Effects of Bilateral and Unilateral Deafness Observed from Cortical Responses Evoked in Children with Bilateral Cochlear Implants

by

Sho Tanaka

A thesis submitted in conformity with the requirements for the Master of Science degree
The Department of Physiology
University of Toronto

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The Department of Physiology
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2010

Abstract

This study examined the effects of bilateral and unilateral deafness by measuring cortical auditory evoked potential (CAEP) responses in children at initial stages of bilateral cochlear implant (CI) use. We recorded cortical responses evoked by right and left CI stimulation in 127 children with early onset (< 12 months) deafness, with 72 children receiving the two devices in the same surgery (simultaneously implanted) and 55 children receiving the devices in separate procedures (sequentially implanted).

Three different types of responses were identified in children with bilateral CIs. No significant effects of duration of deafness, age at implantation, or duration of unilateral CI use were found on response latencies and amplitudes within each type of cortical response, but there were clear differences in responses types between groups and ears. In the context of these findings, the effects of bilateral and unilateral deafness to the auditory pathways were discussed.
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<tr>
<td>ABR</td>
<td>Auditory Brainstem Responses</td>
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<td>ANOVA</td>
<td>Analysis of Variance</td>
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<td>CAEP</td>
<td>Cortical Auditory Evoked Potential</td>
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<td>CI</td>
<td>Cochlear Implant</td>
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<td>CN</td>
<td>Cochlear Nucleus</td>
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<tr>
<td>CNS</td>
<td>Central Nervous System</td>
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<tr>
<td>EABR</td>
<td>Electrically Evoked Brainstem Responses</td>
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<tr>
<td>FM</td>
<td>Frequency Modulation</td>
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<tr>
<td>fMRI</td>
<td>Functional Magnetic Resonance Imaging</td>
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<tr>
<td>ICA</td>
<td>Independent Component Analysis</td>
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<tr>
<td>ISI</td>
<td>Interstimulus Interval</td>
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<td>MLR</td>
<td>Middle Latency Response</td>
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<td>NH</td>
<td>Normal Hearing</td>
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<td>Principal Component</td>
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<td>PET</td>
<td>Positive Emission Tomography</td>
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Chapter 1 - Introduction

1.1 Cochlear Implants and Cortical Auditory Evoked Potentials

Cochlear implants allow children who are deaf to hear by stimulating the auditory nerve with electrical pulses. The development of hearing relies on the transmission of this electrically evoked activity to more central areas of the auditory system including the auditory cortex. Cortical auditory evoked potential (CAEP) responses are one of the few non-invasive measures which can be used to image cortical function in cochlear implant (CI) users. In this thesis, we used CAEPs to study the effects of bilateral and unilateral deafness on cortical maturation and function in children who received bilateral CIs. We focused on the first day of bilateral cochlear implant use in order to study the deprived auditory system. We recorded responses in children who had been bilaterally deaf early in life (probably from birth) and had received bilateral cochlear implants simultaneously or after a period of unilateral CI use (sequential procedures). The latter group of children provided a means to explore the effects of unilateral CI use and unilateral deafness.

1.2 Research Objectives

We asked three research questions in this thesis:

1) Does bilateral deafness arrest auditory development resulting in persistently immature responses to CI stimulation from the auditory cortex?

2) Does a period of unilateral CI use promote more mature responses from the auditory cortex?

3) Does a period of unilateral cochlear implant use affect cortical responses evoked by CI stimulation of the naïve contralateral deaf ear?

These are important questions to be addressed because we currently lack a thorough knowledge regarding the effects of deafness in the auditory cortex. Since we cannot use imaging
devices, such as functional magnetic resonance imaging (fMRI), in CI users because of the metallic component within their prosthesis, electrophysiological measures are the most direct and non-invasive method of assessing the effect deafness in these individuals. Thus, we performed these experiments in hopes of gaining further insight into the developmental pattern of the auditory cortex in children with bilateral CIs. We reveal a variety of cortical responses from the deaf auditory cortex under differing conditions of auditory deprivation, and speculate on how the two auditory cortices might reorganize during a period of bilateral and unilateral deafness.

1.3 Thesis Outline

In this chapter, we present the motivation behind our research. In the second chapter, we discuss the background information to each of the three experimental questions. In the third chapter, we detail experimental methods that are common to the three experiments. We give a description of the participants, apparatus, stimuli, procedure, and data analyses. In the fourth chapter, we present and statistically analyze our experimental results to each of the three experiments. In the final chapter, we discuss our experimental findings from each of the three experiments and direction of future research.
Chapter 2 - Background

In this chapter, we review the framework for each of the three main experimental studies. First, we discuss cortical responses from normal hearing (NH) individuals, prematurely born NH infants, and cortical responses evoked from new CI users. Second, we review cortical responses evoked from experienced CI users. We conclude the chapter by discussing the effects of unilateral deafness to the auditory cortex.

2.1 Responses from Bilaterally Naïve Auditory Cortex

For our first question, we asked the following: “Does bilateral deafness arrest auditory development resulting in persistently immature responses from auditory cortex?” Our hypothesis to this question was that cortical responses to CI stimulation from bilaterally deaf children would resemble immature cortical responses from young NH children. Although the mechanisms are not clear, the auditory late latency response, reflecting cortical activity to sound, changes with age. Responses evoked by CI in children have been reported to be delayed in latency relative to NH children of similar ages suggesting either delayed or abnormal development.

2.1.1 Cortical Responses from Normal Hearing Adults

In normal hearing (NH) individuals, mature, adult cortical responses are characterized by multiple peaks, which are labeled P1-N1-P2-N2 for their positive and negative amplitudes with respect to the latency at which they occur (Figure 2.1). The first positive peak, P1, occurs around 40-60 ms and its generator is understood to be associated with the excitatory inputs from the thalamus to the pyramidal neurons in cortical layers III and IV (Ponton et al., 2001; Eggermont et al., 2003, Lippe et al., 2009). In addition, this peak is considered to be analogous to the middle latency response (MLR), which is an evoked potential that follows the auditory brainstem
responses (ABRs) that includes subcortical and cortical generators (Fifer and Sierra-Irizarray, 1988; Frizzo et al, 2007). The first negative peak, N1, occurs around 90-110 ms and its generator, is thought to be a reflection of activity from the superficial layers of the auditory cortex (layers I and II) (Ponton et al, 2001; Eggermont et al, 2003, Lippe et al, 2009, Naatanen and Picton, 1987).

In contrast to the two former peaks, P2 and N2 peaks have been less studied. The second positive peak, P2, is often seen around 140-200 ms in latency (Ponton et al, 2000, Lippe et al, 2009). The early latency maturation of P2 has hinted at the strong association of P2 generator with the auditory brainstem-reticular activating system pathways, with the generator possibly being near the insular cortex (Ponton et al, 2000). The second negative peak, N2, occurs around 220-270 ms (Ponton et al, 2000). The generator of N2 has not been studied nor speculated on in the current literature. However, it has been reported that both P2 and N2 are influenced by different types of stimuli (Perrault and Picton, 1984; Ceponiene et al, 2005), which suggests the involvement of association cortical areas.

Figure 2.1

**Figure 2.1** Typical cortical response morphology from a NH adult to 2kHz pure tone for a duration of 36ms, presented at 1Hz from an electrode placed at the midline cephalic location (Cz) on the scalp.

Cortical responses from young children have a different morphology compared to adult
responses. Specifically, a large number of studies report that the response recorded at the midline location consists of a broad positive peak at 200-250 ms, followed by a negative peak at about 300-700 ms, as shown in Figure 2.2 (Sussman et al, 2008; Picton and Taylor, 2007; Lippe et al, 2009; Gilley et al, 2005; Sharma et al, 1997; Barnet et al, 1975; Kurtzberg et al, 1984; Little et al, 1999; Shucard et al, 1987). The latency of these peak values decrease with increase in age, to around 100ms for the positive peak and 250 ms for the negative peak by five years of age, and remains around that latency for a few years (Lippe et al, 2009; Ponton and Eggermont, 2001). At around ten years of age, these responses gain the typical adult morphology consisting of P1-N1-P2-N2 (Ponton and Eggermont, 2001; 1996; Lippe et al, 2009). Some groups call the large positive wave in the immature response from children a P1 and then compare this latency to the mature P1 (Sharma et al, 2005; 2002). Others suggest that the large immature positive peak is an equivalent to P2 which decreases slightly in latency with age and that the P1 and N1 responses emerge separately (Wunderlich et al, 2006). It is also possible that certain peaks cannot be seen until later in childhood; the N1 may appear as the large positive peak seen in NH children bifurcates into the mature response (Ponton et al, 2000) or the mature P1 and P2 peaks may be indistinct in the immature response, combining to make up the dominant positive peak (Ceponiene et al, 2005).
Recently, Lippe and colleagues reported that CAEPs in children under 5 years of age are dominated by low frequency activity (i.e. delta bands: 1-3Hz) as compared to adult responses which have higher frequency (i.e. beta1, beta2 and gamma bands: 13-50Hz) phase locked components at latencies corresponding with P1 and N1 (Lippe et al, 2009). Interestingly, 12 month olds with NH had two clusters of high frequency activity (i.e. alpha and beta bands: 8-32Hz); one which was at the beginning of the dominant positive peak and the other at the end of the same peak response. This is consistent with the view that the positive peak in the immature response reflects the generators of both the mature P1 and P2 (Ceponiene, et al., 2005). Thus, it is possible that there are multiple generators which make up the positive peak of the immature
CAEP. Ponton and colleagues (Ponton and Eggermont, 2001; 2000) have reported that the broad positive peak persists until around ten years of age after which it begins to bifurcate into two smaller peaks contributing to the typical adult cortical response morphology of P1-N1-P2-N2. In terms of amplitude, many researchers have reported that values decrease with increase in auditory experience for P1 and N1 (Gilley et al, 2005; Wunderlich et al, 2006; Pang and Taylor, 2000; Ponton et al, 2000) while that of P2 stays constant (Ponton and Eggermont, 2001). N2 amplitude values seem to increase (Sussman et al, 2008; Gilley et al, 2005, Ponton et al, 2000).

Stimulus presentation rates affect the morphology of CAEP responses. In particular, the first negative peak, possibly the N1, appears to be especially sensitive to rate of stimulus presentation in younger children. At very low rates (2000-3000 ms interstimulus interval (ISI)), children as young as two years show a negative peak at around 100-150 ms which is a similar latency to the mature N1 (Ponton, 2006; Wunderlich et al, 2006, Gilley et al, 2005). In contrast, cortical responses from faster stimulus presentation rates (360 – 1000 ms) do not evoke the N1 peak until about 10-16 years of age (Sussman et al, 2008; Ponton, 2006; Ceponiene et al, 2005; Gilley et al, 2005; Pang and Taylor, 2000). These reports suggest that CAEP morphology is highly influenced by both the length of auditory experience (i.e. influence of age) and stimulus presentation rates in NH individuals.

2.1.2 Cortical Responses from Prematurely Born Normal Hearing Infants

Auditory evoked responses in NH infants may have distinctive morphological features from slightly older children. Lippe and colleagues (2009) showed that cortical responses from NH infants younger than 2 months of age, after full-term pregnancy, have a small negativity that is present around 80 ms and precedes the broad positive peak. More strikingly, it has been reported that cortical responses evoked by auditory input in prematurely born infants show a
broad negative peak at a slightly later latency (~200-250ms) followed by a positive peak (~600ms), as shown in Figure 2.3 (Rotteveel et al., 1987; Weitzman and Graziani, 1968). It is possible that this early negative peak may be an immature form of the MLR (Lippe et al, 2009), and is unlikely to be an equivalent of the adult N1 because a negative peak is not seen in responses evoked by similar stimuli in older children (Sharma et al., 1997; Pateau et al., 1995; Gilley et al., 2005; Ceponiene et al., 2002). The latencies of the positive peak in normal hearing (NH) infants at 1 month of age usually fall between 220-270 ms. These latencies are later than that of the early negative component found in infants (Lippe et al, 2009; Rotteveel et al., 1987; Weitzman and Graziani, 1968) and thus both peaks could be present in this very young group.

Figure 2.3

Figure 2.3—Examples of cortical responses taken from 32, 36, and 42 weeks after conception (i.e. 6, 12 and 18 weeks of age after birth) in a prematurely born infant born at 26 weeks after conception. Responses were evoked by auditory clicks presented at 0.25Hz through a speaker. The numbered cortical responses from 1-10 show responses taken from different recording channels placed on the scalp as indicated (Weizman and Graziani, 1968). Early dominant negative peak present at 32 weeks (6 weeks after birth) gradually becomes a dominant positive peak at 42 weeks after conception, which is near normal age of conception (i.e. approximately 40 weeks). It is important to note the similar response morphology across all electrodes regardless of the location on the scalp.

The electrophysiological changes with age may reflect anatomical changes occurring
during the same period in the cortex. It has been suggested by Vaughan and Kurtzberg (1989) that changes in the cortical response during early infancy parallel changes in the intracortical synaptic organization in layer III of the auditory cortex. This is also around the time when synaptic density rapidly increases in the auditory cortex and reaches its maximum level (Huttenlocher and Dabholkar, 1997). Further electrophysiological changes occurring during childhood can be accounted for by the processes aiding synaptic elimination which continue until about the age of 12 (Huttenlocher and Dabholkar, 1997). There are also reports of laminar changes in the auditory cortex; the deeper layers of the cortex mature prior to superficial layers, in terms of axonal density, and do not become adult-like until around 11-12 years of age (Moore and Guan, 2001). Interestingly, this is also around the time when the CAEP shows adult-like response morphology consisting of the P1-N1-P2-N2 peaks (Ponton et al, 2000; 2001).

2.1.3 Differences between Acoustic Hearing and Cochlear Implants

In NH individuals, sound vibrations cause movement of the tympanic membrane and the middle-ear ossicles that result in fluid within the cochlea to move and ultimately stimulating the hair cells of the inner ear. The movement of the hair cells send action potentials down the auditory nerve, which synapses at the medulla oblongata before moving up to the auditory cortex. In contrast, the use of the outer, middle and inner ears are bypassed in CI users, as the prosthetic device directly stimulates the auditory nerve, where the electrodes are inserted into the scala tympani to replace the function of the hair cells (Papsin and Gordon, 2007).

2.1.4 Naïve Cortical Responses from Cochlear Implant Users

In CI users, there are only a few reports of cortical responses from the naïve auditory cortex and the majority of these are from unilateral device users. These reports show that naïve cortical responses are typically dominated by a broad positive peak on day of device activation.
(Sharma et al, 2005; 2002) which occurs at much later latencies (~400ms) than the positive peak recorded in children with NH between the ages of 0-3 years (~200-250ms), as was shown in Figure 2.2 (Sharma and Dorman, 2006; Wunderlich and Cone-Wesson, 2006, Lippe et al, 2009). However, the waveforms shown in these papers appear to have a negative peak at an earlier latency (~250ms) that precedes the broad positive peak and this resemble responses reported in prematurely born infants with NH, which occurred around 300ms (Rotteveel et al., 1987; Weitzman and Graziani, 1968). Furthermore, the positive peak in children using CIs is significantly delayed relative to the P1 from NH children of the same age. The reported patterns of CAEP development from unilateral CI users from device activation to 18 months of device use is shown in Figure 2.3. Interestingly, children implanted at an early age (defined as below 3.5 years of age) had a much later initial positive peak latency (mean = 375 ms) compared to that of children implanted at a later age of more than 7 years (mean = 250 ms) (Sharma and Dorman, 2006; Sharma et al, 2005; 2002). However, it is not clear that these two peaks represent the same neural generators for early and late implanted children (Sharma and Dorman, 2006). The overall comparison of reported latency values for NH preterm infants, NH children, NH adults, and CI users are given in Table 2.1.
Figure 2.4 – Typical CAEP developmental patterns reported from 12 unilateral CI users who were implanted at ages <3.5 years from the first day to 18 months of device use. These responses were evoked by the speech sound /ba/ for 90ms in duration at a presentation rate of 1.6Hz (Sharma et al, 2005).

Table 2.1

<table>
<thead>
<tr>
<th>Latency (ms)</th>
<th>1st +ve Peak</th>
<th>1st -ve Peak</th>
<th>2nd +ve Peak</th>
<th>References</th>
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<tr>
<td>NH Preterm Infants</td>
<td>---</td>
<td>~200-250</td>
<td>~650</td>
<td>1,2</td>
</tr>
<tr>
<td>NH children (age 5)</td>
<td>~100</td>
<td>~250</td>
<td>---</td>
<td>3,4,5,6,7,8,9,10,11</td>
</tr>
<tr>
<td>NH Adults</td>
<td>(P1) 40-60</td>
<td>(N1) 90-110</td>
<td>(P2) 140-200</td>
<td>5, 12, 13, 14</td>
</tr>
<tr>
<td>CI Users (activation)</td>
<td>---</td>
<td>~250</td>
<td>~400</td>
<td>15, 16</td>
</tr>
<tr>
<td>CI Users (1 year)</td>
<td>~100</td>
<td>~300</td>
<td>---</td>
<td>15, 16</td>
</tr>
</tbody>
</table>


We aimed to further study cortical responses in the bilaterally deprived auditory cortex in children receiving two CIs simultaneously. We expected to find immature CAEPs with no effect of side of CI stimulation (left or right CI).
2.2 Effect of Unilateral Cochlear Implant Use on Cortical Activity

For our second question, we asked: “Does a period of unilateral cochlear implant use promote more mature responses from the auditory cortex? To this question, our hypothesis was that in children who receive a second CI after a period of unilateral CI use, CAEPs evoked by the CI in the experienced ear would resemble mature responses from CI users. If the auditory cortex relies on auditory stimulation to mature, then the same developmental changes in the CAEP should occur in children using CIs. If normally expected maturation of the CAEPs does not occur, this could reflect irreversible effects of deafness and/or differences in activity evoked by electrical versus acoustic auditory input.

