Bilateral Auditory Development and Function in Children with Asymmetric Hearing Loss Who Listen with Electric and Acoustic Hearing

by

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Abstract

This thesis aimed to determine whether treating children who have asymmetric hearing loss with two different, but appropriate auditory prostheses promotes bilateral auditory development and bilateral hearing abilities. Unilateral deafness during development drives extensive reorganization in bilateral auditory pathways, limiting spatial hearing and putting children at risk for social and educational challenges. Providing electric cochlear implant hearing to the deaf ear and acoustic sound through a hearing aid or normal hearing in the other ear (bimodal hearing) restores bilateral access to sound. But it remains unclear how the two very different auditory signals can be processed by the auditory system to prevent abnormal neurophysiological changes from occurring. Hearing development in bimodal users was assessed by measuring evoked electrophysiological changes in the brainstem and cortex, as well as behavioural perception of important differences in sounds between the two ears.

Even though electrical and acoustic hearing are unique and stimulate the auditory system in different ways, symmetric neural conduction in bilateral brainstem pathways and the expected representation of each ear in the auditory cortex were achieved in children who had sufficient

residual hearing in their non-implanted ear. Moreover, most children experienced a bilateral advantage for speech perception over wearing either device alone, benefited from spatial hearing and could detect changes in binaural inter-aural level cues. These findings suggest that bilateral hearing does not need to be restricted to one modality and that the auditory system can integrate bimodal hearing to some extent. However, prolonged experience with asymmetric hearing during development extensively and persistently reorganizes the auditory system, limiting future efforts to restore bilateral and spatial hearing with bimodal devices. These findings are highly relevant to the clinical treatment of asymmetric hearing loss and support the recommendation to provide the most appropriate bilateral auditory prostheses as soon as possible to children who have significant hearing loss.

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Contributions

I, Melissa Jane Polonenko, prepared this thesis. I was involved in all aspects of this work, including planning, equipment development and validation, data collection and analysis, and writing of all original research and publications. The following contributions by other individuals are formally acknowledged:

Dr. Karen Gordon (Primary Supervisor) and Dr. Blake Papsin (Mentor) were the vision behind the studies presented in this thesis and contributed to all aspects of the work. Dr. Robert Harrison and Dr. Claude Alain (Advisory Committee Members) provided guidance and assistance with interpretation of results, as well as thesis preparation. Dr. Andrew Dimitrijevic (Guest of the Final PhD Committee Meeting) assisted with thesis preparation.

Stephanie Jewell and Carmen McKnight helped with some of the EEG recordings presented in Chapters 4-6. The following audiologists in the Cochlear Implant Program at The Hospital for Sick Children measured speech perception and spatial hearing as part of their clinical appointments for the data presented in Chapter 7: Laurie MacDonald, Gina Goulding, Mary Lynn Feness, Susan Druker, Pat Di Santo, Valerie Simard, Rebecca Malcolmson.

Daniel Wong developed the TRACS beamforming method used in Chapters 4-6 and the code used to plot chosen voxel locations on a mesh brain, as shown in Figure 4.3B, Supplemental Figure 4.1B, Figure 5.3A, and Figure 6.2. Alexander Andrews aided equipment development and bimodal stimulus coding used in Chapters 3-6. Alexander Andrews developed code with guidance from Salima Jiwani to extract maximum source activity from the beamforming output for all voxels, which was used in Chapters 4-6. Salima Jiwani, Salim Dharssi, and Catherine McCann developed code to visualize maximum source dipole activity in all voxels of the brain, as shown in Figures 4.3A, Supplemental Figure 4.1A, Figure 5.2C, Figure 6.3C. Carmen McKnight provided modified code to plot topographic maps of surface EEG activity, as shown in Figure 4.2B, Figure 5.2B, and Figure 6.3B. Dr. Vijayalakshmi Easwar assisted with software protocols to extract data logging information shown in Figure 5.1. Dr. Blake Papsin provided and prepared the X-ray used in Figure 2.7.

Permission for reproducing figures within Chapter 2 and reproducing published articles for Chapters 3-6 are provided in the Copyright Acknowledgments Section at the end of this thesis.

Funding and Studentships

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List of Abbreviations

ABR – Auditory Brainstem Response

ANOVA – Analysis of Variance

AVCN – Antero-ventral Cochlear Nucleus

BEM - boundary element model

cCMV - Congenital Cytomegalovirus

CI – Cochlear Implant

CN – Cochlear Nucleus

CU – Current Units

DCN – Dorsal Cochlear Nucleus

EEG – Electroencephalography

ESP – Early Speech Perception test

EVA – Enlarged Vestibular Aqueduct

FDR - False Discovery Rate

GASP - Glendonald Auditory Screening Procedure

GFP – Global Field Power

HA – Hearing Aid

HL – Hearing Level

IC – Inferior Colliculus

ILD – Inter-aural Level Difference

ITD – Inter-aural Timing Difference

IWI – Interwave Interval

LL – Lateral Lemniscus

LNTB – Lateral Nucleus of the Trapezoid Body

LSO – Lateral Superior Olive

MEG - Magnetoencephalography

MGB – Medial Geniculate Body

MLNT - Multisyllabic Lexical Neighbourhood Test

MNI - Montreal Neurologic Institute

MNTB – Medial Nucleus of the Trapezoid Body

MRI – Magnetic Resonance Imaging

MSO – Medial Superior Olive

NH – Normal Hearing

NIC – Nucleus Implant Communicator

PBK - Phonemic Balanced Kindergarten test

PCA – Principal Component Analysis

PROSPER - Pediatric Ranked Order Speech Perception

PTA – Pure Tone Average

PVCN – Postero-ventral Cochlear Nucleus

RAU - Rationalized Arsine Units

SD – Standard Deviation

SDT – Speech Detection Threshold

SE – Standard Error

SNR – Signal/Speech-to-Noise Ratio

SOC – Superior Olivary Complex

SRT – Speech Recognition Threshold

SSD – Single Sided Deafness

TRACS - Time-Restricted, Artefact and Coherent Source Suppression

WIPI - Word Identification by Picture Identification

Thesis Roadmap

This thesis is organized into 10 chapters. Chapter 1 sets the stage for the content of this thesis by describing the aims and hypotheses of this research and outlining the general approach to answering the specific questions explored in Chapters 3-7. Chapter 2 reviews the relevant background literature concerning the mechanisms and importance of binaural hearing during development, the consequences of not having binaural hearing, the efforts to restore binaural hearing in children who have significant hearing loss, and the methods to measure binaural development. Chapter 3 characterizes the unique challenges of combined electric-acoustic hearing and explores the consequences of this bimodal hearing on bilateral brainstem development and behavioural perception of binaural cues. This paper is published in *Audiology & Neuro-Otology*. Chapters 4-6 assess cortical development and neuroplasticity with bimodal hearing. These three papers are published in *NeuroImage: Clinical, Nature Scientific Reports,* and *Hearing Research*. Chapter 7 explores whether the electrophysiological findings from Chapters 3-6 are corroborated by behavioural outcomes of speech perception and spatial hearing. This paper has been submitted to *Scientific Reports* and is currently under review. Chapter 8 provides a general discussion of the findings from the 5 main chapters. Chapter 9 describes current projects and future directions that extend the findings of this thesis. Finally, Chapter 10 concludes this thesis by summarizing the findings and impact of this thesis.

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Chapter 1
Overview

</div>

1   Aims and Hypotheses

1.1   Main objective and impact

The main objective of this thesis is to examine whether symmetric bilateral auditory development and hearing abilities could be protected in children with asymmetric hearing loss. Thus, children were provided with bilateral auditory prostheses that were appropriate for the hearing loss in each ear: electrical stimulation of the auditory nerve with a cochlear implant (CI) in the deaf ear and amplified acoustic sound through a hearing aid (HA) in the other ear (termed electro-acoustic or bimodal hearing).

This thesis adds to the understanding of bilateral auditory development and the consequences of sensory deprivation. Furthermore, it informs on the optimal timing of treating deafness during development with different auditory prostheses (progression from bilateral hearing aids to bimodal devices to bilateral cochlear implants). The results of this thesis are already changing how bilateral sound is provided to children with significant and permanent hearing loss.

1.2   Rationale

Children with severe to profound hearing loss can learn speech (Gordon and Papsin, 2009; Harrison et al., 2005; Sarant et al., 2001) and language (Boons et al., 2013; Hess et al., 2014; Nicholas and Geers, 2007; Tobey et al., 2013) using electric hearing through one cochlear implant (CI). However, lack of stimulation from the non-implanted ear deprives the auditory system of binaural (two ears) cues. These binaural cues are essential for navigating and interpreting complex listening environments that have multiple sound sources, such as the playground and classroom. Bilateral (two-sided) hearing can be re-established by providing a second electric cochlear implant or an acoustic hearing aid (HA) in the other ear. However, it is important that sufficient hearing is provided to each ear at the right time for binaural hearing to occur because the developing auditory system must integrate small timing and level differences in sound delivered from both ears to the auditory brainstem and cortex (reviewed by Grothe et al., 2010). Without binaural integration of sound, children cannot locate and listen to a speaker in

the presence of multiple sounds (noise) as well as their peers with normal hearing, which challenges education and social interactions (Bess and Tharpe, 1986; Borton et al., 2010; Kuppler et al., 2013; Lieu et al., 2013, 2010). Furthermore, prolonged unilateral stimulation from one cochlear implant beyond a sensitive period of 1.5 years abnormally strengthens neural pathways from the stimulated ear (Gordon et al., 2013b, 2012, 2007b; Kral et al., 2013a, 2013b). This reorganization creates a system that remains preferential to the first stimulated ear (reviewed by Gordon et al., 2015; reviewed by Kaplan et al., 2016), which impedes later efforts to restore binaural hearing with a second implant in the other ear (Gordon et al., 2013a, 2013b; Jiwani et al., 2016).

Previous studies focused on bilaterally deaf children and animal models who became unilateral listeners through one cochlear implant. Another important group at risk for unilateral listening is the children who have one deaf ear and various degrees of residual hearing in their other ear, because they are not candidates for cochlear implantation using standard criteria (Cadieux et al., 2013). However, given the consequences of unilateral hearing in development, it is imperative that hearing loss be treated with the most appropriate device for each ear (Gordon et al., 2015). Thus, we sought to promote bilateral hearing development in children with asymmetric hearing by providing electric hearing with an implant in the deaf ear and amplified acoustic hearing with a hearing aid in the better ear (bimodal devices). Providing bimodal devices may restore bilateral access to sound, but it remains unclear how the two very different signals are processed and combined by the auditory system to (1) limit unilaterally driven reorganization in the brainstem and cortex, or to (2) promote symmetric speech perception and spatial hearing in children with asymmetric hearing. In the experiments of this thesis, I explored the utility of bimodal devices to protect and promote symmetric bilateral auditory development and function, thereby creating the capacity for binaural hearing to develop.

The acoustic hearing histories of children with asymmetric hearing loss are very heterogeneous and the etiology of deafness is often associated with acquired and/or progressive hearing loss (Arndt et al., 2015; Clemmens et al., 2013; Lin et al., 2017; Paul et al., 2017; Polonenko et al., 2018a; Sokolov et al., 2017). Hence, clinical management of asymmetric hearing loss has often been ambiguous and variable: to date, there are no established guidelines for treating pediatric asymmetric hearing loss. Only recently in 2016, there was a consensus about which outcomes should be measured and suggestions were given about trials with different auditory prostheses in

an effort to elucidate best treatment options (Van de Heyning et al., 2016). Having access to one of the largest cohorts of children with asymmetric hearing loss who use both a cochlear implant and hearing aid, I had a unique opportunity at SickKids Hospital to use their heterogeneous hearing histories to investigate which factors may best predict symmetric auditory development and function. By defining neurophysiological and perceptual asymmetries and characterizing several predictive factors, this thesis ultimately aimed to contribute to the discussion towards development of a guideline for treating asymmetric hearing loss in children.

1.3   Main hypothesis

Considering the importance of bilateral input to development, I hypothesized that providing adequate bilateral access to sound in each ear with bimodal devices protects the auditory pathways from reorganization and promotes symmetric function in children with asymmetric hearing. I also hypothesized that bimodal hearing would be particularly protective for those children with better hearing in their non-implanted ear and who consequently achieve adequate audibility to sound with a contralateral hearing aid.

1.4   Questions and hypotheses

At the beginning of my doctoral studies, we asked whether we should be providing a cochlear implant (and therefore, bimodal devices) to children with some residual hearing. Bilateral hearing aids were not providing sufficient bilateral input or satisfactory clinical outcomes; children were abandoning or rejecting a hearing aid in their deaf ear and only wearing one hearing aid in their other ear. But many of the children were not eligible for a cochlear implant in their deaf ear because of their residual hearing in the other ear. We first implanted children who had a significant hearing loss in the non-implanted ear, as they were close to eligibility with the standard implantation criteria ("traditional" group shown in blue in **Figure 1.1**). We termed this group "traditional" because previous studies of clinical outcomes in bimodal users focused on these children with limited residual hearing (Ching et al., 2014, 2007; Holt et al., 2005; Luntz et al., 2005; Simons-McCandless and Shelton, 2000). Following preliminary results from these children and through the course of my doctoral studies, the implantation criteria were expanded at The Hospital for Sick Children to include children with various degrees and configurations of residual hearing ("non-traditional" groups shown in **Figure 1.1**), eventually including children with normal hearing in the non-implanted ear (i.e., single-sided deafness). This latter group of

children with single-sided deafness provided a unique opportunity to study the consequences of congenital unilateral deafness with acoustic stimulation (as opposed to congenital bilateral deafness with unilateral electric implant stimulation) and the ability of a cochlear implant to work with acoustic hearing that is not affected by the physiological sequelae of hearing loss in the non-implanted ear.
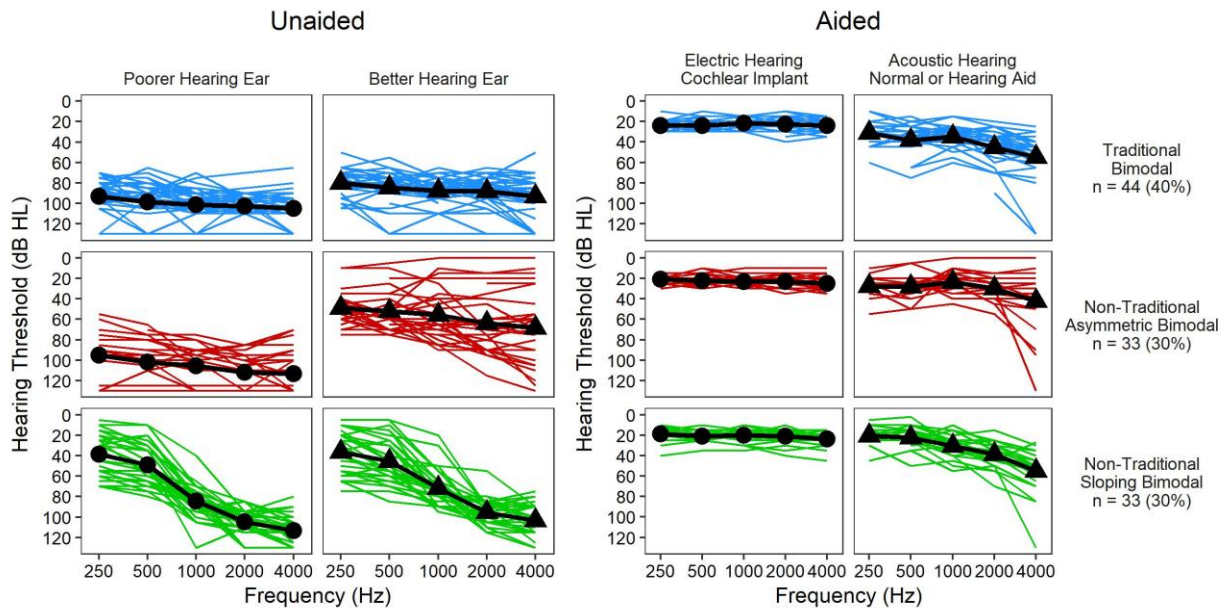
Figure 1.1. Hearing configurations of three bimodal groups.
The left panel shows pre-implantation unaided hearing thresholds for the poorer and better hearing ears of the 110 children who received bimodal devices at SickKids Hospital from 2012 to 2017. The right panel displays post-implantation hearing thresholds while wearing each device (aided) for the implanted and non-implanted ear. Three similarly sized groups were identified based on the configuration of hearing loss. Traditional bimodal users (blue) had significant bilateral hearing loss but slightly better hearing in one ear. The two non-traditional bimodal groups clearly had significant residual hearing, either in the non-implanted ear (asymmetric group; red) or in the low-frequencies of both ears (sloping group; green). For this last group, aided hearing became asymmetric due to better high-frequency audibility with the implant.

I developed unique but necessary equipment to study neurophysiological development of the bilateral auditory pathways from the brainstem (Chapter 3) to the cortex (Chapters 4-6) and the ability of children to lateralize binaural cues (Chapter 1), perceive speech (Chapters 4 & 7), and

benefit from spatial hearing (Chapter 7). By conducting the experiments within this thesis, I was able to begin answering questions about whether bimodal hearing should be given to children and in what timeframe during development. The experiments also enabled assessment of whether the goals were achieved of promoting symmetric neurophysiological development and symmetric auditory behavioural perception in children with asymmetric hearing. In Chapters 3-7, I specifically asked and hypothesized the following:

Chapter 3:

> Thesis Question 1: Does bimodal hearing preserve and protect bilateral symmetry in the auditory brainstem?

I hypothesized that absolute brainstem latencies will be asymmetric due to differences in stimulus conduction time and neural synchrony evoked by electric and acoustic stimuli. However, inter-wave latencies (reflecting neural transmission through the brainstem after accounting/correcting for much of the stimulus conduction differences) will develop symmetrically for children with better residual acoustic hearing.

Chapters 4, 5 & 6:

> Thesis Question 2: Can bimodal hearing prevent and/or reverse cortical reorganization and promote symmetric development in the cortex?

> Thesis Question 3: What factors prevent expected cortical development in children provided with bimodal hearing?

I hypothesized that bimodal stimulation limits cortical reorganization in children with asymmetric hearing loss by providing bilateral access to sound with the most appropriate hearing device for each ear. The ability of bimodal hearing to protect against and/or reverse cortical reorganization will depend on the duration and extent of asymmetric hearing prior to implantation.

Chapter 7:

> Thesis Question 4: Does bilateral input through bimodal devices or bilateral cochlear implants work to provide symmetric bilateral and spatial hearing?

Thesis Question 5: What factors best predict asymmetric perception of auditory input in children using bilateral devices?

I hypothesized that providing bimodal devices with limited delay to children with better residual hearing will prevent asymmetric speech perception, improve speech detection in noise, and enable spatial hearing.

1.5 Overview of methods
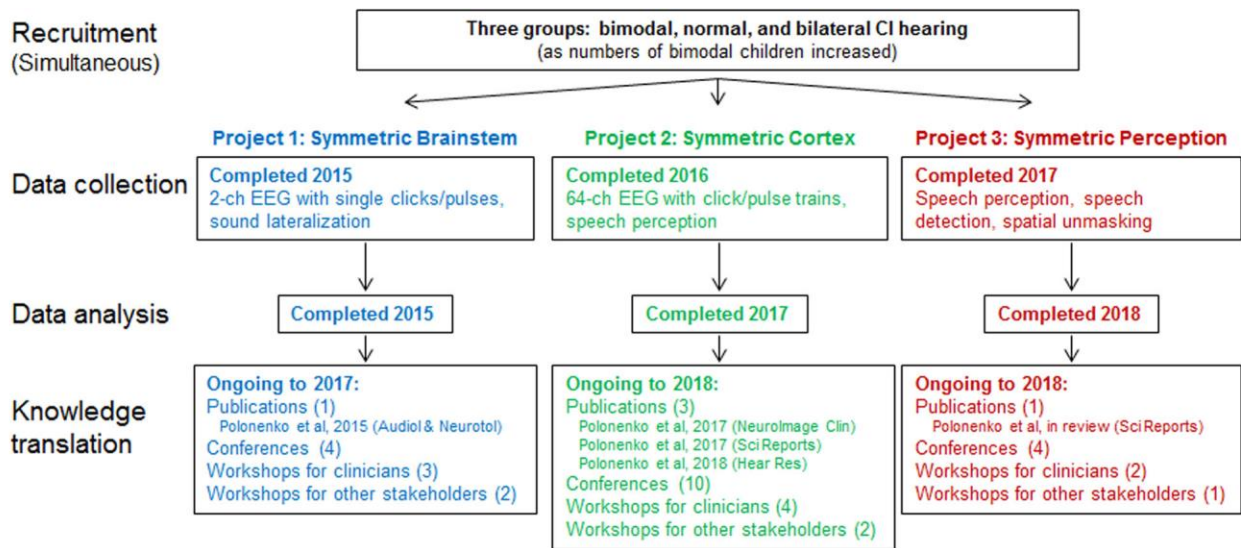
Figure 1.2. Study design and timeline.

Briefly, a cohort design was used to test whether bilateral auditory symmetry could be promoted and/or rescued in children who use bimodal devices. Longitudinal measures were completed for subsets of this cohort to evaluate plasticity with bimodal devices (Chapters 5-7). This group of pediatric bimodal users was compared to a control group of age-matched typically developing children with normal hearing, as well as to previously studied groups of similarly matched children who use two cochlear implants (**Figure 1.2**). Development of symmetric bilateral pathways and function was assessed using established electroencephalographic (EEG) measures of evoked activity in the auditory brainstem (Gordon et al., 2007a, 2007b) (Chapter 3) and cortex (Easwar et al., 2017b; Gordon et al., 2013b; Jiwani et al., 2016; Wong and Gordon, 2009) (Chapters 4, 5 & 6). Furthermore, behavioural measures of sound lateralization of inter-aural level and timing cues (Gordon et al., 2014; Salloum et al., 2010) (Chapter 3), speech perception

(Gordon and Papsin, 2009; Trimble et al., 2008) (Chapters 4 & 7) and spatial hearing (Chadha et al., 2011; Polonenko et al., 2016a) (Chapter 7) were also examined.

1.6   Summary of findings

1)   Bimodal hearing promotes symmetric bilateral auditory development of the brainstem and cortex with benefits for bilateral speech perception and spatial hearing in children who have asymmetric hearing loss. This occurs if bimodal hearing is provided without delay and to children who have sufficient residual hearing in their non-implanted ear. These findings suggest that bilateral hearing does not need to be restricted to one modality and that the auditory system can integrate electrical and acoustic hearing to some extent.

2)   There are limitations of bimodal hearing to reversing or preventing asymmetrically-driven reorganization of the auditory system when long periods of asymmetric hearing exist either pre- or post-implantation. Both neurophysiological and functional (behavioural) aural preference for the better hearing ear persists despite the use of bimodal devices, limiting bilateral advantages for speech perception in quiet and noisy situations and affecting spatial hearing.

3)   Bimodal hearing can re-establish bilateral hearing but there are remaining challenges for binaural hearing. Bimodal users cannot detect inter-aural timing differences, which is not surprising given the large mismatches in inter-aural place of stimulation and neural conduction in bilateral brainstem pathways. These mismatches may be further distorted by independently working processing in their two devices. Advances in device programming are required to correct for these differences, thereby optimizing capacity for binaural processing.

Chapter 2
Literature Review

2   Introduction

2.1   Binaural hearing is important during development

Humans are sensory beings that interact with their complex and multi-sensory environments. We are simultaneously exposed to a wide range of complex sounds from all directions in our environment. Appropriately distinguishing and perceiving these sounds is important for signaling danger and survival, oral communication and social interaction, navigation through acoustic space, and even pleasure, such as musical enjoyment and dancing. The auditory system is intricately designed and finely tuned to identify, segregate, process, interpret and respond to multiple sounds that comprise these rich acoustic landscapes in which we live.

Like its visual counterpart, the auditory system uses information from two sensory organs. But unlike vision, auditory information leaving these sensory organs does not explicitly convey spatial information. The auditory system must extract, transform and reconstruct an auditory spatial map. This in turn allows complex auditory perception, sound segregation and navigation to occur. Thus, two ears do not simply provide redundant sound information or aesthetic symmetry, but they also deliver signals that are compared and integrated by the bilateral auditory pathways (binaural hearing). This integration allows sound localization, spatial hearing and listening in complex environments (Grothe et al., 2010). These hearing abilities allow us to accurately understand, perceive and interact in the complicated environment that surrounds us.

Because these binaural hearing abilities are integral to daily living, disrupted or impaired hearing from one or both ears during childhood can have detrimental consequences on speech and oral language development (Nott et al., 2009; Tomblin et al., 2015; Yoshinaga-Itano et al., 2010, 2000, 1998). These impairments in turn place children at risk of social and educational challenges (Bess and Tharpe, 1986; Borton et al., 2010; Culbertson and Gilbert, 1986; Kuppler et al., 2013; Lieu et al., 2010; Ruben and Schwartz, 1999; Yoshinaga-Itano, 2003). Indeed, even transient minimal unilateral hearing loss during development can permanently change auditory neurophysiology (Buran et al., 2014; Keating and King, 2013; Polley et al., 2013; Popescu and Polley, 2010). Without consistent and adequate bilateral input during key sensitive periods, the

auditory system becomes persistently preferential to information from the better/dominant/stimulated ear, distorting and disrupting binaural representation of sound, and in so doing, compromising binaural hearing. This lasting developmental problem is termed the "aural preference syndrome" (reviewed by Gordon et al., 2015) or "amblyaudia" (reviewed by Kaplan et al., 2016). This is not a trivial or rare issue. Approximately 0.06% and 0.17% of babies in developed countries are born with permanent unilateral or bilateral hearing loss respectively (Berninger and Westling, 2011), and 0.04% are born with bilateral deafness (Smith et al., 2005). Thus, the prevalence of any type of permanent hearing loss is estimated to begin at 1.33 to 1.86 per 1,000 births, and then with progressive and acquired losses, the prevalence increases to 2.83 per 1,000 children in elementary school and then 3.5 per 1,000 adolescents (Fortnum et al., 2001; reviewed by Korver et al., 2017; Mehra et al., 2009; reviewed by Morton and Nance, 2006; Watkin and Baldwin, 2012). Hence, centres around the world have developed programs to identify hearing loss early in development in an effort to intervene with auditory prostheses as soon as possible.

Both cochlear implants (CIs) and hearing aids (HAs) are auditory prostheses designed to provide sound to children with hearing loss. Some children can successfully use a hearing aid, which delivers amplified acoustic sound to the auditory system. However, when the hearing loss is too profound for a hearing aid to provide adequate access to sound, a cochlear implant is used to translate acoustic sound into electric pulses. These pulses bypass the ear and directly stimulate the auditory nerve. Each device provides children with access to sound, thus promoting speech and language development (Ching et al., 2007, 2005; Gordon and Papsin, 2009; Harrison et al., 2005; Holt et al., 2005; Nittrouer and Chapman, 2009). There are some concerns about the capability of these auditory prostheses to promote binaural hearing development and to prevent the language and educational sequelae of the aural preference syndrome. To this end, bilateral implantation has become standard treatment for bilateral deafness (Cullington et al., 2017; Illg et al., 2017; Papsin and Gordon, 2008; Ramsden et al., 2012). However, there are currently no such established guidelines for children who have some residual hearing in at least one ear (asymmetric hearing loss) and who do not benefit from two hearing aids (Van de Heyning et al., 2016). Under standard implantation criteria, these children are not eligible for implantation of their deaf ear. This thesis fills this gap by measuring the developmental consequences of asymmetric hearing and examining the utility of implanting the deaf ear of these children.

Before delving into the utility and mechanisms by which these auditory prostheses attempt to re-establish binaural hearing, I briefly review normal auditory neurophysiology, mechanisms of binaural hearing, pathophysiology of hearing loss, and consequences of not having binaural hearing.

2.1.1 Normal auditory neurophysiology requires intact structures and involves parallel pathways

Normal hearing requires intact structures at each level of the auditory system. Moreover, from the outer ear to the auditory cortex, structures of the auditory system both transmit and transform sound information. Therefore, dysfunction in any structure alters the normal auditory experience.

2.1.1.1 Outer and middle ears transmit and transform acoustic pressure vibrations into mechanical and hydrodynamic vibrations

Sound waves consist of vibrations in pressure. These waves are first collected by the pinna of the outer ear and then transmitted through the external auditory meatus (ear canal) to vibrate the tympanic membrane (eardrum). Natural resonances of the concha (bowl of the pinna at the opening of the external auditory meatus) and external auditory meatus boost the incoming sound waves by 10-15 dB from 1-7 kHz (Shaw, 1974). The concha and cartilaginous folds of the pinna also change the amplitudes and phases of frequencies that comprise the incoming sounds based on where the sound is located. These head-related transfer functions give primarily monaural (one ear) cues that help localize sound coming from the front versus the back, and the location of sounds in the vertical plane (reviewed by Grothe et al., 2010; Shaw, 1974).

Vibrations of the tympanic membrane are then transmitted to the cochlea of the inner ear via mechanical vibration of the middle ear ossicular chain (malleus, incus and stapes). The footplate of the stapes is implanted into the fenestra ovalis (oval window) of the cochlea and its vibration displaces the fluid within the cochlea. The lever action of these three bones, the buckling action of the tympanic membrane, and the large surface area differential between the tympanic membrane and stapes footplate act to overcome the large impedance mismatches between air and fluid by increasing pressure 44-fold at the oval window (translates to approximately 33 dB). This pressure also increases as a function of frequency due to mass and stiffness properties of the middle ear system (Nedzelnitsky, 1980). Therefore, transfer functions of the outer ear and middle ear together shape the frequency range to which the auditory system is most sensitive. Vibration

conduction efficiency by the ossicular chain is modified with loud sounds by contractions of the tensor tympani and stapedius muscles which attach to the malleus and incus respectively. This acoustic reflex can be measured as a change in impedance of the middle ear system, which is one of many useful clinical tools to assess auditory function.

2.1.1.2   The cochlea transmits and transforms hydrodynamic mechanical vibrations into electrical neural signals according to frequency

The cochlea is the primary acoustic organ of the inner ear, which resides in the temporal bone of the skull. Also housed within the inner ear are the vestibular organs of the otoliths (utricle and saccule) and three orthogonal semicircular canals. These structures sense gravity and linear and angular accelerations of the head respectively. The vestibular and cochlear labyrinths are connected, contain membranous sacs filled with fluid, and use hair cells as sensory receptors that transduce mechanical motion into electrochemical signals. It is worthwhile mentioning the close anatomical and neurophysiological association of the cochlea and vestibular organs, because 20-70% of children with sensorineural hearing loss also experience vestibular impairment (Buchman et al., 2004; Cushing et al., 2013, 2008; Licameli et al., 2009; Selz et al., 1996). Furthermore, as discovered in Chapters 4 and 7 of this thesis, children with asymmetric hearing loss are more likely than children with bilateral deafness to have cochlear-vestibular abnormalities as the etiology of deafness (Polonenko et al., 2018a). Recent studies of children who have unilateral hearing loss or single sided deafness also report a 10% to 35% incidence of cochlear-vestibular abnormalities (Arndt et al., 2015; Fitzpatrick et al., 2017; Lin et al., 2017; Sokolov et al., 2017). The remainder of this literature review focuses on auditory neurophysiology.

The cochlea is a snail-shaped organ with just over 2.5 turns (ranges from 2.2 to 2.9 turns; Erixon et al., 2009) that measures on average 42.0 mm along the outer wall in humans, but cochlear length can vary from 38.6 to 45.6 mm (Erixon et al., 2009; Erixon and Rask-Andersen, 2013; Nadol, 1988; reviewed by Pujol et al., 1991; Pujol and Hilding, 1973; Rask-Andersen et al., 2012; von Békésy and Wever, 1960). The spiral turns of the cochlea transversely divide into three fluid-filled spaces: the scala vestibuli which connects with the fenestra ovalis (oval window) and contains perilymph fluid; the scala media which contains the organ of Corti and endolymph fluid; and the scala tympani which connects with the fenestra rotunda (round window) and contains perilymph fluid. The scala media is a sealed membranous sac separated

from the scala vestibuli by Reissner's membrane and from the scala vestibuli by the basilar membrane. The scala media is also bound by the modiolus down the centre axis of the cochlea, and the spiral ligament and stria vascularis on the outer axis of the cochlea.

Vibration of the stapes footplate into the fenestra ovalis creates hydrodynamic vibrations in the perilymph of the scala vestibuli, which subsequently vibrates the endolymph of the scala media. Perilymph vibrations continue through the helicotrema (a hole at the cochlear apex) and through the scala tympani to dispel pressure through the fenestra rotunda. The endolymphatic vibrations create a traveling wave along the basilar membrane that propagates from the cochlear base to the apex (von Békésy and Wever, 1960). Because stiffness of the basilar membrane decreases towards the apex (thin and narrow at base to thick and wide at the apex), the position of maximum displacement along the basilar membrane depends on the frequency composition of the sound. Higher frequencies maximally displace the stiffer basal end of the basilar membrane whereas the more flaccid/flexible apical end responds maximally to lower frequencies. Therefore, receptor hair cells at different places along the cochlea will respond to different frequencies, resulting in a cochleotopic mapping of frequency (i.e., tonotopic map) (reviewed by Lim, 1986; von Békésy and Wever, 1960). Also due to the tonotopic nature of the basilar membrane and the traveling wave, higher intensity sounds (i.e., louder) that are lower in frequency will activate a larger population of receptors and nerve fibres along the length of the cochlea than high-frequency sounds.

Endolymph fluid vibrations are transduced into electrochemical signals within the organ of Corti of the scala media. Lining the basilar membrane are approximately 15,000 hair cell receptors arranged into three rows of outer hair cells and one row of inner hair cells (reviewed by Lim, 1986). Atop these hair cells are 40-150 stereocilia shaped into rows with a "V" or "W" pattern, which are connected to an overlying tectorial membrane. Vibration of the basilar membrane displaces the hair cells and exerts a shearing motion with the tectorial membrane, which together bend the stereocilia. When stereocilia bend in the direction of the tallest stereocilia (the kinocilium), mechanically-gated potassium (K^+) channels open and K^+ flows against its chemical gradient into the hair cell (which already has a relatively high concentration of K^+). This influx of K^+ occurs because of a strong electrical gradient (+80 mV endolymphatic potential) created by the differing composition of endolymph (high $[K^+]$, low sodium $[Na^+]$) in the scala media (where apical ends of hair cells are located) compared to perilymph (low $[K^+]$, high $[Na^+]$) in the scala

tympani (close to basal ends of the hair cells) (Davis, 1958a, 1958b, 1957). The resulting depolarization of the hair cell potential opens voltage-gated calcium (Ca^{2+}) channels and K^+ channels, creating an influx of Ca^{2+}. This increase in Ca^{2+} further depolarizes the cell and causes neurotransmitter to be released from the basal end of the hair cell. A subsequent efflux of K^+ through the voltage-gated and Ca^{2+}-sensitive K^+ channels repolarizes the cell. Movement of the stereocilia in the opposite direction hyperpolarizes the receptor potential by closing the few mechanically-gated K^+ channels that are open at the resting potential. To allow rapid and continuous mechanoelectrical transduction with vibrations of the organ of Corti, K^+ is recycled through gap junctions in the supporting cells of the basilar membrane, spiral ligament and stria vascularis (Jun et al., 2000; Kelsell et al., 1997). The stria vascularis also provides oxygenated blood which supplies energy to actively pump K^+ back into the scala media against its electrochemical gradient, which maintains the endolymphatic potential. Any genetic mutation or cochlear insult that impairs functioning of any one of these structures will cause a hearing loss.

