line was plotted among all
responses of each individual and its slope was measured. Then, a grand average of the data at both low and high percentage of the DR was calculated. **Figure 3.22b** compares these data, indicating the individual slopes with open symbols (square and triangle) and mean±SD with filled circles. T-test analysis compared the slope of loudness growth at low and high part of the DR and indicated a statistically significant difference between these slopes when the sound was presented only from CI1 (low % of the DR: 0.39±0.20; high % of the DR: 0.84±0.32; \(p=0.0001\)), suggesting that the loudness perception grows faster at the higher levels. Although a similar result was obtained at the side of CI2 (low % of the DR: 0.61±0.25; high % of the DR: 0.76±0.26, \(p=0.01\)), this difference was not as large as that of CI1, suggesting that the loudness grows quickly, even at low input levels at the newly implanted side. Comparing the average values between CI1 and CI2 indicated that perception of sound level grows considerably faster by CI2 than CI1 at the beginning of the DR (\(p=0.0001\)). A brief increment in input level drives a huge change in loudness perception in the naïve ear. On the other hand, loudness perception grows with a similar rate at the higher input levels for both CI1 and CI2 (\(p=0.21\)).

We proposed that this asymmetric perception of sound levels was occurred due to several years of unilateral hearing, and we asked whether aural patching could improve this abnormality. In order to answer this question, all of the above measurements were repeated with the same sequence at month9. **Table 3.12** summarizes the details of prerequisites of loudness growth evaluations and compares the components between CI1 and CI2. The average data, as shown in this Table, indicate that ECAP, T-level, and total indications of upper limit of the DR were obtained with significantly higher input levels by CI1 than by CI2. This result is similar to those of month1, suggesting that removing the first implant while wearing only the new device on the opposite ear for periods in a day is unlikely to impact on psychophysics perception of the sound.
Table 3.12 Mean±SD components of DR measured by CI1 and CI2 at month9. The DR was measured by subtracting the values of shaded cells in the Table. Asterisks show the statistically significant difference between CI1 and CI2.

ESRT was successfully evoked in 12 children at the second evaluation by delivering the electrical stimuli through CI2; 6 children (18.2%) found the sound uncomfortably loud at the first visit before the reflex was evoked. Interestingly, all of these children were in the aural patching group, and the average duration and frequency of patching that was documented by these participants were 2.5±2.1 hours per day and 5.9 days per week, respectively. These responses were evoked with significantly lower levels of CI2 (224.2±13.2 CU) than CI1 (231.7±15.7 CU), (p=0.01). However, the average DR was approximately similar at both sides (p=0.4). Demographic information of these children is shown in Table 3.13.

Table 3.13 Demographic information of children with evoked ESR at month9

<table>
<thead>
<tr>
<th>Children</th>
<th>Etiology of hearing loss</th>
<th>Patching duration (hours/day)</th>
<th>Patching frequency (days/week)</th>
<th>CI1 (CU)</th>
<th>CI2 (CU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CI-4</td>
<td>Unknown</td>
<td>2.3</td>
<td>6</td>
<td>210</td>
<td>210</td>
</tr>
<tr>
<td>CI-5</td>
<td>Progressive</td>
<td>6</td>
<td>7</td>
<td>220</td>
<td>220</td>
</tr>
<tr>
<td>CI-18</td>
<td>Connexin 26</td>
<td>0.4</td>
<td>3</td>
<td>230</td>
<td>215</td>
</tr>
<tr>
<td>CI-20</td>
<td>Unknown</td>
<td>1.3</td>
<td>7</td>
<td>255</td>
<td>245</td>
</tr>
<tr>
<td>CI-23</td>
<td>Unknown</td>
<td>4</td>
<td>7</td>
<td>240</td>
<td>235</td>
</tr>
<tr>
<td>CI-29</td>
<td>Meningitis (at 7 mo)</td>
<td>1</td>
<td>5.4</td>
<td>235</td>
<td>220</td>
</tr>
<tr>
<td>Mean±SD</td>
<td></td>
<td>2.5±2.1</td>
<td>5.9±1.6</td>
<td>231.7±15.7</td>
<td>224.2±13.2</td>
</tr>
</tbody>
</table>
Loudness growth perception again was assessed at month9 with the new defined DR. Figure 3.23 shows the mean±1SE of the children’s judgment against every 20% divisions of the DR at month9. Thirty three children completed this measurement. But the data of one child, because of inaccurate responses during the test, was excluded from averaging.

Figure 3.23 A) Mean±1SE loudness growth by CI1 (grey line) and CI2 (black line) over the DR at month9 measured for 32 children. B) Comparison of loudness growth slope at low % of the DR and high % of the DR between CI1 and CI2. There is a statistically significant difference between loudness perception at low and high % of the DR at both sides.
Repeated measure ANOVA compared the loudness across the DR for CI1 and CI2, and Table 3.14 provides description statistics for both sides. The details of Table 3.14 and Figure 3.23 show that as the input levels increased, the sound was perceived louder. Even though, the average data ±1SE reveals that the asymmetry in loudness between the two ears is still persistent and the sound is heard louder by CI2 than CI1 at every 20% steps of the DR at month9.