2.2.1 Cortical Responses from Experienced CI Users

Cortical responses from children with CIs typically consist of a broad positive peak followed by a negative peak, which is similar to responses found in young NH children between the ages of 3 months to about 10 years of age at stimulus presentation rates with an inter-stimulus interval (ISI) of > 1000 ms (Lippe et al, 2009; Sussman et al, 2008; Ponton, 2006; Gilley et al, 2005; Pang and Taylor, 2000). In NH children, this positive peak is normally bifurcated by the emergence of a negative peak (perhaps the precursor of the N1) at around 10-11 years of age (Sussman et al, 2008; Ponton and Eggermont, 2001). The question remains as to whether this maturational change occurs in children using CIs, even if they have had more than 10 years of device use after being implanted at an early age. It is possible that cortical responses from CI users remain different from normal because: 1) electrical versus acoustic input to the auditory system causes different effects; and 2) children using CIs were deprived of sound during early development.

In NH individuals, sound vibrations cause movement of the tympanic membrane and the
middle-ear ossicles that result in fluid within the cochlea to move and ultimately stimulating the hair cells of the inner ear. The movements of the hair cells send action potentials down the auditory nerve. In contrast, the use of the outer, middle and inner ears are bypassed in CI users, as the prosthetic device directly stimulates the auditory nerve with electrical pulses delivered by electrodes that are surgically placed in the scala tympani of the cochlea. Activity in the primary auditory nerve evoked by electrical stimulation is more synchronized and its excitation spread over a larger range compared to that evoked by acoustic sound (Kral and Tillein, 2006, Kral et al, 1998). However, it is unknown whether such a difference in stimulation would cause differences at the level of the auditory cortex. Both electrical and acoustic stimulations utilize the same auditory nerve fibers, synapse at the brainstem, and most likely lead to the same regions of the auditory cortex. Furthermore, cortical response amplitude, which is considered to be a reflection of synaptic density (Eggermont, 1988), does not differ considerably between NH individuals and CI users, as our group and others have observed (Gordon et al, 2008; Ponton and Eggermont, 2001). Further support that the auditory cortex can respond rather normally to electrical stimulation of the auditory nerve is found in adult CI users. Some of these individuals who had normal hearing throughout childhood but became deaf as adults typically show a normal mature CAEP having the characteristic P1-N1-P2-N2 peaks to CI stimulation (Ponton and Eggermont, 2001). This suggests that mature cortical response seen in NH individuals can be maintained even after late-onset deafness with the use of CIs, and rules out the possibility that cortical morphology difference between NH individuals and CI users arise from difference in stimulation modes.

Moreover, it is unlikely that mature CAEPs seen in NH individuals develop in CI individuals who received CIs as children. In response to electrical pulses presented at rates of 1 –
1.3 Hz, children using unilateral CIs continue to show a dominant positive peak even after 16-17 years of CI experience (Gordon et al, 2008; 2005; Ponton, 2006; Ponton and Eggermont, 2001; Ponton et al, 1999; Singh et al, 2004). This phenomenon has been reported even if the child was implanted early before three years of age (Ponton and Eggermont, 2001; Gordon et al, 2008; 2005), thus suggesting alterations of the neural generators during a period of deafness that produces the cortical response morphology in NH individuals. A support for this theory is also found in animal models. There have been a few studies which used cortical surface recordings and depth recordings of local field potentials in the auditory cortex of deaf cats fitted with CIs (Klinke et al, 1999; Kral et al, 2002; 2000). The report by Klinke et al (1999) show that neural activity in the auditory cortex of deaf cats is immature and restricted to short latencies. This means that activities originating from the subcortical level to layers III/IV (i.e. human equivalent of P1 peak in NH AEP) of the auditory cortex are weak, but present at device activation, and become more robust with increase in auditory experience (Klinke et al, 1999). On the other hand, intracortical connections that originate in the superficial layers of the auditory cortex (i.e. human equivalent of N1 peak in NH CAEP), as represented by longer latency potentials, are known not to mature even after months of device use in cats fitted with CIs (Kral et al, 2000). These developmental restrictions in the auditory cortex that are found from animal models parallel the restrictions seen in CAEP development in children with CIs, as they do not show the emergence of N1 peak found in NH individuals even after years of auditory experience. In contrast, there is also a report that the N1 may begin to emerge in children implanted < 3.5 years of age after 6-9 years of unilateral CI experience (Sharma and Dorman, 2006). However, this finding has not been replicated in other studies (Ponton and Eggermont, 2001; Ponton et al, 1999; Gordon et al, 2008; 2005). Moreover, mature responses may require slower rates of stimulus presentation
(Ponton, 2006) which could indicate differences in neural refractory properties of the auditory cortex in children using CIs (Gilley et al, 2005).

Regardless of whether a negative peak (N1) is eventually found in children using CIs, it is important to determine whether the CAEP changes with CI use, because it might help in determining the maturity of the auditory system. In previous studies, the first dominant positive peak has been the focus with the assumption that any changes to it reflect development of the same neural generators over time. Using this method of characterizing the peaks in the immature and more mature responses, the positive peak decreases in latency with CI use, coming to a plateau around 100-150 ms after 12-18 months for individuals who were implanted before the age of 3.5 years (Sharma et al, 2005; 2002; Ponton and Eggermont, 2001).

There have been two findings which suggest that development of the auditory cortex follows an abnormal trajectory in children using CIs. First, responses from individuals implanted at older ages (i.e. after longer periods of bilateral deafness), were shorter in latency at initial CI activation than responses in younger children (Sharma and Dorman, 2006; Sharma, et al., 2005) but showed little change with implant use (Sharma and Dorman, 2006; Sharma, et al., 2005). This was consistent with smaller changes reported in middle latency responses recorded in children implanted at older versus younger ages (Gordon, et al., 2005). Second, some children using CIs were found to have atypical patterns of cortical response even after several years of CI experience (Gordon et al, 2008, 2005). The atypical response consisted of a negative peak (at approximately 100-150 ms) and a positive peak which occurred at the same latency as the dominant positive peak in the typical experienced responses from CI users, and P2 in normal hearing age-matched children (Gordon et al, 2008; 2005). Interestingly, most of the children who showed the atypical response morphology were found to have poorer speech perception test
scores than the children with Positive peak waveform responses. These differences in CAEPs indicate that CI use may not always promote expected cortical development.

2.2.2 Atypical Cortical Responses from Experienced CI Users

Deviations from normal development of the auditory cortex are likely due to effects of bilateral deafness which become exacerbated over time. Evidence from congenitally deaf cats which received cochlear implants after 5 months of auditory deprivation indicates a delay in the activation of supragranular layers which, in turn, delays activity in the deep layers of the auditory cortex (Kral et al, 2002; 2000; Klinke et al, 1999). To explain this, Kral and colleagues suggested that there might be a functional decoupling of the primary auditory cortex to higher cortical areas during the period of deafness (Kral et al, 2006; 2005). This decoupling could be the result of reorganization promoted by other sensory inputs, which has been seen in some CI users. Specifically, Lee et al (2005; 2001) have shown with a positron emission tomography (PET) scan that late implanted CI users with poor outcomes of device use show greater degrees of metabolic activity in the auditory cortex, which they theorized as evidence for cross-modal takeover that limited auditory development. These reports are supported by studies which have shown that the auditory cortex is strongly susceptible to cross-modal takeover by the visual system during a period of deafness (Finney et al., 2003; 2001; Giraud et al, 2001). Taken together, abnormal cortical responses might be indicative of persistent immaturity or inability to reorganize in a typical way even with years of CI use (Gordon et al, 2008).

Our second objective in the present study was to examine the change in cortical responses in children after unilateral cochlear implant use. Since our study population included children who had a wide range of unilateral CI experience (0.71-11.1 years), we had an opportunity to follow the change in this response over long periods of auditory experience.
2.3 Effect of Unilateral Auditory Experience on Unilaterally Naïve Auditory Cortex

Our final research question asked: “Does a period of unilateral cochlear implant use affect cortical responses evoked by the naïve contralateral ear?” A period of unilateral CI use could affect binaural processing in children who receive bilateral CIs sequentially because of a mismatch in development between pathways from the experienced versus inexperienced ears. At the level of the brainstem, we have reported a delayed latency in responses from the CI stimulation of the unilaterally naïve ear on the first day of device use in sequentially implanted bilateral CI users, indicating immaturity in the unilaterally naïve auditory pathways (Gordon et al, 2007). Such a latency delay at the level of the brainstem could possibly translate to delayed latency values at the cortical level. Based on this report, we hypothesize that cortical responses evoked by unilaterally naïve ears would resemble responses evoked by the newly implanted and naïve ear in CI users.

2.3.1 Influence of Unilateral Hearing Experience to the Auditory Pathways

The influence of unilateral CI stimulation on the organization of the bilateral auditory pathways remains unclear. Normal hearing in both ears should result in relatively symmetrical bilateral auditory pathways, with much of the inputs coming from the contralateral ear due to contralateral dominance of the auditory pathways. Responses taken from the midline cephalic location (Cz) is a reflection of composite activities from both auditory cortices, and thus it is not possible to distinguish whether the activity is originating mainly from one auditory cortex or another. At the same time, however, if the responses evoked by naïve and experienced ear CI stimulation differ in morphology, such a result can be taken as a proof that the underlying components that make the composite activity of two auditory cortices are different, which could possibly indicate maturational differences of the auditory cortices. There are currently no reports
of cortical responses evoked by the unilaterally naïve ear in the literature, but we could speculate the possibilities of responses evoked by the unilaterally naïve ear from electrode placed on the midline cephalic location (Cz).

On one hand, unilaterally stimulated auditory development (i.e. unilateral deafness) is known to cause reorganization along the auditory pathways. In gerbils, unilateral auditory deprivation resulted in abnormal projections from the cochlear nucleus (CN) to nuclei of the superior olivary complex (SOC) (Kitzes et al, 1995) and a substantial increase in the number of projections from the CN to the midbrain ipsilateral to the hearing ear (Moore and Kitzes, 1995). In humans, numbers of groups have explored cortical responses evoked from the hearing ear in NH individuals with unilateral deafness. By using functional magnetic resonance imagining (fMRI) techniques, these studies showed symmetrical patterns of activation in the auditory cortex compared to the asymmetrical activation found in normal hearing individuals (Firszt et al, 2006; Langers et al, 2005; Bilecen et al, 2000). More pertinently, Langers have shown that individuals with childhood onset of unilateral hearing loss also show abnormally symmetrical activation between the two auditory cortices (Langers et al, 2005). Similar reports to those of fMRIs are also found in a study involving CAEPs; late-onset unilateral deafness led to more symmetrical amplitude and synchronous latency activation between the ipsilateral and contralateral sides of the head in adults (Ponton and Eggermont, 2001). Taken together, these data suggest that unilateral deafness leads to a disruption of normally contralaterally dominated auditory projections. Therefore, it is possible that reorganization during unilateral deafness promotes the development of ipsilateral auditory pathways in the Pons, and this pathway might also be stimulated by the contralateral side once a CI is provided in that ear (i.e. unilaterally naïve ear). If so, responses evoked from the naïve ear might be more similar to the responses
evoked by the experienced ear rather than immature responses that are reported from bilaterally naïve ears.

On the other hand, if the unstimulated contralateral pathways are left relatively unchanged during the period of unilateral CI use, we should expect differential responses evoked by the experienced versus naïve ears and the naïve responses to be similar to those from bilaterally deprived individuals. This idea is supported by reports found from the subcortical level in bilateral CI users. We have found that auditory brainstem responses evoked from naïve ear CI stimulation on the first day of bilateral CI use in children with several years of unilateral CI experience were prolonged in latency when evoked by the CI in the newly implanted ear as compared to the responses evoked by the experienced ear (Gordon et al., 2008; 2007). Thus, there is evidence behind auditory immaturity at the subcortical level for the unilaterally naïve pathways, and this could also be translated in the cortical level.

Our third objective was to characterize and study the effects of bilateral and unilateral deafness on cortical responses. This is important in order to predict the potential for binaural processing in children who receive bilateral cochlear implants in sequential procedures.
Chapter 3 - Materials and Methods

In this chapter, we describe the children who participated in this study and the experimental apparatus, design and procedures. Following that, we discuss the methods we used to analyze our data.

3.1 Research Participants

The data describing the participants in this study are described in Table 3.1.

Table 3.1

<table>
<thead>
<tr>
<th></th>
<th>Total</th>
<th>Range of Age at Test (years)</th>
<th>Average Age at Test (years)</th>
<th>Average Age 1st CI (years)</th>
<th>Average Duration of CI #1 Use (years)</th>
<th>Average Duration of CI #2 Use (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simultaneously Implanted</td>
<td>72</td>
<td>0.8-15.5</td>
<td>2.3±2.7</td>
<td>2.3±2.7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Sequentially Implanted</td>
<td>55</td>
<td>1.6-9.2</td>
<td>3.6±2.0</td>
<td>2.0±1.2</td>
<td>1.6±1.0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3.1– Descriptive data for participants in this study. There were 72 simultaneously implanted children and 55 sequentially implanted children.

The cause of deafness varied from one individual to another. Of the 127 participants, 72 children likely were deaf congenitally, whereas 21 children had a period of useable residual hearing (as defined by thresholds of ≤ 40 dB HL with or without hearing aids) for 2.74 ± 3.05 years before becoming severe to profoundly deaf. Of these children, 9 were simultaneously implanted (average duration of usable residual hearing: 3.09 ± 4.45 years, range 0.58-14.75 years) and 12 were sequentially implanted (average duration of usable residual hearing: 2.48 ± 1.55 years, range 0.25-5.08 years). By including the fact that some individuals had a period of moderate hearing, the average duration of bilateral deafness was computed to be 1.9±2.1 years in simultaneously implanted individuals and 1.6±1.1 years in sequentially implanted individuals.

3.2 Evoked Potential Response Recordings

Children wore a single-channel electrocap, created by Compumedics Neuroscan (El Paso,
Texas) and watched a video with closed captioning or played a game with a second tester. Responses were recorded from an electrode placed on the mid-cephalic location (Cz), where maximal potential is seen, and reference electrodes were placed on each earlobe in separate recording channels. Recorded signals passed through an analog low pass filter with a frequency cutoff of 32 kHz to minimize influences from the CI transmitting coil which sends information to the internal device by frequency modulation (FM) waves.

Responses were recorded by Neuroscan 4.3 software and a Synamps I amplifier using a sampling rate of 500Hz. Signals greater than ±100µV were rejected from averaging. Baseline corrections based on the pre-stimulus interval were performed online (-50 to 0 ms). During the averaging process, at least 50 sweeps were accepted and more than one replication of the resultant average cortical responses was taken to confirm the morphology of the cortical responses. The rejection percentage varied between recordings, but in general, about 10-20% of the recorded sweeps were rejected and at least 120-150 sweeps were recorded for each trial.

3.3 Stimuli Evoking Cortical Responses

Electrical pulses were delivered using SPEAR 3 software and processor made by CRC-HEAR, Melbourne (in collaboration with Richard van Hoesel). Trains of electrical pulses were delivered at 250 pulses per second for 36 ms (i.e. 9 pulses per second) from a single CI electrode in the apical end of the array (typically #20). Pulse widths of these stimuli were 25µs for CI device models of N24 and Freedom users. The stimulation mode was set as the default setting for CIs, MP1+2, which was same as the child’s regular implant settings. Current levels (T-levels – minimum amount of current needed for the child to perceive a sound) were determined by using an audiometric technique dependent on the child’s age. Examples include visual reinforcement audiometry (VRA), conditioned play audiometry (CPA), or conventional audiometry.
3.4 Categorization of CAEP Responses

Categorization of the CAEP responses was performed based on wave morphology. Three different types of responses were identified. Examples of these responses are shown in Figure 3.1. The first type had a waveform morphology typically seen from experienced CI users (Positive peak waveform) (Ponton and Eggermont, 2001; Gordon et al, 2008; 2005, Sharma et al, 2005; 2002) and was defined as having a large dominant positive peak (P1ci), followed by a negative peak (N1ci). The second type of cortical response was an atypical response pattern (Negative peak waveform), which we have previously reported (Gordon, 2005). This atypical pattern consisted of a negative peak (N1ci) followed by a positive peak (P2ci). The third type of cortical response (Multi-peak) was multi-peaked with 2 clear positive peaks (P1ci and P2ci) separated by a negative peak (N1ci).