Both afferent and efferent auditory nerve fibres innervate the hair cells (reviewed by Spoendlin, 1985). Of the ~35,000 afferent nerve fibres (Otte et al., 1978), 90% are myelinated type I radial fibres that exclusively innervate one to two inner hair cells (although each inner hair cell is innervated by several type I fibres), whereas the other 10% are unmyelinated type II outer spiral fibres that each innervate many outer hair cells (Ota and Kimura, 1980; Spoendlin, 1972). Cell bodies of these afferents are called the spiral ganglion and are located within the modiolus, running through the centre of the cochlea. Efferent fibres (the olivocochlear bundle) originate from the ipsilateral and contralateral olivary complex of the auditory brainstem, synapsing directly on the outer hair cells and on the afferent fibres from the inner hair cells (Liberman and Brown, 1986; Rasmussen, 1946). Consistent with their innervation, inner hair cells are the primary mechanoelectrical transducers of sound whereas outer hair cells serve to actively increase the sensitivity and frequency resolution of the inner hair cell transduction. This "cochlear amplification" by the outer hair cells is accomplished by their rapid contraction and expansion to stimulation and to efferent control (Brownell et al., 1985; Gummer et al., 1996; Nuttall and Dolan, 1996): outer hair cell motility actively augments the shearing and displacement motions of the basilar and tectorial membranes. By increasing sensitivity, cochlear amplification also expands the dynamic range of intensities to which we are sensitive.

The afferent nerve innervation pattern (many fibres to one inner hair cell) serves multiple purposes, including frequency and intensity coding. Tonotopic organization of the cochlea is retained in the auditory nerve that consists of these fibres. Each afferent nerve fibre responds to a variety of frequencies and intensities, but it will respond best (i.e., greatest change in spontaneous discharge rate with the lowest sound intensity) at its characteristic frequency and location along the basilar membrane and the inner hair cell it innervates (place coding of frequency) (Hind et al., 1967; Liberman and Kiang, 1978; Rose et al., 1971). Furthermore, each nerve fibre discharges at a certain phase with the stimulus (i.e., phase-locked) up until about 5 kHz (temporal coding of frequency) (Rose et al., 1967). Due to refractoriness, each individual neuron may not fire at each cycle of the stimulus (i.e., will skip a phase occasionally). But the combined discharge profile of a group of neurons will faithfully follow each phase of the stimulus, even for frequencies above 5 kHz (population or volley coding of frequency). In addition to frequency coding, conveying this phase information to the brainstem is important for processing binaural inter-aural timing (and thus, phase) differences for sound localization. The discharge rate of an afferent fibre will also increase as a function of stimulus intensity (rate coding of intensity), up to a level 20-50 dB above its threshold (dynamic range). Different nerve fibres innervating the same inner hair cell have different spontaneous discharge rates, and therefore different thresholds to stimulation (high spontaneous rate neurons have low thresholds and low spontaneous rate neurons have high thresholds to stimulation). Consequently, the combined discharge of a population of neurons of low-, medium- and high-threshold fibres can code the entire 140 dB range of intensities to which we are sensitive.

Therefore, the combined anatomical and neurophysiological characteristics of the peripheral auditory system define the frequency and intensity range to which we are most sensitive. Furthermore, the cochlea represents the first site of auditory information transformation and processing, constituting a temporal and frequency analyzer. Any impairment or insult to these structures will cause hearing loss, which will be further described in section 2.2.1.

2.1.1.3 Afferent auditory electrical signals are transmitted and processed in parallel tonotopic pathways through the brainstem, midbrain and thalamus to the cortex

Once transformed into electrical signals in the auditory nerve, auditory information is further transmitted and processed by several parallel pathways and circuits within the central auditory

nervous system. Auditory nerve fibres leave the cochlea via the cochlear/auditory branch of cranial nerve VIII, sending information through the brainstem, midbrain, and thalamus to the cortex. **Figure 2.1** provides a simplified illustration of the ascending auditory afferent pathways.
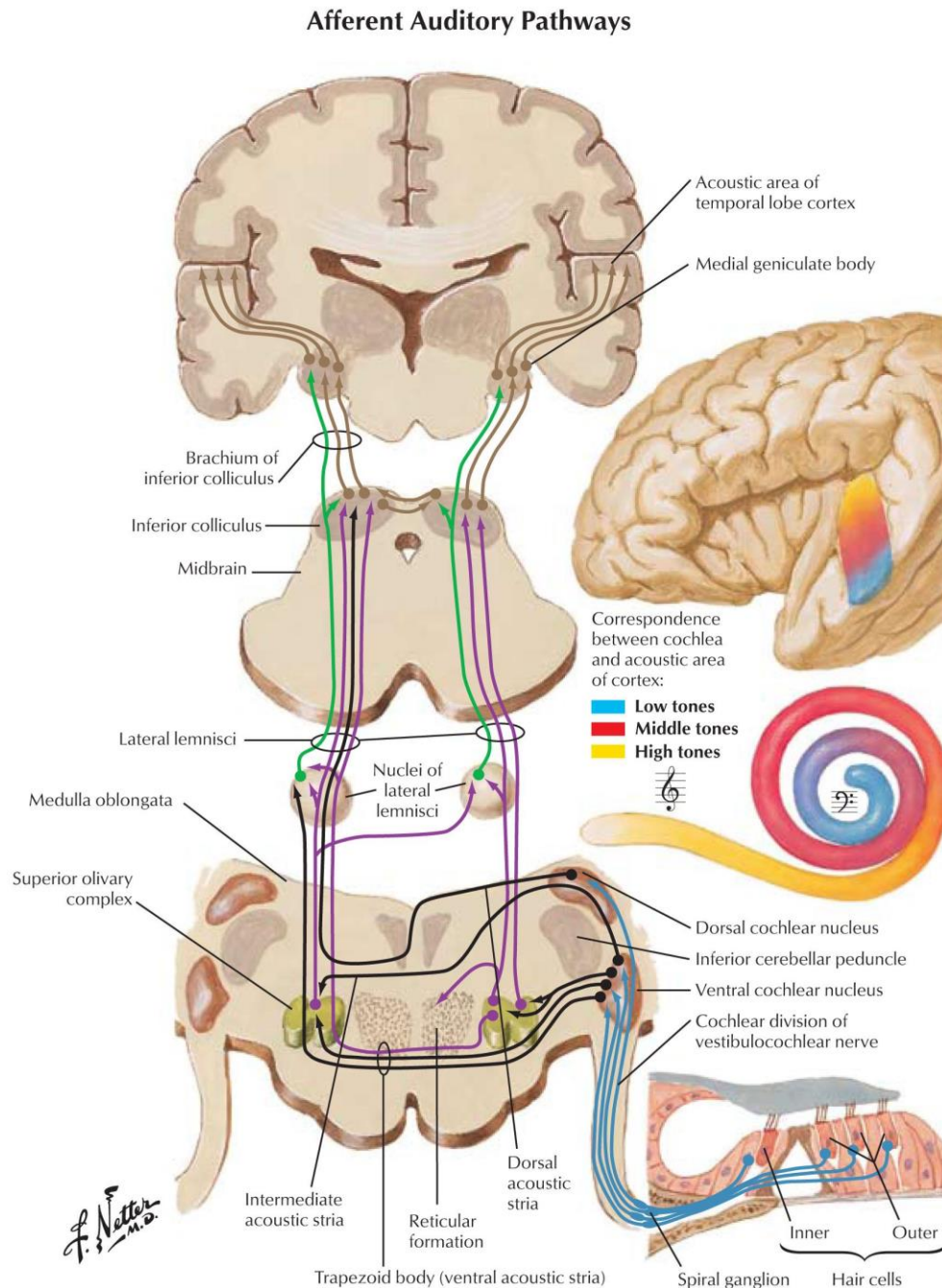
Afferent Auditory Pathways

Figure 2.1. A simplified diagram of afferent auditory pathways from the ipsilateral cochlea to the auditory cortex. Reproduced with permission, Copyright 2018 Elsevier Inc. All rights reserved. www.netterimages.com.

Illustrations of the cochlea and cortex at the top right indicate that tonotopic organization is maintained in the central auditory nervous system. High frequencies are represented in the basal cochlea and the medial primary auditory cortex, whereas low frequencies are located in the apical cochlea and lateral primary auditory cortex. The organ of Corti is shown on the bottom right. In response sound vibrations, vibratory (displacement) and shearing motions of the organ of Corti result in neurotransmitter release from the receptor hair cells, activating auditory nerve fibres. The ipsilateral auditory nerve sends electrical signals to the cochlear nucleus in the brainstem, which then sends both ipsilateral and contralateral projections through the medial nucleus of the trapezoid body to the superior olivary complex, and then through the lateral lemniscus, inferior colliculus of the midbrain, medial geniculate body of the thalamus to the primary auditory cortex in the transverse temporal gyrus (Heschl's gyrus) of the temporal lobe.

Central axons of the spiral ganglion neurons enter the brainstem ipsilaterally, branch and synapse on three cochlear nuclei: the dorsal cochlear nucleus (DCN), antero-ventral cochlear nucleus (AVCN) and postero-ventral cochlear nucleus (PVCN). Consequently, auditory information is differentially processed and transferred to the inferior colliculus (IC) of the midbrain in parallel pathways. Axons originating from the apical end of the cochlea project ventrally and basal axons project dorsally within each cochlear nucleus, thereby preserving tonotopic organization in the brainstem.

The cochlear nuclei contain different cell types with different response properties which serve different purposes. The DCN is a complex structure containing several cell types with complicated response properties. This structural organization enables complex processing of spectral information, including the processing of monaural spectral cues for vertical and front/back sound localization. Output of the DCN bypasses the superior olivary complex (SOC) of the brainstem to directly synapse in the contralateral IC. Some projections synapse in the ventral nucleus of the lateral lemniscus (LL), which in turn confers inhibition to the IC. In contrast, the AVCN primarily contains bushy cells that quickly and securely relay precise timing and intensity information to the ipsilateral and contralateral SOC, where information from both ears is first processed (binaural processing). This dedicated relay is accomplished through large synapses and nerve terminals. Spiral ganglion neurons form giant synapses with bushy cells in the AVCN (called the end bulbs of Held). Bushy cells project their axons to the contralateral medial nucleus of the trapezoid body (MNTB), where they have one of the largest and fastest

nerve terminals observed in the central nervous system (called the calyx of Held) (Kopp-Scheinpflug et al., 2011; von Gersdorff and Borst, 2002). Within the SOC, binaural differences in timing and level are integrated and processed by specialized circuits of excitation and inhibition that are located medially (MSO) and laterally (LSO) respectively. The specific mechanisms of this binaural processing will be described further in Section 2.1.2. The SOC sends projections through the lateral lemniscus to synapse in the central nucleus of the IC. Therefore, at the level of the midbrain, the IC receives converging information sent through these parallel ascending pathways from the CN. The IC further transforms auditory information, such as processing auditory space and complex temporal patterns in sound. Auditory information is then sent to an obligatory relay in the thalamus before projecting to the cortex.

There are distinct and parallel primary (lemniscal) and non-primary (nonlemniscal) thalamocortical pathways (reviewed by Hu, 2003; Kraus and McGee, 1993). The primary pathway is fast and carries specific auditory and tonotopic information that is relayed from the SOC to the central nucleus of the IC, and through the ventral nucleus of the medial geniculate body (MGB) to the middle layers (i.e., III, IV) of the primary auditory cortices (Hu, 2003). Information is then sent for further processing within auditory belt and parabelt association regions (Hu et al., 1994). Conversely, the non-primary pathway includes several thalamic nuclei: the dorsal and medial nuceli of the MGB, posterior intralaminar nucleus (PIN) and suprageniculate nucleus (SG). Responses from these nuclei are slower and more broadly tuned, delivering integrative and multi-sensory information (e.g., Bordi and LeDoux, 1994; Calford and Aitkin, 1983; reviewed by Hu, 2003). Inputs to these non-primary thalamic nuclei come from the dorsal and external-lateral nuclei of the IC, the mesencephalic reticular formation, and spinothalamic tract (Graybiel, 1972; Hu, 2003; Ledoux et al., 1987; McGee et al., 1991). Outputs of these thalamic nuclei project to layer I of auditory association cortices, the limbic system, striatum and cerebellum, which are thought to be involved in multi-sensory integration, temporal pattern or sequence recognition and some forms of learning (reviewed by Hu, 2003). Corticofugal projections also descend from layers V and VI of the auditory cortex onto primary and non-primary thalamic nuclei and to lower brainstem structures, creating a corticothalamic and other corticofugal auditory feedback loops.

2.1.1.4 The auditory cortex is specialized to efficiently process complex aspects of auditory information in parallel

The primary auditory cortex is located in the transverse temporal gyrus (termed Heschl's gyrus) of the temporal lobe. Surrounding the primary auditory cortex are belt and parabelt auditory regions that further process auditory information. As with other sensory cortical areas, the auditory cortex is organized into six layers, arranged from superficial (I) to deep (VI) layers. As mentioned in Section 2.1.1.3, primary thalamic projections enter at layer IV, whereas non-primary thalamic projections enter at more superficial layers (I-III). These superficial layers contain axons that send projections to other auditory and non-auditory cortical areas (cortico-cortical connections) within the same hemisphere and to the contralateral hemisphere via the corpus callosum. Also, as mentioned in Section 2.1.1.3, deep layers (V, VI) send projections to subcortical structures (corticofugal connections). Tonotopic organization is maintained in the primary auditory cortex and some belt/parabelt areas (Harel et al., 2000). As illustrated in the top right panel of **Figure 2.1**, low-frequencies are represented rostrally (towards the front), whereas high-frequencies are represented caudally (towards the back) in the primary auditory cortex. Arranged into these frequency columns are neurons that are excited by both ears (i.e., EE) or excited by one ear and inhibited by the other ear (i.e., EI). Therefore, columns within the auditory cortex respond to both frequency and binaural interactions. Typically, contralateral auditory information evokes stronger and faster activity in the auditory cortex (Gordon et al., 2013b; Jäncke et al., 2002; Khosla et al., 2003; Kral et al., 2009; Ponton et al., 2001; Yamazaki et al., 2018), resulting from the greater number and more efficient transmission of crossed than uncrossed fibres (Jäncke et al., 2002). As a result, each hemisphere preferentially responds to (or has an "aural preference" for) contralateral stimulation and both ears are similarly represented in the auditory cortex (Gordon et al., 2013b; Kral et al., 2013a, 2013b).

Like the subcortical auditory pathways, the auditory cortex is designed to process auditory information in parallel pathways. This specialization facilitates efficient and simultaneous processing of complex auditory input so that responses to sound can be generated within a reasonable timeframe (Zatorre et al., 2002). Like vision, the auditory system sends auditory information to ventral "what" streams that code sound identification and speech meaning, and to dorsal "where" or "how" streams that code spatial and movement aspects of sound and speech (Alain et al., 2001; Belin and Zatorre, 2000; Hickok and Poeppel, 2004; Poeppel et al., 2012).

The left and right hemispheres exhibit distinct neurological roles for processing rapid temporal changes (such as speech) versus slower spectral information (such as music) respectively (Giraud and Poeppel, 2012; Johnsrude et al., 2000; Schonwiesner et al., 2005; Zatorre et al., 2002; Zatorre and Belin, 2001).

Therefore, from spiral ganglion neurons to the cortex, the central auditory system comprises an elaborate system of parallel pathways that transmit, transform, process and integrate complex auditory input.

2.1.2 Binaural processing requires a balance of excitation and inhibition

As mentioned in Section 2.1, binaural hearing is important for sound localization and listening in complex acoustic environments. Sound localization in the horizontal (azimuth) plane requires the auditory system to process and integrate differences in level (ILD) and phase or timing (ITD) of sound reaching the two ears (Grothe et al., 2010; reviewed by Grothe and Pecka, 2014). As shown in **Figure 2.2A**, saliency/relevance of these two binaural cues depends on frequency because of head size (Erulkar, 1972). The head acts as a barrier, attenuating sounds coming from one side of the head. This head shadow effect creates an ILD for sounds that have a wavelength shorter than the width of the head. Thus, for humans, ILDs are more relevant for frequencies greater than 1.5 kHz. For lower frequencies, the auditory system depends on ITD cues. These binaural cues are first processed by circuits in the superior olivary complex of the auditory brainstem which rely on a fine balance of excitation and inhibition. High-frequency ILDs are processed by the lateral superior olive (LSO), whereas low-frequency ITDs are processed by the medial superior olive (MSO). Some low-frequency neurons in the LSO also respond to ITDs (Finlayson and Caspary, 1991; Joris and Yin, 1995; Park et al., 1996; Tollin and Yin, 2002), but the MSO circuit is the predominant ITD pathway (Grothe et al., 2010; reviewed by Grothe and Pecka, 2014).

Figure 2.2B illustrates the LSO and MSO circuits of ILD and ITD processing respectively. Response characteristics of example neurons from each of these circuits are given in **Figure 2.2C**. As briefly mentioned in Section 2.1.1.3, the ipsilateral auditory nerve sends projections to the ipsilateral anterio-ventral cochlear nucleus (AVCN). Input is then sent to both the ipsilateral and contralateral superior olivary complex (SOC), although in different ways and from different cell types for the two different circuits.

The LSO integrates glutamatergic excitatory inputs from spherical bushy cells (SBC) of the AVCN with glycinergic inhibitory inputs from the ipsilateral medial nucleus of the trapezoid body (MNTB). The MNTB receives glutamatergic excitatory inputs from globular bushy cells (GBC) of the contralateral AVCN (Boudreau and Tsuchitani, 1968; Finlayson and Caspary, 1991; Galambos et al., 1959; Tollin, 2003). The larger axons and thicker myelin sheaths of GBCs compared to SBCs (Morest, 1968) enable fast neural conduction from the contralateral AVCN to the ipsilateral LSO, resulting in similar arrival (co-incidence) of the excitatory and inhibitory inputs. Therefore, by integrating co-incident excitatory-inhibitory inputs, LSO neurons respond best to sounds located in the ipsilateral hemisphere (**Figure 2.2C**, left panel). Fibres from the LSO cross as they ascend, giving rise to contralateral representation of sound location in the midbrain and cortex.

On the other hand, the MSO integrates co-incident glutamatergic excitatory inputs from SBCs of both the ipsilateral and contralateral AVCN. Previously, this excitatory co-incidence detection was thought to occur through "delay-lines" of increased axonal length (Jeffress, 1948). However, it is now well established from animal studies that the MSO circuit is not just an excitatory co-incidence detector but involves a finely tuned balance of excitation and inhibition from both sides (Brand et al., 2002; Couchman et al., 2010; Grothe and Sanes, 1993; Jercog et al., 2010; McAlpine and Grothe, 2003; Myoga et al., 2014; Werthat et al., 2008). MSO neurons receive glycinergic inhibition from the ipsilateral AVCN through the ipsilateral lateral nucleus of the trapezoid body (LNTB) (Myoga et al., 2014) and from the contralateral AVCN through the ipsilateral MNTB. Again, because these LNTB/MNTB pathways are mediated by AVCN GBCs, the inhibition may arrive faster than the excitation coming from AVCN SBCs, thereby modulating excitatory inputs to the MSO (Brand et al., 2002; Grothe and Pecka, 2014; Pecka et al., 2008). By this circuitry, MSO neurons respond best to sounds located in the contralateral hemisphere. This contralateral representation is preserved to, and within, the cortex.

Although mediated through different circuits, outputs of both the LSO and MSO result in binaural detectors that are broadly and hemispherically tuned to sound location within the horizontal plane (Hancock and Delgutte, 2004; Harper and McAlpine, 2004; McAlpine et al., 2001; Stecker and Middlebrooks, 2003). According to this "two-channel" system (**Figure 2.2D**), a sound at midline evokes similar activity in ipsilateral and contralateral SOCs (both "channels"). Moving the sound to either side increases the relative activity on one side/channel (reviewed by

Grothe and Pecka, 2014). These responses are dynamic and may code relative rather than absolute sound locations, because previous activity can modify ITD tuning in the SOC to the cortex through GABAergic inhibition (Dahmen et al., 2010; Grothe and Pecka, 2014; Ingham and McAlpine, 2005; Lee and Middlebrooks, 2011; Magnusson et al., 2008; Stange et al., 2013).

This contralateral "two-channel" representation of sound continues upstream into the midbrain and cortex. ILD and ITD information from the SOC converge in the inferior colliculus (IC). Both the IC and auditory cortex contain binaurally sensitive neurons with specific ILD and ITD tuning (Tillein et al., 2016, 2010). Binaural information is combined with monaural spectral information to reconstruct an auditory spatial map of sound location in the colliculi. This auditory spatial map is also combined with visual and somatosensory information in the superior colliculus to build a multi-sensory spatial map. Auditory space is also represented in the auditory cortex, which plays an important role for spatial processing. Evidence for the need of an intact cortex comes from cortical lesion studies, which reveal sound localization deficits in both humans (Adriani et al., 2003; Clarke et al., 2002) and animals (Jenkins and Merzenich, 1984; Malhotra et al., 2004; Neff, 1977). Each auditory cortex represents sound location information from the contralateral hemisphere in animals (Lee and Middlebrooks, 2011; Werner-Reiss and Groh, 2008) and humans (Johnson and Hautus, 2010; Krumbholz et al., 2005; McEvoy et al., 1993). However, this contralateral representation of space may be asymmetric between the hemispheres: the right auditory cortex responds to sound in both hemifields but the left auditory cortex responds primarily to sound in the contralateral hemifield (Briley et al., 2012; Krumbholz et al., 2005; Magezi and Krumbholz, 2010; Malhotra et al., 2004).
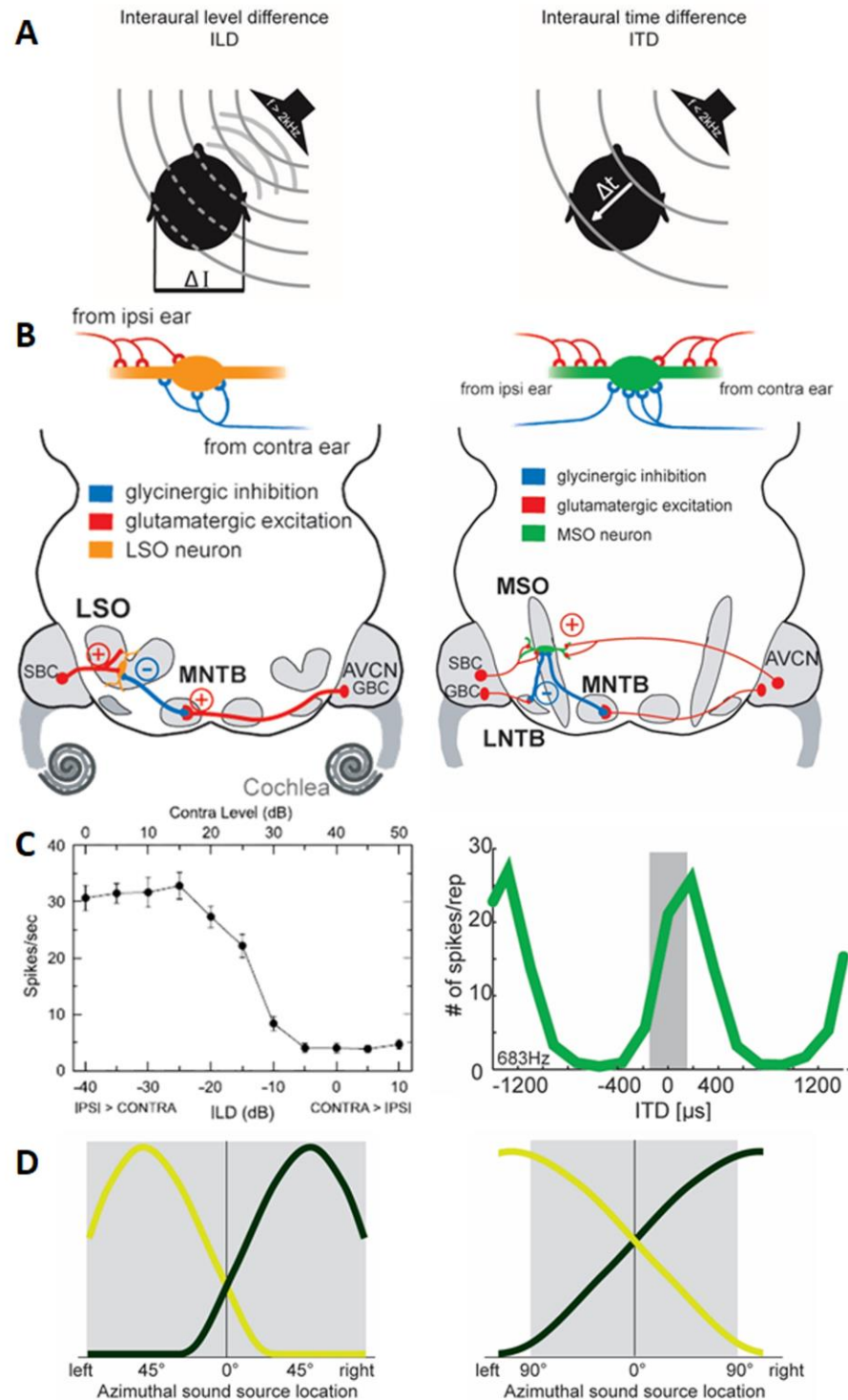
Figure 2.2. Mechanisms of binaural processing in the brainstem. Modified and reproduced with permission from (Grothe and Pecka, 2014), Copyright Frontiers.

(A) Sound localization in the horizontal plane uses binaural cues of inter-aural level (ILD) and timing (ITD) differences in the arrival of sound reaching the two ears. Due to a shadow created

by the head, ILDs are more salient at frequencies higher than 2 kHz, whereas ITDs are more salient at lower frequencies. (B) Binaural cues are first processed in the superior olivary complex of the brainstem using circuits of excitatory and inhibitory synapses. ILDs and ITDs are primarily processed in the LSO and MSO respectively. (C) Example response characteristics of an LSO and MSO neuron to ILDs and ITDs respectively. (D) Location along the horizontal plane is coded by a "two-channel" tuning in both the LSO and MSO. LSO = lateral superior olive; MSO = medial superior olive; MNTB = medial nucleus of the trapezoid body; LNTB = lateral nucleus of the trapezoid body; AVCN = anterio-ventral cochlear nucleus; GBC = globular bushy cell; SBC = spherical bushy cell.

2.1.3 Normal auditory development involves experience-driven refinement and maturation of innate structures

Development of these parallel and complex auditory pathways occurs by a combination of innate embryonic changes, intrinsic neural activity (such as spontaneous discharge), and extrinsic (experience dependent) input-driven processes. Innate and intrinsic activity drives early fetal development, whereas auditory input-driven changes play a larger role following hearing onset. Therefore, auditory input is important during later fetal development, post-natal development, childhood and into adulthood. This is of concern for children who have hearing loss. With deafness, children miss key milestones in fetal and post-natal development while they await input from auditory prostheses (reviewed by Kral and Sharma, 2012). In the case of asymmetric hearing loss, children will have some auditory input to drive development, but this input is abnormal/distorted. Before considering the deleterious effects of hearing loss, a brief overview of normal auditory development will be described, along with the electrophysiological measures that help track these underlying changes.

During the first two trimesters of fetal development (weeks 1-26), peripheral and central auditory structures form, neurons grow and axons begin to mature simultaneously in the absence of auditory input (reviewed by Moore and Linthicum, 2007). These structures connect and exhibit rudimentary function, tonotopy and binaural sensitivity in both normal hearing and deaf animals, suggesting that initial auditory pathways are innate from the cochlea to the cortex (Friauf and Lohmann, 1999; Hartmann et al., 1997; Heid et al., 1998, 1997; Kral and Eggermont, 2007). These initial pathways then undergo auditory experience-driven refinement and maturation, such

as improved neural conduction from the cochlea to cortex, increased complexity of neural response patterns (i.e., complex processing), and refined tonotopic mapping in the auditory cortex (e.g., Harrison et al., 1991; Moore and Linthicum, 2007; Pienkowski and Harrison, 2005; Ponton et al., 2002). These occur through increased myelination, synaptic efficiency, dendritic arborization and synaptogenesis (Huttenlocher and Dabholkar, 1997). Following a period of high synaptic density and plasticity, pathways mature and specialize through synaptic elimination ("pruning"). Synapses follow Hebbian principles, whereby successful repeated synapses gain efficiency while failed or asynchronous synapses become inefficient and latent.

The third trimester of fetal development (particularly weeks 27-30) marks the onset of hearing and the increasing developmental role of auditory input. Behavioural responses, such as facial and body movements, can be observed as early as 25 weeks gestation (Birnholz and Benacerraf, 1983). By 29-32 weeks gestation, these responses become more consistent and indicate some preference, such as to music or the mother's voice (Pujol et al., 1991). Also during this time, electrophysiological auditory brainstem responses (ABR) are first detectable, reflecting neural conduction of auditory input from the auditory nerve to the inferior colliculus (Despland and Galambos, 1980; Ponton et al., 1992; Starr et al., 1977). Not surprisingly, onset of these first responses coincides with the onset of myelination (Moore et al., 1995), highlighting the importance of fast and synchronous transmission of auditory input to the cortex for perception to occur. Thereafter, the temporal lobe of the auditory cortex forms (Moore and Linthicum, 2007), myelination density increases and axons further mature (reviewed by Moore and Linthicum, 2007).

Following birth, the brainstem rapidly matures. Myelination of the spiral ganglion neurons matures within one month, as indicated by adult-like ABR wave I latencies (Amorim et al., 2009; Eggermont and Salamy, 1988). Other ABR waves, reflecting transmission to the cochlear nucleus (III) and inferior colliculus (V), continue to increase in amplitude and decrease in latency over the next five months as myelination density increases. The ABR response essentially becomes adult-like by age 2 years (Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Eldredge and Salamy, 1996; Jiang et al., 2009, 1991; Ponton et al., 1992). Concurrently, axons from the inferior colliculus to the thalamus mature, as indicated by rapid development of the P_0-N_a component of the middle latency electrophysiological response (Moore and Linthicum, 2007). Evidence from animal and human neonates research

suggest that brainstem binaural processing also occurs at these early developmental stages, but further refinement and maturation continues. Collicular (midbrain) neurons in neonatal rats quickly exhibit receptive fields to contralateral space, which undergo further refinement with experience (Vachon-Presseau et al., 2009). Neurons in the cochlear nuclei and inferior colliculus of kittens respond to binaural cues in an adult-like manner (Blatchley and Brugge, 1990). Consistently, binaural brainstem interactions are identifiable in ABR responses of human infants, although latencies and amplitudes reflect immaturity compared to adult responses (Cone-Wesson et al., 1997; Furst et al., 2004; McPherson et al., 1989). Accordingly, adult-like perception of binaural cues (ILDs and ITDs) develops by five years of age (Litovsky, 1997; Van Deun et al., 2009). The later timeframe than brainstem maturation likely reflects the additional role and requirement of cortical development for perception.

Cortical neurons form during embryonic stages, but their axonal maturation follows a longer trajectory than subcortical development. Axonal maturation directly relates to maturation of scaffolding neurofilament proteins, which enlarge axonal diameter and promote myelin sheath development to allow faster and more synchronous neural conduction (Moore and Guan, 2001). Accordingly, these changes are paralleled by the development of sharper and faster electrophysiological middle latency responses (reflecting thalamo-cortical transmission) and cortical evoked potentials (reviewed by Eggermont and Ponton, 2003). Moreover, maturation of these electrophysiological responses into adult-like poly-phasic waveforms (i.e., P1-N1-P2 complexes) follows neurofilament expression and maturation in different layers of the cortex (e.g., Ponton et al., 2002, 2000). These structural and electrophysiological changes correspond to the emergence and progression of complex hearing abilities in children (reviewed by Eggermont and Ponton, 2003).

Over the next five years, mature axons are initially present only in layer I and then emerge in deeper layers (IV-VI) of the auditory cortex (Moore and Guan, 2001). As described in Sections 2.1.1.3 and 2.1.1.4, layer I contains projections from non-primary lemniscal pathways, auditory association areas and other cortical areas (such as the limbic system and reticular activating system, which are involved in arousal), whereas deep layers contain thalamo-cortical and cortico-fugal projections from both primary and non-primary lemniscal pathways. Correspondingly, P2 cortical potentials (Wunderlich et al., 2006) and middle latency responses (Fifer and Sierra-Irizarry, 1988) mature during this time respectively. The faster maturation of

cortical layers associated with the non-primary pathways may result in a relative dominance of this pathway compared to primary lemniscal pathways in younger than older children. This is suggested by the greater influence of wakefulness on MLR responses of younger children (Kraus and McGee, 1993; McGee et al., 1991) and the greater influence of multi-sensory input on auditory perception (Moller and Rollins, 2002). Behavioural perception develops from infants distinguishing different sounds in both their native and non-native languages (Trehub, 1976) to children discriminating auditory input and developing language (reviewed by Eggermont and Ponton, 2003).

Last to develop are the superficial layers III and II. Axonal maturation begins at 5 years and continues to age 12 years (Moore and Guan, 2001). Concurrently, synaptic density decreases, and cortical specialization emerges. A negative N1 peak emerges in the cortical evoked responses, demarcating the immature broad positive peak into its constituent P1 and P2 components (Eggermont and Ponton, 2003). As axons mature in these superficial levels, and the N1 develops, children's hearing abilities improve and become more elaborate. For example, by 12 years, children perceive binaural cues (Litovsky, 1997; Van Deun et al., 2009), make use of spatial hearing (Garadat and Litovsky, 2007; Schafer et al., 2012), perceive degraded speech or speech in challenging listening conditions (Eisenberg et al., 2000; Elliott, 1979), and lateralize frequency-specific (narrow band) noise within continuous broadband background noise (Schneider et al., 1989).