<table>
<thead>
<tr>
<th>Input level (% of DR)</th>
<th>CI</th>
<th>Loudness perception (% of visual scale) (Mean±SD)</th>
<th>p-value</th>
<th>Lower bound</th>
<th>Upper bound</th>
</tr>
</thead>
<tbody>
<tr>
<td>-20</td>
<td>CI1</td>
<td>0.58±0.22</td>
<td>0.59</td>
<td>0.14</td>
<td>1.03</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>0.41±0.22</td>
<td></td>
<td>-0.04</td>
<td>0.86</td>
</tr>
<tr>
<td>0</td>
<td>CI1</td>
<td>4.91±0.76</td>
<td>0.23</td>
<td>3.39</td>
<td>6.42</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>6.21±0.76</td>
<td></td>
<td>4.7</td>
<td>7.73</td>
</tr>
<tr>
<td>20</td>
<td>CI1</td>
<td>12.4±1.32</td>
<td>0.18</td>
<td>9.76</td>
<td>15.04</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>14.94±1.32</td>
<td></td>
<td>12.29</td>
<td>17.58</td>
</tr>
<tr>
<td>40</td>
<td>CI1</td>
<td>20.62±1.94</td>
<td>0.31</td>
<td>16.74</td>
<td>24.49</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>23.43±1.94</td>
<td></td>
<td>19.56</td>
<td>27.3</td>
</tr>
<tr>
<td>60</td>
<td>CI1</td>
<td>29.79±2.4</td>
<td>0.05</td>
<td>24.99</td>
<td>34.58</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>36.47±2.4</td>
<td></td>
<td>31.67</td>
<td>41.27</td>
</tr>
<tr>
<td>80</td>
<td>CI1</td>
<td>49.39±3.03</td>
<td>0.06</td>
<td>43.35</td>
<td>55.44</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>57.69±3.03</td>
<td></td>
<td>51.64</td>
<td>63.73</td>
</tr>
<tr>
<td>100</td>
<td>CI1</td>
<td>67.29±2.78</td>
<td>0.19</td>
<td>61.74</td>
<td>72.84</td>
</tr>
<tr>
<td></td>
<td>CI2</td>
<td>72.48±2.78</td>
<td></td>
<td>66.93</td>
<td>78.03</td>
</tr>
</tbody>
</table>

To answer the second question of the study and to determine whether aural patching was an effective approach to decrease the asymmetric loudness between the two ears, the findings of both time points were compared. In this respect, the difference of loudness perception between CI1 and CI2 at every 20% of the DR was measured at month1 as well as month9. The results
were compared with paired t-test and indicated that the gap between CI1 responses and CI2 responses in terms of loudness score, decreased at month9. The value was significant at higher level of the DR compare to the lower levels (-20%: t(31)=0.62, p=0.5; 0%: t(31)=0.55, p=0.5; 20%: t(31)=0.96, p=0.3; 40%: t(31)=2.4, p=0.03*; 60%: t(31)=3.83, p=0.001*; 80%: t(31)=2.46, p=0.02*; 100%: t(31)=2.41, p=0.02*). **Figure 3.24** shows the loudness growth function by CI1 (left panel) and by CI2 (right panel) at month1 (solid line) and at month9 (dashed lines). These graphs indicate a steady psychoelectric perception of the sound by the experienced ear rather than the naïve ear at which more duration of hearing decreased the loudness. The details of these statistical comparisons are provided in **Table 3.15**.

**Figure 3.24** Loudness growth function across the DR by CI1 (grey lines) and CI2 (black lines) at month1 (solid lines) and month9 (dashed lines). The sound perceived softer at month9 at the higher % of the DR, and the trends of loudness growth tended to be similar at both sides.
Table 3.15 Comparison of loudness perception by CI1 and CI2 between month1 and month9 measurements. Asterisks show significant changes.

The data in Table 3.15 indicate that maximum changes occurred at 40% and 60% of the DR leading to changes in the slope of loudness growth at lower DR (between 0% and 40%). From 32 participants in this part of the study, 25 children followed the aural patching from which 72% indicated smaller slope of the loudness growth at month9 than the first visit. Using the following formula we statistically analyzed the data and found that there was no correlation between changes in loudness score at the second ear with aural patching duration ($p=0.6$) and frequency ($p=0.8$) (Figure 3.25).

“CI2 loudness slope at low % of DR$_{\text{month1}}$ - CI2 loudness slope at low % of DR$_{\text{month9}}$ = CI2 loudness slope changes”

| Implant | T-test |  |  |  |  |  |  |  |
|---------|--------|---|---|---|---|---|---|
| CI1     |        |   |   |   |   |   |   |
| month1  |        |   |   |   |   |   |   |
| (n=41)  |        |   |   |   |   |   |   |
| 0.56±0.2| 4.8±0.7| 12.8±1.1| 20.2±1.6| 33.0±2.4| 53.6±2.8| 69.3±2.9|   |
| month9  |        |   |   |   |   |   |   |
| (n=32)  |        |   |   |   |   |   |   |
| 0.58±0.3| 4.9±0.7| 12.4±1  | 20.6±1.8| 29.8±2.4| 49.4±3.1| 67.3±3.1|   |
| p-value |        |   |   |   |   |   |   |
| 0.9     | 0.9    | 0.8 | 0.9 | 0.4 | 0.3 | 0.6 |   |
| t       | -0.092 | -0.08| 0.245| -0.182| 0.933| 0.994| 0.468|
| df      | 71     | 71  | 71  | 71  | 71  | 71  | 71  |
| CI2     |        |   |   |   |   |   |   |
| month1  |        |   |   |   |   |   |   |
| (n=41)  |        |   |   |   |   |   |   |
| 0.71±0.3| 6.4±0.9| 15.2±1.3| 30.5±1.9| 48.5±2.6| 63.3±2.8| 75.9±2.7|   |
| month9  |        |   |   |   |   |   |   |
| (n=32)  |        |   |   |   |   |   |   |
| 0.41±0.17| 6.2±0.8| 14.9±1.6| 23.4±2.1| 36.5±2.4| 57.7±2.9| 72.5±2.4|   |
| p-value |        |   |   |   |   |   |   |
| 0.4     | 0.9    | 0.9 | 0.9 | 0.01*| 0.001*| 0.2 | 0.4 |
| t       | 0.824  | 0.154| 0.114| 2.511| 3.332| 1.375| 0.914|
| df      | 71     | 71  | 71  | 71  | 71  | 71  | 71  |
Figure 3.25 data points illustrate changes in slope of low % of the DR for CI2 (month1-month9) against the duration of aura patching (left panel), and frequency of aura patching (right panel).