Figure 3.1

Responses were categorized by three independent judges who were blinded to child, ear, and duration of CI use. Correlation between the judges is listed in Table 3.2A to D. These correlations were performed in a subset of our data consisting of 182 responses from 36 simultaneously implanted children and 55 sequentially implanted children. Recordings were evoked by the right and left CI in all children.
Table 3.2A

<table>
<thead>
<tr>
<th></th>
<th>Judge 1</th>
<th>Judge 2</th>
<th>Judge 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judge 1</td>
<td>1.0</td>
<td>0.848</td>
<td>0.83</td>
</tr>
<tr>
<td>Judge 2</td>
<td>0.848</td>
<td>1.0</td>
<td>0.803</td>
</tr>
<tr>
<td>Judge 3</td>
<td>0.83</td>
<td>0.803</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3.2A- Inter-item correlation in sequentially implanted individuals’ responses evoked from experienced ear.
Intra-class correlation coefficient single measures – 0.82
Intra-class correlation coefficient average measures – 0.93
ANOVA with Friedman’s Test – Significance = 0.087

Table 3.2B

<table>
<thead>
<tr>
<th></th>
<th>Judge 1</th>
<th>Judge 2</th>
<th>Judge 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judge 1</td>
<td>1.0</td>
<td>0.836</td>
<td>0.779</td>
</tr>
<tr>
<td>Judge 2</td>
<td>0.836</td>
<td>1.0</td>
<td>0.732</td>
</tr>
<tr>
<td>Judge 3</td>
<td>0.779</td>
<td>0.732</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3.2B- Inter-item correlation in sequentially implanted individuals’ responses evoked from naive ear.
Intra-class correlation coefficient single measures – 0.78
Intra-class correlation coefficient average measures – 0.91
ANOVA with Friedman’s Test – Significance = 0.060

Table 3.2C

<table>
<thead>
<tr>
<th></th>
<th>Judge 1</th>
<th>Judge 2</th>
<th>Judge 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judge 1</td>
<td>1.0</td>
<td>0.819</td>
<td>0.558</td>
</tr>
<tr>
<td>Judge 2</td>
<td>0.819</td>
<td>1.0</td>
<td>0.498</td>
</tr>
<tr>
<td>Judge 3</td>
<td>0.558</td>
<td>0.498</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3.2C- Inter-item correlation in simultaneously implanted individuals’ responses evoked from right ear.
Intra-class correlation coefficient single measures – 0.61
Intra-class correlation coefficient average measures – 0.82
ANOVA with Friedman’s Test – Significance = 0.28

Table 3.2D

<table>
<thead>
<tr>
<th></th>
<th>Judge 1</th>
<th>Judge 2</th>
<th>Judge 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Judge 1</td>
<td>1.0</td>
<td>0.888</td>
<td>0.711</td>
</tr>
<tr>
<td>Judge 2</td>
<td>0.888</td>
<td>1.0</td>
<td>0.64</td>
</tr>
<tr>
<td>Judge 3</td>
<td>0.711</td>
<td>0.64</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 3.2D- Inter-item correlation in simultaneously implanted individuals’ responses evoked from left ear.
Intra-class correlation coefficient single measures – 0.72
Intra-class correlation coefficient average measures – 0.89
ANOVA with Friedman’s Test – Significance = 0.37

3.5 Marking CAEP Responses

The peaks were marked using Neuroscan 4.3 software. Positive and negative peaks as identified in the categorization process were marked for latency (relative to stimulus onset) and amplitude (relative to baseline activity recorded from -50 ms to 0 ms). Only the peaks occurring
>50 ms were considered to avoid mistaking stimulus artifact as a neural response. We have previously shown using independent component analyses (ICA) that this technique is sufficient to avoid artifact created by our short stimulus (Gordon et al., 2008).

### 3.6 Clustering Using Principal Component Analysis (PCA)

We utilized a clustering procedure to determine the reliability of the visual inspection for all responses collected (144 responses from simultaneously implanted users and 110 responses in sequential bilateral CI recipients). This procedure used principal component analysis (PCA) as a way to categorize waveforms that shared a common morphology, and to distinguish one group of responses from another.

Each principle component is an orthogonal basis vector (or eigenvector) which is derived from the cortical response in 2-dimensional space (i.e. x-y plane). The PCA begins by calculating co-variances of each of the time points across the cortical response data set. The structure is calculated based on these correlations, with the idea that variables that are correlated share the same underlying component (Chapman and McCreary, 1995).

The first principal component accounts for the maximum possible variability in the data. Each successive component accounts for as much of the residual variability as possible. Principle component scores represent the strength of the relationship between a given cortical response and the principal components.

Since first 3 principal components accounted for more than 85% of the variability in the data, we used the first 3 principal component scores as coordinates, and displayed the relationship between the 3 scores as a point in 3-dimensional space (see Figures 4.1.4, 4.2.3 and 4.3.3). Each point in the graph represents a cortical response in eigenvector. In addition, it should also be noted that each point belongs to a particular cluster type, as indicated by the different
symbols.

To assess the most optimal number in which the data set clustered into groups, Xie-Beni (XB) index was computed for each cluster number. The greater index of XB values indicate greater degree in which the given dataset clusters into similar groups (Figures 4.1.3, 4.2.2 and 4.3.2).
Chapter 4 - Results

In this chapter, we present the experimental results for each of the three studies that were conducted in this thesis. In the first section, we present our results obtained from bilaterally naïve auditory cortices. In the second section, we present our results from unilaterally experienced auditory cortices. In the third section, we present our results from unilaterally naïve auditory cortices. We then present results of morphology similarity/differences between the experienced and naïve ears in sequentially implanted individuals, followed by overall comparison of three groups in the final section.

4.1 Responses in Children Receiving Bilateral Cochlear Implants Simultaneously After a Period of Bilateral Deafness

For our first study, the experimental question was: “Does bilateral deafness arrest auditory development resulting in persistently immature responses from auditory cortex?” Our hypothesis to this question was that cortical responses from bilaterally deaf children would resemble immature cortical responses from young NH children.

As shown in Figure 4.1.1, there was a high variability in CAEPs recorded in children receiving bilateral CIs simultaneously. In order to explain the data, we divided responses into categories according to wave morphology. As detailed in the methods, three types of waveforms were identified visually: 1) Positive peak responses, 2) Negative peak responses, and 3) Multi-peak responses.
4.1.1 Categorization of Responses

Examples of responses evoked by right and left CI stimulation in simultaneously implanted individuals (n=72) are shown in Figure 4.1.2. The incidence of these combinations of responses is indicated. Negative peak waveform responses were most prevalent (48.6%), followed by Positive peak waveform (26.4%) and Multi-peak waveform (22.2%) responses. The average age of implantation in individuals who showed Negative peak waveform responses were 1.93±1.94 years, individuals with Positive peak waveform responses were 2.79±2.91 years, and Multi-peak
waveform responses were $N=2.63\pm3.38$ years. These demographic details are provided in Table 4.1.1A. ANOVA showed that neither age at implantation for first CI ($F(2,141)=1.9 \ p=0.16$) nor duration of bilateral deafness ($F(2,141)=1.9, \ p=0.16$) was significantly different across the groups.

**Table 4.1.1A**

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Age1st CI</th>
<th>Dur Bilateral Deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>38</td>
<td>2.8±2.9</td>
<td>2.5±3.0</td>
</tr>
<tr>
<td>Negative</td>
<td>70</td>
<td>1.9±1.9</td>
<td>1.7±1.9</td>
</tr>
<tr>
<td>Multi-peak</td>
<td>36</td>
<td>2.63±3.4</td>
<td>1.6±0.9</td>
</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td>$F(2,141)=1.9 \ p=0.16$</td>
<td>$F(2,141)=1.9, \ p=0.16$</td>
</tr>
</tbody>
</table>

*Table 4.1.1A - Demographic details by waveform response type in simultaneously implanted children. Age 1st CI - Age at Implantation for first; Dur Bilateral Deafness - Duration of bilateral deafness.*

*statistically significant

**Figure 4.1.2**

*Figure 4.1.2 Examples of replicated responses evoked in simultaneously implanted individuals (n=72). Mismatched responses between right and left ears are shown in the right panel, and matched response morphologies between right and left ears are shown in the left panel with their respective frequencies.*

Overall, 86.1% (n=62) of the children receiving bilateral CIs simultaneously showed similar response types between the ears, while 13.9% (n=10) of the subjects had different types of responses between the ears. Of the 10 children who had different right and left evoked responses, 4 had Multi-peak waveform left evoked responses and a right evoked Positive peak waveform response; 2 had Multi-peak waveform left evoked responses and right evoked
Negative peak response; 2 with left evoked Negative peak response and right evoked Multi-peak response, 1 child had a left evoked Positive peak waveform response and right evoked Negative peak waveform response, and another child had left evoked Negative peak response and right evoked Positive peak response.

The average age at implantation for individuals who showed similar responses between the ears was 2.42±2.83 years (n=62). In particular, those that showed Positive peak waveform responses had an average age at implantation of 2.99±3.16 years (n=16), Negative peak waveform with 1.93±2.03 years (n=32), and Multi-peak waveform with 2.87±3.87 years (n=14). The 10 children who showed different cortical responses between the ears had an average age at implantation of 1.83±0.85 years (n=10). The differences in age at implantation for individuals who showed similar and different response types between the ears were not found to be significant from one another (t=1.3, df=48, p=0.20, p>0.05).

The average duration of bilateral deafness for individuals who showed similar responses between the ears were 1.93±2.27 years (n=62), as shown in Table 4.1.1B. In particular, those that showed Positive peak waveform responses had an average duration of bilateral deafness of 2.55±3.32 years (n=16), those with a Negative peak waveform (n=32) had 1.76±2.03 years of bilateral deafness, and children with Multi-peak waveforms (n=14) had 1.60±0.97 years of bilateral deafness. The 10 children who showed different cortical responses between the ears had an average duration of bilateral deafness of 1.77±0.81 years (n=10), as shown in Table 4.1.1C. The differences in duration of bilateral deafness for individuals who showed similar and different response types between the ears were not found to be significant from one another (t=-0.40, df=38, p=0.069, p>0.05). For individuals who showed different responses between right and left ear evoked responses, no significant differences in demographic details were observed between
different response combinations. It should also be noted that the combination of Negative peak and Positive peak and Positive peak and Negative peak in left and right ears, respectively, were omitted from the statistical analysis, because only one individual was found in each group.

Table 4.1.1B

<table>
<thead>
<tr>
<th>Match</th>
<th>Number</th>
<th>Age 1st CI</th>
<th>Dur Bilateral Deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>P and P</td>
<td>16</td>
<td>2.99±3.16</td>
<td>2.55±3.32</td>
</tr>
<tr>
<td>N and N</td>
<td>32</td>
<td>1.93±2.03</td>
<td>1.76±2.03</td>
</tr>
<tr>
<td>M and M</td>
<td>14</td>
<td>2.87±3.87</td>
<td>1.60±0.97</td>
</tr>
<tr>
<td>ANOVA</td>
<td>F(2,59)=0.97, p=0.38</td>
<td>F(2,59)=0.82, p=0.44</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1.1B – Demographic details by waveform response type in simultaneously implanted children who show matching morphology between responses evoked by right and left ears.

Table 4.1.1C

<table>
<thead>
<tr>
<th>Mismatch</th>
<th>Number</th>
<th>Age 1st CI</th>
<th>Dur Bilateral Deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>M and P</td>
<td>4</td>
<td>2.11±0.83</td>
<td>2.11±0.83</td>
</tr>
<tr>
<td>M and N</td>
<td>2</td>
<td>1.22±0.21</td>
<td>1.22±0.21</td>
</tr>
<tr>
<td>N and M</td>
<td>2</td>
<td>1.85±1.15</td>
<td>1.85±1.15</td>
</tr>
<tr>
<td>N and P</td>
<td>1</td>
<td>0.87</td>
<td>0.87</td>
</tr>
<tr>
<td>P and N</td>
<td>1</td>
<td>2.88</td>
<td>2.88</td>
</tr>
<tr>
<td>ANOVA</td>
<td>F(2,5)=0.76, p=0.52</td>
<td>F(2,5)=1.1, p=0.41</td>
<td></td>
</tr>
</tbody>
</table>

Table 4.1.1C- Demographic details by waveform response type in simultaneously implanted children who show mismatched morphology between responses evoked by right and left ears. Legends: P – Positive peak response, N – Negative peak response, M-Multi-peak response, ImpAge1st = age at implantation for first CI, ImpAge2nd = age at implantation for second CI, DurUniCI Use = duration of unilateral CI use, DurBiDeaf=duration of bilateral deafness.

4.1.2 Clustering Analyses

To determine the reliability of our visual categorization process, we clustered the responses using PCA. As shown in Figure 4.1.3, XB values were calculated in order to determine how many clusters best explained the variability in the data. The highest XB value was given by a number of 7 cluster groups (XB=1.80). Figure 4.1.4 shows that 87% of the variability in responses collected from from simultaneously implanted individuals can be explained by the first 3 principal components (PCs). The weighting of each response into the 3 PCs is shown by the 2 dimensional scatterplots.
Figure 4.1.3 – Correlation of cluster number and XB values. The highest XB-cluster value was found in a number of 7 cluster groups.
Figure 4.1.4 – Three principle components of the 144 responses were identified, explaining 87% of the response variability. The PC score was determined for each response. The three dimensional relationship between each PC score for all 144 components is represented by the two dimensional scatter plots. Seven different symbols represent the 7 cluster into which responses were grouped.

All 144 responses are shown in Figure 4.1.5 by cluster group. Responses are plotted by normalized amplitude over time in light grey lines and the cluster means are shown by the thicker lines. The clusters reflected 2 of the 3 categories of waveforms identified visually. Specifically, cluster 1 and 5 falls into the category of Positive peak waveform, whereas clusters 2, 3, 6 and 7 shows a mean which falls into the category of Negative peak waveform. In contrast, cluster 4 was Multi-peaked.
Figure 4.1.5– All 144 responses are grouped by cluster group. Individuals responses are shown in light grey and the cluster mean is shown by a ticker black line. Cluster means on the left had one Positive peak (i.e. Positive peak waveform) with the exception of cluster 4, which is Multi-peaked. Cluster means on the right had a Negative peak which in 2 cases preceded a Positive peak (cluster #2 and cluster #7).
4.1.3 Comparing Results from Visual Grouping to Clustering Analysis

Figure 4.1.6A shows the comparison of visual groupings (Positive and Negative peak responses) to cluster groupings and shows a strong agreement between the visual categories and cluster analyses of response types. In general, there was an agreement between the visual grouping and cluster groupings for the Positive peak and Negative peak responses 81.3%, relative to the disagreement of 18.7%.

On the other hand, the responses categorized visually as Multi-peak responses were equally divided in the clustering analyses between Positive and Negative peak clusters. Figure 4.1.6B shows that there was a wide distribution of visually defined Multi-peaked responses across the 7 clusters. Figure 4.1.7 shows the grandmean of response amplitude over time (±S.D.) for all waveforms with a Positive peak and those with a Negative peak as defined by visual categorization and by cluster analysis. Due to the divide in visually categorized Multi-peak responses by the clustering analysis, we omitted Multi-peak responses from the visual grouping (n=36), and cluster #4 (n=24).
Figure 4.1.6A and 4.1.6B

Figure 4.1.6 (A) Visual inspection of positive and negative peaks was mostly in agreement with cluster analyses. The Multi-peak responses as determined visually were divided almost equally into both positive and Negative peak clusters. (B) A closer look at the cluster analysis of responses visually categorized as Multi-peak waveform indicates a broad distribution across all clusters.
Figure 4.1.7

**Visual Grouping (n=108)**

![Graph showing mean and ±1 SD of positive peak waveforms grouped by visual and cluster analyses.]

**Cluster Grouping (n=120)**

![Graph showing mean and ±1 SD of positive peak waveforms grouped by visual and cluster analyses.]

**Figure 4.1.7–** Grandmean and ±1 SD of Positive and Negative peak waveforms are shown as grouped by visual and cluster analyses with good agreement. Stimulus artifact can be seen in 3 of 4 plots and is contained to the first 40 ms of the recording window.

### 4.1.4 Similar Responses Morphology between the Bilaterally Naïve Ears

Similarity between right responses and left responses in simultaneously implanted individuals, based on visual categorization is shown as grand mean average waveforms in Figure 4.1.8. There were 22 Positive peak responses from the right side, and its corresponding response from the left side is also Positive peak waveform. Similarly, Negative peak waveforms (n=34) and Multi-peak waveforms (n=16) from the right side also shows very similar morphology patterns compared to responses from the left side.
Figure 4.1.8– Grandmean and ±1 SD of waveforms grouped by type of response evoked by the right CI. Mean responses from the left CI are similar to the right. Stimulus artifact was clear in some cases and is contained to within the first 40 ms of the recording window.
4.1.5 Latency of Cortical Responses Evoked by Bilaterally Naïve Ears

Mean (±SD) peak latencies are shown in Table 4.1.2. The latency for P1ci in the Positive peak waveform responses (135.7±28.8 ms) and N1ci in the Negative peak waveform response (127.62±33.4 ms) occurred at similar latencies (t=-1.3, df=86, p=0.190, p>0.05), whereas the mean latency for P1ci in the Multi-peak waveform responses occurred earlier (116.8±39.2 ms) and was not significant with respect to Negative peak N1ci (t=-1.4, df=62, p=0.16, p>0.05), but was significant with respect to Positive peak P1ci (t=-2.4, df=64, p=0.02, p<0.05). N1ci values for Positive peak waveform and Multi-peak waveform were 258.0±47.8 ms and 188.5±49.9 ms, respectively with significant differences between the two values (t=6.1, df=71, p=4.6E-8, p<0.05). The mean latencies for P2ci values for Negative peak waveform and Multi-peak waveform waveforms were 238.9±52.1 ms and 285.0±49.7 ms, with a significant difference between the two peaks (t=-4.4, df=74, p=3.0E-5, p<0.05).

Table 4.1.2

<table>
<thead>
<tr>
<th>Average Latency (ms)</th>
<th>P1ci (±S.D.)</th>
<th>N1ci (±S.D.)</th>
<th>P2ci (±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Peak Waveform</td>
<td>135.7±28.8</td>
<td>258.0±47.8</td>
<td>—</td>
</tr>
<tr>
<td>Negative Peak Waveform</td>
<td>—</td>
<td>127.6±33.4</td>
<td>238.9±52.1</td>
</tr>
<tr>
<td>Multi-Peak Waveform</td>
<td>116.8±39.2</td>
<td>188.5±49.9</td>
<td>285.0±49.7</td>
</tr>
</tbody>
</table>

Table 4.1.2 – Latency of cortical response peaks by category for simultaneously implanted individuals.

To determine the effect of age at implantation and duration of deafness on peak latency values of the responses, bivariate correlation was performed. In simultaneously implanted individuals, there was no significant effect of duration of deafness or age at implantation, except for N1ci latency of Multi-peak responses which showed a statistical significance with respect to age at implantation (Spearman 0.42, p=0.011, p<0.05, N=36). Spearman’s rho correlation
coefficients for the non-significant factors ranged from 0.011 to 0.288, p>0.05 for age at implantation and -0.092 to 0.280, p>0.05 in duration of bilateral deafness.