In summary, hearing involves an elaborate system of intact structures and parallel pathways that are innately formed but require auditory experience to mature and increase in complexity. Maturation occurs along different time courses, which is reflected by changes in electrophysiological potentials and behavioural perception. Therefore, disruptions to any part of the system may compromise normal auditory development and function. Because auditory input is integral to maturational processes, the consequences of auditory deprivation through deafness, or distorted auditory input through asymmetric hearing, will be explored next.

2.2   Lack of binaural hearing drives abnormal reorganization in the auditory system with functional consequences to daily functioning/deficits

From Section 2.1, there are clearly several parts of the auditory system that need to be intact, work together with other structures, and receive typical auditory input to achieve normal auditory neurophysiology, development, and function. Hence, absent, deficient or distorted auditory input, or trauma to the auditory system will impair auditory neurophysiology, resulting in hearing impairment and degeneration of the auditory system. Our goal in treating childhood hearing impairment is to promote normal development as much as possible, given the neurophysiological limitations introduced by hearing loss and the current capabilities of auditory prostheses to provide adequate representation of binaural cues and complex auditory input. Before considering how auditory prostheses can be used to treat hearing loss and restore binaural hearing, we must first understand the mechanisms of hearing impairment and the resulting pathophysiology. Impaired binaural hearing occurs with bilateral deafness, unilateral deafness and asymmetric hearing. The consequences of each type of deafness on the developing auditory system will be described, as well as the functional outcomes for children with these types of hearing loss.

2.2.1 Etiology of deafness affects the pathophysiology of hearing loss and the resulting pattern of functional deficits

Hearing impairment can be caused in several ways. This thesis is primarily concerned about permanent sensorineural hearing loss, which affects structures in the cochlea and central pathways. However, it is worthwhile to briefly mention conductive hearing loss because even temporary disruptions to bilateral auditory input during key developmental periods can permanently change auditory processing/functions (Blatchley et al., 1983; Buran et al., 2014; Clopton and Silverman, 1977; Keating and King, 2013; Moore et al., 2003; Polley et al., 2013; Popescu and Polley, 2010; Silverman and Clopton, 1977). Transmission of sound to the cochlea can be disrupted or impeded by outer ear malformations (e.g., malformed pinna/microtia or stenosis/atresia of the external auditory meatus), disruption to the ossicular chain, or fluid build-up in the middle ear space (otitis media with effusion). These impairments to the outer and middle ears dampen, delay and distort sound, thereby disrupting binaural cues. Consequently, children who experience recurrent and persistent otitis media with effusion exhibit long-term deficits in binaural and spatial hearing abilities (Graydon et al., 2017; Hall et al., 1995; Hogan

and Moore, 2003; Jafari et al., 2016; Moore et al., 1991; Tomlin and Rance, 2014), particularly when the conductive hearing loss is asymmetric (Moore et al., 2003). Spatial hearing difficulties and self-reported challenges for listening in noisy environments are also exhibited by children who have unilateral atresia and microtia (Agterberg et al., 2011; Polonenko et al., 2016a). These deleterious effects of conductive hearing loss on binaural auditory development highlight the importance of consistent and early bilateral auditory experience.

As described in Section 2.1.1.2, the inner ear represents the site of mechanoelectrical transduction and where transformation of auditory input first occurs. Therefore, the cochlea represents a vulnerable structure in the auditory system, and any deficiency, impairment or trauma to cochlear processes will impair auditory function. Where and how the impairment occurs in the cochlea will impact the pathophysiology of hearing loss and the resulting functional deficits. For children who have significant cochlear impairment, amplified acoustic sound with a hearing aid insufficiently stimulates the spiral ganglion cells, resulting in poor functional hearing. A cochlear implant can bypass this cochlear dysfunction by directly stimulating the auditory nerve with electric pulses, which will be further described in Section 2.2.3. For children with asymmetric hearing, cochlear impairments are relevant to understanding the remaining hearing challenges they experience while listening with acoustic hearing in at least one ear.

Cochlear impairments can arise from genetic mutations, developmental malformations and trauma. Of particular relevance to congenital hearing loss, genetic factors contribute to almost 50% of hearing impairments, of which 30% are syndromic and approximately 75% are autosomal recessive (Smith et al., 2005). Currently, over 176 genes are known to affect different parts of the cochlea (Meena and Ayub, 2017). **Figure 2.3** provides an overview of several mutations, highlighting the diversity and penetration of genetic mutations to all aspects of cochlear functioning.
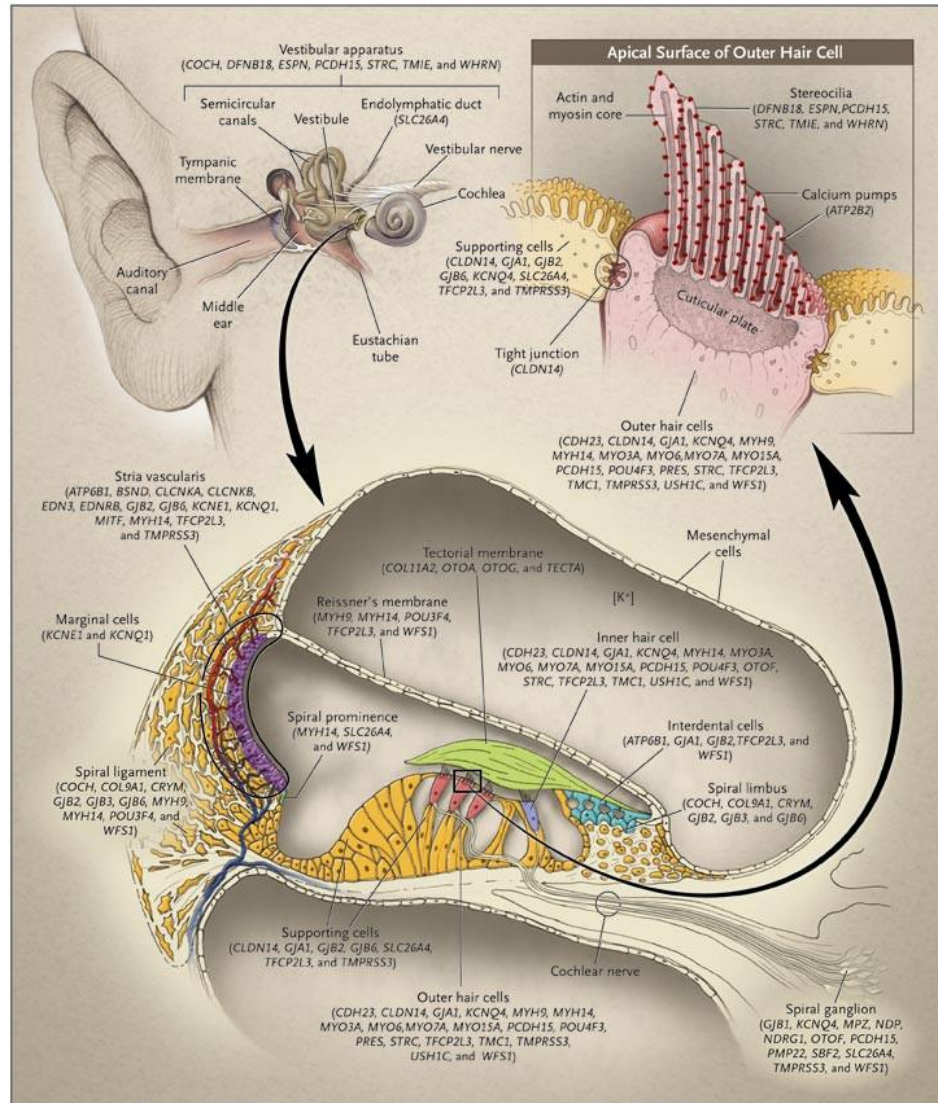
Figure 2.3. Genetic mutations affect several aspects of cochlear functioning. Figure reproduced with permission from (Morton and Nance, 2006), Copyright Massachusetts Medical Society.

Genetic mutations causing hearing loss are located in each cochlear structure, affecting cochlear processes such as ionic flow and the endolymphatic potential, mechanoelectric transduction in the hair cells, and auditory nerve function. These genetic mutations account for up to 50% of hearing impairments.

One of the most well-known genes to cause bilateral deafness is GJB2, which is now routinely screened for in some cochlear implant programs. The 35delG mutation of this gene alone accounts for nearly 80% of the pathogenic deletions identified in a multi-cultural population of children using cochlear implants (Propst et al., 2006b). Other mutations have been identified in children with asymmetric hearing loss (Lin et al., 2017; Song et al., 2009). GJB2 encodes the connexin 26 protein, which forms into gap junctions in the supporting cells, spiral limbus, spiral ligament and stria vascularis. As described in Section 2.1.1.2, these gap junctions are integral to maintaining the endolymphatic potential so that mechanoelectrical transduction can occur in the inner hair cells (Jun et al., 2000; Kelsell et al., 1997). Therefore, with a mutation in this gene, inner and outer hair cells are present but cannot function properly due to loss of the electrochemical gradient driving their function. This in turn limits stimulation of the spiral ganglion cells and perhaps spontaneous activity in ascending pathways, which may have a greater (negative) impact on early development of ascending pathways. In support, children with GJB2 mutations exhibit very immature auditory evoked cortical potentials to initial cochlear implant stimulation compared to similarly aged children without GJB2 deafness (Gordon et al., 2011). Also, unlike non-GJB2 deafness, children with GJB2 mutations exhibit similar evoked neural responses from the cochlear base and apex, suggesting uniform survival of spiral ganglion nerves (Propst et al., 2006a). This consistent survival may inform programming considerations of cochlear implants, such as equal gain applied across electrodes rather than higher gain at basal electrodes.

Chemical composition and fluid dynamics of endolymph are also affected by mutations of the SLC26A4 gene. This gene encodes the pendrin protein, which is an anion (negative ion) exchanger in cell membranes. Mutations of this gene lead to autosomal recessive non-syndromic hearing loss, as well as Pendred syndrome and cochlear abnormalities such as enlarged vestibular aqueduct (EVA) (Meena and Ayub, 2017). It remains unclear precisely how EVA causes hearing loss, but there are three main theories (reviewed by Gopen et al., 2011). First, dysfunctional pendrin impairs ionic movement, which may create toxic byproducts that damage cochlear cells, or create an imbalance in endolymph composition and volume that may overwhelm the ionic pumps in the stria vascularis, thereby affecting the endolymphatic potential (Jackler and De La Cruz, 1989; Levenson et al., 1989). Second, changes to the fluid and pressure dynamics within the inner ear may affect stapes movement or pass along greater intracranial pressure changes into

the cochlea, which in turn may damage hair cells (Lemmerling et al., 1997; Okamoto et al., 1998). Third, EVA may act like a third window to the cochlea, changing the compliance of the system and allowing energy to be lost/transferred out of the cochlea (reviewed by Gopen et al., 2011). Hearing loss associated with EVA tends to progress, especially with trauma to the head (Gopen et al., 2011; Morton and Nance, 2006). Importantly, there is a high prevalence of EVA in children who have asymmetric hearing loss (Chapters 4 and 7) (Arndt et al., 2015; Fitzpatrick et al., 2017; Lin et al., 2017; Polonenko et al., 2018a; Sokolov et al., 2017).

Other well-known genetic mutations affect hair cell and auditory nerve function. Both MYO15A/7A and CDH23 genes affect stereocilia function and are associated with Usher's syndrome, as well as autosomal recessive non-syndromic hearing loss. MYO15A/7A genes encode the myosin protein that helps stereocilia develop and allows hair cell motility. CDH23 encodes cadherin-related protein 23, which is involved in stereocilia and hair bundle formation. As described in Section 2.1.1.2, stereocilia are necessary for mechanoelectrical transduction, and outer hair cell motility is important for hearing sensitivity and frequency resolution. OTOF encodes the otoferlin protein and is expressed in the inner hair cells and spiral ganglion. Otoferlin allows vesicular fusion to the membrane to release neurotransmitter. Therefore, otoferlin dysfunction is associated with abnormal auditory nerve function (neuropathy).

In addition to genetic factors, developmental malformations contribute to congenital hearing impairments. Cochlear-vestibular impairments are present in a significant proportion of children with asymmetric hearing (Chapters 4 and 7) (Lin et al., 2017; Park et al., 2000; Polonenko et al., 2018a). These malformations include EVA, as well as hypoplastic modiolus (incomplete partition of the cochlea), incomplete cochlear turns (1.5 instead of ~2.5), short cochlear duct, and dilated vestibule (collectively called the Mondini malformation). Cochlear-vestibular malformations are also associated with syndromes such as Pendred, CHARGE (*c*oloboma, *h*eart defects, *a*tresia choanae, growth *r*etardation, *g*enital abnormalities, and *e*ar abnormalities), Branchio-Oto-Renal (BOR), X-linked deafness with stapes gusher (Phelp's) and Klippel Feil. Auditory nerve hypoplasia (narrowing) is associated with auditory neuropathy, abnormal brainstem development and poor speech perception outcomes, making children with this etiology poor candidates for cochlear implantation (Valero et al., 2012). While bilateral cochlear nerve hypoplasia is rare (~5%) (Clemmens et al., 2013), unilateral cochlear hypoplasia constitutes the

predominant cause of single sided deafness, with a prevalence of 32-50% (Lin et al., 2017; Paul et al., 2017; Sokolov et al., 2017).

Hearing impairments can also arise from vascular, chemical and mechanical trauma to the cochlea. As the source of energy and the endolymphatic potential, the stria vascularis is vulnerable to vascular trauma from hypoxia (Evans, 1974), loop diuretic medication (Evans and Klinke, 1982; Thalmann et al., 1977), and cytomegalovirus infection (CMV) (Carraro et al., 2016). While some hearing impairments can be reversed once blood flow returns and the endolymphatic potential is restored, some vascular insults permanently damage the cochlea. CMV infection damages the stria vascularis and spiral limbus vasculature, starting at the mid-apical turns and continuing basally (Carraro et al., 2016). As with clinical presentation of hearing loss, damage to the cochlea can be quite variable. Congenital CMV infection can cause bilateral deafness and progressive loss, but as recently discovered, is one of the leading etiologies of single sided deafness in children (Lanzieri et al., 2017; Park et al., 2014; Sokolov et al., 2017). Hypoxia may transiently affect blood flow and the endolymphatic potential, but even three hours of hypoxia selectively damages the inner hair cells and eventually destroys the outer hair cells in both animals and neonates (Amatuzzi et al., 2001; Shirane and Harrison, 1987). The damage is permanent: stereocilia become disarranged and the inner hair cells swell/blebb. Inner hair cells show a similar vulnerability and pattern of damage with poisoning from the cancer drug carboplatin (Harrison, 1998; Hofstetter et al., 1997; Macdonald et al., 1994). Carboplatin also selectively destroys spiral ganglion cells (Ding et al., 1999; Salvi et al., 1999), effectively reducing the number of channels by which auditory information can be delivered to the central auditory system and degrading neural representation of sound. This selective inner hair cell damage with hypoxia and carboplatin results in hearing deficits in animals that parallel those experienced by children with auditory neuropathy (Harrison, 1998; Salvi et al., 1999).

Not all trauma affects the inner hair cells. Aminoglycosides (e.g., gentamycin) are cochleo-toxic antibiotics given for serious infections. They selectively damage the outer hair cells, resulting in elevated thresholds and broad frequency selectivity (Evans and Harrison, 1976; Harrison et al., 1995). As shown in kittens, aminoglycoside poisoning during development can cause long-term deficits to frequency tuning in the auditory cortex, even in areas associated with regions of the cochlea that remain intact (Harrison et al., 1995). Moreover, mechanical damage from loud noise can destroy both inner and outer hair cells and supporting structures (Salvi et al., 1979), or the

synapses between hair cells and spiral ganglion nerve fibres (Liberman and Kiang, 1978). Mechanical damage from temporal bone fractures may disarticulate the stapes, disrupt the cochlear membranes or blood supply, obstruct fluid dynamics or injure the spiral ganglion cells. Therefore, trauma differentially damages the cochlea, causing different hearing deficits depending on the structures affected.

These cochlear impairments arising from genetic, vascular, chemical and mechanical factors ultimately impair transmission and coding of auditory information to central auditory pathways. This stimulation is important for central auditory development (Section 2.1.3). Consequently, absent, insufficient or distorted auditory input drives abnormal development and widespread degeneration of upstream pathways. These central auditory neurophysiological consequences of hearing impairment are described next.

2.2.2 Bilateral deafness causes widespread structural and functional changes to the auditory system

Like other sensory modalities, the auditory system is shaped by experience. Normally, this optimizes our ability to detect and respond to the stimuli to which we are exposed. This neuroplasticity benefits typical development and maturation, as well as provides mechanisms for change with treatment/rehabilitation strategies. But this neuroplasticity also leaves our systems vulnerable to compensatory changes when sensory input is deprived. In the case of bilateral deafness, lack of auditory input drives widespread changes to both structure and function in the auditory system. Considering the importance of experience to development, these changes are more extensive and devastating with earlier onset and longer duration of deprivation (reviewed by Kral and Sharma, 2012).

Much of what we understand about the neurophysiological consequences of bilateral deafness comes from congenitally deaf or early-deafened animal models (mostly kittens) (reviewed by Butler and Lomber, 2013), and from acute electrical stimulation of the deprived auditory system with one or two cochlear implants. However, animal results are often reflected in outcomes of human imaging studies.

Beyond cochlear impairments, extensive deafness-related changes begin with the auditory nerve and continue to association auditory areas. Spiral ganglion cells are reduced in number (Heid et

al., 1998; Ryugo et al., 1998) and show less complex synaptic structure and branching. Compared to cats with normal hearing, the endbulbs of Held in deaf cats exhibit flattened and elongated pre-synaptic densities, increased vesicular density, and no cisternae (Baker et al., 2010; O'Neil et al., 2010; Ryugo et al., 2005, 1997). Less contact is made with bushy cells in the cochlear nucleus (Ryugo et al., 1998), which themselves show larger and flatter post-synaptic densities (Redd et al., 2000; Ryugo et al., 2010). Moreover, bushy cells in the AVCN and pyramidal cells in the DCN are smaller and more dense, contributing to an almost 50% volume reduction of the cochlear nucleus (Hardie and Shepherd, 1999; Saada et al., 1996). The volume reduction is more severe in the AVCN than DCN (Saada et al., 1996), and the magnitude depends on the degree of spiral ganglion loss and length of deafness (Hardie and Shepherd, 1999). Taken together, these changes impact the fidelity of auditory input transmission through these specialized synapses by introducing jitter, delay or failure at synapses (O'Neil et al., 2010). This in turn compromises temporal processing of auditory input, which is necessary for sound localization, feature recognition, and speech perception.

At the level of the brainstem and midbrain the number of projections do not change (Heid et al., 1997; Russell and Moore, 1995) but rather the quality of synapses and neuronal response properties. Neurons in the medial trapezoid body, superior olive and inferior colliculus atrophy without auditory input (Pasic et al., 1994; Russell and Moore, 1999), deliver poorer (yet still rudimentary) tonotopic representation of sound (Heid et al., 1997; Kandler and Gillespie, 2005; Snyder et al., 1991, 1990), and fire with reduced temporal resolution and precision (Leao et al., 2004; Snyder et al., 1990; Vollmer et al., 2005). Deafness also reduces both inhibitory and excitatory input to cell bodies and dendrites of neurons in the MSO (Kandler and Gillespie, 2005; Tirko and Ryugo, 2012) and IC (Vale and Sanes, 2002). These reductions contribute to poorer binaural processing. Contralateral representation of sound is diminished and fewer IC neurons respond to ITDs (Hancock et al., 2013, 2010).

Several changes occur to the auditory cortex with deafness. Like subcortical structures, the auditory cortex exhibits rudimentary but impoverished tonotopic organization (Hartmann et al., 1997; Kral et al., 2001; Tillein et al., 2010) and reduced binaural sensitivity (Kral et al., 2009; Tillein et al., 2016, 2010). There is also a significant increase in the number of non-responsive cortical sites, along with reduced firing rates, smaller dynamic ranges (Tillein et al., 2010) and increased excitability (hypersensitivity) (Kotak et al., 2008, 2005; Kral et al., 2005; Raggio and

Schreiner, 1999). Together, these altered response properties compromise the ability of the auditory system to discriminate and represent different features of dynamically changing auditory stimuli. Representation of auditory input is further compromised by abnormal inhibition and altered maturation of excitatory post-synaptic potentials (Kral and Eggermont, 2007), and by cortical neurons responding more to ipsilateral stimulation and less to contralateral stimulation (Kral et al., 2009; Tillein et al., 2016). Human imaging studies of deafness show a decrease in the white to gray matter ratio in the primary auditory cortices, suggesting impaired myelination (i.e., axonal maturation) and/or synaptic development to/from the auditory cortex (Emmorey et al., 2003; Gilley et al., 2008). While similar cortical layers develop with deafness (Hartmann et al., 1997), activity in mid to superficial layers appears later and remains immature, and activity in deeper layers disappears/decreases (Kral et al., 2000). This follows a delayed period of synaptogenesis and exaggerated pruning (Kral et al., 2005). Consequently, cortical columns decouple/desynchronize, impairing cortico-cortical and cortico-fugal connections that are important for top-down modulation, feedback loops and connection with auditory association areas (Kral et al., 2005). Supporting evidence comes from late-implanted deaf children, who exhibit persistently abnormal evoked cortical responses that do not develop into the typical N1 component (which emerges with cortico-cortical activity in superficial cortical layers, as previously described in Section 2.1.3) (Gilley et al., 2008; Kral and Sharma, 2012; Sharma et al., 2007). Furthermore, deafness alters projections from thalamic nuclei and other auditory areas into the primary auditory cortex, and there is some evidence for small scale cross-modal plasticity with an increase in somatosensory input (Chabot et al., 2015). Therefore, altered connections to, within, and from the primary auditory cortex leave the deaf brain vulnerable to recruitment by other sensory modalities (cross-modal reorganization).

While primary auditory cortices mainly show auditory-specific changes to connections with other cortical areas (Chabot et al., 2015), auditory association areas are susceptible to cross-modal plasticity (reviews by: Butler and Lomber, 2013; Kral et al., 2017). These areas become targets of the visual and somatosensory systems if auditory input is not given within the sensitive period for normal development, which coincides with the period of greatest synaptic plasticity (Huttenlocher and Dabholkar, 1997; reviewed by Kral and Sharma, 2012). This cortical neuroplasticity compensates for hearing deprivation to optimize/enhance the remaining senses for interaction with the world. In deaf cats, visual localization is enhanced by recruitment of the

posterior auditory field (PAF; Lomber et al., 2010) and field of anterior ectosylvian sulcus (FAES; Meredith et al., 2011), both of which are typically involved in sound localization. Visual motion sensitivity improves with recruitment of the dorsal zone (DZ; Lomber et al., 2010) whereas recruitment of the anterior auditory field (AAF; Meredith and Lomber, 2011) improves encoding of somatosensory cues and characteristics of visual movement. Not only are these auditory areas recruited during active tasks such as visual localization, but their connectivity within resting networks also changes with deafness. For example, resting activity of PAF and DZ more strongly couples with activity in cerebellar and collicular networks, which also typically respond to both auditory and visual spatial information (Stolzberg et al., 2018). Reduced resting cortical metabolism (reflecting auditory deprivation) occurs in auditory areas of younger, but not older, children who are deaf, suggesting recruitment of these areas for other purposes for those children who experience longer periods of deprivation (Lee et al., 2001). Deafness also increases resting cortical metabolism in other cortical areas associated with visual processing (occipital-temporal), working memory (pre-frontal) and visual imagery (parietal) (Lee et al., 2005). The extent of these cross-modal changes correlates with the ability of the auditory system to make sense of electrical auditory input following cochlear implantation to restore hearing (Lee et al., 2001, 2005).

Therefore, because of the experience-driven nature of development, the auditory system undergoes extensive structural and functional reorganization in the absence of auditory input. Neuroplastic changes occur at all stages of the ascending auditory pathways. At the level of the cortex, both auditory-specific and cross-modal changes occur. This happens as the auditory system becomes disconnected from other areas of the cortex through abnormal maturation within the deep and superficial cortical layers of the primary auditory cortex.

2.2.3 Cochlear implants provide electrical stimulation to drive auditory development that is subject to sensitive periods

Considering the widespread reorganization and degeneration that occurs in the auditory system with deafness, it is important to restore access to auditory input with auditory prostheses as soon as possible. For children who have significant deafness, a cochlear implant bypasses the cochlea to directly stimulate the spiral ganglion cells with electrical pulses. While hearing can be restored through electrical stimulation, it is important to understand how electric hearing encodes sound, which may affect how an implant drives development.

As illustrated in **Figure 2.4**, a cochlear implant includes an external sound processor that is worn on the ear, a surgically implanted receiver-stimulator that sits within the skull, and an array of 11 to 22 electrodes (depending on the company and electrode length) that is inserted into the scala tympani of the cochlea. Two reference electrodes are situated outside the cochlea. Frequencies are allocated to the different electrodes according to their placement within the cochlea to maintain tonotopic stimulation of the spiral ganglion cells. Electrodes send biphasic electrical pulses (to prevent accumulation of charge that may damage tissue) that vary in magnitude depending on the intensity of the incoming sound. The electrically stimulated spiral ganglion cells then transmit this auditory input to the ascending auditory pathways.

Acoustic sound is detected and digitized by the microphone of the external processor. The input is then filtered into different frequency bands corresponding to each electrode, and low-pass filtered to extract intensity and temporal information from the envelope. Unfortunately, current implants cannot convey temporal fine structure (Zeng, 2004; Zeng et al., 2008), which is important for pitch discrimination and music perception (e.g., Drennan and Rubinstein, 2008; Gfeller et al., 2012; Limb and Rubinstein, 2012). Amplitude compression is applied to ensure the current output at the electrodes does not exceed the dynamic range of electric hearing. The dynamic range for electric hearing is smaller (~20 dB) than for acoustic hearing because a small increase in current provides a greater activation of the neurons (Rubinstein, 2004). This also limits rate coding and perception of loudness growth due to refractory periods (Zeng et al., 2008). The dynamic range is programmed by a clinician, who sets the threshold (T) and maximum comfortable level (C) of stimulation. After processing the input, the external component sends instructions to the internal receiver through a transcutaneous radio frequency transmitting coil, which attaches through a pair of magnets. Electrodes then stimulate the spiral ganglion cells in an interleaved rather than simultaneous pattern, to reduce cross-channel interactions between the electrodes.
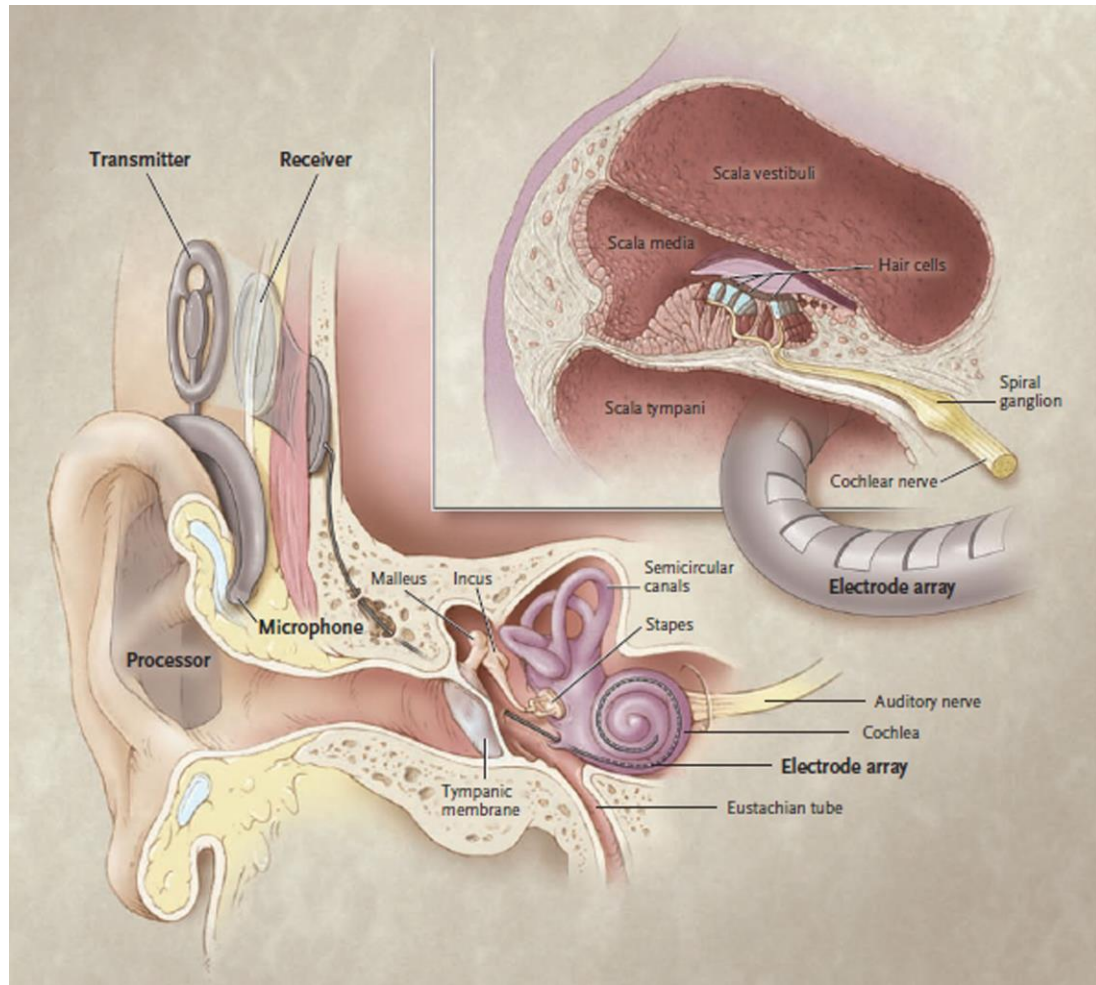
Figure 2.4. The external and internal components of a cochlear implant in a cross-section of the cochlea. Reproduced with permission from (Papsin and Gordon, 2007), Copyright Massachusetts Medical Society.

The external processor of the cochlear implant detects and digitizes sound with a microphone, analyzes the frequency and intensity information the input, and delivers instructions to the internal receiver via a radio frequency signal, which is connected through a skin flap by a pair of magnets. Information is then sent to an array of electrodes implanted into the scala tympani (illustrated in the top right corner), which then send biphasic electrical pulses to stimulate the remaining spiral ganglion cells. Frequencies are allocated to each electrode in a tonotopic fashion, with basal electrodes conveying high frequencies and apical electrodes conveying low frequencies. Intensity of sound is encoded by the magnitude of the electrical pulses.

Although cochlear implants deliver auditory input to the auditory system, electrical representation of sound is not normal. Electrical stimulation provides poorer spatial bandwidth

and frequency resolution because sound is delivered through 22 electrodes compared with ~3,000 inner hair cells in the normal cochlea, and there are fewer spiral ganglion cells to stimulate due to hearing loss (Heid et al., 1998; Ryugo et al., 1998). Moreover, cochlear implants use a monopolar mode of stimulation, which further obscures spatial and spectral resolution. In monopolar stimulation, electric current from the active electrode spreads over a large distance as it returns to the reference electrode, which is placed outside of the cochlea. This larger current spread excites a broader population of spiral ganglion cells along the cochlea, effectively reducing the number of functional channels. Electrical stimulation also evokes greater neural synchrony and phase-locking in the auditory nerve than normal (Rubinstein and Hong, 2003; Zeng, 2004). Instead of a group of neurons combining their firing rates to faithfully convey each phase of the stimulus, neurons phase-lock together and become constrained by group refractoriness. This limits the ability of the auditory nerve to convey phase information, which is important for ITD encoding. Phase information is also obscured due to the inability of electrical stimulation to provide temporal fine structure (Zeng, 2004; Zeng et al., 2008), which is normally conveyed through cochlear vibrations and processes. Cochlear implants are only capable of coding and delivering maximal peaks within the temporal envelope of sound. Therefore, while cochlear implants restore access to auditory input, electrical hearing provides abnormal input to an abnormal system in an abnormal way. This may alter or limit auditory development with electrical hearing.

Regardless of these limitations to electrical hearing, cochlear implants stimulate the auditory system to drive auditory development. Chronic electrical stimulation reverses the morphological abnormalities in the endbulbs of Held if provided early (O'Neil et al., 2010; Ryugo et al., 2005), allowing dedicated transmission of electrical input. A greater area of the auditory cortex responds to stimulation (Kral et al., 2002). Furthermore, cortical neurons develop expanded dynamic ranges and differential responses to different electrical input, which are both important for auditory feature discrimination (Kral et al., 2006). Electrophysiological measures in children who are congenitally deaf indicate that a cochlear implant promotes development of the auditory brainstem (Gordon et al., 2007a, 2007b, 2006, 2003) and thalamo-cortex (Gordon et al., 2008a, 2005a; Jiwani et al., 2016, 2013; Papsin and Gordon, 2007; Ponton and Eggermont, 2001; Sharma et al., 2002a; Sharma and Dorman, 2006). Long-term electrical stimulation can also promote maturation of central auditory pathways and restore some cortico-cortical connections,

as indicated by the emergence and development of the N1 component in adolescents who received a cochlear implant early in life (Gordon et al., 2013a; Jiwani et al., 2016, 2013). Moreover, children using a cochlear implant from an early age make significant gains in speech understanding (Gordon and Papsin, 2009; Sarant et al., 2001) and language development (Boons et al., 2013; Hess et al., 2014; Nicholas and Geers, 2007; Tobey et al., 2013).

However, developmental neuroplasticity with electrical stimulation is constrained by sensitive periods. Best outcomes with cochlear implants are achieved when electrical stimulation is provided before deafness-driven changes become too widespread and permanent. The sensitive period for providing auditory input corresponds with periods of highest synaptic plasticity (Kral and Sharma, 2012), which ranges from ages 2-4 years in humans (Huttenlocher and Dabholkar, 1997). Accordingly, children who are implanted within 3.5 years quickly develop normal cortical response morphology and latency from the stimulated ear (Dorman et al., 2007; Gilley et al., 2008; Gordon et al., 2005b, 2008a; Jiwani et al., 2013; Sharma et al., 2007) and better speech and language abilities (e.g., Geers, 2006; Gordon and Papsin, 2009; Harrison et al., 2005; Niparko et al., 2010) than children who receive an implant after 4-7 years of bilateral deafness. Furthermore, children who experience several years of auditory deprivation before receiving an implant are more likely to exhibit abnormal cortical responses and cross-modal reorganization, which correspond to their poorer speech outcomes (Eggermont and Ponton, 2003; Gordon et al., 2005b; Lee et al., 2001, 2005). Therefore, a cochlear implant, when given within optimal sensitive periods of development, can provide enough stimulation to prevent and/or reverse some of the deafness-related changes to the auditory system.