Furthermore, the relation between changes in loudness slope at low DR and etiology of deafness is shown in Figure 3.26. Y-axis reveals CI2 loudness changes. As shown in this Figure, the majority of the participants of this test became deaf with unknown etiology (n=16), while genetic mutation was the reason of hearing loss in 9 children. Our assessment indicated that hearing experience with the new implant provided greater developmental changes in perceptual function of the latter group (0.2±0.3) which was not statistically significant (p=0.4).
Figure 3.26 Distribution of etiology of hearing loss among the participants of loudness growth measurement at month 9. Y-axis shows average changes (mean±SD) of CI2 loudness slope at lower % of the DR (month1-month9).

3.7. Children and parents satisfaction of aural patching

Parents were asked to complete a satisfaction questionnaire on their last visit. The answers of 6 questions with visual scale were expressed as percentage and plotted in Figure 3.27. X-axis of this graph matches with the scores of visual scale and depicts from 0% as dissatisfied to 100% as very satisfied. The Figure summarizes average ±SD of the answers of 21 parents and the number of responses to each question. Some of the questions were not responded. The bar graphs are shown relative to the visual scale that was used for each question.
Some of the questions were not responded. Each question included a visual scale to be scored by the parents. The tip of the scale shows the minimum (0%) and the wider end shows the maximum (100%) satisfaction.

We also assessed the relation between the above answers with the aural patching performance. **Figure 3.28** illustrates the relation between each question against the aural patching. The left panel shows the distribution of the answers to each question with unfilled circles and the mean±SD of the responses with filled symbols. The right panels includes two groups of data to show the relation between each questions satisfaction score with aural patching duration (the middle panel), and aural patching frequency (the most right panel). So, each row of the data is related to one question.

---

**Figure 3.27** Mean±SD scores of satisfaction questionnaire (n=21). Some of the questions were not responded. Each question included a visual scale to be scored by the parents. The tip of the scale shows the minimum (0%) and the wider end shows the maximum (100%) satisfaction.
As shown in the left panel of Figure 3.28, there was a wide range of responses between 0 to 100% to each question. But even 100% satisfaction did not guarantee the aural patching performance. Interestingly, parents who believed that the new implant would develop the speech and language skill of their children, followed the aural patching more efficiently \((r=0.5; p=0.05)\).

The parents also were asked by a multiple choice question about the reason(s) for which their child(ren) did not have enough level of motivation to follow the aural patching as was requested. The answers were averaged and were plotted in Figure 3.29.
Figure 3.29 Major reasons for low level of motivation to follow the aural patching plan by the children or parents (n=21)

An average of all scores of the questionnaire indicated total satisfaction of aural patching. A total score of 66.6±5.9% indicates that more than half of the participants adhered to the plan and were motivated to improve their hearing skills with the new device.

From 21 answers to question 8 of the questionnaire we noticed that in majority of cases (62.5%) parents reminded the children to remove the first implant.

We recruited 19 answers from question 9 that revealed that 78.9% used the new device alone only at home. One child used only at school and the other one only in the weekends.

Two children (10.5%) did not like to do auditory activities by the new device and preferred to work in silence during the aural patching.
Chapter 4

Discussion

This study mainly focused on asymmetric function of the central auditory pathways in deaf children with bilateral cochlear implants (CIs) who wore one implant for a long period of time before receiving a second implant in the other ear. We hypothesized that this asymmetry would persist for at least a year of bilateral hearing due to the long time period between receipt of the two implants. The study was initiated by evaluating a variety of auditory skills upon the initial activation of the second implant in the naïve ear, in order to provide a baseline measurement of these skills. The persistent asymmetry in the central auditory function was shown by assessment of our control group.

The next part of the study aimed to determine whether removing the first implant in the experienced ear while hearing only through the second implant in the naive ear for periods of time during the day (aural patching) would strengthen the neural pathways in these children. We hypothesized that aural patching would promote auditory development in the naïve ear, which would be reflected in the auditory evoked brainstem potentials, auditory evoked cortical responses, understanding the binaural cues, and loudness growth function. Therefore, all of the initial evaluations were repeated at different time points while the participants followed a patching schedule. The findings were compared in two stages, including comparison between the experienced and naive ears (to assess asymmetric function), and comparison across time points (to show the impacts of aural patching on this asymmetry).

At the end of the study, the psychosocial issues regarding the aural patching were evaluated by a satisfaction questionnaire.
4.1. Changes in the auditory brainstem pathway is not related to the aural patching

Auditory evoked brainstem responses (ABRs) indicate synchronous activity of different generators of the ascending neural pathway. These source dipoles were initially detected by near-field recordings during neurosurgical operations. Comparison of the responses from these intracranial locations with responses from far-field recordings revealed the neural generators of ABR (Burkard et al., 2007, Chapter 16). Irrespective of the evoking stimulus (acoustical or electrical), the auditory nerve generates waves I and II, and the stimulus travels toward the cochlear nucleus to produce wave III. Relays through the lateral lemniscus and inferior colliculus, the inputs create waves IV and V (Gordon et al., 2006). Wave V is the largest and more reliable peak wave among the other brainstem evoked responses and shows the activity in the rostral portion of the midbrain (Burkard et al., 2007, Chapter 6). Therefore, we mainly focused on changes of wave V and recorded the brainstem activity with electrical stimuli (EABR).

For bilaterally deaf children who experienced several years of unilateral hearing with a CI before receiving a second implant, our findings (Figure 3.5, Table 3.3) indicated that eV is significantly delayed in the responses of the newly implanted ear immediately after initial device activation compared to the eV evoked on the more experienced side. The delay was persistent after nine months of bilateral hearing in our control group who were full-time user of both implants. This result, along with the previously published studies (Gordon et al., 2007a; Sparreboom et al., 2010), shows that the evoked potentials of the auditory brainstem is recorded faster through the experienced ear comapre to the newly activated ear, suggesting that development of the rostral portion of the brainstem is activity-dependent. Furthermore, when there is an absence of hearing in one ear for a long duration of time, auditory input to the
working ear develops the ascending neural pathway asymmetrically (Gordon et al., 2006). However, when the deaf side is activated by another CI, a different trend of developmental plasticity occurs in the new brainstem (Gordon et al., 2007a; Gordon et al., 2007b). In this case, the dominant ear restricts changes in the new brainstem pathway (Gordon et al., 2007a; Gordon et al., 2007b) and negatively affects the neural conduction of the contralateral side (Gordon et al., 2007a; Gordon et al., 2007b; Gordon et al., 2011). One proposed mechanism for mammalian brain development is dependence on experience (Greenough et al., 1987). This was also shown in previously reported studies on central auditory pathways (Gordon et al., 2003). However, earlier evidence in children who also received two CIs sequentially indicated that even chronic bilateral time-in-sound did not resolve the asymmetric maturation at the level of the brainstem (Gordon et al., 2007a; Gordon et al., 2007b; Gordon et al., 2008; Gordon et al., 2011).