4.1.6 Amplitude of Cortical Responses Evoked by Bilaterally Naïve Ears

Mean (±SD) of amplitudes for each peak are shown in Table 4.1.3. The smallest mean amplitude value was seen in Multi-peak P1ci (3.6±3.5μV), which was not found to be significantly different from Positive peak P1ci (t=1.83, df=69, p=0.072, p>0.05). For N1ci amplitudes, the largest mean amplitude was seen with Negative peak waveform N1ci (6.2±5.4μV), followed by Multi-peak N1ci (-4.9±6.1μV) and Positive peak N1ci (-4.4±3.7μV).

In terms of differences, Negative peak N1ci and Positive peak N1ci showed a significance (t=-2.1, df=101, p=0.042, p<0.05), while the difference in N1ci between Positive peak and Multi-peak (t=-0.445, df=72, p=0.657, p>0.05) and Negative and Multi-peak (t=1.114, df=104, p=0.268, p>0.05) were not significant. For P2ci, both Negative peak and Multi-peak responses showed similar mean amplitudes (5.2±5.8μV and 5.0±4.6μV, respectively) which was found to be not statistically significant (t=0.20, df=86, p=0.84, p>0.05).

Table 4.1.3

<table>
<thead>
<tr>
<th>Average Amplitude (μV)</th>
<th>P1ci (±S.D.)</th>
<th>N1ci (±S.D.)</th>
<th>P2ci (±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Peak Waveform</td>
<td>5.3±4.5</td>
<td>-4.4±3.7</td>
<td>——</td>
</tr>
<tr>
<td>Negative Peak Waveform</td>
<td>——</td>
<td>-6.2±5.4</td>
<td>5.2±5.8</td>
</tr>
<tr>
<td>Multi-Peak Waveform</td>
<td>3.6±3.5</td>
<td>-4.9±6.1</td>
<td>5.0±4.6</td>
</tr>
</tbody>
</table>

Table 4.1.3 – Amplitude of cortical response peaks by category for simultaneously implanted individuals.

To determine the effect of age at implantation and duration of deafness on peak amplitude values of the responses from simultaneously implanted individuals, bivariate correlation was performed. No significant effects of duration of deafness or age at implantation was seen in most
peak values, with the exception of N1ci in Positive peak waveforms to duration of bilateral deafness (Spearman = 0.4, p=0.004, p<0.01, N=38) and P2ci of Multi-peak waveforms to age at implantation (Spearman=-0.4, p=0.015, p<0.05, N=36). Spearman’s rho correlation coefficients for non-significant factors ranged from -0.132 to 0.225, p>0.05 for age at implantation and -0.197 to 0.308, p>0.05 for duration of bilateral deafness.

In this section, we hypothesized that cortical responses from bilaterally deaf children would resemble immature cortical responses from young NH children. In contrast to our hypothesis, only half of visually categorized responses showed the typically immature response morphology of Negative peak waveform, while the rest showed more mature morphology of Positive peak responses (26%), as well as a previously unreported morphology of Multi-peak responses (25%). We validated our analytic process with the use of statistical test, PCA, which showed a strong correlation with our visual categorization. The evoked response morphology between the right and left ears in simultaneously implanted children were similar in a large majority of cases (86.1%), while there were no demographic differences across the individuals who showed three different response morphologies. Furthermore, we found a significant difference in latency values for P1ci and N1ci of Positive and Multi-peak responses, while a significant difference was found for N1ci of Positive and Negative peak amplitudes. These results from bilaterally naïve ears in simultaneously implanted children are discussed further in Chapter 5, section 1 (5.1).

4.2 Cortical Responses Evoked from Experienced Ears in Children Receiving Second Cochlear Implant Devices After a Period of Unilateral Cochlear Implant Use

For our second study, the experimental question was: “Does a period of unilateral cochlear implant use promote more mature responses from the auditory cortex? To this question,
our hypothesis was that in children who receive a second CI after a period of unilateral CI use, CAEPs evoked by the CI in the experienced ear would resemble mature cortical response morphology.

4.2.1 Categorization of Responses

 Responses from experienced ear CI stimulation in sequentially implanted children showed variability, as shown in Figure 4.2.1. In contrast to the Negative peak grandmean waveform from simultaneously implanted children, the grandmean waveform shows a Positive peak waveform. Since there was variability in responses, we utilized the visual categorization to group similar response morphologies. Most of the responses evoked by the experienced ear were categorized as Positive peak waveform (83.6%), followed by 10.9% Multi-peak waveform and 5.5% of Negative peak waveform.

Figure 4.2.1

**Figure 4.2.1** - 55 responses evoked from experienced side ear in sequentially implanted individuals with grandmean waveform (thick line).
4.2.2 Clustering Analysis

Similar to the clustering analysis we performed on data from simultaneously implanted individuals, we applied the PCA to data from experienced side evoked responses in sequentially implanted children. The highest XB score was obtained in a number of 2 cluster groups (XB=1.80) as shown in Figure 4.2.2

Overall, 88 percent of our data from experienced side responses of sequentially implanted individuals was explained by 3 major PCs as shown in Figure 4.2.3. Overall, 47% of the data was accounted for by the first PC, 25% by the second PC, and 16% by the third PC. Clusters were determined by assessing the relative contributions (PC scores) of each PC in each waveform. The PC scores are plotted across the 3 PCs in the scatterplots.

Figure 4.2.2

Figure 4.2.2- Correlation of cluster number and XB values for experienced side evoked responses in sequentially implanted individuals. The highest XB-cluster value was found in a number of 2 cluster groups.
Three principle components of the 55 responses from experienced side evoked response were identified, explaining 88% of the response variability. The PC score was determined for each response. The three dimensional relationship between each PC score for all 55 components is represented by the two dimensional scatter plots. Two different symbols represent the 2 cluster into which responses were grouped.

All 55 evoked responses from unilaterally experienced side are shown in Figure 4.2.4 by cluster group. Responses are plotted by normalized amplitude over time in light grey lines and the cluster means are shown by the thicker lines. The clusters reflected 1 of the 3 categories of waveforms identified visually. Specifically, both cluster 1 and 2 falls into the category of Positive peak waveform.
Figure 4.2.4- All 55 evoked responses from experienced side from sequentially implanted individuals are grouped into clusters. Individual responses are shown in light grey and the cluster mean is shown by a ticker black line. Two groups of clusters look similar and have a Positive peak waveform morphology.

4.2.3 Comparing Results from Visual Grouping to Clustering Analysis

Figure 4.2.5 shows the comparison of visual analysis (Table 4.2.1) to that from clustering analysis. Since the first and second cluster groups resembled a Positive peak waveform, all 55 evoked responses from the experienced ear were grouped into a single category Positive peak response in the clustering analysis. In contrast, 46 of the responses from the visual analysis were categorized as Positive peak waveform. Hence, there was 84% agreement between the visual and cluster analysis.
4.2.4 Demographic Details by Type

As Table 4.2.1 shows, individuals with Positive peak and Multi-peak responses are younger compared to individuals who showed Negative peak response in demographic details. There was no statistical significance between waveform types in terms of age at implantation for first CI. In contrast, age at implantation for second CI (F(2,52)=6.8, p=0.015), duration of unilateral CI use (F(2,52)=4.6, p=0.01) and duration of bilateral deafness (F=(2,52)=7.5, p=0.002) showed statistically significant differences between the types. More specifically, individuals with Negative peak responses have mean values that are significantly older for three categories of demographic details compared to Positive peak and Multi-peak responses.

We also found statistically significant differences in demographic factors between Positive and Multi-peak responses. While there were no differences in age at implantation for first CI (t=1.0, df=9, p=0.327, p>0.05), there was a difference for age at implantation for second
CI (t=3.8, df=22, p=0.001, p<0.05), duration of unilateral CI use (t=-4.1, df=9, p=0.002, p<0.05) and duration of bilateral deafness (t=3.638, df=10, p=0.005, p<0.05). In general, children with Multi-peak responses were younger compared to children with Positive peak responses.

Table 4.2.1

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Age 1st CI</th>
<th>Age 2nd CI</th>
<th>DurUniCI Use</th>
<th>Dur Bilateral Deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>45</td>
<td>1.6±0.7</td>
<td>2.2±0.6</td>
<td>1.6±0.5</td>
<td>1.6±0.5</td>
</tr>
<tr>
<td>Negative</td>
<td>4</td>
<td>2.9±1.7</td>
<td>5.8±3.4*</td>
<td>2.9±1.7*</td>
<td>2.9±1.7*</td>
</tr>
<tr>
<td>Multi-peak</td>
<td>6</td>
<td>1.6±0.7</td>
<td>2.2±0.6</td>
<td>0.6±0.5</td>
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</tr>
<tr>
<td>ANOVA</td>
<td></td>
<td>F(2,52)=1.6, p=0.20</td>
<td>F(2,52)=6.8, p=0.015 *</td>
<td>F(2,52)=4.6, p=0.01 *</td>
<td>F=(2,52)=7.5, p=0.002 *</td>
</tr>
</tbody>
</table>

Table 4.2.1– Demographic details of response categories evoked from the experienced ear CI stimulation in sequentially implanted children.

4.2.5 Latency of Cortical Responses Evoked by the Experienced Ear

The mean (±SD) values for each peak marked in responses evoked by the experienced ear are shown in Table 4.2.2. The P1ci in Multi-peak waveform responses (95.1±18.6ms) occurred earliest, followed by N1ci for Negative peak waveform responses (103.0±17.0ms) and then the P1ci in Positive peak waveform responses (114.6±19.8ms), which did not show any statistically significant difference (F(2,52)=3.0, p=0.057). No statistically significant differences were observed between Positive peak and Multi-peak P1ci (t=2.4, df=7, p=0.051, p>0.05), Multi-peak P1ci and Negative peak N1ci (t=0.68, df=7, p=0.52, p>0.05), or Positive peak P1ci and Negative peak N1ci (t=−1.29, df=4, p=0.27, p>0.05). In addition, Multi-peak waveform N1ci was seen earlier (164.6±32.2ms) than N1ci in Positive peak waveform responses (235.5±50.7ms), which reached a statistical significance (t=−3.9, df=8, p=0.0012, p<0.05). Furthermore, P2ci in Negative peak waveform responses occurred earlier (220.5±68.6ms) than P2ci in Multi-peak waveform responses (255.9±45.4ms), but were not statistically different (t=−0.91, df=5, p=0.41, p<0.05).
Table 4.2.2

<table>
<thead>
<tr>
<th>Average Latency (ms)</th>
<th>P1ci (±S.D.)</th>
<th>N1ci (±S.D.)</th>
<th>P2ci (±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Peak Waveform</td>
<td>114.6±19.8</td>
<td>235.5±50.7</td>
<td>——</td>
</tr>
<tr>
<td>Negative Peak Waveform</td>
<td>——</td>
<td>103.0±17.0</td>
<td>220.5±68.6</td>
</tr>
<tr>
<td>Multi-Peak Waveform</td>
<td>95.1±18.6</td>
<td>164.6±32.2</td>
<td>255.9±45.4</td>
</tr>
</tbody>
</table>

Table 4.2.2- Latency of cortical response peaks by category for evoked responses from experienced ear in sequentially implanted individuals.

Peak latencies evoked by the experienced ear were compared against age at implantation for the first CI, age at implantation for the second CI, duration unilateral CI use, and duration of bilateral deafness. Statistical significance was only seen with respect to P1ci of Multi-peak responses to age at implantation for 2nd CI (Spearman = 0.94, 0.005, p<0.01, N=6) which increased in latency with increases in age (β=31.3 ms/year). Spearman’s rho correlation coefficients for non-significant factors ranged from -0.37 to 0.12, p>0.05 for age at implantation for first CI, 0 to 0.77, p>0.05 for age at implantation for 2nd CI, -0.007 to 0.6, p>0.05 for duration of unilateral CI use, and -0.07 to 0.6, p>0.05 for duration of bilateral deafness.

4.2.6 Amplitude of Responses Evoked by the Experienced Ear

Mean (±SD) amplitudes for each peak evoked from the experienced side are shown in Table 4.6. The smallest mean amplitude was seen with P2ci of Negative peak waveform (3.0±1.6µV), whereas the largest amplitude was seen in Multi-peak waveform P1ci (6.9±4.7µV). Comparisons between Positive and Multi-peak P1ci values showed no significant differences (t=0.208, df=8, p=0.84, p>0.05). This was also the case for N1ci values among Positive peak, Negative peak and Multi-peak waveforms (F(2,52)=1.2, p=0.31, p>0.05). For P2ci, no statistical difference was seen between Negative peak and Multi-peak values (t=0.80, df=6, p=0.46, p>0.05).
Peak amplitudes evoked by the experienced ear were compared against duration of unilateral CI use, age at implantation, duration of unilateral CI use and duration of bilateral deafness. No statistical significance was seen in any of these bivariate analyses. Spearman’s rho correlation coefficients for these statistically non-significant factors ranged from -0.4 to 0.429, p>0.05 for age at first implantation, -0.4 to 0.371, p>0.05 for age at second implantation, and -0.4 to 0.257, p>0.05 for duration of unilateral CI use and duration of bilateral deafness.

4.2.7 Effect of Duration of Unilateral CI Use on Responses Evoked by Unilaterally Experienced Ears

There was a clear change from multiple response types found in children with no CI experience (simultaneous group) compared to a dominance of Positive peak response types after unilateral CI experience. To further investigate the change in latencies and amplitudes of responses with unilateral CI use, we compared responses evoked in experienced ears of children in the sequential bilateral group with the bilaterally naïve responses from children in the simultaneous bilateral group. The latency of P1ci and N1ci of the Positive peak response significantly decreased in latency with duration of unilateral CI use (P1ci: Spearman=-0.366, p=0.001, p<0.01, N=83, N1ci: Spearman=-0.25 p=0.023, p<0.05, N=83). These findings are shown in scatterplot in Figure 4.2.6. The significant decreases in latencies are evident from the
slope of the trendlines, which was -7.0 for Positive peak P1ci (P1ci: $\beta=-7.0$ ms/year) and -8.1 for Positive peak N1ci (N1ci: $\beta=-8.1$ ms/year). There were no significant effects of unilateral CI use on the latency (Spearman’s rho coefficient values range from -0.23 to -0.091, $p>0.05$) or on the amplitude (Spearman’s rho coefficient values range from -0.078 to 0.238, $p>0.05$) of any of the peaks.

Table 4.2.4A and B shows the details of comparison of peak latency and amplitude values between responses evoked from the simultaneously implanted group and unilaterally experienced sides. As mentioned before, significant differences were only in Positive peak P1ci and N1ci and Multi-peak P1ci latencies, while no significant differences were found in amplitude. Although Multi-peak P1ci latency showed statistically significant differences between responses evoked by unilaterally experienced and unilaterally naïve responses, regression analyses showed no such significance. This was likely caused by a large spread in P1ci latency within the small number of unilaterally experienced side responses ($n=6$).

Table 4.2.4A

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>Sequential Experienced</th>
<th>T-Test</th>
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<tbody>
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</tr>
<tr>
<td>P1ci</td>
<td>38</td>
<td>135.7 ±28.8</td>
<td>45</td>
</tr>
<tr>
<td>N1ci</td>
<td>38</td>
<td>258.0 ±47.8</td>
<td>45</td>
</tr>
<tr>
<td>Negative</td>
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<tr>
<td>N1ci</td>
<td>70</td>
<td>127.6 ±33.4</td>
<td>4</td>
</tr>
<tr>
<td>P2ci</td>
<td>70</td>
<td>238.9 ±52.1</td>
<td>4</td>
</tr>
<tr>
<td>Multi-peak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P1ci</td>
<td>36</td>
<td>116.8 ±39.2</td>
<td>6</td>
</tr>
<tr>
<td>N1ci</td>
<td>36</td>
<td>188.5 ±49.9</td>
<td>6</td>
</tr>
<tr>
<td>P2ci</td>
<td>36</td>
<td>285.0 ±49.7</td>
<td>6</td>
</tr>
</tbody>
</table>

Table 4.2.4A – Mean latency and statistics associated with each comparison.

* statistically significant
Table 4.2.4B

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>Sequential Experienced</th>
<th>T-Test</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>N Mean (µV)</td>
<td>S.D.</td>
<td>N Mean (µV)</td>
</tr>
<tr>
<td>Positive P1ci</td>
<td>38  5.3 ±4.5</td>
<td>45  6.5 ±6.5</td>
<td>t=-1.0, p=0.323</td>
</tr>
<tr>
<td>N1ci</td>
<td>38 -4.4 ±3.7</td>
<td>45 -3.7 ±4.8</td>
<td>t=-0.72, p=0.47</td>
</tr>
<tr>
<td>Negative N1ci</td>
<td>70 -6.2 ±5.4</td>
<td>4   -6.2 ±4.1</td>
<td>t=0.022, p=0.98</td>
</tr>
<tr>
<td>P2ci</td>
<td>70  5.2 ±5.8</td>
<td>4   3.0 ±1.6</td>
<td>t=2.7, p=0.10</td>
</tr>
<tr>
<td>Multi-peak P1ci</td>
<td>36  3.6 ±3.5</td>
<td>6   6.9 ±4.7</td>
<td>t=-1.7, p=0.14</td>
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<tr>
<td>N1ci</td>
<td>36 -4.9 ±6.1</td>
<td>6   -6.6 ±8.1</td>
<td>t=0.49, p=0.64</td>
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<tr>
<td>P2ci</td>
<td>36  5.0 ±4.6</td>
<td>6   5.1 ±6.2</td>
<td>t=-0.05, p=0.96</td>
</tr>
</tbody>
</table>

Table 4.2.4B – Mean amplitude and statistics associated with each comparison.
* statistically significant

Figure 4.2.6

Figure 4.2.6 – Scatterplot of bilaterally naive and unilaterally experienced responses for Positive peak P1ci and N1ci latencies with respect to duration of unilateral CI use.