2.2.4 Unilateral deafness drives reorganization in the auditory system that over-represents the hearing ear and reduces binaural sensitivity

Providing unilateral electrical hearing limits extensive deafness-driven changes by giving some auditory input to facilitate auditory development. However, unilateral hearing creates a new problem because the auditory system is designed to receive binaural input (as described above in Section 2.1.2). Depriving input from one ear restricts access to binaural cues that are necessary for localizing sound and hearing in noisy environments, and consequently, drives abnormal auditory development. The effects of unilateral hearing/unilateral deafness on auditory development are often more dramatic than with bilateral hearing loss (Clements and Kelly, 1978;

Gordon et al., 2015; Keating and King, 2013; Keuroghlian and Knudsen, 2007; Kral et al., 2013b; Silverman and Clopton, 1977).

Unilateral deafness initiates deprivation-related abnormalities in the ipsilateral spiral ganglion cells and CN, which then drive bilateral changes due to binaural circuitry in ascending pathways (see Sections 2.1.1 and 2.1.2). These bilateral changes differ from those driven by bilateral deafness due to an imbalance in excitatory and inhibitory stimulation coming from each ear (i.e., stimulation from one side). The auditory system does not simply adapt to re-map the altered input. Rather, pathways weaken from the deprived ear and strengthen from the stimulated ear, leading to an over-representation of the hearing ear, especially when deafness occurs early in development (Kitzes et al., 1995; Kral et al., 2013a, 2013b; Moore et al., 1995; Moore and Kitzes, 1985; Reale et al., 1987). Similar, but less extensive, changes occur with moderate unilateral hearing loss (Keating and King, 2013; King et al., 2011, 2001; Polley et al., 2013; Popescu and Polley, 2010; Vale et al., 2004; Vale and Sanes, 2002). Developmental over-representation of the hearing ear is called the "aural preference syndrome" (in the case of permanent unilateral stimulation/deafness) or "amblyaudia" (in the case of reversible/temporary unilateral hearing/deafness) (reviews by: Gordon et al., 2015; Kaplan et al., 2016; Keating and King, 2013). The shift from contralateral representation of both ears to aural preference for the hearing ear begins in the brainstem and continues to the auditory cortex.

Similar evidence for unilaterally-driven aural preference comes from different models of unilateral hearing. One model includes unilateral acoustic hearing because of congenital unilateral deafness in children and animals or induced unilateral deafness from ablating the cochlea (unilateral deafness) or ligating or blocking the external auditory meatus (reversible moderate unilateral hearing loss) in animals. The second model involves unilateral electrical hearing from providing one cochlear implant to animals and children who are bilaterally deaf. Effects of these types of unilateral stimulation (i.e., unilateral acoustic or unilateral electrical hearing) on hemispheric reorganization of the auditory system are similar, albeit more extensive with worse deafness and abnormal input (Gordon et al., 2015). In both these conditions, the auditory system receives imbalanced input. Given the binaural organization of the auditory system and the importance of early experience in auditory development, unilateral stimulation leaves pathways from the deprived ear vulnerable to competition. Consequences for pathways from the deprived ear come from studies that restore hearing to the deprived ear by removing the

ligation or by stimulating the deprived ear with a second cochlear implant. Because these two types of unilateral stimulation both drive abnormal aural preference in the developing auditory system, results from studies with both types of unilateral hearing will be discussed together.

Over-representation of the hearing ear (herein referred to as "aural preference") begins by deprivation-induced structural changes in the brainstem and midbrain. Evidence of structural changes in the brainstem and midbrain comes from animal studies that create unilateral hearing loss through ablation of the external auditory meatus or cochlea, surgical ligation of the external auditory meatus, or occlusion of the external auditory meatus. When this type of unilateral loss is introduced neonatally, neurons atrophy within the spiral ganglion, AVCN, DCN and LSO ipsilateral to the deprived ear, as well as the MNTB and IC contralateral to the deprived ear (Blatchley et al., 1983; Sanes et al., 1992; Webster, 1983; Webster and Webster, 1979). Accordingly, AVCN and DCN volumes decrease on the deprived side (Moore and Kowalchuk, 1988; Webster, 1983). Interestingly, neurons in both MSOs do not atrophy, possibly because the AVCN ipsilateral to the intact ear sprouts novel (abnormal) projections to both MSOs during early development with unilateral hearing loss (Russell and Moore, 1995). These novel projections might also affect inhibition within the MSO; only transient changes to synaptic inhibition occur in the MSO, whereas long-term changes occur in bilateral CNs and LSOs (Potashner et al., 2000). Changes to dendritic structure also affect the balance of excitation and inhibition in the SOC. Neurons in the LSO on the hearing side develop a greater number of branches, while dendrites atrophy in the LSO on the deprived side (Sanes et al., 1992). Neurons in both MSOs exhibit asymmetric dendritic atrophy on the sides receiving input from the CN on the deprived side (Russell and Moore, 1999). Furthermore, the numbers of terminals and synapses decrease in the MSO ipsilateral to the deprived ear (Russell and Moore, 2002). These changes decrease excitation in the SOC on the side of deafness and decrease inhibition (increase excitation) in the SOC on the hearing side. Moreover, the CN ipsilateral to the deprived ear sends fewer projections to both ICs, whereas the CN on the hearing side sends more uncrossed projections to the IC (Moore and Kowalchuk, 1988; Nordeen et al., 1983). Neuronal onset responses in the IC become slower and more variable from the deprived ear, reducing the inter-aural differences in responses to binaural stimuli and altering representation of binaural sound (Popescu and Polley, 2010). Fewer neurons respond to binaural input, and more neurons respond with an exaggerated excitatory response to input from the hearing ear (Clopton and Silverman,

1977; Moore and Irvine, 1981; Popescu and Polley, 2010; Silverman and Clopton, 1977). Taken together, these changes in the brainstem and midbrain create ascending pathways that deliver a weakened representation of the deprived ear but a strengthened representation of the hearing ("dominant") ear.

Increased representation of the hearing ear continues into the thalamo-cortex, where extensive changes occur (Polley et al., 2013). Tonotopic and spatial maps in the auditory cortex shift towards an increased representation of the hearing ear and decreased representation of the deaf ear, particularly in the cortex ipsilateral to the hearing ear (Kral et al., 2013a, 2013b; Popescu and Polley, 2010; Reale et al., 1987). Consistent with subcortical changes to projections and the balance of excitation and inhibition, uncrossed pathways from the stimulated ear strengthen in the cortex of unilaterally deaf cats (Kral et al., 2013a, 2013b; Tillein et al., 2016). As summarized in **Figure 2.5A**, more cortical units within both auditory cortices typically respond to contralateral (crossed) stimulation so that both ears are well represented in the auditory cortex. This contralateral aural preference weakens, but does not reverse, with bilateral deafness. Conversely, each cortex responds differently to unilateral deafness. The cortex ipsilateral to the hearing ear reverses to respond favourably to ipsilateral (uncrossed) stimulation while the contralateral cortex exhibits even stronger responses to contralateral (crossed) stimulation; therefore, both hemispheres preferentially respond to the hearing ear rather than to contralateral stimulation (Kral et al., 2013a, 2013b; Tillein et al., 2016). Underlying changes to cortical response latencies suggest a shorter sensitive period for the cortex ipsilateral to the hearing ear than the contralateral cortex (Kral et al., 2013a), also reflecting the differential vulnerability of the two hemispheres to input from the hearing and deprived ears. Because of experience-driven plasticity during key developmental periods, these changes persist, even when hearing is later restored to the deprived ear (Gordon et al., 2013b; Polley et al., 2013). It is important to distinguish though, that unilateral deafness/stimulation weakens, but does not eliminate, representation of the deprived ear. The cortex ipsilateral to the hearing ear still responds to acute stimulation of the deaf ear, but with a preference/stronger activation to input from the hearing ear (reviewed by Gordon et al., 2015, 2013b; Kral et al., 2013a; Polley et al., 2013). This has important implications for attempts to re-establish binaural hearing after a period of unilateral stimulation, which will be discussed further in Section 2.3.

Human imaging studies corroborate these underlying physiological mechanisms of aural preference found in unilaterally deaf animals. Both congenital and late-onset unilateral hearing/deafness disrupts normal hemispheric representation of sound in adults, as indicated by symmetric/bilateral activation of auditory cortices rather than contralateral activation to stimulation of the hearing ear (Bilecen et al., 2000; Chang et al., 2016; Firszt et al., 2006; Fujiki et al., 1998; Hanss et al., 2009; Langers et al., 2005; Ponton et al., 2001; Scheffler et al., 1998; Vasama and Mäkelä, 1997). Children with congenital unilateral hearing also show less activation in contralateral and increased activation in ipsilateral auditory cortices, reflecting an increased representation of the hearing ear (Propst et al., 2010; Schmithorst et al., 2014, 2005). Further support for aural preference comes from children who listen with unilateral electrical hearing before receiving a second cochlear implant. Importantly, cortical representation of the stimulated ear in children increases with longer unilateral electrical hearing and persists despite several years of subsequent bilateral electrical hearing (Gordon et al., 2013b). Moreover, acute stimulation of a long-deprived ear evokes abnormal cortical responses with large and widespread activity, as well as abnormal recruitment of non-auditory areas (Jiwani et al., 2016).

Unilateral deafness/hearing also drives reorganization beyond the auditory cortex. There are some morphological changes to the microstructure of areas within the default mode network (involved with self-monitoring, consistent and efficient goal-directed behaviour, focused attention, etc.) (Yang et al., 2014) and to projections from auditory areas to the cerebellum and auditory association areas (Rachakonda et al., 2014). Children with unilateral deafness also activate auditory association and attention areas to a lesser extent than their peers with normal hearing (Propst et al., 2010). These changes correlate with educational outcomes (Rachakonda et al., 2014), highlighting the deleterious effects of unilateral deafness beyond auditory perception. However, unlike the cross-modal recruitment of auditory areas for non-auditory tasks with bilateral deafness, most extra-auditory changes with unilateral deafness occur to the functional connectivity between areas in different cortical networks. Unilateral deprivation reorganizes cortical networks involved in attention, memory formation, and executive functioning (Schmithorst et al., 2014; Tibbetts et al., 2011; Wang et al., 2014; Yang et al., 2014; Zhang et al., 2015), suggesting extra cognitive demands are required to listen with input from only one ear. Enhanced resting-state functional connectivity to, within and between the auditory cortex and areas involved in the cognitive control and default mode networks may compensate for the

additional challenges of lacking binaural hearing by recruiting cognitive processes to aid listening (Wang et al., 2014).

In addition to changing cortical connectivity and creating aural preference, unilateral deafness/hearing disrupts binaural sensitivity and processing in the auditory cortex. As discussed in Section 2.1.2, binaural hearing requires intact structures and a symmetric balance of excitation and inhibition from each ear. This creates a two-channel, primarily contralateral, system of representing sound. As briefly mentioned above, even a moderate imbalance of input from the hearing and deprived ears reduces the number of binaurally-sensitive neurons in the IC and disrupts binaural representation of sound in the IC and auditory cortex (Polley et al., 2013; Popescu and Polley, 2010). Therefore, abnormal aural preference disrupts this two-channel system and has detrimental effects on binaural development. As shown in **Figure 2.5B**, responsiveness of cortical neurons to contralateral-leading ITDs reduces with bilateral deafness in cats, but flattens across all ITDs with unilateral deafness, particularly for the cortex ipsilateral to the hearing ear (Kral et al., 2015; Tillein et al., 2016). Therefore, the auditory cortex does not simply develop a stronger spatial map of sounds coming from the hemifield of the hearing ear. The number of ITD-responsive units further reduces with unilateral than what occurs with bilateral deafness, and the distribution of best-ITD sensitivity is significantly affected (Kral et al., 2015; Tillein et al., 2016) so that there is no clear sensitivity across the horizontal plane of ITDs. Consequently, as summarized in **Figure 2.5C**, bilateral deafness reduces sound localization sensitivity from ±45˚ to primarily the midline (preferred ITD of 0˚), whereas unilateral deafness reduces localization ability across all ITDs and even responds to non-physiologic ITDs. Developmental changes to binaural processing in the cortex may limit future efforts to restore binaural hearing, which will be discussed further in Section 2.3.
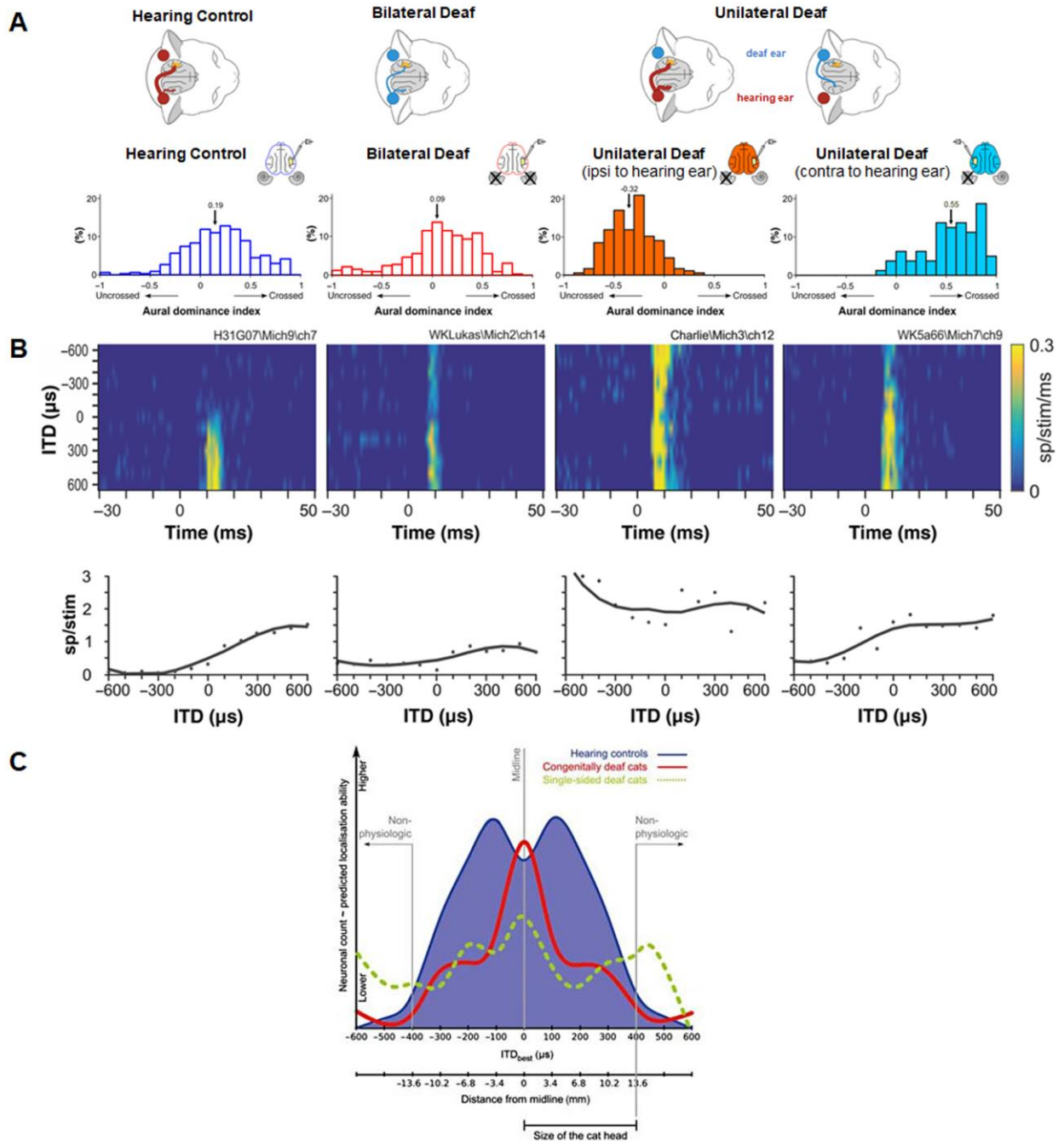
Figure 2.5. Abnormal binaural cortical reorganization is more extensive with unilateral than bilateral deafness. Modified and reproduced with permission from (Gordon et al., 2015; Kral et al., 2015; Tillein et al., 2016), Copyright American Academy of Pediatrics, Oxford University Press, S. Karger AG.

(A) Summary of cortical local field responses and histograms of aural dominance (preference) from the primary auditory cortex (A1) of hearing kittens (unfilled blue), congenital bilateral deaf

(unfilled red), and congenital unilateral deaf kittens (filled bars). Normal hearing kittens show stronger responses to contralateral (crossed) stimulation, indicating contralateral aural preference. Contralateral aural preference is weakened, but not reversed, in congenital bilaterally deaf kittens, but stronger in the cortex contralateral to the hearing ear of the unilaterally deaf kittens. However, aural preference reverses at the cortex ipsilateral to the hearing ear with a shift in favour of uncrossed responses, leading to stronger responses from the hearing ear in both cortices of unilaterally deaf kittens. (**B**) Binaural ITD sensitivity of cortical neurons. The upper panel shows an example of neuron's firing rate (colour) as a function of time for different ITDs. The lower panel shows the corresponding overall changes in firing rate (responsiveness) across ITD: the sensitivity to contralateral leading ITDs is reduced with bilateral deafness but flattened with unilateral deafness, particularly for the cortex ipsilateral to the hearing ear. (**C**) Resulting distributions of the number of neurons responsive to each ITD (best firing rates), assumed to correspond to localization ability. Bilateral deafness reduces localization to the midline, whereas unilateral deafness reduces localization across all ITDs.

Without access to binaural cues, children may learn to use remaining monaural cues to aid horizontal sound localization, if available. Monaural cues are available to children with acoustic hearing in one ear, but not to children with bilateral deafness who electrically hear with one cochlear implant. As discussed in Section 2.2.3, the implant delivers an electrical signal with limited pitch information, which is needed for processing monaural cues. Adults and children with unilateral deafness (Agterberg et al., 2012; Slattery and Middlebrooks, 1994; Van Wanrooij and Van Opstal, 2004) or asymmetric hearing loss (Agterberg et al., 2012; Kumpik et al., 2010; Newton, 1983) localize sound better than peers with normal hearing who have one plugged ear. These findings suggest that the auditory system re-weights cues to some extent to aid localization. The ability to learn to localize with unilateral deafness depends on cortico-collicular connections (Bajo et al., 2010), which may be mediated at the cortex through descending feedback projections to subcortical structures (Bajo and King, 2012). The site of binaural to monaural cue re-weighting may occur in the IC, which receives converging information and integrates different auditory spatial cues (Keating and King, 2013). However, it is important to note that using monaural cues insufficiently compensates for absent binaural cues. Ferrets (Keating and King, 2013) and children (Humes et al., 1980; Newton, 1983) with unilateral or

asymmetric hearing loss still show significantly impaired (and limited) sound localization compared to normal.

Although unilateral acoustic and unilateral electrical hearing drive similar hemispheric organizational changes during development, it is worthwhile noting here that listening with one cochlear implant may have additional detrimental effects on binaural auditory development. This is because of the abnormal input and way in which electrical hearing stimulates the auditory system. Children who are provided with early simultaneous bilateral input through two cochlear implants show preserved (typical) aural preference for contralateral stimulation but impaired ILD and ITD discrimination in the auditory cortex (Easwar et al., 2017c, 2017b, 2018). This could be due to a combination of factors, such as early bilateral deprivation before implantation, independent processing in both cochlear implants that obscures binaural cues, increased neural synchrony evoked by electrical hearing, or some other factor. Therefore, children with electrical hearing experience different auditory development (beyond aural preference) than those who benefit from richer acoustic hearing that includes pitch, temporal fine structure, and phase information. Recognizing that differences may exist between unilateral acoustic and electrical hearing will be important when considering the developmental impacts of combined electric-acoustic hearing through bimodal devices (discussed in Section 2.3.2).

2.2.5 Consequences of asymmetric hearing loss to the developing binaural auditory system remain unclear/unknown

Previous animal and human studies focused on extreme examples of bilateral deafness and unilateral deafness. We are now concerned about the less extreme, and often neglected and unexplored, group of children who have asymmetric hearing ranging anywhere from unilateral deafness to significant (yet slightly asymmetric) bilateral deafness (see **Figure 1.1**). By delivering imbalanced input, asymmetric hearing distorts binaural cues. Monaural cues are also distorted because the better hearing ear often has a hearing loss as well.

For most of the children studied in this thesis, the hearing loss is asymmetric because one ear is deaf, but the other ear has residual hearing. Because of this deaf ear, unilateral deprivation-driven changes may occur. Evidence from animals with moderate unilateral hearing loss suggests that aural preference still develops, but to a lesser extent with less extreme forms of unilateral hearing loss (Kaplan et al., 2016; Keating and King, 2013; Polley et al., 2013; Popescu and

Polley, 2010). On the other hand, children with asymmetric hearing loss also have altered acoustic input from the better hearing ear, which may drive different central auditory development than unilateral stimulation from a normal acoustic ear or from an electric cochlear implant. Therefore, stimulation of the better ear might be limited by deterioration of the cochleae and/or auditory neurons, affecting auditory nerve stimulation and the ascending pathways. Moreover, hearing aids are often not capable of providing enough amplification to the basal cochlea (Stelmachowicz et al., 2004), which is the cochlear region often most affected in individuals with hearing loss (Pittman and Stelmachowicz, 2003). Therefore, children with asymmetric hearing do not benefit from access to high fidelity sound in one or both ears due to hearing loss. Yet, without adequate hearing from one side, they do not have access to bilateral hearing, increasing their listening difficulties and putting them at risk for educational challenges (Kuppler et al., 2013; Lieu et al., 2013, 2010).

Several questions are left unanswered, which this thesis begins to address. Both unilateral deafness and moderate unilateral hearing loss reorganize hemispheric representation of sound. What minimum degree of asymmetry leads to abnormal aural preference and impaired binaural processing? Most studies focus on moderate or severe unilateral deafness with normal acoustic input in the hearing ear. What happens with poorer acoustic hearing in the non-deaf ear? Two case reports of adults with asymmetric hearing suggest deprivation effects (resting hypometabolism in both auditory cortices) and unilateral effects (hypermetabolism in both auditory cortices upon stimulation of the better hearing ear) in the auditory cortex (Cardier et al., 2015). However, more research is required to determine if this generally occurs with asymmetric hearing and in children. Does a hearing loss in the non-deaf ear share similar deficits to the deprived input from unilateral electrical hearing, or is there still advantage to some availability of temporal fine structure and phase information with impaired acoustic hearing? Do the developmental consequences of asymmetric hearing loss follow those of bilateral deafness (because of hearing loss in each ear), or those of unilateral deafness (because of an asymmetry in hearing), or are the consequences of asymmetric hearing different? Are the sensitive periods similar for asymmetric hearing as those of the extreme examples of unilateral deafness? Many etiologies of asymmetric hearing loss are associated with hearing loss progression (Section 2.2.1): does this extend or mitigate some of the deleterious changes that come with an imbalance in stimulation from each ear? The exact nature and trajectory of asymmetric hearing-driven

changes to the developing auditory system remain unclear. Chapters 3-6 of this thesis explore the effects of asymmetric hearing on brainstem and cortical development in children with varying degrees of asymmetric hearing loss.

A few recent studies including children (Gratacap et al., 2015) and adults (Arndt et al., 2017; Mertens et al., 2017; Vannson et al., 2015) indicate poor speech perception in noise, spatial hearing abilities and sound localization when listening with asymmetric acoustic hearing (testing prior to receiving a cochlear implant or when turning a cochlear implant off). For adults with asymmetric hearing, deficits in spatial hearing and sound localization were akin to, or worse than those of adults with unilateral deafness. Moreover, adults with asymmetric hearing loss and unilateral deafness both report difficulties with spatial hearing, speech perception in noise, sound perception, speech production and social interaction (Arndt et al., 2017; Mertens et al., 2017; Vannson et al., 2015). Taken together, these preliminary outcomes suggest that asymmetric hearing loss impairs the auditory system in some way that may correspond to unilateral deafness. Chapter 7 investigates the functional consequences of asymmetric hearing during development for speech perception and spatial hearing in a large group of children with asymmetric hearing.

2.2.6 Lack of binaural hearing impacts speech and language development and challenges quality of daily living

The consequences of lacking binaural hearing extend beyond auditory development. Children who struggle to listen in noise and localize sound also struggle to hear, process, and respond to what a teacher or a friend says. Auditory input during development is necessary for oral speech and language development. Therefore, distorted auditory input through unilateral or asymmetric hearing loss can have far-reaching impacts on language, cognition, socialization and academics, thereby affecting the quality of daily living (reviewed by van Wieringen et al., 2018).

Despite having normal hearing in one ear, children who have unilateral hearing loss achieve lower receptive and expressive language scores (Lieu et al., 2010; Ruben and Schwartz, 1999). Language scores may improve over time (Lieu et al., 2012) but do not resolve into adolescence (Fischer and Lieu, 2014). In fact, the gap between children with unilateral hearing loss and their siblings with normal hearing persists and may even widen (Fischer and Lieu, 2014) as language demands and complexity increase with age. Other specific deficits in complex linguistic skill include: lower scores on morphology (forming sounds into words), syntax (arranging words and

phrases) and expressive vocabulary; incorrect use of the past participle and pronouns; and difficulty formulating sentences (Sangen et al., 2017). Lack of binaural hearing may contribute to some of these challenges, as the same children also report difficulties with spatial hearing and understanding in noisy situations (Sangen et al., 2017).

Impaired speech and language development in turn affects executive cognitive function. Children with unilateral hearing loss consistently have lower verbal IQ scores than peers or siblings with normal hearing (Lieu et al., 2013, 2012; Martínez-Cruz et al., 2009; Niedzielski et al., 2006). Deficits can extend to other functions like verbal working memory (Ead et al., 2013). Which cognitive processes are affected may depend on the side of hearing loss. Some children who have a hearing loss in their left ear struggle with visual memory, spatial imagination, and visual coordination, whereas some children who have right-sided hearing loss show difficulty with verbal processing and abstract reasoning (Niedzielski et al., 2006).

These language and cognitive deficits put children at risk of behavioural and educational challenges. While young children can perform adequately in pre-school years (Kuppler et al., 2013; Lieu et al., 2010), difficulties manifest in elementary school, where both listening and performance demands are greater (Bess and Tharpe, 1986; Culbertson and Gilbert, 1986; Kuppler et al., 2013; Lieu et al., 2010). Children with unilateral hearing loss are up to 10 times more likely (35% versus 3.5%) to repeat a grade than their peers (Bess and Tharpe, 1986; Lieu, 2004; Lieu et al., 2010), and 12-41% of children require additional assistance through speech therapy or individualized education plans (Lieu, 2004; Lieu et al., 2010). Similar challenges are experienced in children with unilateral conductive hearing losses (Jensen et al., 2013; Kesser et al., 2013).

Children with unilateral hearing loss are also at risk of social and emotional problems (Borton et al., 2010). Based on focused group discussions and self-rated questionnaires with children and their parents, children with unilateral hearing loss experience barriers in education and social situations but they learn to adapt. Their social and school functioning scores vary more than those of peers with normal hearing or bilateral hearing loss. "Getting along with other children" and "Getting teased by other children" rate poorer for children with unilateral but not bilateral hearing loss. Children identify challenges with friends becoming angry at having to change sides all the time or thinking that they are ignoring the conversation. Parents of children with unilateral

hearing loss report that their child has more one-on-one interactions and only a few close friends. However, an increase in solitary play and decrease in group play also occurs in children with varying degrees of hearing loss (Ching et al., 2009).

In summary, bilateral and unilateral deafness drive abnormal reorganization of auditory pathways, leading to poor binaural sensitivity. Imbalanced input with unilateral deafness creates new deficits that challenge language development and affect socialization and education. These impacts on daily living highlight the gravity of not having binaural hearing and provide an impetus to treat asymmetric and unilateral hearing loss by proving bilateral input as soon as possible (Gordon et al., 2015). Efforts to restore binaural hearing will be discussed next.

2.3 Bilateral auditory prostheses restore access to bilateral sound, but challenges remain for binaural hearing

Children spend much of their time interacting and learning in dynamic environments, such as the classroom and playground (Ching et al., 2009; Crukley et al., 2011; Easwar et al., 2016). Moreover, unlike adults, children rarely stay in one place and often interact outdoors in groups (Ching et al., 2009). Binaural hearing allows children to listen in these reverberant environments that are riddled with noise and multiple moving sound sources (Crukley et al., 2011). As discussed in Section 2.2, access to sound in only one ear impairs binaural hearing (e.g., Agterberg et al., 2012; Arndt et al., 2015; Hassepass et al., 2013; Humes et al., 1980; Litovsky et al., 2006; Newton, 1983), reorganizes the auditory system (reviewed by Gordon et al., 2015), and challenges children's social and academic functioning (reviewed by van Wieringen et al., 2018). Attempts to prevent these developmental deficits involve restoring bilateral access to sound by providing the most effective treatment for each ear to children with hearing loss (Gordon et al., 2015). This means providing electrical stimulation through a cochlear implant to ears with severe/profound deafness and amplified acoustic sound through a hearing aid to ears with residual hearing. Therefore, children with bilateral deafness receive bilateral cochlear implants, children with less severe bilateral hearing loss receive bilateral hearing aids, and (recently) children with asymmetric hearing can receive one cochlear implant in their deaf ear while continuing to receive acoustic sound through a hearing aid or normal hearing in their other, better hearing ear (bimodal hearing) (Cadieux et al., 2013; Gordon et al., 2015; Gratacap et al., 2015; Polonenko et al., 2015). Providing the appropriate auditory prostheses to each ear may restore

access to bilateral sound, but the timing of balanced auditory input is important for binaural auditory development.

2.3.1 Bilateral cochlear implants promote bilateral auditory development but do not overcome all deafness-related challenges

Bilateral cochlear implants attempt to restore binaural hearing by providing access to sound in both ears. Indeed, compared to listening with one cochlear implant, children using bilateral cochlear implants perform better on tasks of speech perception (Gordon and Papsin, 2009; Illg et al., 2013; Reeder et al., 2017; Strøm-Roum et al., 2012), spatial hearing (Chadha et al., 2011; Ching et al., 2007; Misurelli and Litovsky, 2012; Mok et al., 2010; Murphy et al., 2011), sound localization (Cullington et al., 2017; Ehlers et al., 2017; Grieco-Calub and Litovsky, 2010; Litovsky et al., 2006; Reeder et al., 2017), and even some aspects of music perception (Polonenko et al., 2017a). These improvements attest to the benefits of providing bilateral input during development. However, spatial hearing and binaural hearing remains poorer than normal. This is particularly true depending on when a second device is provided.

Providing bilateral electrical stimulation within the sensitive period of 1.5-2 years reduces the impacts of auditory deprivation by promoting development of auditory pathways from each ear. As shown in **Figure 2.6**, simultaneous bilateral cochlear implantation promotes symmetric neural conduction through the brainstem (Gordon et al., 2007b, 2007c, 2012), as well as normal-like symmetric aural preference for contralateral stimulation in both auditory cortices (Gordon et al., 2013b, 2010). However, this does not occur with longer durations of unilateral electrical hearing prior to receiving bilateral cochlear implants. While the auditory system still responds to electrical stimulation of the second implanted ear (Gordon et al., 2013b, 2012, 2007a; Kral et al., 2013a; Polley et al., 2013), delayed bilateral input cannot prevent or reverse the unilaterally-driven reorganization described in Section 2.2.4. As discussed in Section 2.1.3, myelination rapidly matures in the brainstem, resulting in adult-like auditory brainstem responses by age two years (Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Eldredge and Salamy, 1996; Jiang et al., 2009, 1991; Ponton et al., 1992). A similar trajectory occurs with electrical stimulation, as reflected in decreasing peak latencies of the electrically evoked auditory brainstem response. These latencies stabilize within a year of cochlear implant use. Therefore, unilateral stimulation for longer than 1-2 years drives maturation of brainstem pathways from the stimulated ear while leaving the other ear deprived. Accordingly, peak latencies of brainstem

responses evoked by stimulation of the second hearing ear remain prolonged compared to those of the first hearing ear (**Figure 2.6**), reflecting decreased myelination, longer neural conduction times, slower or weaker synapses, or asynchronous neural activity that comes with immaturity and deafness (Gordon et al., 2007b, 2008b, 2012). Although the auditory cortex follows a longer developmental trajectory than the brainstem (Section 2.1.3), the first few years mark an important time of synaptic plasticity (Huttenlocher and Dabholkar, 1997) and maturation of many projections to and within the cortex (reviewed by Eggermont and Ponton, 2003; Moore and Guan, 2001). Prolonged unilateral stimulation during these developmental periods best predicts persistent over-representation of the first implanted ear in the auditory cortex despite over 3 years of bilateral experience (Gordon et al., 2013b). Therefore, longer delays to bilateral input limit future efforts to promote function in each ear and restore binaural hearing. These electrophysiological data highlight the importance of providing bilateral input as soon as possible in order prevent and/or reverse deafness-related reorganization and to promote capacity for binaural hearing within the auditory system.
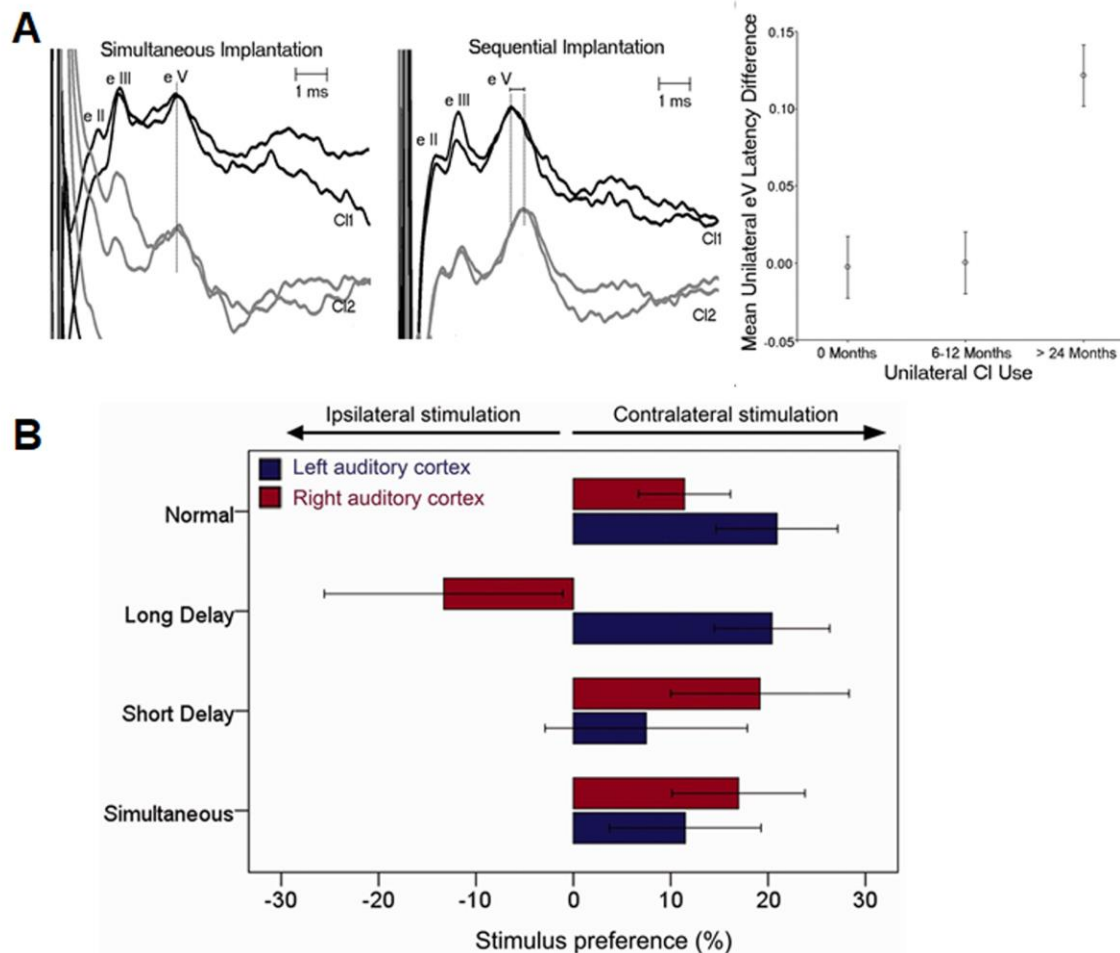
Figure 2.6. Asymmetries persist in the auditory brainstem and cortex with delayed bilateral input. Modified and reproduced with permission from (Gordon et al., 2013b, 2012), Copyright Society for Neuroscience and Oxford University Press.