In the present study we hypothesized that ignoring the input from the previously implanted ear and exposing the new ear with sound would strengthen the immature brainstem. It is expected that this maturation is revealed by decreasing the evoked potentials’ peak latency and increasing the peak amplitude (Sparreboom et al., 2010). Repeated EABR measurements after 9 months of bilateral implant use indicated that this asymmetry was reduced in approximately half of the participants, suggesting that the neural activity increased myelination and improved synaptic efficacy (Gordon et al., 2007). Such changes is normally occur at early ages (Harrison et al., 2005). Consequently, this activity induces faster neural conduction along the pathway, and underlies a sensitive or critical period at which the neural pathway has a greater degree of synchrony (Gordon et al., 2003).

Even though there were changes in eV latency in about 50% of children of patching group (with an age range between 8-18 years old) and 40% of control group, no statistical difference was
found between these two proportions, and no significant correlation was found between these changes with the children’s patching regimen (Figure 3.6). These results suggest that aural patching unlikely restores the asymmetric function of the auditory brainstem.

Parallel studies in amblyopic children indicated that visual acuity in 47% of these children with an age range between 7 to 17 years old improved (Scheiman et al., 2005). Furthermore, occlusion therapy of the poorer eye improved visual acuity in a more limited age range (10 to 16 years old) (Erdem et al., 2011), only if the patients cooperate properly and are sufficiently compliant, suggesting that the quality and quantity of expected experience determines the reorganizational pattern of the developing brain (Greenough et al., 1987).

Furthermore, we found that the children with a shorter inter-implant delay did not have a greater improvement in brainstem development in the naïve ear (Figure 3.7) compared to those with longer duration of inter-implant delay. This finding can be explained by activity dominance of the first ear and abnormal plasticity caused by several years of unilateral hearing (Gordon et al., 2006; Gordon et al., 2007a; Gordon et al., 2007b).

Our participants, on average, followed the patching approach up to 2 hours per day. However, treatment of more severe deficiencies in a sensory system, such as an amblyopic eye, require a more intensive regimen (Stewart et al., 2011; Quinn et al., 2004). Therefore, it seems that a more intensive approach might be more successful for our purposes.

Twenty-seven percent of our participants who were evaluated by EABR had a genetic related hearing loss, with a mutation in the GJB2 gene. These children showed more, but not significant, plastic changes in the auditory brainstem compared to children without a GJB2 mutation. Given that residual hearing in GJB2-related hearing loss at the apical turn of the cochlea (which
is correspond to the electrode #20) is less than in non-GJB2 hearing loss (Propst et al., 2006), improvement in the rostral brainstem in these children (shown by shortening wave eV latency) may have appeared larger than the other participants. We also found that the initial asymmetry between the eV latency from the first and second implants \((eV_{\text{CI1}}-eV_{\text{CI2}})\) measured at initial activation of the second implant (day1), was larger among the children with genetic related deafness compared to those with unknown etiology of hearing loss. (Genetic hearing loss: 0.3±0.3 ms; unknown etiology: 0.2±0.2 ms).

### 4.2. Cortical responses affected by bilateral hearing experiences

Cortical auditory evoked potentials (CAEPs) were measured during the first six months after activation of the new implant. It was expected that the morphology of these evoked potentials would change within the first 6 to 8 months after implantation, as was previously shown in unilateral implantation (Sharma, et al., 2002a; Sharma et al., 2002b). CAEPs in our participants, as shown in Figure 3.9 and Figure 3.10, had different morphologies in each ear. Although two positive peaks appeared in the responses of the first implanted ear \((P1_{\text{ci}}-N1_{\text{ci}}-P2_{\text{ci}})\), the evoked potentials of the naïve ear began with a large and dominant negative peak \((N_{\text{ci}}-P_{\text{ci}})\). This morphology was consistent across the test times. Ponton and Eggermont (2001) suggested that a mature response appears in normal hearing children after 10 years of hearing experience. However, the participants in the present study were deprived from hearing in the implanted ear for more than 7 years. We attempted to induce plastic changes in the cortical responses evoked by the newly activated ear via aural patching, but our effort to record a classical \(P1_{\text{ci}}-N1_{\text{ci}}-P2_{\text{ci}}\) complex from the newly implanted ear was not successful in majority of the children.
The dominant negative peak is also recorded in cortical responses of bilateral deaf children with unilateral cochlear implantation shortly after activation of their device; however, auditory experience with CI causes rapid neural plasticity and diminishes the peak amplitude in these responses (Sharma et al., 2002b). Instead of this negative peak, an early positive peak appears within the first week of CI activation and after 8 months of time-in-sound, the morphology becomes similar to that of an age-matched normal hearing child (Sharma et al., 2002b). Emergence of this positive peak indicates that maturity of layers III and IV axons is starting (Burkart et al., 2007) in the lateral portion of Heschel’s gyrus (Ponton et al, 2002). Our participants had a duration of unilateral hearing experience with their first CI in a range between 4.1 to 14.9 years before receiving the second implant. Therefore, it is not surprising to observe the variability in the waveforms between the ears at the initial activation of the naïve side (i.e., P1_{ci}-N1_{ci}-P2_{ci} in the first ear, and N_{ci}-P_{ci} in the second ear). Recordings from our control group, who used both devices full-time for 9 months, indicated that the chronic exposure to sound would not reorganize the abnormal cortical function.