As for Positive peak P1ci latency, we found it significantly increasing with increase in age at implantation for first CI (Spearman=0.25, p=0.001, p<0.01, N=83). To determine where this discrepancy in trends between duration of unilateral CI use and age at implantation was coming from, we performed a multiple regression analysis for these two factors. The results showed significant differences even when both factors were accounted together (Age at implantation for first CI: β=4.1 ms/year, S.E.= ±1.2, p=0.001; Duration of unilateral deafness: β
=6.7 ms/year, S.E.= ±2.5, p=0.01). To see why this is, we omitted five individuals from the Positive peak response group who had their first CI at age greater than five. By performing the same statistical analysis with five children who were implanted at ages older than five years, the effect of age at implantation on P1ci latency did not come to a statistically significant factor (t=1.4, p=0.18, p>0.05). Thus, children implanted at older ages show a longer latency for P1ci compared to children who were implanted at younger ages (<5 years), which influenced increasing trend of Positive peak P1ci latency.

In this section, we hypothesized that in children who receive a second CI after a period of unilateral CI use, the cortical responses evoked by the unilaterally experienced ear will resemble mature response morphologies. Our results showed that a large majority of responses (83.7%) from the unilaterally experienced ear showed the mature morphology of Positive peak responses, which was also confirmed by the PCA. Statistically significant demographic differences were seen between individuals who showed Negative peak and Multi-peak responses, but given the small number of individuals who showed such responses, the reliability of this data is called into question. These results from unilaterally experienced ears in sequentially implanted children are discussed further in Chapter 5, section 2 (5.2).

4.3 Cortical Responses Evoked from Unilaterally Naive Ears in Children Receiving Second Cochlear Implant Devices After a Period of Unilateral Cochlear Implant Use

For our third study, the experimental question was: “Does a period of unilateral cochlear implant use affect cortical responses evoked by the naïve contralateral ear?” We hypothesized that cortical responses evoked by evoked by unilaterally naïve ears would resemble responses evoked by the newly implanted and naïve ear in CI users.

Evoked responses from the naïve ear in sequentially implanted children showed
variability, as shown in Figure 4.3.1. The grandmean waveform from the unilaterally naïve ear shows a Multi-peak waveform in contrast to Negative peak and Positive peak grandmean waveforms seen from bilaterally naïve and unilaterally experienced ear responses, respectively. Visual categorization of the CAEPs evoked from the newly implanted ear in children receiving bilateral CIs sequentially were most often Multi-peaked (54.5%), with smaller proportions of Positive peak waveform (27.3%) and Negative peak waveform responses (18.2%).

Figure 4.3.1

Figure 4.3.1- 55 evoked responses evoked from naive ear in sequentially implanted individuals with grandmean waveform (thick line).
4.3.1 Clustering Analysis

PC analysis was applied to responses evoked from the unilaterally naive side in sequentially implanted children. As shown in Figure 4.3.2, the highest XB value from unilaterally naïve side responses was found in a number of 4 cluster groups (XB=2.11).

As detailed in Figure 4.3.3, 85% of the variability in responses from the unilaterally naïve side responses in sequentially implanted individuals was explained by 3 PCs. Overall, 40% of the variance was accounted for by the first PC, 27% by the second PC, and 18% by the third PC. The distribution of the waveforms by PC Score is shown in the scatterplots of Figure 4.17.

Figure 4.3.2

![Sequentially Implanted Individuals - Day 1 Naïve Side Response XB-Cluster Correlation (n=55)](image)

Figure 4.3.2- Correlation of cluster number and XB values for evoked responses from naïve ear in sequentially implanted individuals. The highest XB-cluster value was found in a number of 4 cluster groups.
Three principle components of the 55 evoked responses from naïve ear were identified, explaining 85% of the response variability. The PC score was determined for each response. The three dimensional relationship between each PC score for all 55 components is represented by the two dimensional scatter plots. Four different symbols represent the 4 cluster into which responses were grouped.

All 55 evoked responses from unilaterally naïve ear in sequentially implanted individuals are shown in Figure 4.3.4 by cluster group. Responses are plotted by normalized amplitude over time in light grey lines and the cluster means are shown by the thicker lines. The clusters reflected 2 of the 3 categories of waveforms identified visually. Specifically, cluster 1 and 2 falls into the category of Positive peak waveform, whereas clusters 3 and 4 shows a mean which falls into the category of multi-peak waveform.
Figure 4.3.4- All 55 evoked responses from naive ear from sequentially implanted individuals are grouped into clusters. Individual responses are shown in light grey and the cluster mean is shown by a ticker black line. Two groups of clusters look similar, with a Positive peak waveform morphology. The left column represents Positive peak clusters, and the right column represents Multi-peak response clusters.

4.3.2 Comparing Results from Visual Grouping to Clustering Analysis

Figure 4.3.5A shows the comparison of visual groupings (Positive and Multi-peak responses) to cluster groupings and shows a strong agreement between the visual categories and cluster analyses for Positive peak responses, while the visually categorized Multi-peak waveforms equally grouped into Positive and Multi-peak clusters. A high percentage of Negative peak waveforms (n=11) clustered into Multi-peak waveforms (91%).

Looking into visually categorized Multi-peak responses (n=29) further, as shown in Figure 4.3.5B, there was a high number of agreement with Positive peak cluster #2 (10/29) and
Multi-peak cluster #4 (14/29).

Figure 4.3.6 shows the comparison of visual analysis to that from clustering analysis. Since the first and second cluster groups resembled a Positive peak waveform (n=26), they were grouped as a single set, while third and fourth clusters were grouped as Multi-peak waveform (n=29). In contrast, 15 responses from the visual analysis were categorized as Positive peak waveform, while 30 were categorized as Multi-peak response.

Figure 4.3.5A and B

**Figure 4.3.5(A)** Visual inspection of Positive peak was mostly in agreement with cluster analyses while the Negative peak waveforms mostly clustered with Multi-peak clusters. The Multi-peak responses as determined visually were divided almost equally into both Positive and Multi-peak clusters. **(B)** A closer look at the cluster analysis of responses visually categorized as Multi-peak waveform indicates that most visually categorized responses agreed with cluster 2 or 4.
4.3.3 Demographic Details by Type

As Table 4.3.1 shows, individuals with Positive peak responses are older compared to individuals who showed Negative peak response for the demographic details of age at implantation for first and second CI, duration of unilateral CI use, and duration of bilateral deafness. Comparisons of these mean values, however, did not reach any statistically significant values, thus indicating no difference in demographic details between the waveform types.

There was no statistical significance between waveform types in terms of age at implantation for first ($F=(2,52)=0.45$, $p=0.64$) and second CI ($F=(2,52)=0.91$, $p=0.48$), duration of unilateral deafness ($F=(2,52)=0.73$, $p=0.42$) or duration of bilateral deafness ($F=(2,52)=0.88$, $p=0.41$).
Table 4.3.1

<table>
<thead>
<tr>
<th>Type</th>
<th>Number</th>
<th>Age 1&lt;sup&gt;st&lt;/sup&gt; CI</th>
<th>Age 2&lt;sup&gt;nd&lt;/sup&gt; CI</th>
<th>DurUniCI Use</th>
<th>Dur Bilateral Deafness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>15</td>
<td>2.2±1.5</td>
<td>4.1±2.3</td>
<td>1.9±1.0</td>
<td>1.9±1.1</td>
</tr>
<tr>
<td>Negative</td>
<td>11</td>
<td>1.9±1.3</td>
<td>3.4±2.6</td>
<td>1.5±1.5</td>
<td>1.5±1.5</td>
</tr>
<tr>
<td>Multi-peak</td>
<td>29</td>
<td>1.8±1.0</td>
<td>3.4±1.5</td>
<td>1.5±0.8</td>
<td>1.4±0.8</td>
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<td>ANOVA</td>
<td></td>
<td>F=(2,52)=0.45, p=0.64</td>
<td>F=(2,52)=0.90, p=0.49</td>
<td>F=(2,52)=0.73, p=0.42</td>
<td>(F=(2,52)=0.88, p=0.42</td>
</tr>
</tbody>
</table>

Table 4.3.1- Demographic details of cortical responses evoked from unilaterally naïve ear in sequentially
* statistically significant

4.3.4 Latencies of Responses Evoked by the Unilaterally Naïve Side

Table 4.3.2 plots mean (± SD) latency values for each peak evoked by the naïve ear in children receiving bilateral CI sequentially. Latencies occurred earliest for Multi-peak waveform P1ci peaks (92.9±4.0ms) followed by P1ci in Positive peak waveform responses (121.9±38.7ms). These two peaks were found to be significantly different (t=2.69, df=18, p=0.015, p<0.05). In contrast, the comparison of Positive peak P1ci and Negative peak N1ci (135.5±31.2ms) were not significant (t=0.991, df=24, p=0.33, p>0.05), while the comparison between Multi-peak P1ci and Negative peak N1ci was found to be significant (t=4.16, df=14, p=0.0001, p<0.05). The earliest N1ci was in the Negative peak waveform (135.5±31.2ms), preceding Multi-peak waveform N1ci (167.8±39.2ms) and Positive peak waveform N1ci (231.9±57.0ms) peaks. The comparison of N1ci peak values between positive and negative, negative and Multi-peak, and positive and Multi-peak waveforms were all found to be significantly different from one another (t=5.5, df=22, p=1.4E-5, p<0.05; t=-2.7, df=23, p=0.012, p<0.05; t=3.90, df=21, p=0.001, p<0.05, respectively). As for P2ci peaks, mean latencies in the Negative peak waveform responses (225.2±50.3ms) were earlier in latency than in Multi-peak waveform responses (246.5±63.6ms) and they were not found to be significantly different from one another (t=-1.1, df=23, p=0.28, p>0.05).
Table 4.3.2

<table>
<thead>
<tr>
<th>Table 4.3.2</th>
<th>Latency of cortical response peaks by category for evoked responses from naïve ear in sequentially implanted individuals.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average Latency (ms)</strong></td>
<td><strong>P1ci (±S.D.)</strong></td>
</tr>
<tr>
<td><strong>Positive Peak Waveform</strong></td>
<td>121.9±38.7</td>
</tr>
<tr>
<td><strong>Negative Peak Waveform</strong></td>
<td>——</td>
</tr>
<tr>
<td><strong>Multi-Peak Waveform</strong></td>
<td>92.9±21.5</td>
</tr>
</tbody>
</table>

Peak latencies evoked by the naïve ear were compared against age at implantation for first CI, age at implantation for 2nd CI, duration of unilateral CI use and duration of bilateral deafness. Spearman’s rho correlation coefficients ranged from -0.236 to 0.329, p>0.05, for age at implantation for first CI, -0.22 to 0.26, p>0.05, for age at implantation for 2nd CI, -0.39 to 0.16, p>0.05, for duration of unilateral CI use and -0.39 to 0.21, p>0.05, for duration of bilateral deafness. Statistical significance was only seen with respect to P1ci of Positive peak responses to age at implantation for the naïve ear (Pearson =0.52, p>0.05, N=15).

4.3.5 Amplitude of Responses from Unilaterally Naïve Side

The mean (±SD) amplitudes for each response type evoked by the naïve side are shown in Table 4.3.3. In P1ci, Multi-peak amplitude (4.9±6.5μV) was found to be smaller compared to Positive peak amplitude (7.3±8.2μV), but the two were not statistically different (t=0.97, df=23, p=0.34, p>0.05). In N1ci, the comparison between positive (-5.3±5.0μV) and negative peaks (-9.9±6.8μV) and positive and Multi-peaks (-4.7±7.0μV) were not found to be statistically significant (t=-1.89, df=18, p=0.075, 0>0.05, and t=-0.35, df=37, p=0.73, p>0.05 respectively), while the difference between negative and Multi-peaks were found to be statistically different (t=-2.2, df=18, p=0.044, p<0.05). For P2ci amplitudes, value for Multi-peak (3.1±4.7μV) was
found to be smaller than Negative peak (6.6±6.2 µV), but the two were not found to be statistically different (t=1.7, df=14, p=0.11, p>0.05).

Table 4.3.3

<table>
<thead>
<tr>
<th>Waveform</th>
<th>P1ci (±S.D.)</th>
<th>N1ci (±S.D.)</th>
<th>P2ci (±S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Peak Waveform</td>
<td>7.3±8.2</td>
<td>-5.3±5.0</td>
<td>-</td>
</tr>
<tr>
<td>Negative Peak Waveform</td>
<td>-</td>
<td>-9.9±6.8</td>
<td>6.6±6.2</td>
</tr>
<tr>
<td>Multi-Peak Waveform</td>
<td>4.9±6.5</td>
<td>-4.7±7.0</td>
<td>3.1±4.7</td>
</tr>
</tbody>
</table>

Table 4.3.3- Amplitude of cortical response peaks by category for evoked responses from naïve ear in sequentially implanted individuals.

Peak amplitudes evoked by the naive ear were compared against age at implantation for first CI, age at implantation for 2nd CI, duration of unilateral CI use and duration of bilateral deafness. The NIci amplitude of the Negative peak responses decreased significantly with age at second implantation (Spearman = -0.67, 0.023, p>0.05, N=11). Other than this finding, amplitudes were not significantly affected by age at first CI (Spearman=-0.509 to 0.311, p>0.05), age at second CI (Spearman= -0.23 to 0.473, p>0.05,) duration of unilateral CI use (Spearman=-0.44 to 0.26, p>0.05), or duration of bilateral deafness (Spearman=-0.44 to 0.24, p>0.05).

4.3.6 Effect of Duration of Unilateral CI Use on Responses Evoked by Unilaterally Naïve and Bilaterally Naïve Ears

We assessed the effect of unilateral CI stimulation on the contralateral side by comparing latencies and amplitudes of CAEPs evoked by the naïve side in children receiving bilateral CIs sequentially with those receiving bilateral CIs simultaneously. There was little influence of unilateral CI experience on the bilaterally and unilaterally naïve CAEP latencies and amplitudes (latency: Spearman=-0.19 to 0.33, p>0.05, amplitude: Spearman=-0.46 to 0.18, p>0.05). There was a small but significant decrease in the latency and amplitude of the P2ci in the Multi-peaked
response with duration of unilateral CI use (latency: Spearman=-0.33, p<0.05, amplitude: (Spearman=-0.46, p<0.0001). The significant effects of unilateral CI use on Multi-peak P2ci latency and amplitudes are shown in Figure 4.3.7 and 4.3.8 respectively. The slope of the trendline for the peak latency was found to be -18.4 (P2ci: β=-18.4 ms/year) and amplitude was found to be -0.70 (p2ci: β=-0.70 µV/year). For other peaks of evoked responses, no significant effects of unilateral CI use on latency or amplitude values.

Table 4.3.4A and B shows the details of comparison of peak latency and amplitude values between responses evoked from simultaneously implanted group and unilaterally naïve ears. As mentioned earlier, significant differences were in Multi-peak P2ci (t=2.7, df=52, p=0.01, p<0.05) latencies, while no significant differences were found in amplitude values. This is interesting considering the fact that regression analysis showed a significant decrease in amplitude values with respect to duration of unilateral CI use. This discrepancy was caused by the large variability in P2ci response amplitude values between the two groups. In contrast, the t-test showed a statistically significant difference for Multi-peak P1ci latency (t=3.1, df=56, p=0.003, p<0.05), which was not the case with regression analysis.

In this section, we hypothesized that cortical responses evoked by unilaterally naïve ears would resemble responses evoked by the newly implanted and naïve ear in CI users. In sequentially implanted bilateral CI users, cortical responses evoked from the naïve ear showed more variable response morphology than responses evoked from the more experienced ears. The most prevalent response type in the naïve side of the sequential group was the Multi-peak waveform response (53%), followed by Positive peak (27%) and Negative peak (20%) morphologies. These visually categorized responses strongly correlated with the PCA process for the Positive peak morphology, while that was not the case for visually categorized Multi-peak
morphology. No statistically significant differences were found in terms of demographics across the three visually categorized waveforms. These results from unilaterally naïve ears in sequentially implanted children are discussed further in Chapter 5, section 3 (5.3).

Table 4.3.4A

<table>
<thead>
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<th>Simultaneous</th>
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<td>P1ci</td>
<td>N=38</td>
<td>135.7 ±28.8</td>
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</tr>
<tr>
<td>N1ci</td>
<td>N=38</td>
<td>258.0 ±47.8</td>
<td>15</td>
</tr>
<tr>
<td><strong>Negative</strong></td>
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<tr>
<td>N1ci</td>
<td>N=70</td>
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<td>P2ci</td>
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<td><strong>Multi-peak</strong></td>
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<tr>
<td>P1ci</td>
<td>N=36</td>
<td>116.8 ±39.2</td>
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<td>N1ci</td>
<td>N=36</td>
<td>188.5 ±49.9</td>
<td>29</td>
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<tr>
<td>P2ci</td>
<td>N=36</td>
<td>285.0 ±49.7</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 4.3.4A – Mean latency and statistics associated with each comparison.
* statistically significant

Table 4.3.4B

<table>
<thead>
<tr>
<th></th>
<th>Simultaneous</th>
<th>Sequential Experienced</th>
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<tr>
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<td>P1ci</td>
<td>N=38</td>
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<td>N1ci</td>
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<td>-4.4 ±3.7</td>
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<tr>
<td>P2ci</td>
<td>N=36</td>
<td>5.0 ±4.6</td>
<td>29</td>
</tr>
</tbody>
</table>

Table 4.3.4B – Mean amplitude and statistics associated with each comparison.
* statistically significant
Figure 4.3.7  Scatterplot of bilaterally naïve and unilaterally naïve responses for Multi-peak P2ci latencies with respect to duration of unilateral CI use.