(**A**) Latencies of wave eV of electrically evoked auditory brainstem responses are similar for the first and second cochlear implants (CI) when they are provided simultaneously (left panel) but remain asymmetric (delayed for CI2; middle panel) if the period of unilateral stimulation exceeds 1 year (right panel). (**B**) Children with normal hearing or who receive bilateral CIs within 1.5 years of each other (simultaneous or short delay) develop cortical aural preference for contralateral stimulation. Unilateral stimulation exceeding 1.5 years (long delay) reverses preference in the right cortex leading to an abnormal aural preference in both cortices for stimulation from the first implant, which persists for years after receiving bilateral implants.

These electrophysiological findings are reflected in behavioural outcomes with bilateral cochlear implantation. Children benefit from bilateral implants despite a period of unilateral stimulation, but longer delays to providing bilateral input impairs speech perception in the second hearing ear (Cullington et al., 2017; Gordon and Papsin, 2009; Illg et al., 2017, 2013; Kocdor et al., 2016; Strøm-Roum et al., 2012). While performance with the second implant may improve with bilateral hearing experience, function often remains poorer (Cullington et al., 2017; Easwar et al., 2017a; Sarant et al., 2001). This creates asymmetric abilities between the two ears for understanding speech (Gordon and Papsin, 2009; Illg et al., 2017, 2013; Kocdor et al., 2016; Strøm-Roum et al., 2012) and an asymmetric preference for a better signal at the first implanted ear for spatial hearing (Chadha et al., 2011; Ching et al., 2017; Cullington et al., 2017; Galvin et al., 2017; Killan et al., 2015b; Litovsky et al., 2006; Murphy et al., 2011; Peters et al., 2007; Sparreboom et al., 2011). However, only two of studies include children with simultaneous implantation (Cullington et al., 2017; Gordon and Papsin, 2009). More studies of speech perception, spatial hearing and sound localization abilities of children with no delay to bilateral input are necessary to fully understand whether simultaneous electrical input, and in which timeframe, can prevent the effects of aural preference on behavioural outcomes. In order to understand the optimal timing for bilateral input, as well as to provide a benchmark against which to compare children with bimodal devices, Chapter 7 investigates speech and spatial hearing outcomes in a large cohort of children who received bilateral cochlear implants simultaneously and with a variable length of inter-implant delay.

Bilateral cochlear implants may restore access to bilateral sound and improve hearing abilities, but they do not establish normal binaural hearing. Children with bilateral cochlear implants continue to perform poorer than their peers with normal hearing, even when these implants are provided early and simultaneously (Chadha et al., 2011; Ehlers et al., 2017; Gordon et al., 2014; Litovsky et al., 2010; Misurelli and Litovsky, 2012). This reflects the lingering challenges to early deafness and the limitations of auditory prostheses to provide normal binaural input (as described in Section 2.2.3). Children with bilateral cochlear implants quickly detect ILDs, but continually struggle with perceiving even large ITDs (Gordon et al., 2014; Salloum et al., 2010). Children are biased towards cues from the side of their first implant (Gordon et al., 2014; Grieco-Calub and Litovsky, 2010), indicating effects of neurophysiological aural preference on binaural processing. Although the auditory brainstem shows some capacity to integrate bilateral electrical

input (Gordon et al., 2007c, 2008b, 2012), children do not perceive bilateral input as a fused sound image (Steel et al., 2015). Larger brainstem asymmetries with sequential implantation further disrupt perceptual fusion. This, along with impaired cortical processing of binaural ILD and ITD cues and recruitment of other cortical areas (Easwar et al., 2017c, 2018), suggests that children with bilateral cochlear implants use a different mechanism to localize sound. Adding to impaired neurophysiological processing and development, bilateral cochlear implants further obscure binaural cues (reviewed by Gordon et al., 2017). Currently, the two cochlear implants do not communicate with each other (i.e., are not linked). Independently operating (i.e., differing) automatic gain control (Wiggins and Seeber, 2013, 2012, 2011), adaptive directionality and frequency compression (Brown et al., 2016) between the two implants variably distort binaural cues. Moreover, there may be mismatched interaural places of stimulating the spiral ganglion cells due to differing cochlear anatomy, insertion depths of the internal electrode arrays, or the degree of neural survival in each ear. These tonotopic mismatches also impair fusion (Reiss et al., 2011; Steel et al., 2015), perception (Kan et al., 2015), and integration (Gordon et al., 2012; Hu and Dietz, 2015) of binaural input. Therefore, while bilateral cochlear implants improve hearing abilities and promote bilateral auditory development with restricted durations of unilateral hearing, there are remaining challenges for re-establishing binaural hearing.

2.3.2 Bimodal hearing provides access to bilateral sound, but it remains unknown how the bilateral auditory system develops with these two different types of hearing

Previous studies focused on children who were bilaterally deaf and became unilaterally hearing with a cochlear implant before receiving a second cochlear implant. We are presently asking whether children who have significant hearing loss in one ear and various degrees of residual hearing in the other ear (asymmetric hearing) will experience the same developmental changes with the same sensitive period. We are also asking about the utility of electro-acoustic (bimodal) hearing (from a cochlear implant in the deaf ear and normal hearing or a hearing aid in the other ear) for promoting bilateral auditory development and binaural hearing in these children.

Children with asymmetric hearing loss, including the extreme case of single sided/unilateral deafness, do not meet standard cochlear implant candidacy because of the degree of residual hearing in their better hearing ear (Cadieux et al., 2013). At the same time, there are no established guidelines for treating pediatric asymmetric hearing loss. Yet more children are being

identified with asymmetric hearing loss through screening and early intervention programs. Moreover, this group of children is quite heterogeneous, with hearing ranging from normal to severe hearing loss (see **Figure 1.1**). Their hearing loss can be acquired or can be progressive due to the higher prevalence of etiologies, such as enlarged vestibular aqueduct and congenital cytomegalovirus (Section 2.2.1; Chapters 4 and 7) (Arndt et al., 2015; Lin et al., 2017; Paul et al., 2017; Sokolov et al., 2017). Therefore, limited information exists to guide clinicians in how to remediate binaural hearing in this heterogeneous group of children. Consequently, treatment of asymmetric hearing loss has been ambiguous and variable. This means that children are often left with significant hearing impairment in one ear, placing them at risk of the educational and social challenges experienced by children with unilateral hearing loss (as described in Section 2.2.6). Only recently has a consensus been reached about which tests should be performed in order to aid our current understanding of how a cochlear implant can be used to effectively treat asymmetric hearing (Van de Heyning et al., 2016).

As the deleterious and far-reaching effects of unilateral hearing are becoming known, centres around the world are starting to implant these children in an effort to restore bilateral hearing. However, it remains unclear what should be the new implantation criteria. Many questions remain unanswered, which this thesis begins to address. When will children benefit from receiving bimodal devices? Can electrical and acoustic sound be integrated to aid binaural hearing? Can this very different electrical stimulation (as described in Section 2.2.3) work together with the impaired acoustic stimulation from the other ear to drive bilateral auditory development? What degree of residual hearing in the better hearing ear is sufficient to work together with the cochlear implant? Should children with severe hearing loss continue to use a hearing aid in the contralateral ear for a period of time before receiving bilateral cochlear implants? Does limited acoustic hearing help mitigate unilaterally-driven changes to the auditory system that occur with unilateral cochlear implant use?

The first children to receive bimodal devices had a severe/profound hearing loss in the non-implanted ear because they were close to meeting the candidacy criteria. Therefore, most studies with outcomes in bimodal users focus on children with limited residual hearing and may not represent the full benefits of bimodal hearing. That said, even a short period of limited acoustic hearing facilitates slightly better language acquisition (Nittrouer and Chapman, 2009) and music perception in children who proceed to bilateral cochlear implantation (Hopyan et al., 2012). This

likely reflects the phase and temporal fine structure that can be delivered through acoustic hearing, which are not currently available through electrical hearing with a cochlear implant (Rubinstein, 2004; Zeng, 2004). Like bilateral implant users, children using bimodal devices show highly variable but overall poorer than normal sound localization abilities (Ching et al., 2001, 2005; Choi et al., 2017; Litovsky et al., 2006) and speech perception in quiet and noisy environments (Ching et al., 2007, 2005; Chmiel et al., 1995; Dettman et al., 2004; Holt et al., 2005; Litovsky et al., 2006; Luntz et al., 2005; Simons-McCandless and Shelton, 2000). More importantly however, these children benefit from wearing both devices over using only a hearing aid or cochlear implant (Ching et al., 2007; Choi et al., 2017; Mok et al., 2007, 2010; Nittrouer and Chapman, 2009; Straatman et al., 2010). Comparison across studies suggests there are similar binaural advantages for children with bimodal hearing and bilateral cochlear implant hearing (Ching et al., 2007; Choi et al., 2017). These studies with children who have limited residual hearing provide encouraging evidence supporting potential success of bimodal device use in children with better residual hearing. Indeed, initial studies of implanting children with better, even normal, residual hearing, suggest early benefits of bimodal hearing for improving spatial hearing and speech perception in quiet and in the presence of noise (Arndt et al., 2015; Cadieux et al., 2013; Gratacap et al., 2015; Greaver et al., 2017; Hassepass et al., 2013; Rahne and Plontke, 2016; Tavora-Vieira and Rajan, 2016; Thomas et al., 2017). Taken together, these studies of behavioural outcomes suggest that children experience difficulties when listening with asymmetric hearing, which can be alleviated to some degree with bimodal devices. Furthermore, bilateral benefit compared to listening with either device alone suggests that the combined electrical and acoustic hearing is integrated to some degree somewhere in the auditory system.

Treating asymmetric hearing loss with bimodal devices may restore bilateral access to sound, but it remains unclear whether this bimodal input can be combined to limit unilaterally driven reorganization or promote binaural hearing in children. One case report suggests that implantation of a child with unilateral deafness can reduce cross-modal plasticity of the auditory cortices over time (Sharma et al., 2016). Little else is known about the neurophysiological development and changes that occur with bimodal hearing for the broad range of children with asymmetric hearing. It is important to assess whether bimodal hearing can restore/promote bilateral auditory development, and during which sensitive periods, to help understand functional outcomes and capabilities with bimodal hearing, as well as to guide treatment decisions.

Children with bimodal devices experience device and stimulation related challenges in addition to (and including) the challenges of independent processing strategies and interaural place mismatches that children with bilateral cochlear implants experience. Electrical input from the cochlear implant is quite different from acoustic input from a normal hearing ear or a hearing aid. As discussed in Section 2.2.3, a cochlear implant delivers a degraded signal with a wide spread of neural excitation and synchrony, which may interfere with the acoustic information delivered by the other ear to the brainstem, distorting binaural processing. Binaural input could also be affected by the hearing loss in the non-implanted ear, which may limit audibility and distort phase information. Often the hearing loss is most severe at the cochlear base where high frequencies are represented (Pittman and Stelmachowicz, 2003). Due to acoustic limitations, hearing aids often cannot provide sufficient amplification to adequately stimulate the high frequencies (Stelmachowicz et al., 2004). In this case, the cochlear implant may deliver high frequency input that may not be delivered by the hearing aid, creating asymmetries that vary with frequency, even after bimodal devices are provided.

As illustrated in **Figure 2.7**, the cochlear implant and hearing aid (or normal hearing) deliver sound to the auditory system in different modalities (electrical current versus acoustic sound pressure), at different places in the auditory system (spiral ganglion cells versus outer ear canal), with different timing (peripheral acoustic delay) (Zirn et al., 2015), and with different degrees of evoked neural synchrony (Rubinstein and Hong, 2003; Zeng, 2004). Despite different insertion depths of the electrode array, default frequency allocations are often provided across electrodes, which can be perceived up to 1-2 octaves lower than suggested by the tonotopic location in the cochlea (Landsberger et al., 2015; Peters et al., 2016). Interaural pitch mismatches are experienced by adult bimodal users with varying degrees of residual hearing (Landsberger et al., 2015; Reiss et al., 2014a, 2015; Vermeire et al., 2015), which affects their binaural fusion/integration (Reiss et al., 2014a). All previous animal models compared neurophysiological responses to stimulation in the same modality (e.g., Kral et al., 2013a, 2013b; Polley et al., 2013; Popescu and Polley, 2010; Tillein et al., 2010). It remains unclear how the auditory system processes and integrates the different input and different response properties being evoked by electrical and acoustic stimulation. Moreover, it remains unknown whether auditory development is similar enough with bimodal stimulation to compensate for asymmetries resulting from these electrical versus acoustic stimulus differences or to enable binaural hearing.
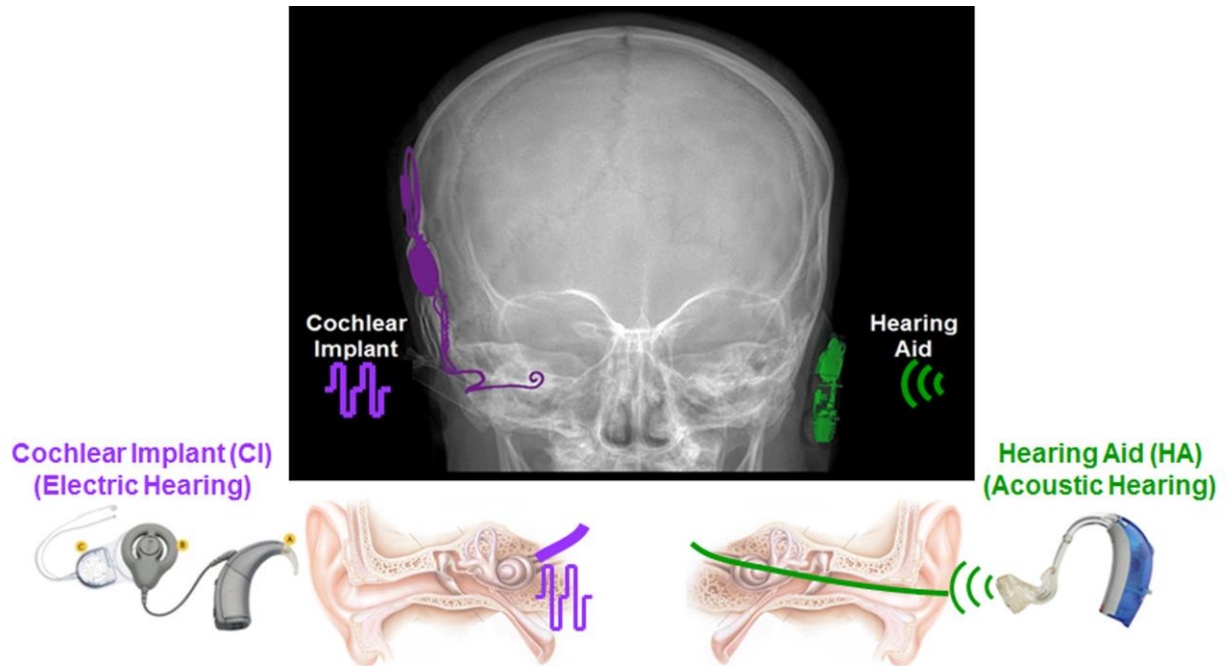
Figure 2.7. Sites and mode of electrical cochlear implant and acoustic normal or hearing aid stimulation differ.

A cochlear implant is surgically placed within the cochlea (as seen in purple in the X-ray, top panel) and delivers auditory input with biphasic electrical pulses that directly stimulate the auditory nerve. Acoustic sound begins at the outer ear (green; top panel). Acoustic sound waves are transduced through the outer, middle and inner ear before mechanoelectrical transduction occurs to stimulate the auditory nerve. These introduce an internal acoustic peripheral timing delay that varies by frequency and hearing loss.

Therefore, considering the reported benefits, potential challenges, and the gaps in our current understanding of bimodal hearing for auditory development and function in children with a wide range of residual hearing, we sought to: 1) determine whether unilaterally- or bilaterally-driven reorganization occurs with asymmetric hearing and can be reversed or prevented with bimodal hearing; 2) corroborate these neurophysiological findings with speech perception and spatial hearing outcomes in a large group of bimodal users who have a wide range of residual hearing; and 3) identify which factors of the highly heterogeneous hearing histories of children with hearing loss are essential for bilateral auditory pathway development. By doing so, this thesis aimed to determine the optimal timing of treatment with bimodal and bilateral cochlear implantation, in order to guide the current treatment of significant hearing loss in development.

To achieve these objectives, I conducted five studies in three main projects. *First*, I used evoked auditory brainstem responses (e.g., Eggermont and Salamy, 1988; Gordon et al., 2006; Zirn et al., 2015) to quantify peripheral delays between electrical and acoustic stimulation and to measure brainstem development by comparing timing of neural conduction through the brainstem. I compared asymmetries in these brainstem responses to the abilities of the same children to perceive binaural cues with a lateralization task (Gordon et al., 2014; Salloum et al., 2010). *Second*, I conducted three studies using the TRACS beamforming method (e.g., Easwar et al., 2017b; Gordon et al., 2013b; Jiwani et al., 2016; Wong and Gordon, 2009) to determine which areas of the cortex respond to electrical and acoustic stimulation and the extent to which the auditory cortices are activated by each stimulus in order to quantify the hemispheric representation of sound. This allowed me to determine if abnormal aural preference for the better hearing ear or for the cochlear implant developed or was restored or prevented with bimodal hearing. In the first study I measured cortical aural preference in children who used bimodal devices for a period of time and investigated whether the children also experienced preference for one ear when perceiving speech. The next two studies investigated longitudinal changes in cortical aural preference following initial cochlear implant activation to determine whether typical or abnormal cortical aural preference was initially present and did/could not change with bimodal use or whether bimodal use promoted neuroplasticity within the auditory cortex. The second study focused on a small homogeneous group of children with single sided deafness whereas the third study expanded the cohort to include children with a variable degree of asymmetric hearing. *Third*, I corroborated the electrophysiological data from the previous four studies by measuring whether children with bimodal devices and bilateral cochlear implants develop perceptual aural preference for perceiving speech and for spatial hearing. I quantified the diverse hearing histories of all bilateral device users to elucidate which factors were most predictive of persistent perceptual asymmetries.

2.4   Electrophysiological and behavioural measures of auditory development and aural preference

The studies in this thesis include neuroimaging measures of auditory development and plasticity, which are corroborated with behavioural measures of hearing function (see **Figure 1.2** for an overview). Development of symmetric bilateral auditory pathways was assessed using established electroencephalographic (EEG) measures of obligatory evoked activity in the

auditory brainstem (Beiser et al., 1985; Campbell et al., 1981, 2015; Eggermont and Salamy, 1988, 1988; Gordon et al., 2006, 2003; Jiang et al., 2009, 1991) (Chapter 3) and cortex (Gordon et al., 2013b, 2010; Jiwani et al., 2016; Wong and Gordon, 2009; Yamazaki et al., 2018) (Chapters 4-6). Development of symmetric hearing abilities was assessed using behavioural measures of sound lateralization of binaural cues (Gordon et al., 2014; Grantham et al., 2008; Salloum et al., 2010; van Hoesel and Tyler, 2003) (Chapter 3), speech perception using standardized tests (Gordon and Papsin, 2009; Trimble et al., 2008) (Chapters 4 and 7), and spatial release from masking (Chadha et al., 2011; Garadat and Litovsky, 2007; Litovsky et al., 2006; Misurelli and Litovsky, 2012; Mok et al., 2010, 2007; Murphy et al., 2011) (Chapter 7).

2.4.1 Electrophysiological neuroimaging techniques assess development of the auditory brainstem and cortex in children with cochlear implants

Auditory neurophysiology can be measured using a variety of imaging techniques, some of which have already been mentioned in the Sections of this Chapter. Non-invasive techniques include positron emission tomography (PET), functional magnetic resonance imaging (fMRI), functional near infrared spectroscopy (fNIRS), magnetoencephalography (MEG) and electroencephalography (EEG). PET, fMRI and fNIRS measure changes in energy supply as a proxy of neural activity through decay in radioactively labelled glucose (used in metabolism; PET) or the changes in blood flow by the difference in oxygenated and deoxygenated blood (the blood-oxygen-level-dependent signal; BOLD). The BOLD signal is detected by differences in the magnetic properties (fMRI) or optical absorption (fNIRS) of de/oxygenated blood. By measuring changes in energy or blood flow, these three techniques operate on a slower timescale and therefore, have poor temporal resolution. But PET and fMRI have high spatial resolution, allowing accurate identification of active locations in the subcortex and cortex. PET is not entirely non-invasive because a radioactive tracer must be injected. fNIRS cannot detect deeper activity due to optic limitations and has poorer spatial resolution, but is a relatively cheaper and more mobile option than fMRI. MEG and EEG also have poorer spatial resolution, but because they measure primary effects of neural activity (their magnetic fields and electrical current fields respectively), they have good temporal resolution on the order of milliseconds. The magnetic component of the cochlear implant receiver-stimulator precludes testing in the magnetic field required for fMRI and MEG techniques. Of the PET, fNIRS and EEG options, the temporal

resolution of EEG makes this technique ideal for studying event-related (i.e., sound evoked) neural activity in the auditory brainstem and cortex.

2.4.1.1 Neural activity generates electrical fields that can be recorded as electrophysiological signals at the surface of the head

Neural activity generates electrical currents which can be detected by an array of sensors on the surface of the head as electrophysiological signals (i.e., EEG). The central auditory system consists of interconnected neurons that each have a cell body, axon and dendritic tree. Neurotransmitter released from the pre-synaptic cell binds to receptors on neural dendrites, resulting in changes to ionic flow into and out of the neuron. Depending on the type of neurotransmitter, ionic flow will result in post-synaptic potentials (PSP) that are depolarizing (excitatory; EPSP) or hyperpolarizing (inhibitory; IPSP). When sufficient dendritic depolarization occurs to raise the resting potential above a threshold, action potentials are generated and propagated along the neuronal axon. The EPSP/IPSP currents within the neuron generate a primary electrical current, which are matched by an opposite flow of ions in the surrounding environment to return current flow (current source and sink). Movement of these ions create a secondary current, which gives rise to an electrical field that can be measured by EEG as electrophysiological signals. One neuron does not evoke enough current to measure a signal at the scalp. Rather, EEG recordings reflect the summed activity across populations of synchronized neurons that are located together and oriented similarly (otherwise activity would cancel out what can be recorded at a distance). Propagation of these secondary electrical currents through varying conductivities of the brain, skull and scalp smears spatial representation of the potentials recorded across the surface of the head but maintains good temporal resolution.

Temporal resolution of EEG allows recording of auditory evoked potentials, which can be used to understand underlying responses of the auditory system to sound and to track development of the auditory pathways. Auditory stimulation results in time-locked fluctuations in neural activity, which can be measured as multi-peaked electrophysiological responses with a certain morphology. In this way, neural activity within the ascending pathways can be measured by evoked auditory brainstem responses (ABR) and cortical auditory evoked potentials (CAEP). Peak amplitudes and latencies reflect the underlying sources giving rise to the responses, as well as developmental changes to myelination, neural conduction times, synchrony, and synaptic strength and efficiency (e.g., Eggermont and Ponton, 2003; Eggermont and Salamy, 1988;

Gordon et al., 2003; Picton, 2011; Ponton et al., 2002, 2000, 1992). Latencies reflect neural transmission and are essentially impervious to noise. On the other hand, noise affects amplitude, which also reflects the number of active neurons, the degree of synchronization, orientation and distance.

2.4.1.2 Auditory brainstem responses (ABR) track development and neural conduction of acoustic and electrical auditory input

Surface morphology of the ABR provides information about neural activity between and within brainstem nuclei. Five positive peaks typically characterize the ABR (I, II, III, IV, V), which appear to have similar sources for both acoustic and electrical stimulation (Gordon et al., 2006, 2003). Peaks I and II arise from the distal and proximal sections of the auditory nerve respectively. In the electrically evoked ABR (eABR), the electrical artifact generated by the cochlear implant hides peak eI and sometimes eII; this occurs despite established recording parameters that minimize the artifact (Gordon et al., 2006). Peak III/eIII is generated in the cochlear nucleus, IV/eIV by the superior olivary complex and lateral lemniscus, and V/eV by the lateral lemniscus and inferior colliculus (Møller and Jannetta, 1983). Peaks III/eIII and V/eV are most often easily distinguished, but eIV is rarely observed. Presence of these peaks has been used extensively in research and clinic to assess hearing status and development (e.g., Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Gordon et al., 2007a, 2007b, 2006; Jiang et al., 1991). Because latencies decrease with maturation of myelin and increased synaptic efficiency (reviewed by Eggermont and Ponton, 2003), they provide a good biomarker of brainstem development. Indeed, as shown in **Figure 2.6**, children who experience long durations of unilateral electrical hearing prior to receiving a second cochlear implant exhibit persistently asymmetric brainstem latencies from each ear (Gordon et al., 2012).

Although absolute brainstem peak latencies provide useful information about sources within the brainstem, they are impacted by hearing loss (Rosenhamer et al., 1981) and site of stimulation (Gordon et al., 2006). Both factors are important to consider when using the ABR as tool to measure brainstem development in bimodal users. For acoustic ABRs evoked by broadband click stimuli, increasing the level of stimulation will decrease peak latency as more neurons within a cochlear site and across the cochlea are activated. With a sufficiently high enough level, normal-like latencies can be evoked with hearing loss depending on which location of the cochlea is impaired and to what degree. Most hearing impairments however, are most severe at the cochlear

base where high frequencies are represented (Pittman and Stelmachowicz, 2003). Consequently, even at high stimulation levels, ABR peaks are often delayed due to the shift towards a greater contribution from the cochlear apex, where the traveling wave is slower and neurons fire less in phase. Therefore, the degree of hearing loss between ears can produce an acoustically evoked inter-aural asymmetry in peak V latency of 0.2 to 0.4 ms or greater (Bauch and Olsen, 1989, 1988; Selters and Brackmann, 1977). This asymmetry, then, reflects both peripheral and developmental differences.

As shown in **Figure 2.7** and discussed in Section 2.3.2, a cochlear implant stimulates the auditory system in a different place and with a different degree of neural synchrony. This impacts the eABR, which shows faster, steeper and larger peaks than the acoustically evoked ABR. Reflecting this direct stimulation, eII peaks at ~1.3 ms (Gordon et al., 2006) compared with the acoustic peak II at ~ 2.7 ms (Jiang et al., 1991). Therefore, given these peripheral timing delays between acoustic versus electric stimulation, it is reasonable to expect that greater brainstem asymmetries will exist in bimodal users than previously documented for children with normal hearing, asymmetric hearing loss, or bilateral electrical hearing. These asymmetries will be characterized in Chapter 3 for bimodal users who have varying degrees of hearing loss in their non-implanted ear. These peripheral delays will be further affected in real-life situations by the specific processing strategies employed by each hearing aid and cochlear implant device, which can vary by individual and by frequency (Zirn et al., 2015). Considering these factors, peripheral timing delays for bimodal users can be accounted for by measuring the inter-peak latencies, reflecting primarily neural conduction between the neural generators of the ABR peaks. Specifically, the acoustically evoked III-V or electrically evoked eIII-eV interval reflects neural transmission through the brainstem to midbrain and can be used as a biomarker for brainstem development with electro-acoustic stimulation.

2.4.1.3 Multichannel EEG recordings allow for source localization analyses that estimate underlying cortical source location, activity and development

As discussed in Section 2.1.3, morphology of CAEPs correspond to maturation of cortical layers and the emergence of more complex hearing abilities in children (Eggermont and Ponton, 2003; Moore and Guan, 2001). For both acoustic (Eggermont and Ponton, 2003; Jiwani et al., 2013; Yamazaki et al., 2018) and electrical (Jiwani et al., 2013) auditory stimulation, children under 7

years exhibit a large positive peak from ~50-150ms, which begins to bifurcate from 7-12 years old into a multi-peak P1-N1-P2-N2 response. The N1 continues to develop thereafter. While morphology of surface evoked CAEP responses are helpful to track the status of maturation, they provide limited information about the location and strength of cortical activity. To investigate whether cross-modal recruitment or aural preference occurs in the cortex, source localization algorithms can be applied to multichannel recordings to estimate the location and activity of underlying cortical sources (Ponton et al., 2000).

Presence of the cochlear implant artifact poses a problem for source localization analyses. The artifact is much larger than the evoked potentials, time-locked to the stimulus, and lasts for the duration of the stimulus. This artifact must be suppressed or removed to avoid contamination that obscures and distorts source estimates, or falsely identifies the artifact as a source. Several options have been used. The subtraction technique involves recording responses in different conditions or with different inter-stimulus intervals and then subtracting responses from each other (Friesen and Picton, 2010). This assumes that artifact remains the same even if the neural responses differ. However, extra testing time is required to record the additional conditions and more sweeps due to the noise introduced into the difference response. Two other methods are commonly used. Neither of these methods completely remove all artifact but they remove enough (>92%) to accurately locate sources (Viola et al., 2012; Wong and Gordon, 2009). First, the recorded EEG can be decomposed into different independent components (ICA) based on statistical techniques (Debener et al., 2008; Viola et al., 2012, 2011). This theoretically separates out cortical data from non-biological activity such as electrical artifact, but assumes that the neural sources and artifact are independent of each other. Care must also be taken when removing components to ensure important cortical data is not removed along with the cochlear implant artifact. ICA must be performed before using two of the common source localization techniques. Briefly, the equivalent current dipole (ECD) estimation method assumes the spatial distribution across the surface of the head (topography) is represented by a fixed number of sources that are determined by a priori knowledge or by decomposition methods like ICA. Standardized low resolution brain electromagnetic tomography (sLORETA) estimates neural activity distributed in points (voxels) within the brain's volume by assuming maximal spatial smoothness (Grech et al., 2008; Pascual-Marqui, 2002). The second method of dealing with the cochlear implant artifact is employed in this thesis. Location (signal space) of the artifact can be

estimated during a recorded period with no evoked cortical data (i.e., directly preceding and up to 10 ms during stimulus presentation, given that cortical responses typically do not occur before 30 ms). This signal space can then be suppressed while estimating neural activity (Wong and Gordon, 2009). Therefore, employing this artifact suppression method requires use of a source analysis method that incorporates spatial filtering properties, such as the linearly constrained minimum variance (LCMV) beamformer.

In this thesis a modified LCMV beamformer is utilized to localize underlying cortical activity. The time-restricted, artifact and coherent source suppression (TRACS) beamformer (Wong and Gordon, 2009) does not assume a fixed number of neural generators but estimates activity in all points (voxels) within the volume of the brain, and uses adaptive spatial filtering that can be harnessed to suppress the cochlear implant artifact and coherent sources (Wong and Gordon, 2009). These features are important when studying development in children with deafness because of the known consequences of cross-modal plasticity and recruitment of other areas for hearing (Section 2.2). Suppressing the artifact avoids the subjectivity of choosing which, and how many, artifact ICA components to remove. The adaptive spatial filters estimate dipole activity in one voxel (unit space in the brain) by blocking the contributions from all other sources while applying unit gain. This method enables TRACS to add vectors to additionally nullify contributions from the signal space (areas) encompassing the cochlear implant artifact (corresponds to 4 vectors representing 97% of the artifact) and regions that may have coherent activity (Wong and Gordon, 2009). Coherent sources are a problem for source localization because leakage between to the two sources disrupts/suppresses the source estimation, effectively canceling out the sources (Dalal et al., 2006). Because activity in the two auditory cortices could be coherent, these sources could be incorrectly identified by the beamformer (often at a middle location in the brain). Hence, when estimating source activity in each voxel of a hemisphere, activity in the contralateral auditory cortical area (20x20x20 mm region) is suppressed (Dalal et al., 2006; Wong and Gordon, 2009).

A boundary element head model is used to account for head geometry and differing tissue conductivities. Because MRIs cannot be obtained for children using cochlear implants, the head models used in this thesis were constructed from age-appropriate Montreal Neurologic Institute (MNI) MRI templates generated with the Template-O-matic toolbox (Wilke et al., 2008). The head model divides the brain into 3x3x3 mm points in space (voxels). Lead field potentials are

the unit gain applied to each voxel representing the contribution of a dipole moment (source) within the centre of this voxel to the surface potential. With LCMV beamforming, sources are estimated by applying weights to lead field potentials. Because this beamformer uses adaptive filters, the weights are based on covariance in the data, and will vary depending on direction and magnitude of environmental and background brain noise for each recording. Event-related beamforming improves localization accuracy by selecting weights based on covariance measured across all trials instead of an average, thereby gaining a better estimate of noise (Wong and Gordon, 2009). Lead potentials are updated based on region suppression and the dipole orientation that gives the strongest signal that can explain the surface potentials. Because there are potentially multiple sources with different orientations over time (as reflected in multiple peaks in the surface responses), the time-window for computing dipole orientation is constrained over a peak (e.g., P1) in the averaged surface potential (Wong and Gordon, 2009).