We hypothesized that eliminating the dominant ear from hearing and delivering the sounds only through the newly implanted ear would provide plastic changes in the central pathway. As shown in Figure 3.11 morphology of the responses in four children was changed and a new early positive peak was appeared in the third visit for cortical recording. Given that all of these children followed the patching plan, the first reason for this morphologic change might be due to their adherence with this approach. However, this claim might not be supported strongly for two reasons. First, due to the number of children there is not sufficient evidence to approve the contribution of patching adherence in the morphologic changes. Second, the early positive peak (P1) requires at least 10 years of hearing experience to be elicited even in normal hearing.
children (Ponton & Eggermont, 2001). This was also shown in CI users with 10 years of time-in-sound (Jiwani et al., 2013). It is worth noting that these children had an average duration of unilateral deafness of 6.6 years (Table 3.4). We know from previous data that cortical plasticity occurs faster in children with CIs than in age-matched normal hearing children (Sharma et al., 2002b). The short duration of deafness in the above children might explain the driven neural plasticity. Meanwhile, in all of these children EABR eV latency decreased over time. This could be explained by similar time course in maturation of P2 and wave V in normal development (Burkart et al., 2007).

There were also four more children in the patching group who had a range between 4.1 to 6.7 years of unilateral hearing and their aural patching report were available, but did not have any change in morphology of their cortical potentials. The reason for this inter-subject variability is not clear at this time, but it might be due to variability in maturation of cortical responses in children who received a CI between 3.5 to 7 years old (Sharma et al., 2009). Overall, only 50% of children with the shortest duration of unilateral deafness in the present study showed plastic changes in cortical potentials, but because of small number of these children it is hard to decide whether these changes were due to the aural patching.

Related studies that evaluated visual evoked potentials (VEP) indicated variable discussions in term of efficiency of these responses in individuals with amblyopia. VEP is the gross electrical signal generated by the occipital cortex as a result of visual stimuli (Datta et al., 1998). Therefore, its results are comparable with auditory evoked cortical responses. Light is used as a visual stimulus to evoke the pattern VEP (pVEP) which has small amplitude but delayed latency in an amblyopic eye compared to a normal eye (Chung et al., 2008). One study indicated that even a successful clinical result of occlusion is not necessarily reflected in a VEP, and the central
visual pathway indicates asymmetric neural conduction in amblyopic and fellow eyes of 7 to 11 years of age (Watt et al., 2002). In contrast, Chung and colleagues (2008) claimed that VEP efficiently predicts outcomes of occlusion therapy, and that a greater decrease in latency of P100 resulted in a greater improvement of visual acuity (Chung et al., 2008).

Our findings indicated that the N_{ci}-P_{ci} amplitude of the CAEP diminishes as hearing experience increases (Figure 3.13), whereas the pVEP increases in amplitude as the treatment improves the visual acuity (Chung et al., 2008). This comparison suggests that the initial dominant negative peak in the CAEP is an immature response, and the decreasing amplitude reveals the improvement of cortical function across the aural patching period. However, a six month follow up evaluation of this evoked potential did not show strong evidence that the N_{ci} is going to be replaced with a P1_{ci} (except the four children with shorter inter-implant delay). There is no consensus information at this time about the origin of N_{ci}, but P1 originates from cortical deep layer III and IV axons (Ponton & Eggermont, 2001), and normally matures after a decade of hearing experience (Burkart et al., 2007, Jiwani et al., 2013). This maturation occurs along with an increase in the amplitude. The absence of this positive polarity of cortical activity even after the aural patching in the majority of children may be due to a longer maturational process required by these layers (Ponton et al., 2001) in the newly activated hemisphere.

4.3. Binaural cues

The role of binaural cues (ILD and ITD) for localizing sound sources and facilitating speech perception in noisy environments has been well documented (Litovsky et al., 2006; van Hoesel 2004). Delayed bilateral implantation restricts normal binaural fusion. Even though these CI recipients have two active ears to hear, they may be deprived from some benefits of binaural
hearing. Similarly, experiments on amblyopic eyes also suggest that the absence of binocular interaction in this visual deficit also may result in difficulties in mismatching the images coming from each eye (Birch, 2013).

The relative dominance of binaural cues is different between normal hearing individuals and CI users. While the ITD plays the most important role in sound localization for normal hearing individuals (Seeber & Fastl, 2008), its importance is decreased for CI users, and alternatively, the ILD plays the major role for this latter group of listeners (Seeber & Fastl, 2008; Grantham et al., 2008). The reason for importance of ILDs for CI users in sound localization may be attributed to consistent sensitivity to this cue rather than ITD across the electrode array (Seeber & Fastl, 2008). However, other experiments indicated that adult CI users who were unsuccessful in detecting timing cues had greater difficulty localizing the sound in free field relative to those who were able to detect the ITDs (Schoen et al., 2005).

4.3.1. One month of bilateral hearing experience allows children to identify inter-implant level differences (ILD)

A behavioral lateralization task was completed in 39 children one month post-activation of the new device. As mentioned in chapter 2, a balanced level in 75% of the children was predicted by matching the eV amplitude elicited from both ears, while the remaining children behaviorally judged the balanced level, as was done already by the other researchers (Litovsky et al., 2010). More than half of the children (56.4%) successfully lateralized bilateral stimuli using ILD cues. This result conflicts with previous findings suggested that more than six months of hearing with bilateral devices in sequential CI users was required to enable children older than 5 years to localize the sound (Galvin et al., 2007). The success of our experiment might be attributed to the use of electrical stimuli presented directly to the implants rather than acoustic sounds presented
via loudspeakers, as in Galvin’s study. While we delivered the stimuli with a defined ILD, the
binaural cues (ILDs and ITDs) were not seperated in Galvin’s experiment. Meanwhile, their
participants were using their own speech processor with a daily program, and experienced
asymmetric loudness with them. In the present study, only 23% of the participants were unable
to undersatand the task, which may be attributed to the variability in achieving early binaural
skills.