Figure 4.3.8  Scatterplot of bilaterally naïve and unilaterally naïve responses for Multi-peak P2ci amplitudes with respect to duration of unilateral CI use.
4.4 Differences in Response Types between Evoked responses from Experienced and Naïve Ears

In sequentially implanted individuals, 36 children (65.5%) showed different types of response waveforms between the experienced and naïve ears, while 19 children (34.5%) showed similar responses between experienced and naïve ears at this early stage of bilateral CI use. As indicated in Figure 4.4.1, the most common waveform combination was a Positive peak waveform response evoked by the experienced side and a Multi-peak waveform response evoked by the naïve side (49.1%, n=27). Four children (7.3%) had experienced-naïve combinations of Positive and Negative peak waveforms, 4 had Multi-peak and Negative peak waveform combinations (7.3%), and 1 child had a Negative peak waveform in the experienced ear but a Positive peak waveform in the newly implanted ear (1.8%). Of the 19 children (34.5%) with similar response morphology evoked by the two sides, it was most common to find Positive Peak waveform responses bilaterally (25.5%). Two of these children with similar response morphology from the experienced and naïve ear CI stimulation had Negative peak waveform responses (3.6%) in both ears and 3 children (5.4%) had Multi-peak waveform responses in both ears.

Overall, the differences in age at implantation for the first CI and second CI for individuals who showed similar and different response types between the ears were not found to be significantly different from one another (t=-1.3, df=53, p=0.21, p>0.05 and t=-1.7, df=53, p=0.10, p>0.05, respectively). Similarly, the differences in duration of unilateral deafness and duration of bilateral deafness for individuals who showed similar and different response types were not found to be significantly different (t=1.7, df=53, p=0.87, p>0.05, and t=1.9, df=53, p=0.68, p>0.05, respectively).
Table 4.4.1A and B provides demographic details for each response pattern across the entire group of 55 children in terms of mismatched/matched responses between the sides (as shown in Figure 4.4.1). In individuals who showed similar response morphology between the experienced and naïve ears, no statistical significance was seen in any of the demographic details for a given waveform morphology, as indicated in Table 4.4.1A. By contrast, in children who showed different response morphology between the ears, a significant difference was found in terms of duration of unilateral CI use \((p=0.039, p<0.05)\), as the response combination of Positive peak in experienced and Multi-peak response in naïve ear showed an higher mean compared to other two combinations. It should be noted that the combination of Negative peak in experienced and Positive peak in naïve ear was omitted for the purposes of statistical analysis, as it only contained one individual.
Table 4.4.1A

<table>
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<th>Number</th>
<th>Imp 1&lt;sup&gt;st&lt;/sup&gt; CI</th>
<th>Imp 2&lt;sup&gt;nd&lt;/sup&gt; CI</th>
<th>DurUniCI Use</th>
<th>DurBiDeaf</th>
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</thead>
<tbody>
<tr>
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<td>14</td>
<td>2.19±1.56</td>
<td>4.09±2.41</td>
<td>1.90±1.02</td>
<td>1.85±1.10</td>
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<td>N and N</td>
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<td>6.30±4.00</td>
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<td>M and M</td>
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<td>1.73±0.31</td>
<td>0.52±0.62</td>
<td>0.54±0.65</td>
</tr>
</tbody>
</table>

Statistics

F(2,16)=0.93, p=0.41  
F(2,16)=2.8, p=0.18  
F(2,16)=1.9, p=0.073  
F(2,16)=3.1, p=0.090

Table 4.4.1A – Demographic details by waveform response type in sequentially implanted children who show matching morphology between responses evoked by unilaterally experienced and unilaterally naïve ears.  
* statistically significant

Table 4.4.1B

<table>
<thead>
<tr>
<th>Mismatched</th>
<th>Number</th>
<th>ImpAge1st</th>
<th>ImpAge2nd</th>
<th>DurUniCI Use</th>
<th>DurBiDeaf</th>
</tr>
</thead>
<tbody>
<tr>
<td>P and M</td>
<td>27</td>
<td>1.87±1.03</td>
<td>3.49±1.47</td>
<td>1.62±0.80</td>
<td>1.50±0.84</td>
</tr>
<tr>
<td>M and N</td>
<td>4</td>
<td>1.75±0.84</td>
<td>2.43±0.55</td>
<td>0.69±0.55</td>
<td>0.69±0.55</td>
</tr>
<tr>
<td>P and N</td>
<td>4</td>
<td>1.35±0.51</td>
<td>2.29±0.64</td>
<td>0.94±0.52</td>
<td>0.94±0.52</td>
</tr>
<tr>
<td>N and P</td>
<td>1</td>
<td>2.21</td>
<td>4.42</td>
<td>2.22</td>
<td>2.2</td>
</tr>
</tbody>
</table>

Statistics

F(2,32)=0.51, p=0.60  
F(2,32)=2.4, p=0.13  
F(2,32)=2.2, p=0.039 *  
F(2,32)=3.6, p=0.11

Table 4.4.1B – Demographic details by waveform response type in sequentially implanted children who show mismatched morphology between responses evoked by unilaterally experienced and unilaterally naïve ears.  
* statistically significant

Legends: P – Positive peak response, N – Negative peak response, M-Multi-peak response, ImpAge1st = age at implantation for first CI, ImpAge2nd = age at implantation for second CI, DurUniCI Use = duration of unilateral CI use, DurBiDeaf=duration of bilateral deafness

4.5 Overall Comparison across Three Groups

By combining our responses from bilaterally naïve, unilaterally experienced and unilaterally naïve sides, we see a marked difference in the incidence of cortical response waveforms, as shown in Table 4.5.1. The highest prevalence of Positive peak response was seen in sequentially experienced ear evoked response, whereas bilaterally and unilaterally naïve ear evoked responses show lower prevalence. The highest prevalence of Negative peak waveform was seen in bilaterally naïve ear evoked responses, followed by unilaterally naïve, and unilaterally experienced ear evoked responses. Multi-peak responses were seen most prevalently in unilaterally naïve ear evoked responses, followed by bilaterally naïve and unilaterally experienced ear responses.
Table 4.5.1

<table>
<thead>
<tr>
<th>Type</th>
<th>Simultaneous (n=144)</th>
<th>Seq Experienced (n=55)</th>
<th>Seq Naïve (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive peak</td>
<td>26% (n=38)</td>
<td>82% (n=45)</td>
<td>27% (n=15)</td>
</tr>
<tr>
<td>Negative peak</td>
<td>49% (n=70)</td>
<td>7% (n=4)</td>
<td>20% (n=11)</td>
</tr>
<tr>
<td>Multi-peak</td>
<td>25% (n=36)</td>
<td>11% (n=6)</td>
<td>53% (n=29)</td>
</tr>
</tbody>
</table>

Table 4.5.1– Overall incidence of waveform morphology for different conditions of auditory deprivation based on visual categorization.

4.5.1 Latency Comparison Across Groups

Table 4.5.1 and 4.5.2 provide descriptive statistics for all peaks described and the same data are shown in Figures 4.5.1 and 4.5.2. Comparison of mean latencies across the groups showed that Positive peak P1ci (F(2,95)=6.4, p=0.002, p<0.05), Multi-peak P1ci (F(2,68)=4.9, p=0.011, p<0.05), and Multi-peak P2ci (F(2,68)=4.0, p=0.023, p<0.05) showed statistically significant differences across the groups. All other peak latencies across groups showed no statistically significant differences across groups.

Table 4.5.2

<table>
<thead>
<tr>
<th>Latency</th>
<th>Number</th>
<th>Mean Latency (±S.D.)</th>
<th>95% Confidence Interval</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sim</td>
<td>Exp</td>
<td>Naïve</td>
<td>Sim</td>
<td>Exp</td>
</tr>
<tr>
<td>Pos P1ci</td>
<td>38 45 15</td>
<td>135.7 (±28.8)</td>
<td>114.6 (±20.0)</td>
<td>121.9 (±38.7)</td>
</tr>
<tr>
<td>Multi P1ci</td>
<td>36 6 29</td>
<td>116.8 (±39.2)</td>
<td>95.1 (±18.6)</td>
<td>92.9 (±21.5)</td>
</tr>
<tr>
<td>Pos N1ci</td>
<td>38 45 15</td>
<td>258.0 (±47.8)</td>
<td>235.5 (±50.7)</td>
<td>231.9 (±57.0)</td>
</tr>
<tr>
<td>Multi N1ci</td>
<td>36 6 29</td>
<td>127.6 (±33.4)</td>
<td>102.9 (±17.0)</td>
<td>135.5 (±31.2)</td>
</tr>
<tr>
<td>Neg N2ci</td>
<td>70 4 11</td>
<td>188.5 (±49.9)</td>
<td>164.6 (±32.2)</td>
<td>167.8 (±39.2)</td>
</tr>
<tr>
<td>Multi P2ci</td>
<td>36 6 29</td>
<td>285.0 (±49.7)</td>
<td>255.9 (±45.4)</td>
<td>246.5 (±63.6)</td>
</tr>
</tbody>
</table>

Table 4.5.2– Comparison of peak latency values in responses evoked by bilaterally naïve, unilaterally experienced and unilaterally naïve ears. Legends: Pos = Positive peak waveform, Neg = Negative peak waveform, Multi = Multi-peak waveform, Seq E = Sequentially Implanted Experienced Ear, Seq N = Sequentially Implanted Naïve Ear, Sim = Simultaneous Implanted Ear.

* statistically significant
Figure 4.5.1— Comparisons of mean latency values with 95% confidence intervals between three groups for each waveform types. Figure legends: Sim = simultaneously implanted children, Exp = unilaterally experienced ear of sequentially implanted children, Naïve = unilaterally naïve ear of sequentially implanted children.

4.5.1 Amplitude Comparison Across Groups

In contrast, comparison of mean amplitude across the groups showed no statistically significant differences across the groups (Table 4.5.3).
Table 4.5.3

<table>
<thead>
<tr>
<th>Amplitude</th>
<th>Number</th>
<th>Mean Latency (±S.D.)</th>
<th>95% Confidence Interval</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sim</td>
<td>Exp</td>
<td>Naïve</td>
<td>Sim</td>
</tr>
<tr>
<td>Pos P1ci</td>
<td>38</td>
<td>45</td>
<td>15</td>
<td>5.3 (±4.5)</td>
</tr>
<tr>
<td>Multi P1ci</td>
<td>36</td>
<td>6</td>
<td>29</td>
<td>3.6 (±3.5)</td>
</tr>
<tr>
<td>Pos N1ci</td>
<td>38</td>
<td>45</td>
<td>15</td>
<td>-4.4 (±3.7)</td>
</tr>
<tr>
<td>Neg N1ci</td>
<td>70</td>
<td>4</td>
<td>11</td>
<td>-6.2 (±5.4)</td>
</tr>
<tr>
<td>Multi N1ci</td>
<td>36</td>
<td>6</td>
<td>29</td>
<td>-4.9 (±6.1)</td>
</tr>
<tr>
<td>Neg P2ci</td>
<td>70</td>
<td>4</td>
<td>11</td>
<td>5.2 (±5.8)</td>
</tr>
<tr>
<td>Multi P2ci</td>
<td>36</td>
<td>6</td>
<td>29</td>
<td>5.0 (±4.6)</td>
</tr>
</tbody>
</table>

*statistically significant differences

Figure 4.5.2

Figure 4.5.2- Comparison of mean amplitude values with 95% confidence intervals between three groups for each waveform types. Figure legends: Sim = simultaneously implanted children, Exp = unilaterally experienced ear of sequentially implanted children, Naïve = unilaterally naïve ear of sequentially implanted children.
Chapter 5 - Discussion

In this chapter, we discuss the results obtained from the three studies in an effort to interpret our findings. The first 3 sections will discuss the findings from the three questions that we asked in this study. These were: 1) Does bilateral deafness arrest auditory development resulting in persistently immature responses from auditory cortex?, 2) Does a period of unilateral cochlear implant use promote more mature responses from the auditory cortex?, and 3) Does a period of unilateral cochlear implant use affect cortical responses evoked by the naïve contralateral ear? In the fourth section, we discuss the response differences that were seen from responses evoked by experienced and naïve ears in sequentially implanted children, and compare that to findings from simultaneously implanted children. In the final section, we discuss future directions and potential applications from the findings of these studies.

5.1 Question 1: Does bilateral deafness arrest auditory development resulting in persistently immature responses from auditory cortex?

5.1.1 Discussions of Responses Evoked by Bilaterally Naïve Ears

To answer this question, we measured cortical responses on the first day of bilateral CI use in simultaneously implanted children. Our hypothesis to this question was that cortical responses from bilaterally deaf children would resemble immature cortical responses from young NH children. Contrary to our expected findings, a variety of cortical responses were evoked in the bilaterally naïve auditory cortex. Without knowing the neural generators for each of these responses, we elected to categorize these responses. Since responses from CI users have primarily reported a dominant positive peak (P1ci), we categorized these waveforms as Positive peak waveform, which also resembles the typical CAEP morphology taken from NH hearing children under the age of around ten (Ponton and Eggermont, 2001; 1996; Lippe et al, 2009).
Responses containing a negative peak (N1ci) preceding a positive peak (P2ci) was considered to be atypical as we have previously reported (Gordon, et al., 2008; 2005) and called Negative peak waveform responses. A third category was categorized by multiple positive peaks (P1ci and P2ci) with an intervening negative peak (N1ci) and called Multi-peak waveform.

To determine the reliability of our visual categorization process, we utilized the statistical test of PC analysis to categorize our response waveforms into similar morphology groups. Interestingly, in the simultaneously implanted group, the responses categorized visually as multi-peak responses were equally divided in the clustering analyses between positive and negative peak clusters. Due to this difficulty in distinguishing multi-peak waveform from the other two response types, multi-peak responses identified visually were omitted from the clustering analysis. Even so, the application of PC analysis showed a strong agreement with the visual categorization.

Our data from bilaterally naïve auditory cortices showed a high prevalence of Negative peak waveform morphology (48.6%), which is consistent with the waveform previously reported at early stages of unilateral CI use as well as prematurely born NH infants (Sharma 2005; 2002; Rotteveel et al., 1987; Weitzman and Graziani, 1968). However, there were also a fair proportion of Positive peak waveform (26.4%) and Multi-peak waveform (22.2%) responses. The Positive peak waveform morphology (i.e. P1ci-N1ci) has been reported previously from experienced CI users (Ponton et al, 2001; Sharma et al, 2005; 1996, Gordon 2008; 2005), but we now show that it can be present even at an initial stage of CI use. The Multi-peak waveform morphology (i.e. P1ci-N1ci-P2ci), which resembles Positive peak waveform morphology except for the extra positive peak (P2ci), has not been reported before now to our knowledge. Upon further inspection of our data from simultaneously implanted children, we found a lack of
significant difference in age at implantation (Positive peak waveform: 2.84 years; negative peak waveform: 1.91 years; Multi-peak waveform: 2.63 years) and duration of bilateral deafness (Positive peak waveform: 2.47 years; Negative peak waveform: 1.75 years; Multi-peak waveform: 1.63 years) between the different groups of responses. This is an especially interesting finding, considering the fact that each morphology group shared a narrow range for these demographic factors. The variation in cortical responses from the bilaterally naïve auditory system suggests that there are multiple effects of bilateral deafness to the central auditory pathways, including the relay nuclei and the auditory cortex, which cannot be clearly explained using the demographic information available to us.

The Negative peak waveform response found at this initial stage of CI use in children receiving bilateral CIs simultaneously may reflect the extreme end of cortical developmental immaturity. According to such an idea, the Negative peak waveform results from desynchronized activity among the cortical layers in the naïve auditory cortex, which increases in synchrony with increase in auditory experience (Kral et al, 2005; 2000; Klinke et al, 1999). More specifically, there is a delay in the activation of cortical neurons in the superficial layers and lack of activity in the deeper layers (layers V and VI) of the auditory cortex in deaf animals (Kral et al, 2005). Cortical responses from normal hearing infants do not show the negative peak that characterizes Negative peak waveform morphology. Rather, the normally immature response evoked by slow stimuli presentation rates of 0.25-0.5 Hz consists of a broad positive peak at 200-250 ms followed by a negative peak at 300-550 ms (Barnet et al., 1975, Kurtzberg et al, 1984, Little et al, 1999; Rotteveel et al., 1986, Shucard et al, 1987; Weizman and Graziani, 1968). However, cortical responses from NH premature infants (conceptual ages of 23-26 weeks) have been reported to have a negative peak between 130-200 ms (Rotteveel et al, 1987; Weitzman and
Graziani, 1968) which may be similar to the response recorded in almost half of the children who had no prior CI experience. In our study (which we evoked the responses by stimulating CI electrodes at 1Hz), the mean latency for the negative peak (N1ci) in Negative peak waveform responses was 127.6 (±33.4) ms, which seems to occur on the early end of the range reported in preterm infants (around 200 ms). Interestingly, as NH premature infants reached the period corresponding to the last 4-5 weeks of gestation, their predominantly negative cortical response changed to the more Positive peak waveform P1-N1 morphology seen in full term infants (Weizman and Graziani, 1968; Little et al, 1999; Rotteveel et al, 1986). Based on these reports, there is a possibility that the Negative peak waveform response recorded prior to any CI experience in our group of children, reflects a truly naïve state of auditory cortex which is not typically seen in full term NH infants. Taken together with our data, this suggests that activity is required for the auditory brain to develop from this very immature state.

On the other hand, we also report positive peak waveform and multi-peak waveform responses from bilaterally naïve auditory cortices in simultaneously implanted children. These response types have not been previously reported in the literature for naïve responses from CI children (Sharma et al, 2005; 2002), although there is a brief mention about a polyphasic waveform/low amplitude waveform in late-implanted children (Sharma and Dorman, 2006; Sharma et al, 2007). Interestingly, when all the cortical responses from simultaneously implanted individuals are added together in our study, the resultant grand mean waveform morphology resembles the negative peak waveform (Figure 3). This is in accordance with previous reports of cortical response morphology in naïve CI users (Sharma et al, 2005; 2002), but also suggests that other response morphologies that we report in this study were either not seen, or were lost as a result of creating grand average waveforms. The variable responses morphology that we report
point to the possibility that there are multiple factors that influence the cortical responses from the deaf auditory cortex. It is possible that variable cortical responses are influenced by the cause the deafness, which might differ from one child to another. However, this is beyond the scope of our current study, but they will be addressed in our future studies.