To locate and visualize the largest contributing sources to the observed evoked surface potentials, the lead potentials must first be normalized. This is to avoid over-representation of deep sources, which have weaker signals (farther from the sensors) and poorer signal-to-noise ratios (Wong and Gordon, 2009). Normalization occurs relative to the pre-stimulus baseline (in our data, this is -200 to -80 ms) using a pseudo-Z statistic (like a signal-to-noise ratio), calculated as a ratio of the mean signal to the standard deviation of the pre-stimulus baseline (Vrba and Robinson, 2001). Because adaptive filters are used, baseline brain activity can vary. To avoid accepting spurious sources and background noise, a threshold level of evoked source activity is determined using a one-tailed omnibus *t*-test (Petersson et al., 1999) on a signal-free/noise-only dataset achieved by taking a plus-minus average of the EEG data. Then non-normalized activity (i.e., dipole moments) can be extracted from voxels with pseudo-Z values greater than this omnibus threshold level (representing baseline brain activity) and used to calculate relative strength of activity evoked by each ear and in each hemisphere. These can be used to evaluate whether aural preference develops, and whether pathways from one ear are strengthened or weakened.

2.4.2 Behavioural measures of functional consequences of neurophysiological aural preference in development

Well established behavioural measures of hearing function are used to corroborate the electrophysiological findings. These measures include binaural sound lateralization (Chapter 3),

speech perception in quiet and in noise (Chapters 4 and 7), and spatial release from masking (spatial hearing; Chapter 7). By measuring binaural hearing, asymmetric function, or better use of signals in one ear over the other for spatial hearing, the functional consequences of abnormal auditory development and aural preference can be evaluated.

As discussed in Section 2.1.2, binaural integration and processing of binaural inter-aural level (ILD) and timing (ITD) cues first occur in the brainstem. To assess the consequences of brainstem development and electro-acoustic peripheral delays on binaural processing, I used a previously established task of perceived lateralization to ILD and ITD cues (Gordon et al., 2014; Salloum et al., 2010). Similar binaural lateralization tasks have been used by other groups to study binaural hearing of children using bilateral cochlear implants (Grantham et al., 2008, 2007; Laback et al., 2004; Seeber and Fastl, 2008; van Hoesel and Tyler, 2003). During the forced choice task, children indicate from which side of their head they hear the sound by raising the respective hand or pointing to that side of the head. Trial runs are completed to ensure that the children understand the task, and a child's responses are considered valid if at least 75% of the unilaterally presented stimuli are accurate. There are at least three advantages to measuring sound lateralization over sound localization with an array of loudspeakers. First, lateralization enabled us to isolate the children's abilities to perceive each type of cue. Sound localization requires an array of speakers, and sound reaching each ear contains both an ILD and ITD. Bilateral cochlear implant users can learn to proficiently use, and depend upon, ILD cues but struggle to perceive ITDs (Section 2.3.1). Furthermore, I expect bimodal users to find ITD perception particularly challenging given their projected peripheral delays (Section 2.3.2). Bimodal binaural processing could be better characterized by independently changing one cue at a time. Second, sound localization requires the children to listen with both of their devices. By conducting a lateralization task, I was able to remove the additional variability and challenges related to independent device processing (which also differs for each child) by directly stimulating the electrode array with a research processor and using an insert earphone to deliver acoustic sound. Third, by using research equipment rather than the children's own auditory devices, I was able to use similar, controlled stimuli for the electrophysiological and behavioural measures.

Cortical development is associated with the emergence and progression of complex hearing abilities in children (Section 2.1.3) (reviewed by Eggermont and Ponton, 2003). Moreover,

cortical activity evaluated by source localization methods has been shown to correlate with standardized measures of speech perception in children using bilateral cochlear implants (Gordon et al., 2013b; Jiwani et al., 2016). Accordingly, I compare cortical activity with speech perception in Chapter 4. Standardized and age-appropriate tests of speech perception (Gordon and Papsin, 2009; Trimble et al., 2008) provide a good measure of functioning with each device, the asymmetry in function between ears, and the benefit from using both devices together. Speech perception is clinically relevant and extensively used to measure outcomes of bilateral implantation (e.g., Cullington et al., 2017; Gordon and Papsin, 2009; Illg et al., 2017, 2013; Kocdor et al., 2016; Strøm-Roum et al., 2012) and bimodal hearing (Ching et al., 2007, e.g., 2005, 2001; Chmiel et al., 1995; Dettman et al., 2004; Gratacap et al., 2015; Holt et al., 2005; Luntz et al., 2005; Mok et al., 2010; Simons-McCandless and Shelton, 2000).

In the last study of this thesis (Chapter 7), I corroborate the electrophysiological aural preference findings with behavioural measures of bilateral and spatial hearing. Even if children cannot perceive binaural cues for accurate sound lateralization or localization, children can take advantage of bilateral hearing for better speech perception and better use of spatial cues. Spatial/binaural hearing is evaluated by measuring speech recognition in difficult noise conditions (speech-in-noise) or while listening with both ears over each ear alone (binaural benefit) and measuring the ability to better detect or understand speech when noise comes from different directions than the target speech (spatial unmasking). Behavioural/functional preference for one ear can be calculated as asymmetric speech perception (using the same standardized and age-appropriate tests), and an asymmetric ability to make use of spatially moving noise to either ear (spatial unmasking). Both these measures are used in Chapter 7 to characterize behavioural aural preference as a potential consequence to asymmetric hearing.

By using standardized speech perception tests and measuring speech detection in noise (for spatial unmasking), I was able to include a larger number of children within our multicultural site with a wide range of age, native language and developmental ability. Speech detection in noise has been used to assess spatial hearing in children with bilateral cochlear implants (Chadha et al., 2011; Galvin et al., 2017; Murphy et al., 2011). As the auditory system develops and matures, the ability to detect and understand speech in noisy situations improves (Chadha et al., 2011; Garadat and Litovsky, 2007; Schafer et al., 2012). Significant changes occur over the first 5 years (Garadat and Litovsky, 2007; Schafer et al., 2012), making spatial unmasking a useful

measure to track bilateral changes in hearing following implantation. Absolute degree of spatial unmasking and speech perception accuracy depends on several factors, including task (detection versus recognition), stimulus (words versus sentences), as well as the number of competing sounds and their similarity (information versus energetic masking) (reviewed by Litovsky et al., 2017). However, these factors affect performance across sessions/tests/centres, but not the relative performance between conditions in the same test session (i.e., asymmetry in speech perception or spatial unmasking when moving the noise to either ear). I confirmed that the administration differences for speech perception in noise did not affect calculated asymmetry or bilateral advantage (Chapter 7 supplementary material). To answer our question about whether children develop functional aural preference, we primarily focused on asymmetries rather than absolute values.

In summary, a battery of established electrophysiological measures and techniques, as well as standard tests of behavioural perception were used to address our main objective of examining whether bimodal hearing can protect symmetric bilateral auditory development and hearing abilities in children with asymmetric hearing loss.

Chapter 3
Paper 1

I first sought to quantify stimulus and peripheral conduction times unique to bimodal hearing and to examine the combined effects of these peripheral asymmetries on brainstem development. Then I evaluated the consequences of these brainstem asymmetries for the integration of bilateral electro-acoustic sound by testing the ability of children to perceive differences in timing and level of sound reaching their two ears (binaural cues).

3 The Effects of Asymmetric Hearing on Bilateral Brainstem Function: Findings in Children with Bimodal (Electric and Acoustic) Hearing

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3.1 Abstract

As implantation criteria are broadening to include children with asymmetric hearing loss, it is important to determine the degree of residual hearing needed to protect the bilateral auditory pathways for binaural hearing and whether there is a sensitive period in development for implantation in these children. We have been studying these questions in a growing cohort of children. In the present study, auditory brainstem responses were recorded in 21 children who had 2.2 ± 2.2 years of bimodal hearing. Responses were evoked by 11 Hz acoustic clicks presented to the non-implanted ear and with biphasic electrical pulses presented to the implanted ear. Twelve of these children also completed a behavioral task in which they were asked to which side of their heads bilaterally presented clicks/pulses that varied in interaural level or timing lateralized. All children experienced a delay in the non-implanted ear that resulted in 2.0 ± 0.35 ms longer peak latencies. These were further prolonged in 7 children as measured by longer interwave latencies from this ear than from the implanted ear. Despite large asymmetries in timing of brainstem activity between the two ears, all children perceived changes in interaural

level differences. They were unable to detect differences in interaural timing cues. Symmetric brainstem function suggests bilateral development was preserved in some children. Future work will explore whether these children have better potential for developing binaural hearing using bimodal input.

3.2 Introduction

Children with significant and permanent hearing loss were traditionally provided with only one cochlear implant (CI) to promote speech and language (Gordon and Papsin, 2009), as well as development of the auditory brainstem (Gordon et al., 2007a, 2006, 2003) and cortex (Gordon et al., 2005a, 2005b). Although there are benefits to using one CI, it has become clear that the immature auditory system requires input from both ears. Lack of stimulation from the non-implanted ear not only restricts access to the binaural cues necessary for navigating and interpreting complex acoustic environments, but also drives abnormal reorganization in the developing auditory system (Gordon et al., 2013b; Kral et al., 2013a, 2013b). In recent work, a sensitive period of 1.5 years was defined as a time window within which to provide two CIs in order to promote symmetric brainstem development and avoid reorganization of the cortex toward an abnormal "aural preference" for the hearing ear (Gordon et al., 2013b). A second CI provided beyond this sensitive period was unable to change the unilaterally driven cortical reorganization; both auditory cortices remained preferential to the first implanted ear (Gordon et al., 2013b; Kral et al., 2013a, 2013b). The degree of persistently abnormal reorganization significantly correlated with poorer speech perception in the second implanted side relative to the first.

Because the previous studies focused on children who were bilaterally deaf and became unilaterally hearing through a cochlear implant, we are presently asking whether children who are unilaterally deaf with various degrees of residual hearing in the other ear will experience the same developmental effects with the same sensitive period. We hypothesized that bimodal hearing (electrical hearing with a CI in one ear and acoustic hearing in the other ear) will protect the bilateral auditory pathways from developing asymmetric function at young ages.

3.3 Methods

3.3.1 Participants

The Cochlear Implant Program at The Hospital for Sick Children currently follows 73 children who use one cochlear implant and a hearing aid in the non-implanted ear, called bimodal hearing. Twenty-one of these children who have worn both devices for at least 9 months participated in this study. Most children had early-onset hearing loss, with the exception of two children: one child had recurrent middle ear infections and subsequent mastoiditis, and the second child had a sudden onset single-sided deafness of unknown origin. Right CIs were provided to 38% of the children and 48% of the children were male. Biographical details of each child, as well as the group mean and standard deviation are listed in **Table 3.1**. Hearing aid settings were verified to be appropriate using the Desired Sensation Level (DSL) Method and targets prescribed by DSL v5.0a (Scollie et al., 2005). Written consent was obtained from the caregivers and assent from the children before participation in the study, according to protocols approved by Research Ethics at The Hospital for Sick Children (approved study #2954).

Table 3.1. Biographical information for each child and the group mean ± standard deviation.

Subject code	Gender	CI ear	CI type	Aetiology of hearing loss	Age, years at test	Age, years at CI	Bimodal experience, years	Deprivation, years bilateral	Deprivation, years unilateral	PTA, dB HL non-CI	PTA, dB HL CI
16028	Female	Left	CI24RE (CA)	Mondini m., EVA, Pendred syndrome	8.9	7.8	1.1	0.2	0.1	78	95
22691	Female	Right	CI24RE (CA)	Mild right EVA	3.1	1.3	1.8	0.3	0.2	73	118
26308	Female	Right	CI422	Mondini m., EVA	15.3	13.7	1.4	0.3	0.2	73	85
26570	Male	Right	CI24 (CA)	Mondini m., EVA	11.0	2.5	8.3	1.5	0.3	82	103
40745	Male	Right	CI24RE (CA)	Unknown	10.7	9.7	0.8	0.0	0.4	70	73
41522	Female	Left	CI24RE (CA)	GJB2 mutation	3.1	1.9	0.8	0.7	0.6	63	123
42607	Female	Left	CI422	Mondini m., EVA	13.0	12.3	0.6	0.0	0.1	70	93
44907	Male	Right	CI513	Mondini m., EVA, Pendred syndrome	6.2	4.1	2.0	0.3	0.1	83	90
49137	Male	Left	CI422	Unknown	7.4	6.6	0.8	0.0	0.1	38	48
58171	Female	Left	CI24RE (CA)	Unknown	15.2	14.2	0.9	0.0	0.1	2	92
62848	Female	Right	CI422	Right mastoiditis	14.0	12.5	1.5	0.0	0.1	43	130
62882	Female	Left	CI24RE (CA)	Waardenburg syndrome	6.8	4.1	2.5	0.3	0.2	88	98
63763	Male	Left	CI24RE (CA)	Mondini m., EVA	8.5	7.2	1.3	0.0	0.1	83	95
64711	Male	Left	CI24RE (CA)	GJB2 mutation	6.0	4.3	1.7	0.1	0.1	63	110
67574	Female	Right	CI24RE (CA)	Mondini m., EVA	11.1	3.0	7.7	1.2	0.5	85	130
71183	Male	Left	CI24RE (CA)	Left EVA	17.2	15.9	1.1	0.8	0.3	75	80
72949	Male	Left	CI24RE (CA)	Mondini m., EVA	5.1	2.8	2.0	0.6	0.4	72	120
80770	Female	Left	CI24RE (CA)	Unknown	11.0	2.4	4.9	1.4	3.8	93	103
81119	Female	Left	CI24RE (CA)	Unknown	6.2	5.2	1.0	0.0	0.1	78	77
88069	Male	Left	CI24RE (CA)	Meningitis	9.5	3.2	3.5	0.0	2.9	78	88
94129	Male	Right	CI24RE (CA)	Meningitis	4.1	2.4	1.6	0.0	0.2	75	100
Mean ± SD					9.2±4.1	6.5±4.7	2.2±2.2	0.4±0.5	0.5±1.0	79±20	98±20

PTA = Pure-tone average at the non-CI or CI ear; (CA) = with Contour Advance; EVA = enlarged vestibular aqueduct; m. = malformation.

3.3.2 Electrophysiological Recordings

EEG measures of obligatory evoked activity in the auditory brainstem (ABR) were recorded from a midline cephalic recording electrode (Cz) referenced to the ipsilateral earlobe while children sat in a soundproof booth and watched a movie with captioning but no sound. Responses were evoked using single 100 μs acoustic clicks or 25 μs pulse width biphasic electric pulses presented at 11 Hz. Matlab (MathWorks) and Nucleus Implant Communicator (NIC; Cochlear Limited, Melbourne) software programs were created to deliver both the electrical pulses to an apical electrode (#20) through the L34 processor and acoustic clicks through Etymonic Research (ER-3A) insert earphones. A standard 0.9 ms correction factor to account for the additional propagation delay of the earphone tubing (Picton, 2011, pp. 125–126) was subtracted from the acoustically evoked response latencies. The 0.9 ms was further verified by measuring the delay through an oscilloscope. Applying this correction was done so that latencies would be reported in reference to stimulus presentation to the auditory system (i.e., acoustic click to the ear canal and electric pulse to the internal electrode array). The level of stimulation was increased until the amplitude of wave V saturated, a myogenic response was obtained, or the child expressed discomfort. Established recording parameters were used that minimize the CI artifact (Gordon et al., 2003). At least two replications were recorded to ensure response repeatability. Although other peaks were sometimes present beyond the stimulus artifact, the criteria for analyzing peaks were focused to include waves III/eIII and V/eV when they were: 1) visually detectable, 2) replicable over the noise floor, and 3) occurring at expected wave latencies. These waves were chosen as prominent ABR waves that are standardly used to evaluate brainstem function (Jiang et al., 1991). Earlier waves II and eII are small and wave II has variable morphology that significantly affects peak latency during all stages of maturation (Jiang et al., 1991).

3.3.3 Behavioural Lateralization Measure

Twelve of the 21 children were also tested for their ability to detect binaural cues using a previously established task of perceived lateralization to interaural timing differences (ITD) and interaural level differences (ILD) (Salloum et al., 2010). During the forced-choice task, children indicated from which side of their head they heard the sound by raising the respective hand or pointing to that side of the head. Trial runs were completed to ensure that the children understood the task. A child's responses were considered valid if at least 8 out of the 10

unilaterally presented stimuli were accurate. Stimuli were presented using the same equipment as in the electrophysiological testing. Acoustic clicks and electric pulses were delivered at 250 Hz in 36 ms trains presented at 1 Hz. Levels used for the ABR -10% of the dynamic range (level for maximum activity – level for threshold activity) were used to account for temporal integration of the click/pulse trains. The stimuli were presented bilaterally while varying ILDs (± 10, ± 5, 0 current units, CU) and ITDs (± 1, ± 0.4, 0 ms). Each condition was repeated ten times in order to calculate the proportion of responses the child indicated hearing the sound to the non-implanted and implanted sides. During ILD conditions, the acoustic level was held constant while the electric level varied around the level determined by the ABR, in order to maintain similar units (clinical units of current) of stimulation for all ILD conditions, and to ensure that balanced levels were used during the ITD testing (i.e., the closest level of electric stimulation that resulted in 50% lateralization to either side, considered "0 CU ILD"). In most cases, this level was equal to that set by the ABR.

3.4   Results

ABR responses to both electric and acoustic stimulation were present in all 21 children. Example recordings from two children are shown in **Figure 3.1**. These examples illustrate that regardless of whether the child had considerable residual hearing (**Figure 3.1A**) or poor residual hearing (**Figure 3.1B**) in the non-implanted ear, large differences existed in wave latencies when evoked by electric versus acoustic stimulation (**Figure 3.1C,D**). Some differences were expected since the two types of stimulation deliver sound to the auditory system in different modalities (electric current versus acoustic sound pressure) and at different places in the auditory system (acoustic nerve versus outer ear canal). Timing differences to the brainstem can be accounted for by measuring the latency of wave V relative to the peak latency of wave III (**Figure 3.1E,F**). In the first example, these normalized waveforms now overlap, indicating similar neural conduction through the brainstem for electric and acoustic stimulation (**Figure 3.1E**). But for some children, as in the second example (**Figure 3.1F**), the acoustically evoked waveform continued to be delayed relative to the electrically evoked response despite normalization to wave III peak latencies, indicating slower neural conduction on that side from brainstem to midbrain and, thus, asymmetric bilateral brainstem function.
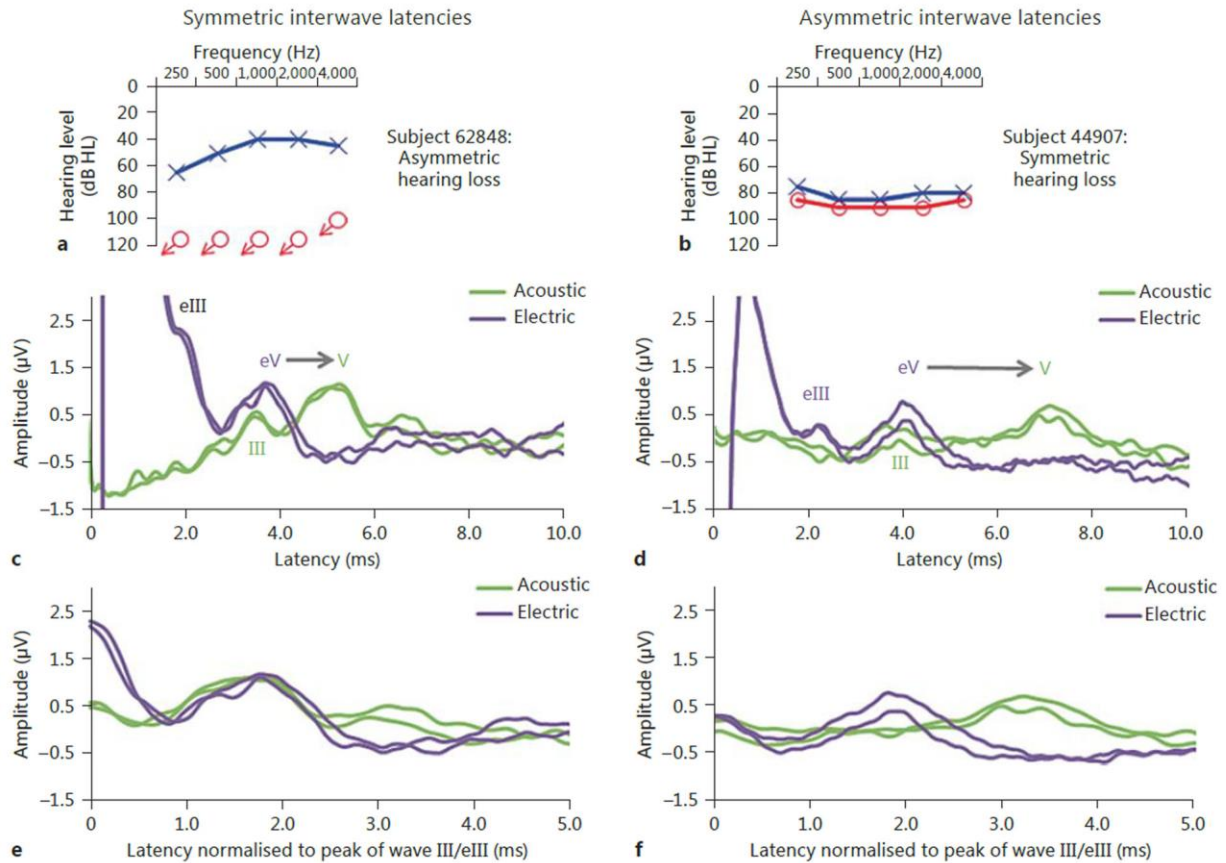
Figure 3.1. Example brainstem recordings from two bimodal users.

Example recordings from two bimodal users: 1 child with asymmetric hearing loss (**A**) and 1 child with symmetric bilateral severe hearing loss (**B**). Peak ABR responses to acoustic stimulation were delayed compared to electrically evoked responses in both children (**C,D**). However, once responses to each mode of stimulation were normalised to begin at the peak of wave III/eIII, the latency to wave V/eV was either symmetric (**E**) or asymmetric (**F**) within a child.

3.4.1 Brainstem latencies are asymmetric in bimodal users

Since hearing loss is one factor known to affect ABR responses (Rosenhamer et al., 1981), wave eIII/III and eV/V latencies were compared across unaided hearing levels (pure tone averages) in the non-implanted ear and preoperative unaided hearing levels for the implanted ear (**Figure 3.2A**). A wide range of asymmetric hearing loss was represented in this group of bimodal users, with most of the children having a severe or profound hearing loss in the implanted ear, and

anywhere from normal hearing to a profound hearing loss in the non-implanted ear (**Table 3.1, Figure 3.2A**). Across all degrees of hearing loss, the acoustically evoked wave latencies were shifted later than the electrically evoked wave latencies (**Figure 3.2A**). Linear regression analysis indicated that poorer hearing levels did not affect latencies of electrically evoked waves eIII ($R = 0.10$, $p = 0.66$) and eV ($R = 0.003$, $p = 0.99$), or the acoustically evoked wave III ($R = 0.18$, $p = 0.43$). Acoustically evoked wave V latencies became more variable with greater hearing loss, but non-linear regression indicated that the exponential relationship was not significant ($R = 0.55$, slope 95% confidence interval: -0.03 to 0.10). Overall, mean latencies of waves eIII and eV were within 2 SD of previously reported normative values in children using unilateral cochlear implants (Gordon et al., 2006), whereas the latencies of III and V were prolonged (Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Jiang et al., 2009), especially for wave V (**Figure 3.2B**). Some wave-V latency delays were expected given the hearing loss in that ear (Rosenhamer et al., 1981). Repeated measures analysis of variance was conducted using wave (III/eIII or V/eV) and mode of stimulation (electric, acoustic) as within-subject factors, and sex and implanted ear as between-subject factors. Brainstem latencies were significantly different in response to electric and acoustic stimulation in the 21 bimodal users ($F(1,17) = 179.8$, $p < 0.0001$) (**Figure 3.2B**), and there was a significant interaction between mode and wave ($F(1,17) = 3.4$, $p = 0.006$). Post-hoc paired t-tests using Bonferroni corrections for multiple comparisons indicated a mean ± SD acoustic delay of 2.1 ± 0.37 ms for wave III/eIII ($t(20) = 26.0$, $p < 0.0001$) and 2.9 ± 1.3 ms for wave V/eV ($t(20) = 10.1$, $p < 0.0001$). There were no significant effects of gender ($F(1,17) = 0.38$, $p = 0.55$) or implanted ear ($F(1,17) = 0.34$, $p = 0.46$), or interactions with mode of stimulation (gender: $F(1,17) = 0.42$, $p = 0.44$; implanted ear: $F(1,17) = 0.16$, $p = 0.63$) or wave (gender: $F(1,17) = 0.21$, $p = 0.41$; implanted ear: $F(1,17) = 0.007$, $p = 0.88$).
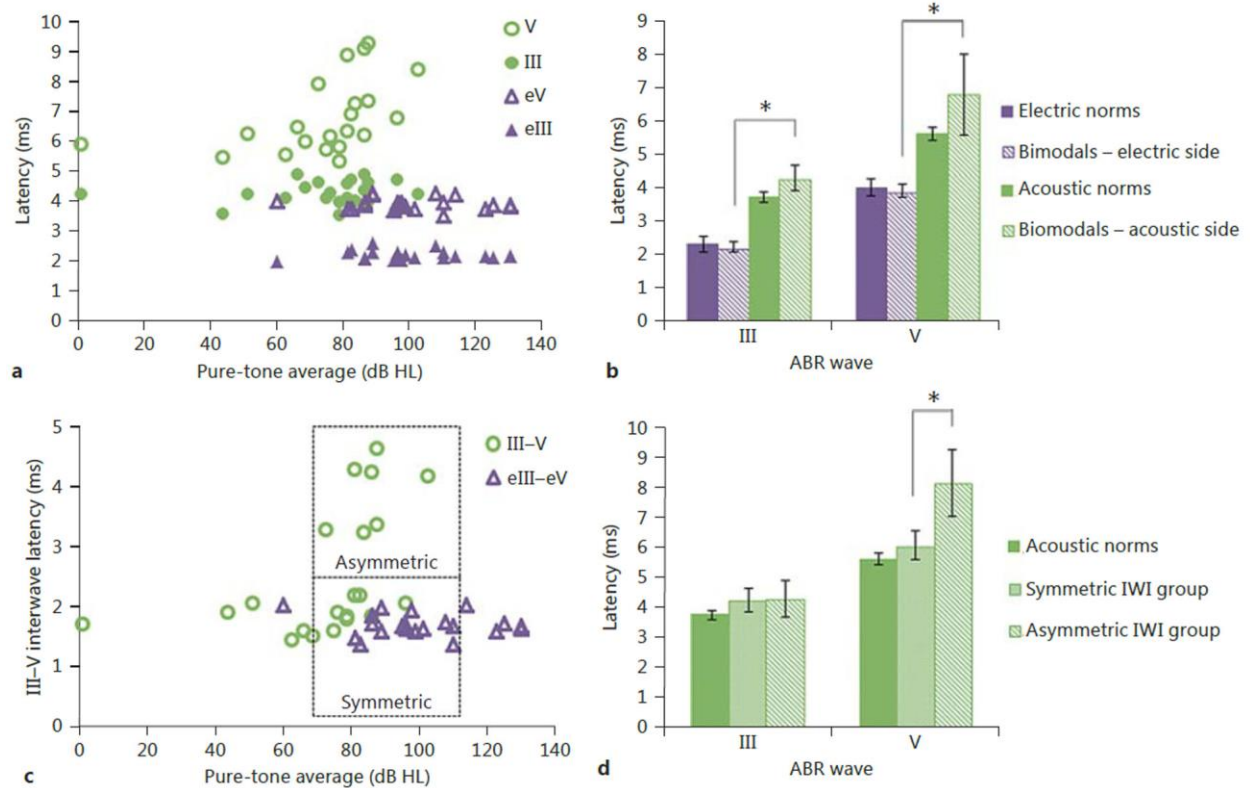
Figure 3.2. Differences in ABR responses to electric versus acoustic stimulation.

(**A**) ABR wave III (solid symbols) and V (open symbols) latencies to electric (triangles) and acoustic (circles) stimulation were not similarly affected by hearing loss. Poorer preoperative hearing does not impact electrical stimulation of the brainstem, whereas hearing loss differentially affects acoustic stimulation of the brainstem. (**B**) Mean wave latencies were significantly shorter to electric than acoustic stimulation, but were comparable to normative values (Gordon et al., 2006) with electric stimulation, but not with acoustic stimulation (Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Jiang et al., 2009, 1991) (**C**) Interwave latencies were similar for electric and acoustic stimulation except for seven children with severe to profound hearing loss in the non-implanted ear. (**D**) Children with asymmetric interwave intervals (IWI) had normal acoustically evoked wave III latencies but prolonged wave V latencies. *$p = .000$

3.4.2 Symmetric brainstem function is preserved in only a portion of bimodal users

Given the large asymmetry in timing of neural conduction into the brainstem between electric and acoustic stimulation (wave eIII/III), latencies were normalized to reflect transmission of auditory information through the brainstem by calculating the wave III-V interwave latency (**Figure 3.2C**). Again, there were no significant effects of hearing loss on electrically ($R = 0.08$, $p = 0.73$) or acoustically ($R = 0.43$, $p = 0.05$) evoked interwave latencies, although variability increased with hearing loss with acoustic stimulation. Interwave latencies were compared with previously reported normative values for electric stimulation (Gordon et al., 2006) and acoustic stimulation (Beiser et al., 1985; Campbell et al., 1981; Eggermont and Salamy, 1988; Jiang et al., 2009). All 21 children had electrically evoked interwave latencies within the normative range ($+2$ SD $= 2.48$ ms) (Gordon et al., 2006); however, only 14 of the 21 children had interwave latencies that were within the normative range for acoustic stimulation, when compared to the largest (most conservative) normative estimate ($+2$ SD $= 2.31$ ms) (Eggermont and Salamy, 1988). Seven children had abnormally prolonged (> 2.31 ms) acoustically evoked interwave latencies (**Figure 3.2C**, upper dashed box) and therefore did not have bilaterally normative, or symmetric, brainstem function. Although symmetric brainstem function was evoked in the majority of the bimodal users, the proportion was not significant ($\chi^2(1) = 2.3$, $p = 0.13$). On average, the interaural interwave difference was 0.11 ± 0.08 ms for the children with both acoustic and electric interwave latencies within the normative range for each mode of stimulation, and 2.23 ± 0.28 ms for the children with abnormally long acoustic III-V intervals. Of particular note was the group of 16 children with severe to profound hearing loss (**Figure 3.2C**, dashed boxes), in which a similar number of children had symmetric ($n = 9$, lower dashed box in **Figure 3.2C**) and asymmetric ($n = 7$, upper dashed box in **Figure 3.2C**) interwave latencies ($\chi^2(1) = 0.25$, $p = 0.62$). Independent t-tests with Bonferroni corrections for multiple comparisons indicated similar wave III latencies between these two groups of children ($t(14) = -0.85$, $p = 0.82$), but significantly different wave V latencies ($t(14) = -6.53$, $p < 0.0001$), which primarily contributed to the prolonged interwave latencies in these children (**Figure 3.2D**). Additionally, acoustically evoked wave III and V latencies were more similar to the normative values for children in the symmetric group. There were no significant differences in number of right CIs (Fisher's Exact $p = 1.00$) or females (Fisher's Exact $p = 1.00$) between the symmetric and asymmetric groups of children.

Repeated measures analysis of variance was conducted again in only the 14 children with symmetric interwave latencies, using wave (III, V) and mode of stimulation (electric, acoustic) as within-subject factors. As expected, brainstem latencies were significantly different in response to electric and acoustic stimulation ($F(1,13) = 402.6$, $p < 0.0001$), but there was no longer a significant interaction between mode and wave ($F(1,13) = 1.8$, $p = 0.20$), indicating that neural conduction from caudal to rostral auditory brainstem was similar regardless of stimulus modality in these children. Post-hoc paired t-tests using Bonferroni corrections for multiple comparisons indicated a mean ± SD acoustic delay of 2.0 ± 0.35 ms for wave eIII/III ($t(13) = 21.3$, $p < 0.0001$) and 2.1 ± .47 ms for wave eV/V ($t(13) = 1.3$, $p < 0.0001$). On the other hand, paired t-tests with Bonferroni corrections completed for wave asymmetries in the 7 children with prolonged interwave latencies had a mean ± SD acoustic delay of 2.22 ± 0.14 ms for wave eIII/III ($t(6) = 15.6$, $p < 0.0001$) and 4.45 ± 0.39 ms for wave eV/V ($t(6) = 11.4$, $p < 0.0001$).

3.4.3 Asymmetric brainstem function is difficult to predict in bimodal users

To determine which demographic features differentiated whether a child with severe to profound hearing loss would develop symmetric brainstem function with bimodal stimulation, independent-samples Mann-Whitney U tests were used, since most demographic variables were not normally distributed (one-sample Kolmogorov-Smirnov tests $p > 0.05$). Only total deprivation was significantly distributed differently between symmetric and asymmetric interwave latency groups ($p = 0.02$). All other factors were not significant ($p > 0.05$), including unilateral and bilateral deprivation, auditory experience, age of implantation, acoustic pure tone average, and pure tone average asymmetry.