Comparison of the mean cumulative Gaussian curve of ILD task after one month of bilateral CI
use showed a slight difference between EABR-based and Behavioral-based groups (Figure
3.17). Equal response probability to either the right or left responses was occurred at negative
ILDs leading toward CI1 in the EABR-based group (Figure 3.17b), suggesting that the children
needed higher CI1 input to perceive the bilateral sounds equally with both ears. However, in the
Behavioral-based group this point was very close to zero. Perhaps this difference occurred due to
the large steps of current (10 CU) that were used in the electrophysiological measurments,
leading to missing the fine changes in the waveforms. On the other hand, smaller step sizes (5
CU) were used in the Behavioral-based group.

In the lateralization task in month1, about 40% of the children were excluded from the average
and statistical analysis, because of inabilty in understanding the task or partial ability of doing
the task. However, a similar study that was completed in our laboratory had only 21% outliers
due to their unreliable lateralization of the unilateral stimuli (Salloum et al., 2010). Given that the
participants in that study had approximately two years of bilateral hearing experience, it seems
that more auditory activity with two ears allows children to complete this task with a higher
degree of confidence.
This was confirmed with our findings at nine months post-activation of CI2. At this later test time children were more familiar with the concept of the binaural cues, and only six children (19%) were excluded from the statistical analysis with similar reason as month1, from which all but two were in the patching group. In fact, these children did not achieve the ability of lateralization of the inter-implant level differences. This number of outliers may be explained by inter-subject variability, insufficient patching regimen, or their limited hearing activity during the patching. Similarly, the role of active and attentive vision in treatment of amblyopia has been previously mentioned (Birch, 2013). Another reason for an inability to perform this task may be attributed to the several years of unilateral hearing with the first CI. These CI users have been adapted with the limitations of monaural hearing and do not expect to localize the sound source with single side hearing. Indeed, location of the sound source has not been defined for sequential bilateral implanted children shortly after receiving the second implant. Providing the new auditory input from the second ear introduces a new concept of “where is the sound coming from?” The novelty of this experience decreases considerably at the first year of bilateral hearing (Litovsky et al., 2006) and their performance improves gradually.

An additional finding in the lateralization task was that the measured balanced levels for successful children did not change significantly at the two test times, or across the methods (Tables 3.9 and 3.10). Therefore, when EABR data are not available, at least in the older children, the behavioral judgment would be a useful approach for finding the bilaterally balanced level. Similarly, the behaviorally balanced level was previously performed in different studies with post-lingually deaf adults who had a minimum of six months of bilateral hearing with their CIs (Litovsky et al., 2009).
4.3.2. Perception of inter-implant timing differences (ITD) might require more hearing experience and was not improved efficiently by aural patching

Our experiment indicated that none of the sequential bilaterally implanted children were able to lateralize pulses with ITDs when they had one month of bilateral hearing experience. This result was not surprising given our previous report. Our laboratory showed that timing cues were not detectable by children who received bilateral CIs sequentially, even after two years of hearing with their naïve ear (Salloum et al., 2010). Other investigators also observed similar findings in adults (Seeber & Fastl, 2008; Grantham et al., 2008; Van Hoesel & Tyler, 2003).

The medial superior olive (MSO) in the mammalian brainstem receives projections from both the ipsilateral and contralateral cochlear nuclei (CN). This specific anatomical structure tunes the MSO as the major location for detecting the timing cues (Altschuler et al., 1991, Chapter1). Glutamergic neurons deliver excitatory inputs to the MSO neurons (Grothe et al., 2010), while inhibitory inputs are received by GABAergic neurons to suppress the out-of-phase signals (Altschuler et al., 1991, Chapter1) via activation of potassium channels (Hassfurth et al., 2010). However, studies on gerbils indicated that just after onset of hearing, input from the lateral nucleus of trapezoid body (LNTB) to the MSO do not provide enough GABA to activate the receptors in the MSO. Regulation of these receptors is activity dependent, however, excessive excitation and elevated glutamate levels down-regulate GABA receptors expression (Hassfurth et al., 2010). The clinical observation of this physiological abnormality is an inability to identify the ITDs.

Our unpublished data indicated that children receiving their second implant on the opposite ear with a long inter-implant delay were able to detect timing cues after at least four years of hearing.
with both their devices, suggesting that chronic exposure to the auditory stimuli might improve the physiology of MSO (Hassfurth et al., 2010).

In the present study we proposed that the function of the MSO could be developed if auditory input is removed from the dominant side and is only driven by the newly activated side. We therefore re-evaluated the ability of children to process the pulses with ITDs after a period of aural patching. The findings indicated that most of the children were unable to lateralize the stimuli with different ITDs after the aural patching. Only two children succeeded in this evaluation. They used both of their implants full-time rather than aural patching, and had experience with acoustic hearing from two conventional hearing aids prior to receiving their first implant. There were also two more children who showed partial ability on this task. Interestingly, they were compliant with aural patching and followed the plan (>3 hours/day in ≥4 days/week). Their successful result might be due to several reasons, including compliance with the aural patching, limited inter-implant delay (<6 years), and receiving the second implant at younger age (<12 years old).

Overall, our results suggest that the ability to lateralize ITDs in children with long sequential bilateral CIs may depend on a foundation of acoustic hearing prior to receiving a CI. Perhaps aural patching improves this skill, but there are some considerations in this regard. First, the number of successful children after the aural patching was too small to strongly support the positive effect of the aural patching on the newly achieved skill. Second, their successful performance was partial. We do not know whether this result would be improved if the children had a more intensive regimen of aural patching or if they were required to continue the plan to stabilize the result.
4.4. Children still suffer from loudness asymmetry of both sides