Since we do not know the source of neural generators for Multi-peak responses, we must closely analyze the uniqueness of this response morphology. Although Sharma and Dorman (2006) describe polyphasic responses from naïve auditory responses of late-implanted children (implanted after at least 7 years of auditory deprivation), and we report a similarly polyphasic (Multi-peaked) pattern of activity from a much younger population (mean implanted age of 2.6 years). Within the simultaneous group, the Multi-peak waveform response was characterized by an earlier P1ci than that from Positive peak waveform P1ci, and Multi-peak waveform N1ci peak was between the earlier Negative peak waveform N1ci and later Positive peak waveform N1ci, and Multi-peak P2ci occurred later than Negative peak waveform P2ci.

If we consider the Multi-peak waveform N1ci to come from a distinct population of cortical neurons from those generating the P1ci, it is possible that this response bifurcates the Positive peak waveform P1ci peak creating 2 separate positive peaks. The same phenomenon reportedly explains the normal maturation of the immature P1 response to the mature P1-N1-P2 response (Ponton and Eggermont, 2001). In that case, it is the N1 which is responsible for the change from a single positive peak to 2 positive peaks. A possible association between the N1ci of the Multi-peaked response and the normal N1 requires further study. However, a closer analyses of the mean amplitude values show that mean multi-peak waveform P2ci value (5.0±4.6µV) are similar to positive peak waveform P1ci (5.3±4.5µV) whereas the P1 is typically smaller in amplitude (≈1.6µV) compared to P2 (≈2.0µV) in NH individuals between the ages of

74
five to adulthood (Ponton et al, 2000).

Alternate explanations include the possibility that the Multi-peak waveforms reflect a combination of Positive Peak and Negative Peak responses or that this reflects an entirely separate developmental course. This notion is supported by studies in congenitally deaf white cats who show abnormal activity from the auditory cortex with acute CI stimulation. Whereas electrically evoked activity of the auditory nerve in previously hearing cats travels in a clearly defined spatio-temporal pattern in the auditory cortex, such activity in the same area was found to be more synchronous and spread over a wider cortical area in congenitally deaf animals (Kral et al, 2009). This could be due to differences in deprivation as well as stimulation differences between acoustic and electrical input. By considering this possibility, it is plausible that Multi-peaked response that we report from bilaterally naïve auditory cortex in children is the result of difference in how the naïve auditory system preserved or developed differentially during a period of auditory deprivation.

Another possible source of Multi-peak responses arises from the difference in mode of auditory stimulation that is specific to CI users. In NH individuals, sound vibrations cause movement of the tympanic membrane and the middle-ear ossicles that result in fluid within the cochlea to move and ultimately stimulating the hair cells of the inner ear. The movement of the hair cells send action potentials down the auditory nerve, which synapses at the medulla oblongata before moving up to the auditory cortex. In contrast, the use of the outer, middle and inner ears are bypassed in CI users, as the prosthetic device directly stimulates the auditory nerve, where the electrodes are inserted into the scala tympani to replace the function of the hair cells (Papsin and Gordon, 2007). Thus, the electrical pulses that are sent from the electrodes to the auditory nerve are different from action potentials that result from normal hearing because of
direct auditory nerve stimulation in CI users. More specifically, the action potentials from electrical stimulation are also more synchronized and its excitation is spread over a larger range compared to acoustic hearing (Kral and Tillein, 2006, Kral et al, 1998). A larger excitation area in the cortex from CI users could certainly evoke regions that are not normally stimulated in NH individuals. However, it is unknown whether such a difference in stimulation would cause differences at the level of the auditory cortex. Both electrical and acoustic stimulations utilize the same central nervous system (CNS) structure, where the auditory nerve synapses at the brainstem and leads to the auditory cortex. Furthermore, cortical response amplitude, which is considered to be a reflection of synaptic density (Eggermont, 1988), does not differ considerably between NH individuals and CI users in experienced auditory responses, as our group and others have observed (Ponton and Eggermont, 2001).

Now that we have categorized these peaks, we can, in future studies, begin to address the similarities and differences more specifically by identifying the neural sources of these peaks.

### 5.1.2 Similarity in Responses evoked by Right versus Left Cochlear Implants

Since both ears from simultaneously implanted children were naïve at the time of test, it was not surprising to find a high prevalence of similar responses evoked by the left and right CIs (67%). On the other hand, it is more challenging to explain the reasons behind why a third of simultaneously implanted children showed different responses between right and left ear CI stimulations. Statistical analyses found no significant difference in age at implantation and duration of bilateral deafness between individuals who showed similar and different morphology between the ears. This suggests that it is unlikely that auditory deprivation caused such similarity/differences in cortical responses between the ears. It is possible that this difference stemmed from difference in etiology between the right and left auditory pathways that caused
bilateral deafness. Another possibility is the possibility of asymmetrical effects of deafness which might have resulted in different periods of residual hearing in each ear. We were not able to find any demographic explanations for why some children had similar types of responses evoked by both sides and others had different types. One possible explanation might be the individual differences in placement of the CI electrodes within the cochlea that resulted in different cortical response morphology. However, given the number of synapses and neurons that each auditory signal recruits along the auditory pathway, the placement of CI electrode within the cochlea seems unlikely to cause differences at the cortical level. Within those individuals who showed similar response types between the ears, we found no statistically significant differences in age at implantation or duration of bilateral deafness across response types. Similarly, no statistically significant differences were found for demographic details across different combination patterns in individuals who showed differential responses. Thus, there are likely to be factors yet unknown regarding the etiology of deafness that remain to be found.

5.1.3 Latency and Amplitudes of Responses at Initial Cochlear Implant Use

Given that we do not know the source of neural generators for the peaks of the three identified waveforms, it was important to compare latency and amplitude values of a given peak between different waveform types.

We begin by comparing Negative peak responses to Positive peak responses. While Negative peak responses have been reported from naïve auditory systems, Positive peak responses have only been reported in experienced CAEPs, and not from naïve CAEPs in CI users. Between these two waveforms, peaks occurring at more similar latencies were: 1) Positive peak P1ci (135.7±28.8ms) and the Negative peak waveform N1ci (127.6±33.4ms) and 2) the Positive peak waveform N1ci (258.0±47.8ms) and Negative peak waveform P2ci (238.9±52.1ms). One
suggestion for these similarities is that the Negative peak waveform response found in children at
the initial stage of CI use is a reversed polarity of the Positive peak waveform response. Such a
reversal could reflect differences in dipole orientation within the activated area which reportedly
may be possible if a group of activated neurons are located near the curved part of the cortex
(Pang and Taylor, 2000).

Another possible interpretation can be found in amplitude value differences between the
Positive peak and Negative peak waveforms. The only statistically significant difference in mean
amplitude values was between N1ci of the two morphology groups. This difference could have
arisen from the presence of a neural generator that produced the large positive amplitude, P1ci, in
positive peak responses, and lack of such neural generators in Negative peak waveforms. This
explanation points to differences in areas of cortical activity rather than differences in dipole
orientation (Pang and Taylor, 2000). At the same time, however, it is also important to note the
lack of statistical significance among other peak amplitude values of different waveforms.
Ultimately, this suggests that mean amplitude values may not be suitable for peak identifications
and characterizations in children with CIs.

We also compared Positive peak responses to Multi-peak responses. Whereas Positive
peak responses have not been reported from naïve CAEPs, Multi-peak responses have been
reported from naive CAEPs in older children (Sharma and Dorman, 2006). The mean difference
between P1ci responses in Positive peak waveform (135.7±28.8ms) and Multi-peak waveform
responses (116.8±39.2ms) was approximately 20 ms, and showed statistically significant
differences. In other peaks, comparisons of N1ci values between Positive peak (258.0±47.8ms)
and Multi-peak waveforms (188.5±49.9ms) also showed statistically significant differences. If
we assume that different neural generators result in different peak latencies, these differences in
peak latency values between Positive peak and Multi-peak responses suggests that the two have different sources of neural activity that are producing these peaks.

Furthermore, previous reports of Multi-peak responses, or polyphasic responses, as Sharma and colleagues discussed (Sharma and Dorman, 2006; Sharma et al, 2007) were characterized by low amplitude values, compared to the typical positive peak response amplitudes. In our case, such difference in amplitude was not found, and children with Multi-peak responses were not statistically different in age at implantation from other morphology types. Thus, there exists a discrepancy between the literature and our findings, which points to the possibility that Multi-peak responses that we report might be different from the previous reports of polyphasic waveforms from naïve cortical responses of older children with CIs (Sharma and Dorman, 2006; Sharma et al, 2007).

In addition, we also compared peaks from Negative peak waveform to Multi-peak waveforms. These two waveforms show significant differences in P2ci latency. This significance is exemplified by the marked difference in mean latency values for P2ci in Negative peak waveform and Multi-peak waveforms, which were 238.9±52.1ms and 285.0±49.7ms, respectively. Again, this difference could be interpreted with the idea that generators for P2ci are different between these two waveforms. In contrast, it could also be argued that the lack of significant difference in latency between Negative peak waveform N1ci and Multi-peak waveform P2ci also points to the possibility that these two peaks are opposite in polarity, while sharing a similar neural generator (Pang and Taylor, 2000). A lack of significant differences in amplitude values between these two waveforms also supports our position that amplitude values in CI users may not be the most suitable factor to consider when characterizing responses.

To determine the effect of age at implantation and duration of deafness on peak values,
we performed bivariate statistical analyses on these demographic factors. Of the seven peaks that constituted our categorized responses, only multi-peak waveform N1ci showed a statistically significant increase in latency with respect to age at implantation. Similarly for amplitude values, one peak showed significance with respect to duration of bilateral deafness (positive peak waveform N1ci) and another one with respect to age at implantation (multi-peak waveform P2ci). Such a lack of significant effect of duration of bilateral deafness and age at implantation suggests that waveform morphology differences between simultaneously implanted individuals are not caused by a period of auditory deprivation, or age at implantation within narrow range studied in this group of children.

On the other hand, it is more difficult to discern why a few peaks showed effects of auditory deprivation and age at implantation. It might be possible that those particular peaks are sensitive to such conditions, but a lack of coherence between latency and amplitude to those effects suggests otherwise. One solution to this remaining question might be to track these peak latency and amplitude values in our future studies with these children, and to measure the effects of auditory experience on these values.

In sum, approximately half of responses evoked from bilaterally naïve ears from CI users show Negative peak morphology, which has been previously reported at initial stages of CI use (Sharma 2002; Sharma 2005). On the other hand, we also report cortical responses that have been reported as a mature response (i.e. Positive peak morphology) (Ponton and Eggermont, 2001; Gordon et al, 2008; 2005; Sharma et al, 2005, 2002) and polyphasic responses that have been seen only from late implanted children (Multi-peak responses) (Sharma and Dorman, 2006, Sharma et al, 2007). If we assume that cortical response morphology is an accurate indicator of cortical maturation, then our results suggests that bilateral deafness arrested preserved the
auditory cortex in an immature state only in half of our tested children, whereas the remaining
children who did not show Negative peak morphology had 1) cortical reorganization due to a
period of bilateral deafness, 2) unaccounted period of hearing prior to bilateral deafness or 3)
there are multiple responses morphology associated with bilateral deafness. A lack of significant
differences in demographic details among the morphology types suggests that morphology
differences alone cannot explain the state of cortical immaturity. In essence, this points to a
complex mechanism that underlies cortical response morphology from bilaterally naïve auditory
cortices, and highlights the importance of tracking cortical responses as simultaneously
implanted individuals gain auditory experience.

5.2 Question 2: Does a period of unilateral cochlear implant use promote more mature
responses from the auditory cortex?

5.2.1. Discussions of Responses Evoked from Unilaterally Experienced Ears in Sequentially
Implanted Children.

To this question, our hypothesis was that in children who receive a second CI after a
period of unilateral CI use, CAEPs evoked by the CI in the experienced ear would resemble
mature cortical response morphology. As hypothesized, the auditory cortex began to respond in a
more predictable fashion after long term unilateral CI stimulation. The majority of responses
(83.7%) from the experienced ear CI stimulation in sequentially implanted individuals showed
the positive peak morphology that is typical of cortical responses after unilateral CI use, as
reported from past studies (Sharma et al, 2005; 2002; Ponton and Eggermont, 2001; Gordon
2008). This was confirmed using PCA based clustering analyses. The change from more
variable responses from naïve ears to a less variable response occurs during the early stages of
unilateral CI use, given that some children had under a year of unilateral CI experience (range:
0.17-4.01 years).
The low numbers of children who showed Negative and Multi-peaked responses made it difficult to fully assess differences in demographics between response types. However, comparison of demographic details showed that individuals with Negative peak responses had longer duration of bilateral deafness, duration of unilateral CI use, and older age at implantation for 2nd CI compared to the children with Multi-peaked responses. These differences were statistically significant compared to demographic details from Positive and Multi-peak responses. Considering the fact that typical cortical response from CI users develop from the Negative peak to Positive peak morphology within a year of auditory experience (Sharma et al, 2007; 2005), it was interesting to find a few individuals who showed Negative peak responses even after years of auditory experience. In fact, our previous study have shown that some individuals with unilateral CIs exhibit Negative peak waveform responses even after years of CI use, suggesting abnormal cortical maturation despite auditory input from a CI (Gordon 2008; Gordon et al., 2005). If that is indeed the case, it is promising to find that most (45/55) children showed Positive peak waveform morphology in the responses evoked from the experienced ear, and that only 4 children showed the atypical Negative peak response morphology.

On the other hand, we also show statistically significant differences in demographic details between Positive and Multi-peak responses in terms of duration of bilateral deafness, duration of unilateral CI use and age at implantation for second CI. Children with Multi-peak responses were younger compared to children with Positive peak responses. Given the similarity in morphology between the Positive peak and Multi-peak responses with younger demographic details of Multi-peak responses, it is possible that Multi-peak response morphology is in the process of becoming a Positive peak response. Moreover, this idea for Multi-peak developmental
course is in contrast with the idea that Negative peak responses will be arrested in that state (Gordon 2008; 2005).

5.2.2 Effects of Unilateral CI use on Response Latencies and Amplitudes

Since we do not know the source of neural generators for the peaks of the three identified waveform morphologies evoked from the experienced ear, it was important to compare latency and amplitude values for a given peak between different waveforms. This method of analysis assumes that peaks occurring at different latencies have different underlying neural generators.

We begin by comparing the mature response morphology of Positive peak, typically seen in experienced ear evoked responses to the Negative peak responses, which has been characterized as atypical in evoked responses from experienced ears. No statistically significant differences were seen in latency or amplitude between these two morphology groups. This raises two possibilities. First, it could be that Negative peak responses reflect differences in dipole orientation within the activated cortical area (Pang and Taylor, 2000) compared to Positive peak responses. This explains similar latency and amplitude values between the two waveform types, but it does not explain why a larger number individuals (n=45) show Positive peak responses compared to a small number of individuals with Negative peak responses (n=4). Second, it is possible that the generator for P1ci and N1ci in Positive peak waveform is simply different from the generator of N1ci and P2ci in Negative peak waveform. Although we currently lack the ability to test this idea with our single-channel test setup, it is possible that individuals with Negative peak responses have developed an abnormal auditory cortex due to longer periods of auditory deprivation. This idea is supported by our previous study, which reported poorer speech perception skills in children who showed Negative peak responses even after years of CI use (Gordon et al, 2005). Unfortunately, current imagining technologies, such as MEG and fMRI,
cannot be used in CI users because of interference with the magnetic component of CIs. Thus, it is currently not possible to confirm this data through the MEG or the fMRI. However, there have been a few studies that employed the PET scan, which showed abnormal activity in the auditory cortex in poor device users (Lee et al, 2005; 2001), and activity in the visual cortex in response to auditory stimuli (Giraud et al, 2001). These studies lend support to the idea that some CI users do have abnormal activities of the auditory cortex.

We also performed latency and amplitude value differences between Positive and Multi-peak responses. It is in N1ci latency between these two response morphology that we find the only statistically significant difference. As mentioned previously, this significant difference between N1ci values might be indicating distinct neural generators for N1ci peaks between the two waveforms. It follows that there is a possibility that Multi-peak responses from the experienced ear have an extra neural generator that Positive responses lack. Alternatively, it is possible that Multi-peak responses are in the process of becoming Positive peak waveform, given the younger demographic details associated with individuals showing Multi-peak responses. In this case, Multi-peak responses arise because there are contributions from neural generators that produce both Positive peak and Negative peak morphology. The overlap of these two neural generators will result in some phase cancellation, resulting in Multi-peak morphology. If Multi-peak cortical responses follow this mechanism, the reliability of peak latency and amplitude comparison comes into question, because there is a second factor of phase cancellation to consider.

Since the responses evoked by the experienced side CI stimulations were from children who had a range of cochlear implant experience, we also analyzed the effects of demographic factors including duration of unilateral CI (inter-implant delay) use on peak latency and
amplitude values. CAEP responses taken from the experienced ear CI stimulation in sequentially implanted individuals showed that there was no significant effect on any of the demographic factors on peak latencies across different waveform types except P1ci of Multi-peak responses to age at implantation for 2nd CI. However, this increase in P1ci latency is hard to interpret, as the number of individuals with Multi-peak responses was small (n=6), and no statistical significance was reached for duration of unilateral CI experience, which should be a stronger indicator of auditory deprivation. In terms of amplitude, we did not find any statistically significant effects to demographic details, thus providing further support that amplitude may not be suitable as an analytic factor.