3.4.4 Bimodal users were able to detect level cues but not timing cues

All 12 children completed behavioral testing with ITD cues (interwave ABR latency groups: symmetric $n = 8$, asymmetric $n = 4$), and eight of these children also listened for ILD cues (symmetric group $n = 6$, asymmetric group $n = 2$). Detection of these binaural cues was measured as the proportion of responses that children indicated that they heard the sound on the CI, or electric, side. Positive values of binaural conditions indicated when the electrical stimulation led in time (ITD, **Figure 3.3A**) or was at a greater level (ILD, **Figure 3.3B**) than the acoustic stimulation, and vice versa for negative ITD and ILD values. A generalized linear, mixed model with random intercept and slope effects was used to fit binary logistic functions to

each child for ITD and ILD lateralization and compare ITD slopes in the symmetric versus asymmetric groups, using the symmetric group as the reference. The symmetric group ITD slope did not significantly differ from zero ($p = 0.86$), and was not significantly different from the asymmetric group ITD slope ($p = 0.11$). A similar model was used to determine that the group slope for ILD lateralization was significantly positive ($p < 0.0001$). The average ILD that generated a predicted response rate of 0.5 (i.e., the ILD at which bilateral input was perceived as balanced or neither coming from left or right), using the binary logit equations, was -0.14 ± 0.70 CU and ranged from -2.9 to +3.7 CU.
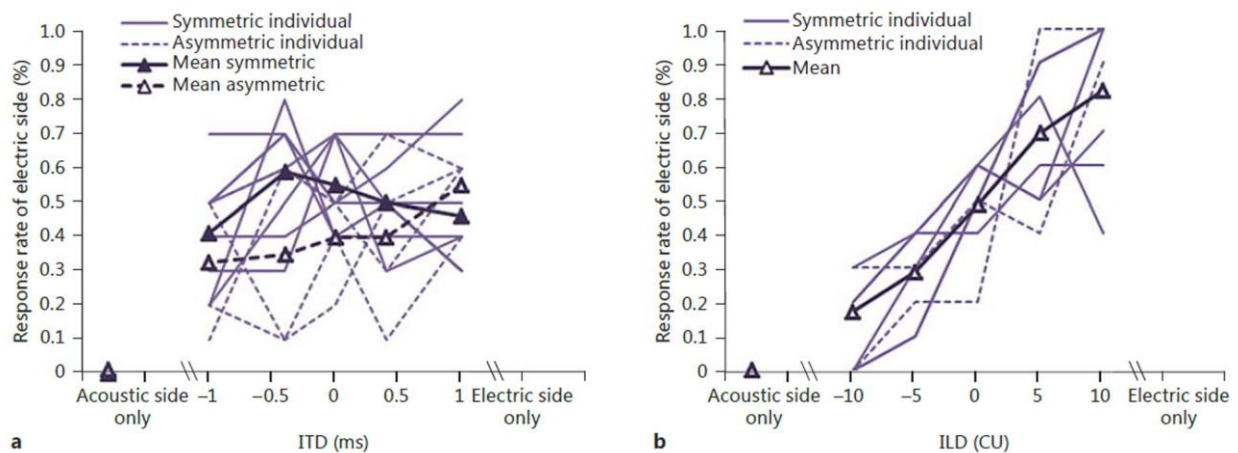
Figure 3.3. Behavioural lateralization of binaural cues.

Group and individual behavioural responses to inter-aural timing differences (ITDs) (**A**) and interaural level differences (**B**). The proportion of responses that children indicated they heard the sound towards the CI (electric) side is plotted against changes in each binaural cue, with positive cue values representing when CI electrical stimulation led in time (ITD) or was greater in level (ILD). Children were not able to lateralize bilaterally presented sounds when timing cues were changed, regardless of whether the child had symmetric inter-wave latencies (solid lines and closed symbols) or asymmetric inter-wave latencies (dashed lines and open symbols; **A**). On the other hand, all children were able to significantly detect level cues (**B**). Only the overall group mean is shown for ILDs since there were only two children in the asymmetric group that completed this task.

3.5 Discussion

In the present study, we examined whether bimodal stimulation protects the bilateral auditory brainstem from developing asymmetric function. Overall differences were expected in absolute latency of evoked activity in the brainstem due to delayed stimulus conduction time and reduced neural synchrony evoked by acoustic rather than electrical stimuli. Indeed, latency asymmetries for both waves eIII/III and eV/V in these bimodal users were even longer than previously recorded in bilateral CI users (Gordon et al., 2007b, 2007c, 2008b) and bilateral hearing aid users who had an asymmetric hearing loss (Bauch and Olsen, 1989, 1988; Selters and Brackmann, 1977). Asymmetries were three times longer in the bimodal users with symmetric interwave latencies, and seven times longer in those children with asymmetric interwave latencies. Furthermore, asymmetries in both these bimodal groups were even larger than interaural timing differences experienced in the environment (reviewed by Grothe et al., 2010). In some bimodal users, these large asymmetries likely represented a peripheral delay; once the information reached the caudal brainstem, the information transfer through the brainstem to the midbrain was symmetric (**Figure 3.1E, Figure 3.2C,D**). Even some children with severe-to profound hearing loss in the non-implanted ear had interwave latencies within normative ranges for both electric and acoustic stimulation. However, in other children the acoustic delay was further prolonged through the brainstem, as indicated by the longer acoustically evoked interwave latencies (**Figure 3.1F, Figure 3. C,D**). In this subgroup of bimodal users, the evoked activity was not a simple difference in peripheral timing between the two types of stimulation, but also neural conduction in the brainstem. Transmission through the brainstem remained within the normative electric range but was significantly abnormal when evoked by acoustic stimulation, creating asymmetric bilateral brainstem function. Although both groups of bimodal children had larger interaural differences in interwave latency (III-V minus eIII-eV) than previously reported for bilateral acoustic hearing in neonates (Eldredge and Salamy, 1996; Sininger and Cone-Wesson, 2006), on average, the children with bilaterally normative interwave latencies (symmetric group) had similar interaural interwave differences to children who received two CIs either simultaneously or with a short delay between surgeries (Gordon et al., 2008b). On the other hand, interaural interwave differences were about twenty times larger in the bimodal users with abnormally prolonged acoustic interwave latencies than even the children who received a second CI after a long duration of unilateral CI use (Gordon et al., 2008b). It is important to note,

however, that previously reported values for interaural interwave differences to bilateral acoustic or bilateral electric stimulation may not directly apply to bimodal stimulation; there will likely remain a larger range of acceptable interaural difference due to different stimulation modalities, particularly because the normative ranges for electric and acoustic interwave latencies differ. Testing of more bimodal children is required to further understand functional implications of the bimodal interaural interwave difference. Regardless, it is clear that bimodal children with prolonged interwave latencies on their acoustic side have significantly larger interaural asymmetries than previously reported for any peak latency or interwave latency, including I-V (Eldredge and Salamy, 1996; Gordon et al., 2008b; Rosenhamer et al., 1981; Sininger and Cone-Wesson, 2006). Therefore, despite introducing larger absolute brainstem asymmetries than previously reported in children and adults with hearing loss, bimodal stimulation can provide some protection of bilateral auditory brainstem function in a portion of children.

Preservation of normative brainstem function in only a portion of children using bimodal stimulation raises the question of whether there was some factor or sensitive period that affected brainstem development in these bimodal users. Unfortunately, this is not an easy question to answer, as it is extremely difficult to quantify what differentiates these two groups of bimodal users due to the large variations in hearing history. Several factors likely contribute to the differences in evoked activity with acoustic and electric stimulation, and bimodal users with asymmetric hearing loss are inherently more variable (see **Table 3.1**) than traditional pediatric bilateral CI users, who had restricted access to acoustic sound in both ears and from an early age. How bilateral auditory brainstem function could be protected in some bimodal users is unclear, but input to the auditory system likely plays a significant role. The type of input could be spontaneous and/or evoked and could have occurred any time during development including the pre-natal period of hearing. Even children with congenital deafness could have experienced spontaneous activity before birth, depending on their etiology of hearing loss. In addition, many children in our cohort of bimodal users had progressive and/or fluctuating hearing loss due in 10 cases to enlarged vestibular aqueducts. Questions about this input remain due to unclear and variable histories around the deterioration of hearing and consistency of hearing aid use. Our best estimate of total auditory deprivation indicated differences between the two groups of bimodal users (as indicated in the results), highlighting the importance of minimizing auditory deprivation in children with asymmetric hearing loss.

The question remains whether those children with symmetric brainstem development were potentially better able to benefit from spatial hearing than those with asymmetric brainstem function. Despite significant peripheral acoustic delays (>2 ms) all eight children were able to significantly detect level cues (**Figure 3.3B**), but only one of the 12 bimodal users were able to detect timing cues (**Figure 3.3A**). This poorer ability to detect ITDs than ILDs is not surprising, given the significant peripheral delays, which would have a greater effect on the coincident detection mechanisms for processing ITDs in the medial superior olive (Brand et al., 2002; Grothe and Sanes, 1994; Jeffress, 1948; Jercog et al., 2010) than the integrative mechanisms of processing ILDs in the lateral superior olive (Finlayson and Caspary, 1991). Furthermore, preferential use of ILD cues is consistent with previously documented lateralization abilities of children and adults using bilateral CIs (Grantham et al., 2008, 2007; Laback et al., 2004; Salloum et al., 2010; Seeber and Fastl, 2008; van Hoesel and Tyler, 2003). Comparison across studies of binaural hearing suggests there are similar binaural advantages for children with bilateral CIs and bimodal hearing (Ching et al., 2007), although several of our children had greater residual hearing than previously studied bimodal groups. Pediatric bimodal users also show highly variable sound localization abilities (Ching et al., 2005, 2001; Litovsky et al., 2006), and the present findings suggest that bimodal users may be relying on ILD cues and perhaps other cues or strategies to locate a sound. Additionally, the bimodal asymmetries may be compounded when listening through their own devices, rather than the direct stimulation provided in the present study which was delivered through research equipment. Cochlear implant processors and hearing aids are currently independent, and their automatic gain control processing would differentially affect sound reaching both ears, thereby reducing level differences and further skewing timing differences reaching the auditory brainstem. Regardless, in early stages of bimodal hearing (2.2 ± 2.2 years), integrating the information from both sides is challenging for these children, even with symmetric activation through the brainstem.

This study is part of a larger, on-going investigation of bilateral auditory development in bimodal users, including measures of cortical activity and other behavioural outcomes. Future investigations focus on whether we can compensate for these large asymmetries in stimulation and neural conduction, and whether children using a cochlear implant and a hearing aid can develop a fused binaural image or obtain true binaural hearing. It may be that children require greater lengths of experience to use ITD and ILD cues, as we have seen in bilaterally deafened

children with a long delay between receiving their two CIs (Gordon et al., 2014). These children were able to detect some ITD cues only after several years of using bilateral CIs, although sensitivity remained abnormal. Perhaps bimodal users with symmetric brainstem function will be more likely to use the information after long durations of bimodal use. Even if we are not able to restore true binaural hearing to these children, we know that providing a longer period with acoustic hearing can have positive benefits on performance with bilateral CIs for tasks such as identifying different characteristics of music (Hopyan et al., 2012). We are, therefore also asking whether bimodal use, even in those children with asymmetric brainstem function, primes the auditory system to function better with a second CI, thereby lengthening the critical period for bilateral implantation.

3.6   Conclusions

Results from this study demonstrated that bimodal stimulation can protect bilateral symmetry in auditory transmission through the brainstem in a portion of children, but this protection cannot be generalized to the whole population of bimodal users. Despite whether this protection occurs, peripheral asymmetries from electric versus acoustic stimuli still remain for all children. Regardless of whether symmetric brainstem function was preserved, children were able to detect level cues but not timing cues for lateralization of sound. Given the variability in responses and hearing histories of bimodal users, a clear sensitive period within which to implant cannot be determined at this point in time.

3.7   Acknowledgments

3.8   Conflicts of Interest

Both the second and last authors are on speaker's bureau with Cochlear Limited.

<div align="center">

Chapter 4
Paper 2

</div>

Chapter 3 identified subcortical consequences of bimodal hearing, particularly in children with poor residual hearing. I then asked if bimodal hearing could protect auditory cortical development and whether the extent of this protection also depended on residual hearing and durations of asymmetric hearing.

4 Delayed Access to Bilateral Input Alters Cortical Organization in Children with Asymmetric Hearing

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4.1 Abstract

Bilateral hearing in early development protects auditory cortices from reorganizing to prefer the better ear. Yet, such protection could be disrupted by mismatched bilateral input in children with asymmetric hearing who require electric stimulation of the auditory nerve from a cochlear implant in their deaf ear and amplified acoustic sound from a hearing aid in their better ear (bimodal hearing). Cortical responses to bimodal stimulation were measured by electroencephalography in 34 bimodal users and 16 age-matched peers with normal hearing, and compared with the same measures previously reported for 28 age-matched bilateral implant users. Both auditory cortices increasingly favoured the better ear with delay to implanting the deaf ear; the time course mirrored that occurring with delay to bilateral implantation in unilateral implant users. Preference for the implanted ear tended to occur with ongoing implant use when hearing was poor in the non-implanted ear. Speech perception deteriorated with longer deprivation and poorer access to high-frequencies. Thus, cortical preference develops in children with asymmetric hearing but can be avoided by early provision of balanced bimodal stimulation. Although electric and acoustic stimulation differ, these inputs can work sympathetically when used bilaterally given sufficient hearing in the non-implanted ear.

4.2 Introduction

Children who have one deaf ear with better hearing in their other ear are at risk for unilateral listening and abnormal cortical development because they are not candidates for cochlear implantation using standard criteria (Cadieux et al., 2013). Yet, the most effective treatment for each ear should be provided to children with hearing loss (Gordon et al., 2015). Whereas symmetric hearing loss can be treated with similar devices in each ear (two cochlear implant (CIs) for severe/profound deafness or two hearing aids (HAs) for less severe hearing impairments), children with asymmetric hearing loss may require electrical stimulation of the deaf ear with a CI and amplified acoustic sound through a HA in the better ear (Arndt et al., 2015; Cadieux et al., 2013; Ramos Macías et al., 2016). It is not clear, however, that this bimodal input (electrical CI in one ear and acoustic HA in the other) can be combined to limit unilaterally driven reorganization or promote binaural/spatial hearing in children. The concern is that electrical CI hearing completely differs from listening to amplified sound through a HA and thus could provide unbalanced or even conflicting bilateral access to sound. To test this clinical recommendation, we asked: 1) can bilateral cortical development be protected in children with asymmetric hearing loss through bimodal hearing; and 2) what factors prevent expected cortical development in children provided with bimodal hearing? We hypothesized that bimodal stimulation with limited delay restricts cortical reorganization underlying preference of one ear by providing bilateral access to sound.

Young children with asymmetric hearing loss have impaired access to bilateral access to sound and are at risk of developing poor sound localization and speech detection in noise (Gordon et al., 2014; Litovsky et al., 2010), as well as social, educational and language deficits (Kuppler et al., 2013; Lieu et al., 2013, 2010). These hearing difficulties and associated challenges likely reflect cortical reorganization with prolonged unilateral hearing. In children with congenital bilateral deafness, early hearing through one CI for >2 years increases activity in the contralateral auditory cortex (Gordon et al., 2013b; Jiwani et al., 2016) and both left and right auditory cortices develop an abnormal preference for stimulation from the hearing ear (Gordon et al., 2013b). These effects are consistent with abnormal strengthening of uncrossed pathways from the stimulated ear in unilaterally hearing cats with congenital deafness (Kral et al., 2013a, 2013b; Tillein et al., 2016). Importantly, cortical representation of the stimulated ear in children increases with delay to bilateral implantation and persists despite several years of bilateral CI use

(Gordon et al., 2013b). Unilateral deprivation also reorganizes cortical networks involved in attention and executive functioning (Tibbetts et al., 2011; Wang et al., 2014; Yang et al., 2014). Given that impairments in these networks correlate with educational outcomes (Rachakonda et al., 2014), and that bilateral hearing is important for social and educational development (Lieu et al., 2013), it makes sense to avoid cortical reorganization resulting from unilateral hearing in children.

Treating asymmetric hearing loss with bimodal devices may restore bilateral access to sound, but it remains unclear how the two very different signals are processed and integrated in the cortex. Contributions from the CI could disrupt information from the better hearing ear. Sound frequencies are more poorly translated by CIs than by HAs to the auditory pathways which impairs CI users' perception of pitch and music (Gfeller et al., 2002, 2012; Hopyan et al., 2012; Limb and Rubinstein, 2012; Polonenko et al., 2017a), and emotion in speech and music (Giannantonio et al., 2015; Hopyan et al., 2016; Volkova et al., 2013). On the other hand, acoustic stimulation of the non-implanted ear might be limited by deterioration of the cochleae and/or auditory neurons, affecting auditory nerve stimulation (reviewed by Korver et al., 2017). Moreover, HAs often are not capable of providing enough amplification to the basal cochlea (Stelmachowicz et al., 2004) which is the cochlear region often most affected in individuals with hearing loss (Pittman and Stelmachowicz, 2003). In addition, bimodal hearing could also be detrimental for binaural/spatial hearing by introducing large asymmetries in timing of input between the ears (direct CI stimulation of the auditory nerve is ~1.5 ms faster than acoustic input) (Polonenko et al., 2015; Zirn et al., 2015) and large mismatches in inter-aural place of stimulation which potentially compromise integration/fusion of bilateral input (Landsberger et al., 2015; Reiss et al., 2014a).

To evaluate the potential benefits and limitations of bimodal hearing for bilateral auditory development, we examined cortical activity and functional outcomes in children with asymmetric hearing loss who use bimodal devices. The present findings demonstrate that bimodal stimulation can promote typical cortical activity when: 1) delay to implantation is limited and 2) bilateral access to sound through the HA and CI is balanced. When these conditions are not met, prolonged asymmetric hearing restructures auditory cortices, creating a preference for the better hearing ear. Speech perception skills depended on access to high-

frequency information in each ear independently rather than on broadband-evoked aural preference measures.

4.3 Materials and Methods

Parental/guardian written informed consent and child assent were obtained under study protocol #1000002954 approved by the Hospital for Sick Children Research Ethics Board.

4.3.1 Participants

Sample size calculations for sufficient power ($1 - \beta \geq 0.8$, $\alpha = 0.05$) were completed a priori using G*Power v3.1.7 software (Faul et al., 2007), based on partial eta-squared values estimated from previous work (Gordon et al., 2013b, 2010). Accordingly, 50 children aged 1.3 - 12.9 years were recruited: 34 bimodal users (mean ± SD: 6.8 ± 3.2 years old) who wore both devices for > 6 months and 16 peers with normal hearing (6.4 ± 3.5 years old). Audiometric screening confirmed normal hearing (≤ 20 dB HL) thresholds at 250 - 8000 Hz prior to testing. The implanted ear in the bimodal group was evenly split (17 left, 17 right). Ages between the three groups (Normal Hearing, Left CI/Right HA, Left HA/Right CI) were similar (one-way ANOVA: $F(2,47) = 0.03$, $p = 0.97$). Responses were compared to the same measures collected in 28 bilateral implant users (6.7 ± 2.4 years old) who were part of a previously reported cohort (Gordon et al., 2013b). Bilateral implant users received their first (right) implant at 1.8 ± 1.1 years old; 12 received both CIs simultaneously and 16 waited 2.3 ± 1.6 years to receive a left implant. Although mean cortical responses of the bilateral CI group were previously reported, aural preference measures per subject and the analysis of change over time are provided here for the first time.

Details of several demographic variables are provided in **Table 4.1**. Most variables were similar between the two bimodal groups ($p > 0.05$). Both groups were implanted over a similar range of ages, but the left implanted group was implanted later and had longer bilateral HA use on average than the right implanted group ($p < 0.05$).

Table 4.1. Bimodal group mean ± SD demographic information and categorization by principal component analysis (PCA). Shaded regions and bolded text denote which variables significantly load to the component (factor loading > 0.3).

Variable	Left CI / Right HA (n = 17)	Left HA / Right CI (n = 17)	Statistics	PCA: Pattern Matrix Pre-CI Deafness	PCA: Pattern Matrix Pre-CI Hearing	PCA: Pattern Matrix Post-CI Hearing	PCA: Score Coefficient Matrix Pre-CI Deafness	PCA: Score Coefficient Matrix Pre-CI Hearing	PCA: Score Coefficient Matrix Post-CI Hearing
Duration of Unilateral Deafness (years)	1.2 ± 2.3	0.8 ± 0.7	$t_{(18.8)} = 0.8, P = 0.44$	**0.96**	-0.06	0.00	**0.47**	-0.03	-0.01
Duration of Asymmetric Hearing (years)	1.7 ± 2.3	1.0 ± 0.9	$t_{(21.1)} = 1.1, P = 0.27$	**0.97**	0.10	0.03	**0.47**	0.03	0.01
Unaided Hearing Loss in CI Ear (dB HL)	98.4 ± 23.5	105.2 ± 19.6	$t_{(31.0)} = -0.9, P = 0.37$	**0.33**	**-0.75**	-0.01	**0.16**	**-0.30**	-0.02
Duration of HA Use Pre-CI (years)	3.2 ± 1.9	1.9 ± 1.0	$t_{(24.9)} = 2.4, P = 0.02$	0.03	**0.90**	-0.15	0.01	**0.35**	-0.08
Age Implanted (years)	4.7 ± 2.6	3.0 ± 2.1	$t_{(30.7)} = 2.1, P = 0.05$	0.29	**0.88**	-0.01	0.13	**0.34**	0.00
Asymmetry in Bimodal Hearing (dB) (CI-HA)	7.8 ± 7.1	5.8 ± 7.3	$t_{(29.3)} = 0.8, P = 0.42$	-0.05	**0.53**	**0.55**	-0.03	**0.21**	**0.34**
Unaided Hearing Loss in HA Ear (dB HL)	62.5 ± 19.9	71.7 ± 17.9	$t_{(31.7)} = -1.4, P = 0.17$	0.01	0.08	**0.85**	-0.01	0.04	**0.52**
Duration of CI Use (years)	1.9 ± 1.3	3.4 ± 3.4	$t_{(20.5)} = -1.8, P = 0.09$	0.05	-0.34	**0.78**	0.02	-0.13	**0.47**

CI = cochlear implant; HA = hearing aid

4.3.2 Hearing history categorizes into pre- and post-CI hearing experience components

Candidacy for bimodal implantation continues to evolve, resulting in a cohort with more varied hearing histories than bilateral CI users. Some of this variability can be explained by etiology of deafness (**Figure 4.1**). Bimodal users tended to have etiologies associated with progressive and asymmetric deafness (i.e., inner ear malformations; 11 (32%) bimodal: 4 (14%) bilateral CI; *OR* = 2.8, *p* = 0.14), whereas more bilateral CI users had genetic mutations causing congenital bilateral deafness (e.g., *GJB2/6*; 5 (15%) bimodal: 11 (39%) bilateral CI; *OR* = 0.3, *p* = 0.04). All other etiologies were similar between the groups (*OR* ~ 1, *p* > 0.05). To better characterize these complex histories, an oblique principal component analysis (PCA) using promax rotation with Kaiser normalization was completed. Only components with eigenvalues > 1 were included. PCA analysis identified three components related to hearing experience (**Table 4.1**). Variables included in two pre-CI components related to deafness or hearing asymmetry while waiting to receive an implant. Variables included in the post-CI component related to hearing asymmetry

during the period of bimodal hearing. Because components did not correlate with each other ($R <$ 0.01), only the pattern matrix was shown along with the component score coefficient matrix used to create component scores for each child. Component scores were used for regression analyses of cortical activity and correlational analyses with speech perception scores.
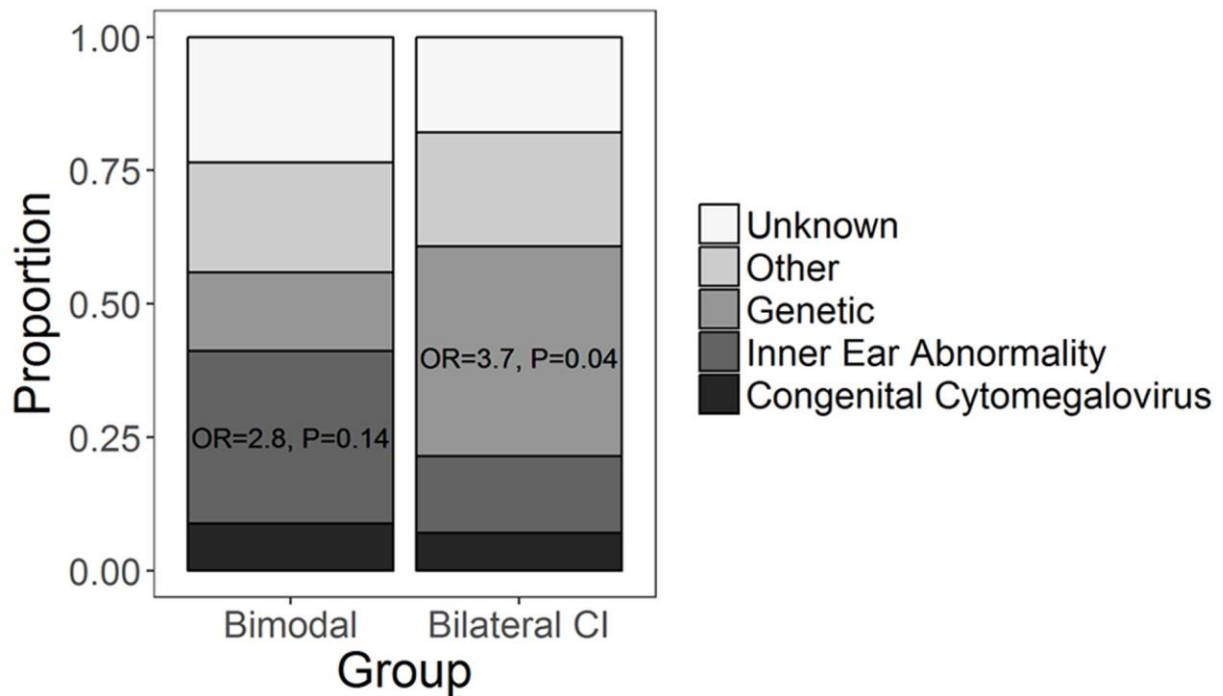
Figure 4.1. Distribution of hearing loss etiology.

Proportions of bimodal and bilateral cochlear implant (CI) users with each known and unknown etiology are shown. The odds of an inner ear abnormality were greater for bimodal users whereas the odds of a genetic etiology were greater for bilateral CI users. OR = odds ratio.

4.3.3 Cortical recording

EEG measures of evoked cortical activity were recorded across 64 scalp electrodes including those from the standard 10-20 configuration referenced to the right earlobe. Responses were measured using the NeuroScan-4.5 system and Synamps-II amplifier (Compumedics USA, Inc., Charlotte, NC), sampled at 1,000 Hz and online band-pass filtered between 0.15 - 100 Hz. Responses were common referenced and filtered offline from 1 - 30 Hz for source analysis. A minimum of 220 sweeps with at least two visually replicable responses were collected. Rejected epochs included eye blinks in frontal electrodes or activity in a midline cephalic electrode (Cz) greater than $\pm100\,\mu V$.

Matlab (MathWorks) and Nucleus Implant Communicator (NIC; Cochlear Ltd., Melbourne, Australia) programs were created to deliver monaurally presented stimuli while children sat in a soundproof booth watching a captioned movie without sound or reading a book. Stimuli were presented at 1 Hz and included 36 ms trains of 250 Hz biphasic electric pulses (57 µs) delivered through an L34 research processor to an apical electrode (#20) of the internal device in the implanted ear, and 250 Hz acoustic clicks (100 µs) delivered to non-implanted ears through an Etymonic Research (ER-3A) insert earphone. Loud but comfortable levels were confirmed using maximum auditory brainstem response wave eV/V amplitude, thereby ensuring similar activation of both ears at the upper part of the dynamic range (Gordon et al., 2013b; Polonenko et al., 2015). Brainstem responses were recorded from CZ referenced to the ipsilateral earlobe using 11 Hz single pulses/clicks, averaged across trials, and filtered from 10 - 3,000 Hz. Rejected epochs contained responses over ±30-40 µV. Levels determined from single pulses/click evoked brainstem responses were reduced by 10 current units (CU) (20.96 µA) or dB on each side for pulse train evoked cortical responses to account for temporal integration and ensure comfortable stimulation.

4.3.4 Source localization

The time-restricted, artefact and coherent source suppression (TRACS) linearly constrained minimum variance type beamformer (Wong and Gordon, 2009) was used to estimate source dipole activity underlying latency windows encompassing the first visually identified positive (P1) and negative (N2) peaks of the immature cortical waveform (**Figure 4.2**), as previously described (Easwar et al., 2017b; Gordon et al., 2010, 2013b). Briefly, application of the time-restricted artefact suppression algorithm maintained evoked responses while suppressing ~97% of the CI artefact corresponding to the four largest singular vector values between -80 to 10 ms (Wong and Gordon, 2009). Because an internally implanted magnet precludes MRI testing for implanted children, age-appropriate Montreal Neurologic Institute (MNI) head model templates created using the Template-O-matic toolbox (Wilke et al., 2008) were used to construct a 3-layer boundary element model (BEM) mesh. This mesh accounted for age-dependent head geometry and tissue conductivities through the brain, skull and scalp when calculating lead potentials for dipoles in ~64,000 3x3x3 mm voxels. Source activity in each hemisphere was evaluated by suppressing the other hemisphere (Dalal et al., 2006).

The signal-to-noise ratio of evoked source activity relative to baseline activity in the pre-stimulus interval (-200 to -80 ms) was normalized using a pseudo-Z statistic (Vrba and Robinson, 2001). A one-tailed omnibus-noise T-test (Petersson et al., 1999) calculated a statistical threshold pseudo-Z value ($p \leq 0.0005$) reflecting baseline activity (omnibus value). Pseudo-Z values were corrected relative to this omnibus value. Group average corrected pseudo-Z values for each voxel were plotted on the average age-appropriate head model for each condition (**Figure 4.3A**), in order to identify consistently activated cortical areas. Maximum dipole strength (nAm) and latency were extracted for all voxels, and the voxel with the largest corrected pseudo-Z value in both the left (MNI coordinates $X \leq -55$, $-35 \leq Y \leq 5$, $-10 \leq Z \leq 20$) and right (MNI coordinates $X \geq 55$, $-35 \leq Y \leq 5$, $-10 \leq Z \leq 20$) auditory cortices was chosen for each condition and child (Easwar et al., 2017b; Jiwani et al., 2016). For children in which stimulation of one ear evoked activity with pseudo-Z values above omnibus in only one auditory cortex, the peak dipole moment associated with the highest pseudo-Z value (although below omnibus) was chosen in the less-activated hemisphere to calculate aural preference. Aural (stimulation) preference (%) of each auditory cortex was calculated as: 100 x (dipole magnitude evoked by contralateral stimulation – dipole magnitude evoked by ipsilateral stimulation) / (ipsilateral + contralateral evoked dipole magnitudes). Positive aural preference scores indicated preferential stimulation by the contralateral ear while negative scores indicated preferential stimulation by the ipsilateral ear.

4.3.5 Speech perception to assess functional outcomes

Functional outcomes with bimodal devices were evaluated using age- and language-appropriate speech perception tests. Words were presented at 0º azimuth in quiet to each device separately. Speech scores were available for both devices in all but five bimodal users. Scores were obtained in a limited number of conditions in four of the five children with missing data, reflecting the young age of these five participants (5.2 ± 2.8 years). The following tests were used for the remaining 29 children: Early Speech Perception test (ESP; $n = 1$), Word Identification by Picture Identification (WIPI; $n = 1$), Glendonald Auditory Screening Procedure (GASP; $n = 7$), Multisyllabic Lexical Neighbourhood Test (MLNT; $n = 5$), and Phonemic Balanced Kindergarten test (PBK; $n = 16$). Children responded by either pointing to a picture best representing the heard word from a group of pictures (closed-set: ESP, WIPI) or repeating the heard word (open-set: GASP, MLNT, PBK). Because number of words varied across tests (12 to 25 words), percent correct scores were transformed to rationalized arsine units (RAU) and then

corrected for guessing on closed-set tests (Sherbecoe and Studebaker, 2004). Speech perception tests were often not completed on the same day of cortical recording due to length of testing, but the two tests were within 5.0 ± 1.9 months of one another.

4.3.6 Statistical analysis

To evaluate differences in evoked surface and source activity for each peak time window (P1 and N2), mixed repeated measures ANOVA were used with hearing group (Normal, Left CI/Right HA, Left HA/Right CI) as a between-subject factor. One within-subject factor was included for comparing surface peak amplitudes and latencies (ear) as well as cortical aural preference (cortex). Two within-subject factors (ear and cortex) were included for confirming similar voxel locations were chosen for further analyses and for comparing peak dipole moments and latencies. Greenhouse-Geisser corrections for lack of sphericity were used when indicated. Post-hoc two-tailed paired *t*-test tests were completed using false discovery rate (FDR) corrections (Benjamini and Hochberg, 1995) for multiple comparisons. Multiple linear regressions were used to assess changes in aural preference with implanted ear (i.e., bimodal group), PCA component scores, and demographic variables. Pearson correlations were used to assess associations between speech perception scores and PCA component scores, demographic variables, and aural preference. Partial and bivariate R^2 and FDR-corrected *p*-values were provided. PCA was completed using SPSS Statistics v.23 (IBM Corp, Somers, NY, USA); all other analyses and graphics were completed using R v3.3.1 (R Core Team, 2016).