Loudness growth functions were evaluated between two extremes, hearing threshold level and maximum comfortable level. These lower and upper limits were elicited at significantly lower CUs in the naïve ear compared to the experienced ear one month post-activation of the second implant, resulting in a similar dynamic range for both ears. This result was achieved regardless of using objective (ECAP, ESRT) and subjective measurements (T-level, children’s judgment about the level of the sound). Our lab previously reported different levels required for eliciting the responses by CI1 and CI2 in children who did not receive both of their implants in a single surgery (Gordon et al., 2012b). As was also concluded in that paper, this difference can be a consequence of using devices from two different generations of technology. While straight electrode arrays tend to reside slightly distant from the modiolus, pre-curved electrode arrays were designed in a way to sit closely to the inner cochlear wall. This modiolar proximity provides several advantages. First, there is less resistance against the implant insertion compared to the free-fit (straight) arrays, which is a safety advantage during the surgery and results in maintenance of residual spiral ganglion cells (Tykocinski et al., 2000; Briggs et al., 2001). Second, the minimal positioning resistance leads to deeper insertion of the array toward the apical portion of the cochlea (Briggs et al., 2001), which usually has more residual active neurons. Third, the straight arrays contain full platinum bands (Hughes et al., 2006) while the pre-curved arrays have half-band electrodes faced toward the cochlear inner wall (Briggs et al., 2001, Hughes et al., 2006), resulting in less electrical energy required to evoke an auditory nerve action potential (Hughes et al., 2006).
The difference between the two implanted sides in objective and subjective measurements remained consistent for nine months, and CI2 which is chronologically newer device than CI1 still required less electrical energy than CI1 to elicit an ECAP, ESRT, and T-level. Interestingly, at the second visit for this evaluation, an ESRT was evoked in more ears compared to at the first visit. This might be due to more cooperation from the children to sit still and quiet during the test, fewer middle ear infections, and more success in sealing the ear to perform the ESRT test.

The loudness growth functions showed that the input was perceived as louder by the second implant relative to the first implant across the dynamic range (DR). Given that the DR for the two ears of our participants was not statistically different, the derived difference between the CI1 and CI2 responses may be related to the physiological changes caused by a long duration of unilateral deafness in the un-implanted ear. Studies of deaf cats indicated that damaged inner hair cells resulted in loss of spontaneous discharges in the auditory nerve (Ryugo et al., 1998). Lack of this spontaneous activity changes post-synaptic density, and in turn unilateral auditory stimulation induces some plastic changes in the contralateral un-implanted ear (O’Neil et al., 2010). Considering the high level of synchrony among the auditory nerves at the initial exposure to electrical stimulation, the newly activated fibers respond abnormally to the amplitude changes and drive an excessive action potential by a large number of fibers (Hong & Rubinstein, 2005).

Our earlier study compared the perceptual loudness of the experienced unilateral CI users with normal hearing peers. In that study we showed that the loudness growth had a similar pattern for the two groups, suggesting that chronic CI use provides cross-modality matching when the stimulus level is increased (Steel et al., in review). Therefore, mismatched loudness growth in the present study might be related to abnormal function of the newly implanted side. We proposed that aural patching would improve the function of the naïve ear and decrease the excessive
loudness growth on this side. Repeated measurements after nine months of aural patching indicated that the gap between CI1 and CI2 responses decreased significantly, but the sound was still perceived as louder in the naïve ear.

We also investigated further details of the pattern of loudness growth across the DR at both test times, and found that the loudness sensation grows at a greater rate with higher input levels on both sides than with softer sounds at the first evaluation (month1) (Figure 3.22b). There are three possibilities for this break point in the loudness function: 1) At low levels, slightly above the threshold, only a small patch of related nerve endings is activated, while higher levels activate the whole nerve and cause a rapid loudness growth. 2) In contrast with the low levels, there is a tight phase lock between the neural response and the electrical stimuli at the higher levels. This high degree of synchrony is interpreted as a loud sound by central nervous system. 3) The nerve produces multiple action potentials at the high levels, resulting in a faster loudness growth (Shanon, 1985).

Upon more precisely comparing the loudness function between the two ears at month 1, we found that the loudness sensation grows quickly in the naïve ear, not only with high-amplitude sounds but also with softer sounds (Figure 3.22). Interestingly, as the time-in-sound of the second ear increased, this asymmetric response decreased, and at the second test time more matched responses between the two ears were seen (Figure 3.23). This improvement was observed in 76% of the patching group (n=24) and 57% of the control group (n=8). Given that the changes were not related to the aural patching regimen (Figure 3.25), and the improvement in loudness growth perception were observed in both aural patching and control group without significant difference between the two proportions, it seems that decreasing the loudness
sensation in the naïve ear corresponds to the more experience with the second implant rather than aural patching.

Meanwhile, the improvement in the loudness function slope for CI2 among different etiologies of deafness was similar to our findings for EABR responses, as previously discussed, suggesting that genetic-related hearing loss was associated with more changes in the results than those of the other etiologies. However, this improvement would not be necessarily leading to a normal loudness growth perception for this population.

4.5. *Aural patching provided similar satisfaction as eye patching among the participants*

Using results from the correlation between the duration and frequency of aural patching (Figure 3.1), we found that a regimen lasting longer would not negatively affect the frequency of the aural patching. In contrast, a UK study indicated that high dose rates (hours/day) of eye patching reduces compliance with the treatment (Stewart et al., 2007). Less adherence with the aural patching, however, might be due to the users’ greater dependency on the first implant for oral communication. Meanwhile, all of the participants were full-time students, and spent most of the day at school. Thus, either children or their parents hesitated to remove the better hearing from the first implant in the educational environment, and their aural patching hours were limited to the times that they were at home. This may explain why the children did the aural patching on average only two hours/day. On the other hand, the average frequency of aural patching was better at the beginning of the study and then decreased over time (Figure 3.2). Similarly, lower eye patching adherence than the prescribed schedule has also been reported in amblyopia therapy (Webber, 2007).
To increase compliance with the aural patching regimens we used several approaches: 1) Following up with in-person appointments in the laboratory, with a more intense schedule at the beginning and later every 3 months. This was also similar to the eye patching program (Stager et al., 1990). 2) Splitting the aural patching hours. Previous studies on amblyopia also indicated that splitting the occlusion therapy not only has similar effects as continuous treatment but also improves the children’s adherence with the schedule (Sachdeva et al., 2013). 3) Monitoring the performance with telephone interviews and e-mails.