To further examine the effect of auditory experience, we compared the responses from unilaterally experienced sides to those from bilaterally naïve side responses. Analyses were completed for each of the three types of waveform responses separately. These categorization gave confidence that same generator was being tracked over time. No differences were found between Negative peak responses evoked from bilaterally naïve ears and experienced ear for both latency and amplitude. In contrast, we found a significant difference in latency for P1ci in Multi-peak responses and P1ci and N1ci in Positive peak responses. This suggested that auditory experience does change latency values for certain peaks within a given morphology type. This phenomenon of decreases in latency of peaks with increase in auditory experience is in accordance with reports from other studies involving cortical responses from CI users (Sharma et al, 2005; 2004; Ponton and Eggermont, 2001). This raises the possibility that in some individuals, waveform morphology might stay the same as they gain auditory experience, while decreasing peak latencies. In contrast, some individuals would change cortical response morphology as they gain auditory experience, as indicated by the differences in prevalence of morphology types.
between responses evoked from bilaterally naïve ears (most prevalent: Negative peak morphology—49%) and experienced ears (most prevalent: Positive peak morphology—82%). Considering the fact that some sequentially implanted individuals had only a few months of unilateral CI experience, it is likely that changes in latencies of Positive peak responses occur quickly.

This idea of fast change in latencies in the Positive response types is consistent with the rapid change from more frequently found Negative peaked responses to a dominance of Positive response types within the first 6 months of unilateral CI use and consistent with previous reports (Sharma et al, 2005, 2002). It should be noted that the time course is remarkably similar to changes occurring subcortically. In NH individuals, ABRs are reported to reach adult values within 2-3 years of age (Ponton et al, 1996; 1992). Moreover, our group has reported that the auditory brainstem shows the largest developmental changes in the auditory brainstem, measured by electrically evoked auditory brainstem responses (EABRs), during the first 6 months of unilateral CI use: (Gordon et al, 2006). Thus, the developmental trajectory of the electrically stimulated auditory brainstem and cortex, as measured by EABRs and CAEPs, respectively, shows a remarkable similarity. Longitudinal studies would be helpful to confirm our idea about the latency and amplitude changes in responses evoked from bilaterally naïve ears, and how such responses might become similar to mature responses (i.e. responses evoked from unilaterally experienced ears).

In sum, many responses evoked from unilaterally experienced ears from CI users show Positive peak morphology, which has been previously reported in a number of studies (Ponton, 2006; Ponton and Eggermont, 2001; Gordon et al, 2008; 2005; Sharma et al, 2005; 2002). On the other hand, we also report Negative peak and Multi-peak responses evoked from experienced
ears. Negative peak morphology has been reported before in experienced CI users who performed poorly on speech perception tests, thus pointing to limited auditory capability in this context (Gordon et al, 2008; 2005). Multi-peak response has not been reported from responses evoked by the experienced ears, but the younger demographic details in this group suggest the possibility that it may be in a developmental stage into the mature Positive peak response. Comparison of morphology peak values between evoked responses from bilaterally naïve and unilaterally experienced responses indicate that certain peak latencies decrease with increase in auditory experience. By combining this fact with the large change in the prevalence of waveform morphology between the naïve and experienced ears, we come to the conclusion that auditory experience does promote the development of evoked responses into more typical Positive peak morphology.

5.3 Question 3: Does a Period of Unilateral Cochlear Implant Use Affect Cortical Responses Evoked by the Naïve Contralateral Ear?

5.3.1 Discussions of Responses Evoked by Unilaterally Naïve Ears in Sequentially Implanted Children

To this question, we hypothesized that cortical responses evoked by unilaterally naïve ears would resemble responses evoked by the newly implanted and naïve ear in CI users. We formed our hypothesis for unilaterally naïve responses in sequentially implanted bilateral CI users based on the findings from one of our previous studies. On the first day of bilateral CI use, ABRs evoked by unilaterally naïve ear CI stimulation in sequentially implanted children show a delay in latency compared to the responses evoked by the unilaterally experienced side (Gordon et al, 2007), most likely due to slower conduction speed of the action potentials from less myelinated neurons in the unilaterally naïve pathway. In sequentially implanted bilateral CI users, cortical responses evoked from the naïve ear showed more variable response morphology than
responses evoked from the more experienced ears. This is similar to what we have reported in simultaneously implanted children with bilaterally naïve auditory systems. However, the most prevalent response type in the naïve side of the sequential group was the Multi-peak waveform response (53%), in contrast to Negative peak waveform responses (49%) seen from responses evoked by bilaterally naïve ears. The high prevalence of Multi-peak responses in children from the unilaterally naïve side indicates a uniquely different state of auditory immaturity compared to bilaterally naïve auditory systems. There are several possibilities behind the high prevalence of Multi-peak waveform in responses evoked by unilaterally naïve ears.

First, it is possible that a period of unilateral CI experience from the opposite ear promoted the development of the unilaterally naïve auditory cortex. Sequentially implanted individuals go through a period of unilateral deafness. During this time, it is possible that this unique environment cause changes in the normally contralaterally dominant auditory pathways to have more influential effects on the unilaterally naïve auditory cortex. There have been a number of studies which explored cortical responses evoked from unilaterally experienced ears in unilaterally deaf individuals. Many imaging studies have reported that a period of unilateral deafness leads to symmetrical activation patterns in the auditory cortex compared to the asymmetrical activation patterns of normal hearing individuals with the use of functional magnetic resonance imagining (fMRI) (Langers et al, 2005; Bilecen et al, 2000). More symmetrical activation in the auditory cortex is also reported in a study involving CAEPs, where late-onset unilateral deafness led to more symmetrical amplitude and synchronous latency activation between the ipsilateral and contralateral sides in adults (Ponton et al, 2001). This report of more symmetrical auditory pathway during a period of unilateral deafness suggests that the unilaterally naïve auditory cortex is not isolated from auditory experience and it is perhaps
for this reason that responses evoked by unilaterally naïve ear show a higher prevalence of Multi-peak responses compared to responses evoked by bilaterally naïve ears.

Second, as discussed in the previous section, it is possible that Multi-peak responses are in the process of becoming Positive peak waveform. To reiterate this idea, Multi-peak responses arise because there are contributions from neural generators that produce both Positive peak and Negative peak morphology. The overlap of these two neural generators will result in some phase cancellation, resulting in Multi-peak morphology. Given the difference in prevalence of Multi-peak responses evoked by unilaterally experienced ears (11%) and unilaterally naïve ears (54%), and combining this with the idea that unilateral CI experience promoted some cortical development in the unilaterally naïve pathways, this theory seems plausible. Thus, as an individual gains auditory experience, contribution from neural generators of Negative peak response gets suppressed, while the contribution from Positive peak response becomes more dominant. During the time when the suppressive effects have not fully come into effect, Multi-peak responses arise. While this idea seems plausible, the earlier peak latencies of Multi-peak responses compared Positive peak waveform refutes it. The two waveform types show statistically significant differences in P1ci values, where Multi-peak P1ci (92.9±4.0ms) occurs much earlier compared to P1ci of Positive peak waveform (121.9±38.7ms). This discrepancy cannot be explained by the phase cancellation theory, because it fails to address the earlier peak latency of Multi-peak waveform P1ci, which is not present in the Positive peak waveform at that latency. Thus, the source of Multi-peak responses is difficult to explain at the current stage of our study.

We also wondered whether demographic details could be associated with a particular waveform type. By comparing the demographic details across different response morphology
evoked from unilaterally naïve ears, we found no statistically significant differences in age at implantation at first and second CI, duration of unilateral deafness, or duration of bilateral deafness, which is similar to what we have found in responses evoked by bilaterally naïve ears. However, this is in contrast to the findings we found from responses evoked by unilaterally experienced ears, where waveform morphology types showed statistically significant differences in demographic factors of age at implantation for second CI, duration of unilateral deafness and duration of bilateral deafness. Thus, this suggests that although responses evoked by the naïve ears are similar to those found from experienced ears, they might have fundamental differences in the production of such cortical responses, such that typical morphology type in one state might be abnormal in another. For example, the neurogenerator that produces Positive peak response evoked from experienced ear might be following a normal cortical development for CI users, while neurogenerator that produces Positive peak evoked response in naïve ears might be indicative of abnormal state of cortical immaturity. Although we currently lack the technique of proving this theory, we believe that such a finding is the first step in better understanding the complexities of cortical development in children with CIs, and highlights the importance of tracking the development of these cortical responses.

5.3.2 Effects of Unilateral Auditory Deprivation on Response Latencies and Amplitudes

To study the effects of unilateral auditory deprivation in the unilaterally naïve auditory cortex, we compared responses evoked from unilaterally naïve ears to that from bilaterally naïve ears. Interestingly, the only statistically significant differences were found between P1ci and P2ci latencies of Multi-peak responses between the responses evoked by unilaterally and bilaterally naïve ears. More specifically, peaks from Multi-peak waveforms consistently occurred earlier in responses evoked by unilaterally naïve ears compared to unilaterally experienced ears. This
suggests a difference in development due to unilateral CI use for Multi-peak responses, where Multi-peak responses evoked from unilaterally naïve ears might have decreased in latency due to auditory input from the contralateral side, while that was not the case in children with bilaterally naïve ears. Reasons behind why such latency changes occur in Positive peak and Negative peak waveforms are more difficult to explain. It is possible that individuals who show Multi-peak responses are more susceptible to auditory development during a period of unilateral hearing experience, compared to other waveform morphology types. This could be further supported by the idea that there might be differences in etiology of deafness between the different morphology types, but this is beyond the scope of this study.

In summary, we report for the first time responses evoked by unilaterally naïve ears after a period of unilateral auditory deprivation. These responses show a high prevalence of Multi-peak morphology (53%) compared to Positive peak (27%) and Negative peak morphologies (20%). This difference in prevalence of response morphology type evoked by unilaterally naïve ears (most prevalent: Multi-peak waveform—53%) compared to bilaterally naïve ears (most prevalent: Negative peak waveform – 49%) alone suggests that period of unilateral hearing promotes the development of naïve auditory cortex to an extent. Analyses of demographic details showed no statistically significant differences between waveform types, which is similar to what we have found in responses evoked from bilaterally naïve ears. To see the effects of unilateral CI experience, we also compared peak latencies and amplitudes for a given waveform type between responses evoked by the unilaterally naïve and bilaterally naïve ears. Statistically significant differences were only found P1ci and P2ci latencies of Multi-peak responses. This suggests that unilateral auditory experience may only promote auditory development in individuals who show Multi-peak morphology while not in individuals with Positive peak or Negative peak
morphology. It is possible that these response differences arise not only from state of cortical immaturity, but it might also be influenced by differences in etiology of deafness. Further analysis of such a factor should be performed in our future studies.

5.4 Response Difference/Similarities between experienced and Naïve Side Evoked responses

Unlike simultaneously implanted children, a majority of whom showed similar response types between the ears (67%), only 34% of sequentially implanted individuals showed similar response types between the ears. The fact that a majority of sequentially implanted individuals (66%) showed different response morphology between the experienced and naïve ear evoked response points to the likelihood that unilateral hearing experience promotes the development of the auditory cortex in one side, while having an effect on the opposite side.

Comparisons of demographic details between individuals who showed similar responses and differential responses between the experienced side and naïve side evoked responses showed no statistically significant differences. Similarly, there were no statistically significant differences in demographics between the waveform types within individuals who showed similar response morphology between the experienced and naïve ear evoked responses. In individuals who showed differential responses, however, statistical significance was reached for duration of unilateral CI use (duration of unilateral CI use) between the different combination patterns. This arose from the fact that four individuals who showed a combination of Multi-peak and Negative peak (experienced and naïve ears, respectively) had a shorter delay compared to other combination patterns. Since the number of individuals being compared differs considerably between one combination to another (ex. 27 versus 4 individuals), the reliability of such a finding is questionable.

Since there were generally no differences in demographic details from one group to
another, we can begin to speculate why some individuals showed similar response patterns, and why others showed differential patterns between the ears.

The development of contralateral dominance in NH animals and lack thereof in deaf animals has been shown in animal models. In cats, Kral and colleagues (2009) have shown that evoked response from the contralateral ear was found to have a greater response amplitude in the rostral areas of the cortical hemisphere than ipsilaterally evoked response in previously NH cats to CI stimulation (i.e. deafened NH cats implanted with CIs). In contrast, congenitally deaf cats fitted with CIs did not show such a specialization to the side of CI stimulation on the first day of device use (Kral et al, 2009). Thus, a period of deafness affects the organization of normal auditory pathways.

In our study, sequentially implanted individuals go through a period of unilateral deafness, as they have little to no auditory experience in the naive side prior to the day of testing. There is a possibility that unilateral CI stimulation could cause changes in the contralateral pathways in such a way that reorganizes the unused unilaterally naïve auditory pathway. In other words, for individuals who showed similar response morphology between the ears, one cannot rule out the possibility of strengthened ipsilateral auditory pathways, which could be utilizing the auditory pathways already established by the unilaterally experienced ear. Such a phenomenon is known to occur in individuals with unilateral deafness. Many imaging studies have reported that a period of unilateral deafness leads to symmetrical activation patterns in the auditory cortex compared to the asymmetrical activation patterns (i.e. contralateral dominance) of NH individuals with the use of functional magnetic resonance imagining (fMRI) (Langers et al, 2005; Bilecen et al, 2000). More symmetrical activation in the auditory cortex was also found in a study involving CAEPs, where late-onset unilateral deafness led to more symmetrical
amplitude and synchronous latency activation between the ipsilateral and contralateral sides in adults (Ponton et al, 2001). Together, these data suggests that unilateral deafness leads to a disruption of normal contralaterally dominated auditory projections, which may mean that cortical responses from experienced and naïve side evoked responses might be similar in response due to heavy reliance on the experienced auditory pathway. Considering the fact that central nervous system is more plastic during childhood compared to adulthood, unilateral deafness might cause more drastic changes in the auditory pathways during a period of deafness in children with unilateral CI experience than reported for adults (Ponton and Eggermont, 2001).

There are currently no studies that have examined the effects of unilateral deafness on responses from unilaterally naïve ear evoked response in humans. However, there is a similar study that was done in an animal model. With congenitally deaf cats which were sequentially implanted with bilateral CIs, Kral et al showed that CI stimulation of the naïve ear activated the ipsilateral auditory cortex relative to the experienced ear (i.e. activated the auditory cortex contralateral to naïve ear) (Kral et al, 2002). This result suggests that a period of unilateral CI use during cortical maturation do not result in a complete functional suppression of the naïve auditory pathways (Kral, 2002), thus preserving the normal, contralateral projections to a certain degree. This idea gives support to the possibility of the naïve auditory cortex receiving some auditory input, while maintaining at least some normal-like projections during a period of unilateral deafness.

Based on the current literature, it is possible that some sequentially implanted children exhibited symmetrical activation, as perhaps evidenced by similar waveform morphology between experienced and naïve ear evoked responses. However, we are unable to prove this idea from our test setup consisting of single channel cortical recording. At the same time, our study
refutes the idea that symmetrical activation might lead to similar response morphology between experienced and naïve sides. Our data showed two-thirds of sequentially implanted children with differential responses between the ears. This phenomenon must be accounted for by the fact that unstimulated contralateral pathways remain immature relative to the experienced pathways. On the other hand, to what extent unstimulated naïve pathways remain naïve is more difficult to discern. It is unlikely that the naïve pathways remain independent of auditory inputs from the experienced side, as our data showed higher prevalence of Multi-peak waveform responses in the unilaterally naïve side compared to bilaterally naïve side responses in addition to the likelihood of symmetrical activation in other unilaterally deaf auditory cortices (Langers et al, 2005; Bilecen et al, 2000, Ponton and Eggermont, 2001). In other words, if unilaterally naïve pathways were truly naïve, then they should have shown a higher prevalence of Negative peak waveform responses, while exhibiting different response morphology between the ears. Thus, we speculate that there is probably an influence of auditory input in the unilaterally naïve auditory cortex, possibly resulting from the symmetrical activation of the auditory cortex (Langers et al, 2005; Bilecen et al, 2000, Ponton and Eggermont, 2001).

It is also important to address whether response differences between the ears in sequentially implanted individuals will ever resolve after a period of bilateral CI use. We have previously reported differences in EABR latencies from the first day of bilateral CI use between simultaneously implanted and sequentially implanted individuals have also shown differences in latency (Gordon et al, 2008; 2007). Whereas simultaneously implanted bilateral CI users only had small differences in latency between the ears, sequentially implanted children with longer duration of delay between the first and second CIs had an especially large latency difference between the experienced and naïve ears (Gordon et al, 2008; 2007). In this respect, differential
responses at the brainstem level in sequentially implanted users are likely to have influenced the
differential cortical responses to some degree. Longitudinal studies of brainstem latency
differences in bilateral CI users have shown to decrease in simultaneously implanted and
sequentially implanted individuals with short delays after 9 to 30 months of device use (Gordon
et al, 2008, 2007). In sequentially implanted children with long delays, however, latency
differences persisted. Factoring in such results from the brainstem, it is likely that cortical
response differences will persist even after several months of bilateral CI use, especially for
those who show a difference at the subcortical level.

5.5 Concluding Remarks

Cortical responses from children using bilateral CIs showed clear differences in
prevalence of wave morphology under different deaf conditions. First, not all responses evoked
from bilaterally naïve ears show the typically naïve, Negative peak response, which suggests that
there are multiple effects of bilateral deafness to the deaf auditory cortex. Second, a period of
unilateral hearing experience leads to a development of typically mature Positive peak responses,
which was seen in a large majority of responses evoked by the unilaterally experienced ear. Third,
a period of unilateral CI use does affect cortical responses evoked by the naïve ear, as evidenced
by a large prevalence of Multi-peak responses compared to responses evoked by bilaterally naïve
ears.

Moreover, this study highlights the importance of tracking the development of cortical
responses as these children with bilateral CIs gain auditory experience. Such longitudinal studies
should help us answer some of the remaining questions we have at the end of our study. These
include 1) Where are the neurogenerators that are producing the three different evoked response
morphologies? 2) How will the three different waveform morphologies change with increase in
auditory experience? 3) Are Multi-peak responses an intermediate state of auditory development, as it becomes the Positive peak responses?

By combining our current results with results from our longitudinal study in the future, we hope to isolate the neurogenerators that are giving rise to different types of response morphology. This would provide us with a clearer picture of the effects of deafness in the auditory cortex in order to achieve our ultimate goal of improving the success rate of CI device use in deaf children.
Chapter 6 - References


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