Aural patching was a challenging plan for the parents and children. However, in eye patching the parents may have less difficulty than with aural patching, since the treatment commonly is performed before school-age. This, however, does not mean that occlusion therapy is a completely successful treatment. Generally, 15-50% of amblyopic treatments might fail. Several reasons were given for this failure. Perhaps the treatment was started too late and after the sensitive period (beyond 7 years of life). Poor compliance with treatment in older children is another reason for poor response to treatment. Another possible reason for failure to achieve normal vision is that the current treatment is inadequate. Finally, there might be subtle deficits in the retina, optic nerve or gaze control that limit the potential for recovery of visual acuity (Birch, 2013).

We did not find negative correlation between ages at which the children received the second implant (equal to the age at which the aural patching was started) and aural patching adherence (Figure 3.3). Conversely, studies on amblyopia indicated that age at the eye patching has a negative effect on the compliance with the treatment (Webber et al., 2007; Erdem et al., 2011).
Considering the satisfaction questionnaire (Figure 3.27), writing the patching report had the smallest score (58.5%) and parents’ feeling about the children’s speech perception with the new implant had the highest score (76.6%) among the other questions. Moreover, in more than 60% of cases, parents reminded the children to do the aural patching. These results suggest that: 1) the aural patching performance should be monitored with a more attractive method than writing. Perhaps a special program on the speech processor would be a useful way to record the hours that the device is on or off, working similarly to an actimeter (a sensor for monitoring the muscles activity cycles). Studies on eye patching were also shown that only 50% of children returned their daily records about the patching performance (Scheiman et al., 2005). 2) Setting an extra program for the CI1 speech processor with a softer sound, and asking the children to use this program for a few hours per day, rather than removing the first device. This approach might increase the motivation of children to follow the instructions, by eliminating the anxiety associated with losing the dominant ear. Investigators in a newly published study attempted to improve the visual acuity in adult amblyopic brain via low resolution video games. They suggested that dichotic training rather than monocular stimulation by occlusion therapy, would restore part of abnormality in visual function, however, this approach was not resulted in a normal binocular vision for the participants (Li et al., 2013). 3) Parents’ view and psychological force on the children’s performance with the new implant plays an important role for the input (encouraging the children to do the aural patching) and the output (feeling about the speech perception with the new implant after aural patching).
Chapter 5
Conclusions

In the present study we demonstrated that when two cochlear implants are not provided simultaneously, children would suffer from asymmetric function in different auditory skills. Mismatched responses were recorded from the auditory brainstem, and auditory cortices. Moreover, regardless of using two implants, the children were not able to perceive the binaural timing cues, which are critical components for localizing sounds and for speech perception in noisy environments. Furthermore, loudness was not perceived as balance with the two implants.

In an attempt to improve these skills, we proposed that aural patching, similar to a common treatment for amblyopia, would reduce the mismatched auditory functions. We found that there is a limited range of aural patching adherence including 2 hours per day and 4 days per week, suggesting that the children are still dependent on their first implant. Some of the auditory skills in children with bilateral cochlear implants who did not receive both implants at the same surgery improved within the first 9 months of bilateral hearing experience, but these changes were not related to the aural patching regimen. Electrophysiological measurements indicated that evoked potentials of the rostral portion of the brainstem elicited by stimulation of the naïve ear were recorded slightly faster in month9 than the initial activation. However, asymmetry in this part of the brainstem did not further develop by the aural patching. Furthermore, asymmetry in cortical responses after 9 months of bilateral implant use was persistent, and cortical development on the second side was not improved by periods of aural patching. Even though timing cues were successfully perceived by a few individuals, on average the children remained disable to perceive this localization cue after 9 months of bilateral hearing. Furthermore,
asymmetry in loudness perception between the ears decreased with bilateral implant use. However, this improvement was not related to the aural patching.

Overall, we are relying on children and parents to do the aural patching, and their reports reveal that there is a good compliance with the aural patching approach. This performance was not affected by children’s age. However, children had better compliance with the aural patching shortly after activation of the naïve ear. This performance was reduced following the first few months. Therefore, more restricted and intensive follow-up of aural patching within this period of time, along with auditory activities, might improve the results.

Since there was an appropriate compliance with aural patching, it could be a recommended approach for children with bilateral cochlear implantation who received their second implant with a long inter-implant delay. However, in clinical application providing a few modifications in the performance might improve the results, including stricter rehabilitation sessions early after onset of hearing in the second ear, monitoring the aural patching adherence with an on-line program, and using a program with a softer sound level for the experienced ear that is used along with the new implant in the naïve ear (partial versus complete patching).

The limitation of this study is related to the children’s compliance with the aural patching that was affected by their attendance at school. Therefore, the effects of the aural patching might be in part restricted as a result of lower patching regimen. In order to overcome to this problem we suggest that the second surgery be scheduled during the summer break of school program to maximize the aural patching adherence.

This study can be continued in the future with assessments of dipole locations of the cortical areas affected by activation of the new implant. This would give us an overview of aural
patching-related changes of the higher order of the central nervous system in sequentially bilateral cochlear implantation. Furthermore, assessment of middle latency evoke responses of the auditory brainstem provides information about thalamo-cortical pathway. Comparing speech perception scores with newly implanted ear before and after the duration of aural patching indicate whether ignoring the dominant ear would improve children’s speech skill.

Results of the present study were presented in four conferences as follows:

1- Unbalanced loudness growth in children receiving bilateral cochlear implants sequentially with long inter-implant delay. SENTAC conference, Kansas City, United States, Dec 2011 - Awarded as the best paper

2- Using loudness measurements to balance bilateral implants. The 12th international conference on cochlear implants and other implantable auditory technologies, Baltimore, United States, Apr 2012

3- Can we restore binaural hearing to children with bilateral cochlear implants by removing the first implant? SENTAC conference, Charleston, United States, Dec 2012

4- Can we strengthen pathways from the deprived ear after unilateral cochlear implant use in children? The University of Toronto, Percy Ireland day, Toronto, Canada, May 2013

Furthermore, a clinical application of this study was written and will be submitted for Ear & Hearing Journal.
Chapter 6

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