4.4 Results

4.4.1 Children show immature P1-N2 cortical responses to both electric and acoustic stimulation

Children in all three groups exhibited immature cortical responses at Cz characterized by a positive (P1) then negative (N2) peak (**Figure 4.2A**, top), which resembled cortical responses recorded in other studies with young children (Easwar et al., 2017b; Gordon et al., 2013b; Ponton et al., 2000, 2002). Corresponding peaks were evident in the global field power (GFP; **Figure 4.2A**, bottom) and were analysed. Mean $\pm$ SD peak amplitudes and latencies are provided in **Supplemental Table 4.1**. Despite having similar peak amplitudes irrespective of ear (left/right) or stimulation mode (acoustic (HA)/electric (CI)) (all $p > 0.05$), groups differed by early peak latencies (P1: $F(2,46) = 4.0$, $p = 0.02$; N2: $F(2,46) = 0.5$, $p = 0.60$). Specifically, P1

latencies were faster for children with normal hearing than bimodal users (left CI: $t(28.4) = -2.6$, $p = 0.04$; right CI: $t(29.8) = -2.3$, $p = 0.04$), but similar for both bimodal groups ($t(31.2) = 0.1$, $p = 0.90$). For all three groups, average-referenced topographical maps of surface EEG activity at group-specific peak latencies (**Figure 4.2B**) indicated positive and negative bilateral activation at fronto-temporal electrodes for P1 and N2, respectively.
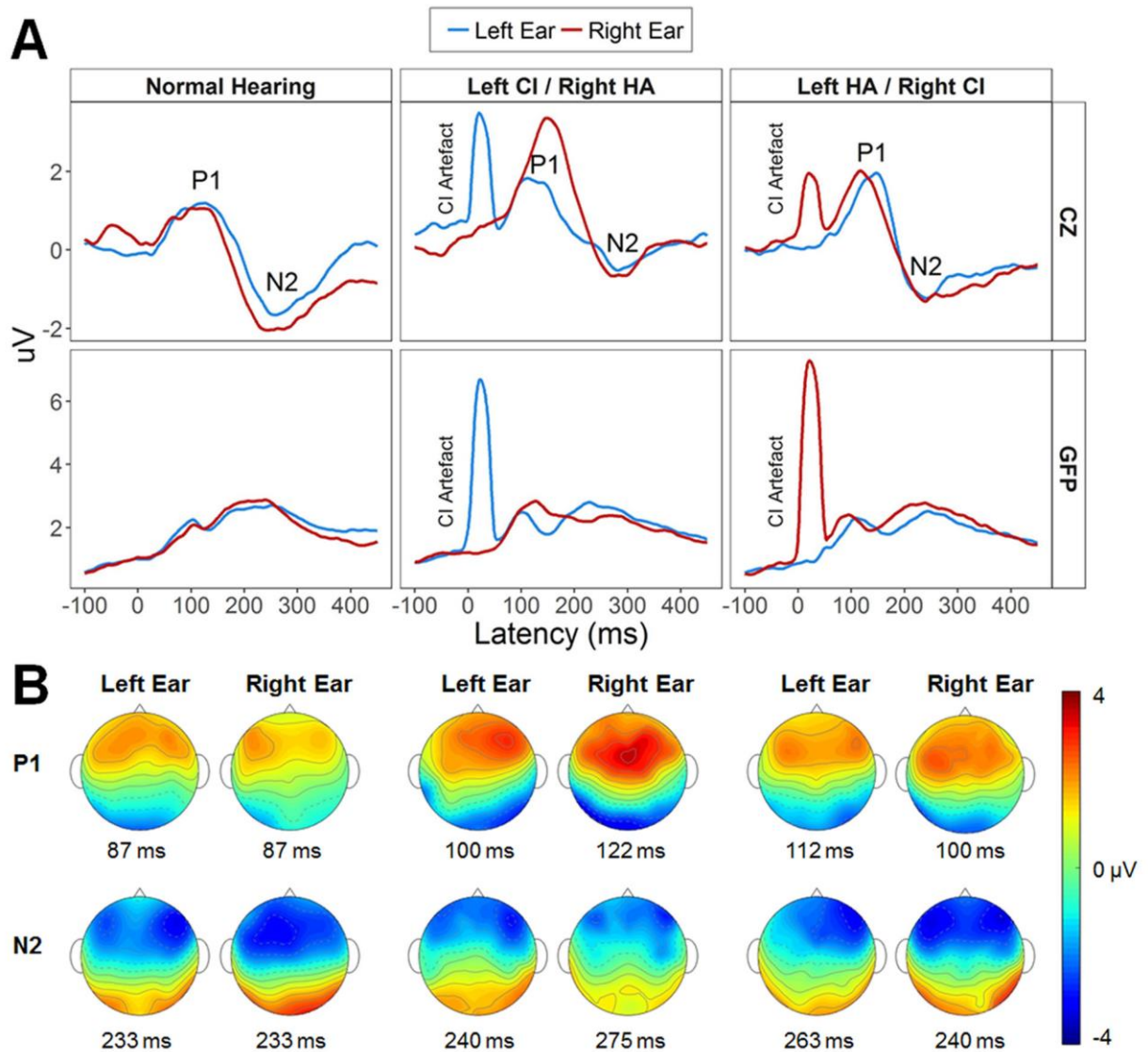
Figure 4.2. Evoked surface activity.

(**A**) Mean common-reference cortical responses at a cephalic electrode (Cz; top row) and mean global field power (GFP; bottom row) in response to stimulation of the left ear (blue) and right ear (red) for children with normal hearing ($n = 16$), and bimodal hearing ($n = 34$; $n = 17$ each for left or right CI). The first positive (P1) and negative (N2) peaks are labelled for responses

recorded at Cz. In general, responses were similar in amplitude across groups but slower in the bimodal groups. (**B**) Group average common-reference head topographic maps display the distribution of EEG activity across the surface of the head at GFP peak latencies for P1 and N2 peaks. CI = cochlear implant; HA = hearing aid.

4.4.2 Auditory cortices respond more quickly to electrical than acoustic stimulation

Axial views of mean omnibus-corrected pseudo-Z maps showed similar activated regions (higher pseudo-Z in red) underlying P1 upon stimulation of each ear for each group (**Figure 4.3A**). Due to similarity of outcomes between P1 and N2, N2 results are provided in the supplementary material. Voxels chosen for further analyses had similar coordinates (group: $F(2,97) = 0.05$, $p = 0.95$; ear: $F(1,97) = 0.02$, $p = 0.87$) within auditory cortical areas (**Figure 4.3B**). Furthermore, the centroid location of these peak voxels were within 3 voxel spaces of one another (6.1 ± 1.4 and 6.3 ± 3.9 mm between the normal hearing group and the left CI/right HA and left HA/right CI groups respectively, and by 4.5 ± 1.0 mm between bimodal groups), and variation around these centroids were similar (group: $F(2,47) = 0.2$, $p = 0.83$; ear: $F(1,47) = 0.01$, $p = 0.91$; cortex: $F(1,47) = 0.5$, $p = 0.48$).

Peak dipole moments (**Figure 4.3C**) from voxels in each cortex were stronger for contralateral versus ipsilateral stimulation (ear: $F(1,47) = 14.0$, $p < 0.001$) in all groups (ear x group: $F(2,47) = 0.2$, $p = 0.81$; group: $F(2,47) = 0.2$, $p = 0.84$). By contrast, peak dipole latencies (**Figure 4.3D**) did not follow the same pattern in each group (3-way interaction: $F(2,47) = 5.4$, $p = 0.007$). Children with normal hearing tended to have faster peak latencies in each cortex to contralateral stimulation (left cortex: $t(15) = 2.1$, $p = 0.21$; right cortex: $t(15) = 0.80$, $p = 0.52$) whereas peak dipole latencies in bimodal users tended to be slower in response to HA than CI stimulation; this was only significant in the right auditory cortex in children with left HA/right CI ($t(16) = -3.5$, $p = 0.04$).
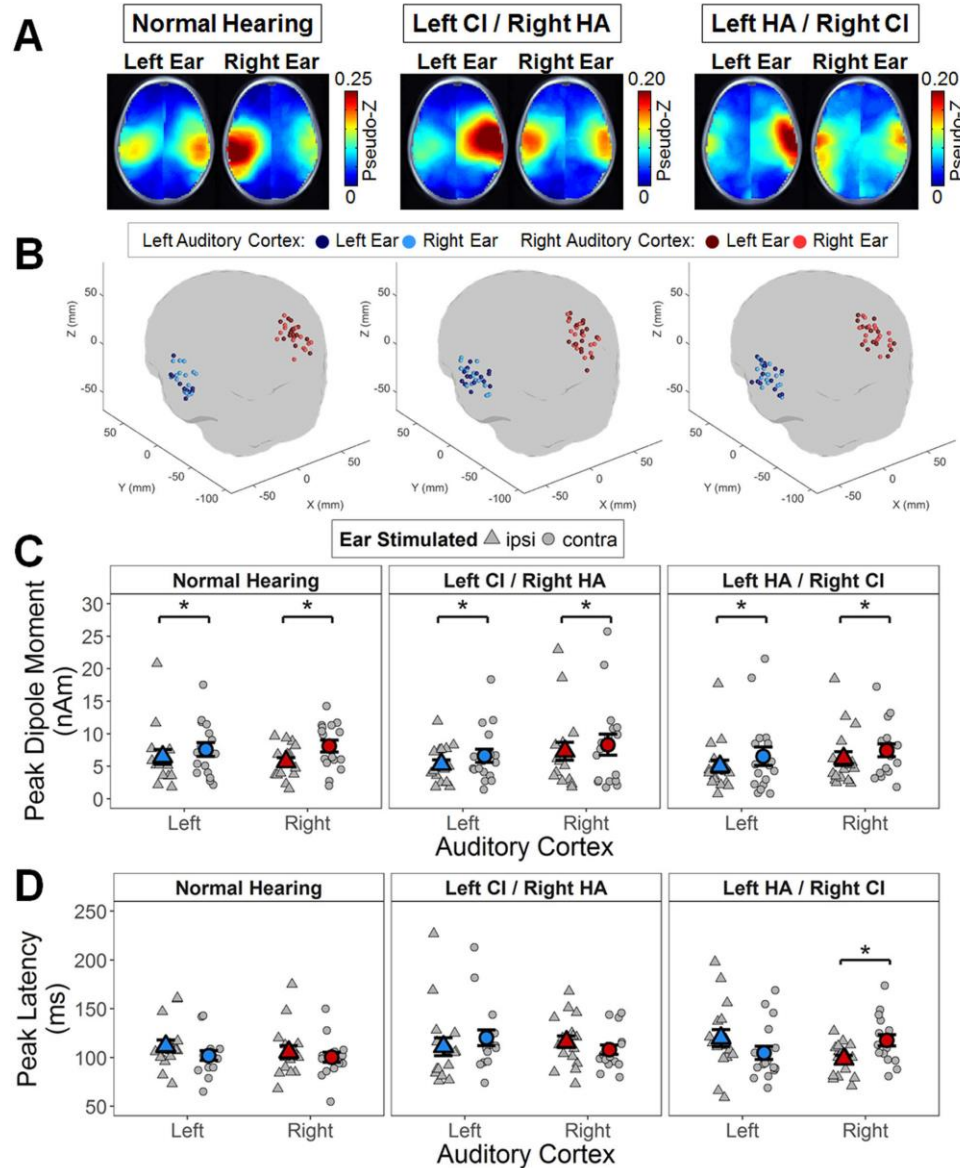
Figure 4.3. Evoked source activity for P1.

(**A**) Axial views of each group mean omnibus-corrected pseudo-Z (higher signal-to-noise-ratio in red) maps show regions of activation during P1 upon stimulation of the left and right ears. Activity localized to both auditory cortices in all conditions and groups. (**B**) Peak dipoles were located at similar locations in the left (blue) and right (red) auditory cortices upon stimulation of the left (dark colour) and right (light colour) ear. For each group, the mean ± SE (coloured) and individual (gray) maximum peak (**C**) dipole moments (nAm) and (**D**) latencies extracted from chosen voxels are shown for the left (blue) and right (red) auditory cortices upon stimulating the ipsilateral (ipsi; triangles) and contralateral (contra; circles) ear in each group. CI=cochlear implant; HA=hearing aid; * $p < 0.05$.

4.4.3 Some bimodal users have abnormal preference for input from one ear

Aural preference was calculated for each cortex to evaluate the relative cortical representations of each ear. On average, all three groups ($F(2,47) = 0.68$, $p = 0.51$) developed expected contralateral aural preference in both cortices ($F(1,47) = 0.18$, $p = 0.67$). Aural preference for cortices ipsilateral to each type of device (e.g., ipsilateral to CI is the left cortex for left implanted children) are plotted for each child in **Figure 4.4**. Many bimodal users (filled circles) developed primarily contralateral aural preference in both cortices, like their peers with normal hearing (open circles) (**Figure 4.4**) but 9 (26.5%) bimodal users developed abnormal preference in both cortices for stimulation from one ear ($n = 6$ for the HA ear; $n = 3$ for the ear with CI).
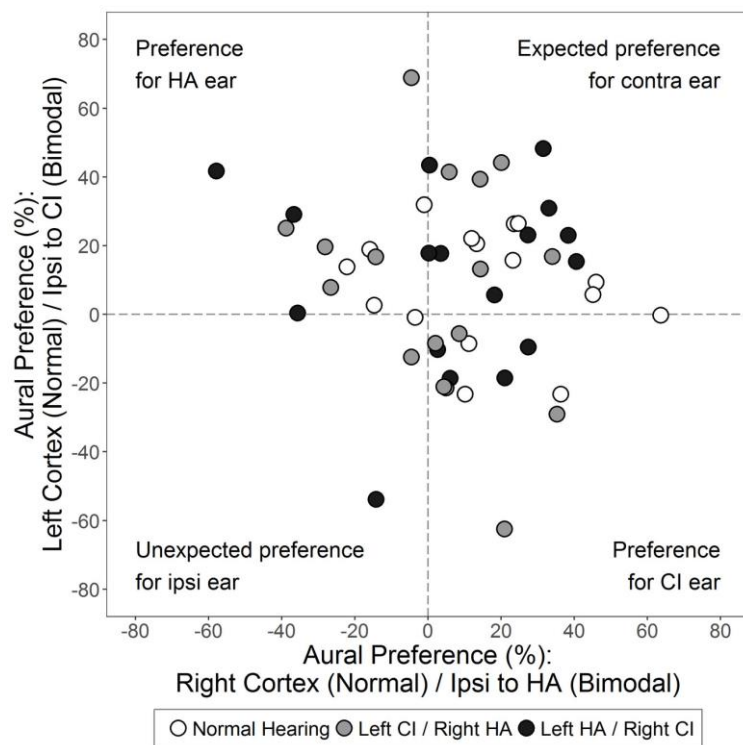
Figure 4.4. Aural Preference for P1.

Aural preference (%) for each auditory cortex is plotted for each child with normal hearing (white), a left cochlear implant (CI)/right hearing aid (HA) (gray), and a left HA/right CI (dark gray). For bimodal users, aural preference was calculated for cortices ipsilateral (Ipsi) to each type of device to evaluate whether some children preferred stimulation from one ear (e.g., Ipsi to CI is the left cortex for children with a left CI). Positive values indicate preference for stimulation of the contralateral ear.

Multiple linear regression analyses were completed to identify relationships between the aural preference measures and the pre- and post-implant PCA components. Aural preference of the cortex ipsilateral to the HA reversed to abnormally prefer this better hearing ear as the pre-CI hearing experience component increased (**Figure 4.5A**). The cortex ipsilateral to the CI abnormally preferred the implanted ear as the post-CI experience component increased (**Figure 4.5B**). These findings were independent of implanted ear (unstandardized β $p > 0.05$). Bivariate and partial R^2 values and corresponding p-values are provided in **Table 4.2**.

Table 4.2. Multiple regression parameters for significant predictors of aural preference.

Cortex	Predictor	Bivariate		Partial		
		R^2	P-value	R^2	P-value	Adjusted P-value
Ipsilateral to HA	Component: Pre-CI hearing experience	0.15	0.03	0.13	0.04	0.08
	Duration of hearing aid use before implantation	0.24	< 0.01	0.26	< 0.01	0.02
Ipsilateral to CI	Component: Post-CI hearing experience	0.14	0.04	0.17	0.02	0.06
	Duration of implant use	0.10	0.07	0.12	0.05	0.08

Effects of individual variables comprising the pre- and post-CI components on aural preference measures were then assessed. Two significant variables were identified in multiple regression analyses; both were based on experience with auditory prostheses (**Figure 4.5C,D**). In the auditory cortex ipsilateral to the HA, aural preference abnormally reversed to favour this better hearing ear at a rate of -7.5 $\pm$ 2.3%/year of asymmetric hearing prior to implantation (delay to implant) (**Figure 4.5C**). In the auditory cortex ipsilateral to the CI, most children had normal aural preference for the contralateral HA ear. Those children with abnormal aural preference for the implanted ear tended to have longer implant experience (**Figure 4.5D**). The rate of change was -24.4 $\pm$ 13.8%/log10(year of CI use) which corresponds to a change of -7.4% per doubling of time of CI use. Bivariate and partial R^2 values and corresponding p-values are provided in **Table 4.2**. Pre-implant unaided hearing loss in the CI and HA ears did not significantly predict abnormal cortical reorganization ($p > 0.05$), although children with abnormal aural preference tended to have a severe/profound hearing loss ($n = 3$; deaf ear: 102.1 $\pm$ 6.4 dB HL; better ear: 77.5 $\pm$ 9.8 dB HL).
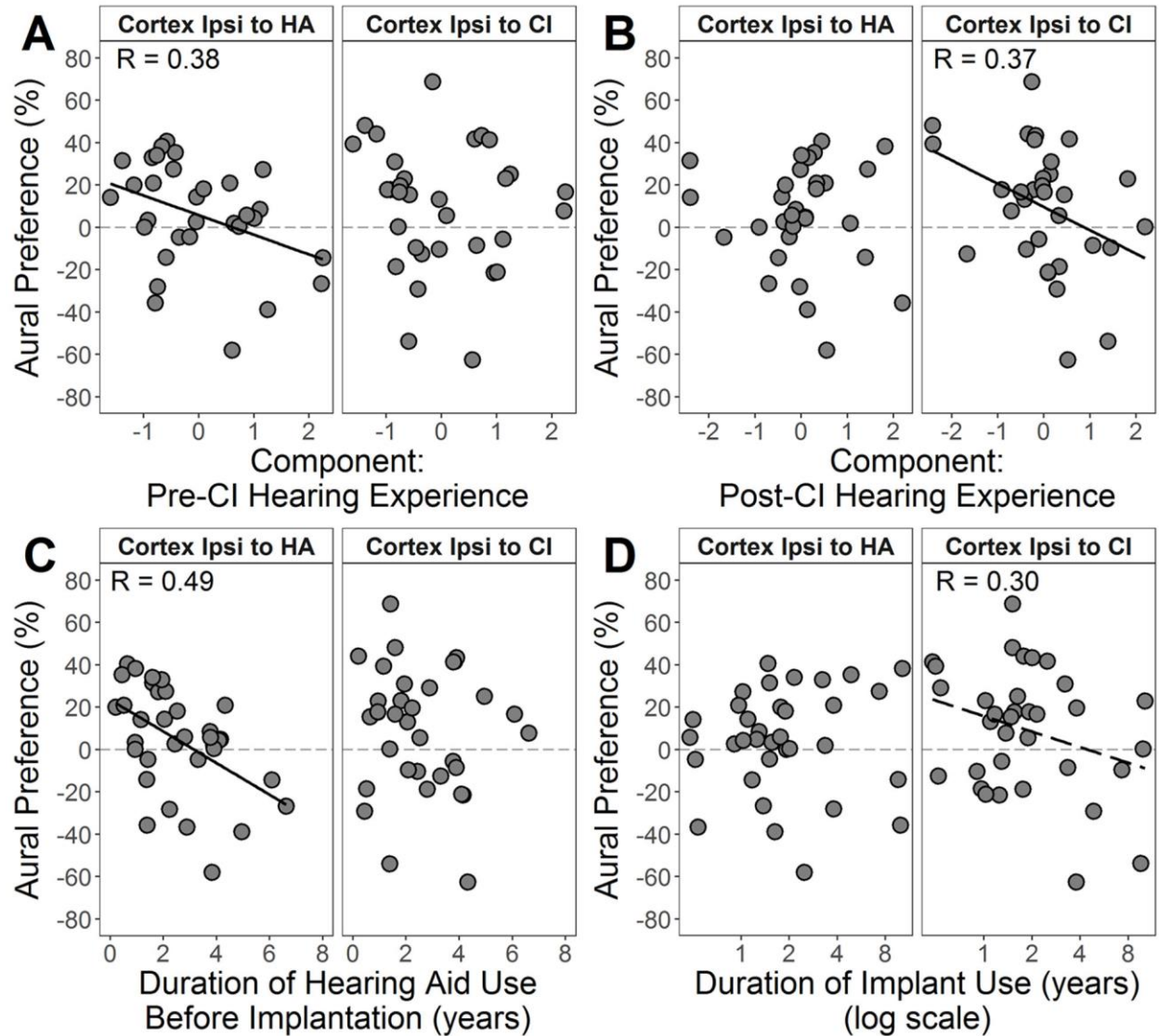
Figure 4.5. Changes in Aural Preference for P1.

(**A**) Aural preference in bimodal users is shown for the cortices ipsi to the HA and ipsi to the CI as a function of the pre- (**A**) and post- (**B**) implant hearing experience components identified by Principal Component Analyses (PCA), and as a function of (**C**) duration of HA use before implantation, and (**D**) duration of CI use (log scale). Positive values indicate preference for stimulation of the contralateral ear. Solid regression line: $p < 0.05$; dashed regression line: $p < 0.1$.

4.4.4 Reorganization follows a similar time course for unilateral deafness and asymmetric hearing

Cortical development in bimodal users was compared to responses from a cohort of children with bilateral implants to determine if effects were similar for asymmetric and unilateral CI hearing. Aural preference for each child in the bimodal and bilateral CI groups are plotted for the left versus right cortex (ipsilateral to CI versus HA for bimodal users) in **Figure 4.6A**. Some children using bilateral implants ($n = 4$) and bimodal devices ($n = 6$) had similar abnormal preference for the first (i.e., first CI) or better hearing (i.e., HA) ear respectively (**Figure 4.6A**, top left quadrant). Multiple linear regressions were used to compare changes in aural preference with duration of device use prior to bimodal/bilateral CI hearing (aural preference ~ time x group). The rate of change in aural preference for the cortex ipsilateral to HA (bimodal users) or first implanted (bilateral CI users) ear was similar (multivariate regression: $F(3,58) = 7.7$, $R^2 = 0.28$, $p < 0.001$; time: $p = 0.004$; group: $p = 0.84$, time x group: $p = 0.44$). Prior to bilateral input, the rate of change toward abnormal preference for the better hearing ear was $7.4 \pm 2.3\%$/year in the bimodal group (bivariate regression: $F(1,32) = 10.2$, $p = 0.003$, $R^2 = 0.24$; light gray line in **Figure 4.6B**) and $10.4 \pm 3.0\%$/year in the bilateral CI group (bivariate regression: $F(1,26) = 11.8$, $p = 0.002$, $R^2 = 0.31$; dark gray line in **Figure 4.6B**). The x-intercepts calculated from the full model for bimodal and bilateral CI users differed by 1.1 years (3.2 versus 2.1 years respectively).
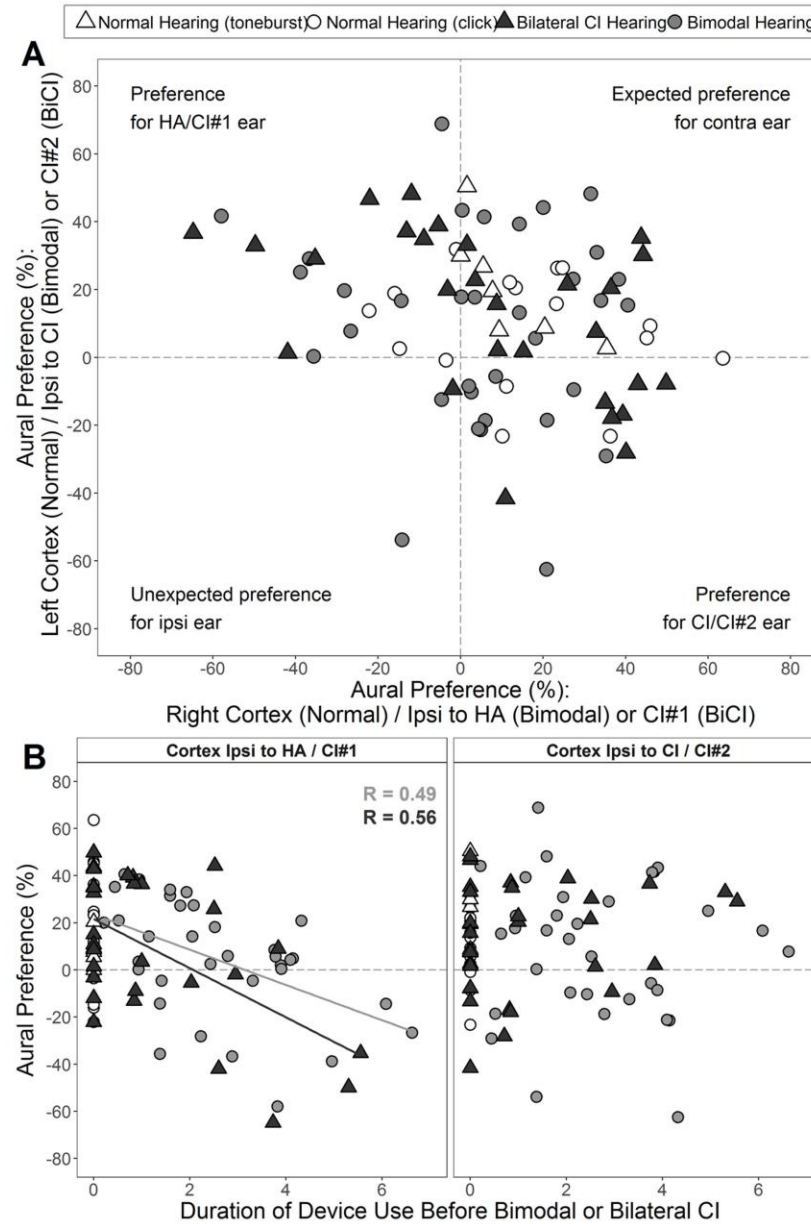
Figure 4.6. Aural preference (%) in children with normal, bimodal and bilateral implant hearing.

(**A**) Aural preference for P1 is plotted for left versus right auditory cortex (ipsilateral to CI versus HA for bimodal users and CI#2 versus CI#1 for bilateral implant users) for each child with normal hearing (white), bilateral implants (dark gray) and bimodal devices (gray) in the current study (circles) and a previous study (triangles) (Gordon et al., 2013b). (**B**) Relationship between aural preference and duration of device use before receiving bimodal devices or bilateral CIs. Significant regression lines ($p < 0.05$) are shown. HA = hearing aid; CI = cochlear implant; Ipsi = ipsilateral.

4.4.5 Speech perception accuracy increases with early access to high frequencies

Figure 4.7 plots speech perception accuracy when listening through each device in 29/34 bimodal users. Results varied substantially (**Figure 4.7A**) but on average, bimodal users perceived speech 16.1 ± 0.5 RAU more accurately with their CI than HA ($t(28) = -4.0, p < 0.001$). Many children ($n = 20, 69\%$) exhibited similarly good (> 60 RAU; $n = 8$) or similarly fair (< 60 RAU, $n = 12$) accuracy in each ear (**Figure 4.7B**) and scores with each device alone were correlated ($R = 0.55, p = 0.002$; **Figure 4.7B**). Thus, consistent with cortical preference data, most bimodal users developed symmetric/balanced function from each of their two ears. Asymmetry in speech perception favoured the implanted ear: of nine (31%) children with asymmetric speech perception, eight had better CI scores and only one had better HA scores. These data did not reflect cortical findings; no significant association was found between unilateral speech perception scores and aural preference in either auditory cortex (ipsi to HA: HA scores: $R = 0.31, p = 0.12$; CI scores: $R = 0.07, p = 0.71$; ispi to CI: HA scores: $R = 0.35, p = 0.06$; CI scores: $R = 0.19, p = 0.31$).

Like cortical aural preference, speech perception was predicted by hearing experience, as characterized by the PCA post-CI ($R = -0.44, p = 0.03$; **Figure 4.7C**) and pre-CI ($R = -0.49, p = 0.03$; **Figure 4.7D**) components. The major difference was that time-based factors relating to asymmetric hearing in the PCA components predicted reversal of contralateral aural preference (**Figure 4.5C,D**) whereas unilateral speech perception depended on factors involving access to high-frequency sound in each ear independently (**Figure 4.7E,F**). In particular, accuracy with the HA increased with better hearing in that ear as measured by unaided hearing thresholds at 2 kHz ($R = -0.44, p = 0.03$; **Figure 4.7E**) and 4 kHz ($R = -0.43, p = 0.03$), and aided thresholds at 4 kHz ($R = -0.43, p = 0.01$). Scores when using the CI decreased as low-frequency access in that ear pre-implantation increased (0.5 kHz: $R = 0.38, p = 0.04$; **Figure 4.7F**). This may reflect later implantation of children with better low-frequency hearing ($R = -0.56, p = 0.007$), as speech perception with the CI also worsened with older age at implantation ($R = -0.52, p = 0.02$). Given that all children had profound hearing loss in the deaf ear at high frequencies (2 kHz: 112.5 ± 15.4 dB HL; 4 kHz: 112.8 ± 16.7 dB HL), children implanted with minimal delay consequently received access to high-frequency hearing with the CI at earlier ages.
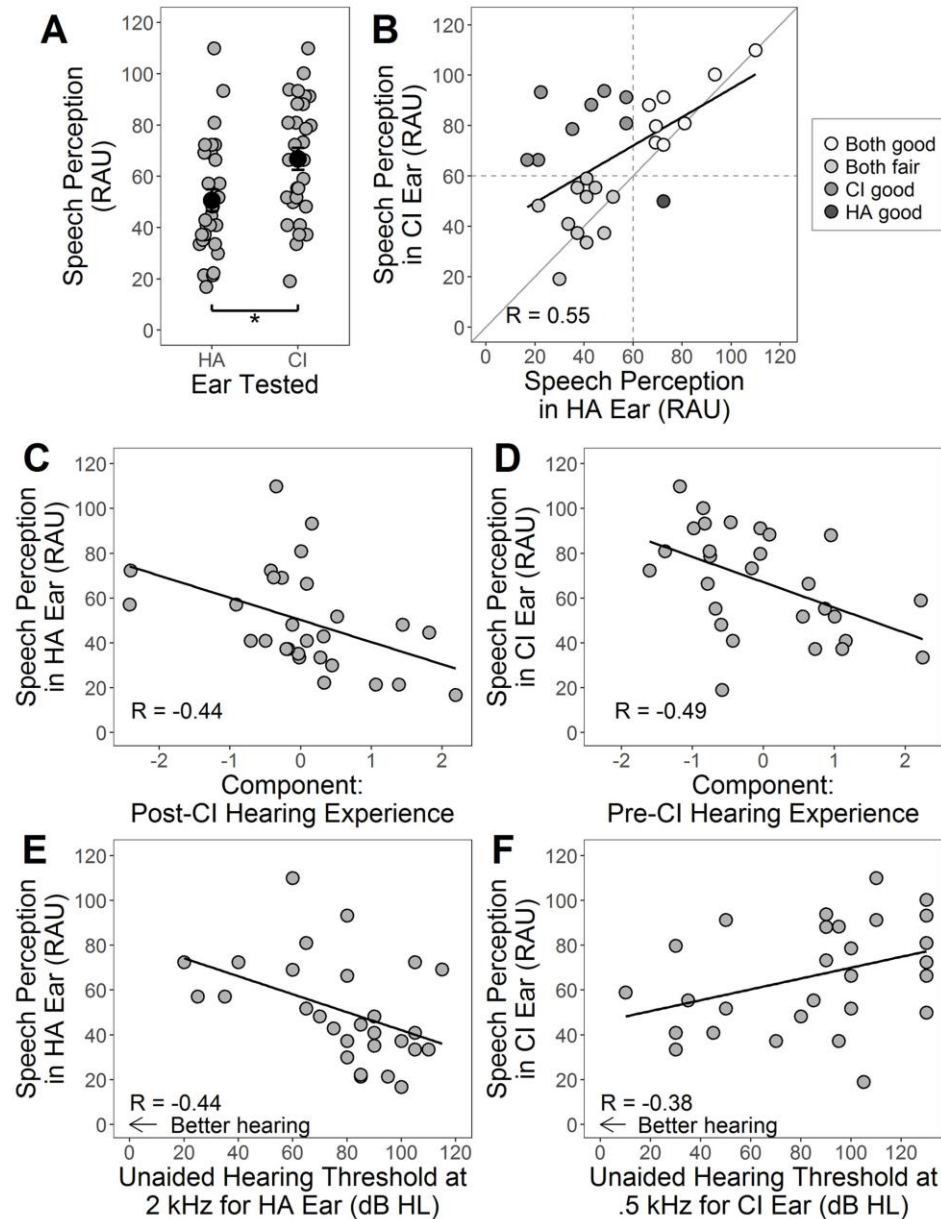
Figure 4.7. Speech perception of bimodal users.

(**A**) Speech perception in rationalized arsine units (RAU) is plotted for individuals (gray) and the group mean (black) upon monaural testing of the hearing aid (HA) ear and cochlear implant (CI) ear. (**B**) Speech perception for the CI ear is plotted in relation to speech perception for the non-implanted HA ear. Dashed lines denote the cut-off (60 RAU) of how speech perception compares in each ear; whether both ears have good scores (white) or poor scores (light gray), or whether only one ear has a good score (medium gray: CI better; dark gray: HA better). Speech perception for each ear correlated with principal component analysis (PCA) demographic components (**C,D**) and with individual predictors (E,F). *$p < 0.05$.

4.5 Discussion

This is the first study to address cortical development driven by bimodal stimulation in children with asymmetric hearing loss. Although electric and acoustic inputs each have unique and distinct effects on auditory stimulation in each ear, expected preference for contralateral stimulation in both auditory cortices was achieved in many children. On the other hand, an increasing cortical preference for stimulation from the better hearing ear occurred with ongoing asymmetric hearing loss either with delays to implantation of the deaf ear (preference for better hearing ear) or with CI use if acoustic input in the non-implanted ear was relatively weak (preference for implanted ear). Speech perception in bimodal users strongly depended on access to high frequency sound on each side independently rather than on the bilaterally sensitive measure of aural preference evoked by broadband stimuli.

4.5.1 Bimodal use can protect symmetric cortical activity and speech perception

Bimodal hearing preserved cortical responses with similar surface waveform morphology to peers with normal hearing (**Figure 4.2A**) and symmetric source activity in most children (25/39, 64.1%) despite lagging response latencies of 10.5 - 14.1 ms from the acoustic relative to implanted ear (**Figures 4.2A, 4.3D**). These latency delays exceed previously characterized latency differences between contralateral/ipsilateral stimuli and between ears in young children (Easwar et al., 2017b) and kittens (Kral et al., 2013b). Causes for latency differences within this study and across studies include rapid electrical stimulation of the auditory nerve, which occurs at least 1 ms before acoustic stimulation (Gordon et al., 2006; Polonenko et al., 2015), and greater synchrony across broad populations of electrically evoked neurons (Hartmann et al., 1984; Kral et al., 2009). Compounding the problem, neural synchrony from the acoustic hearing ear is compromised by deterioration of cochlear structures and/or auditory neurons with hearing loss, particularly in basal cochlear regions which respond most quickly (Polonenko et al., 2015; Rosenhamer et al., 1981). Yet, these factors did not affect response magnitude; source dipole activity did not significantly differ between the implanted and normal hearing groups and, in both groups, was larger in response to contralateral than ipsilateral stimulation **(Figure 4.3C)**. Moreover, many bimodal users (25/34, 64.1%) showed expected contralateral aural preference in both auditory cortices (**Figure 4.4**) and similar speech perception abilities when using each device separately (20/29, 69.0%; **Figure 4.7B**). Symmetrical activity measured from both ears in

bimodal users thus provides the first evidence that bilateral input with limited delay does not need to be restricted to a single modality to protect against development of a cortical or functional preference for one ear.

4.5.2 Delays to bimodal hearing alter auditory development and compromise speech perception

Some children showed abnormal aural preference for the better non-implanted ear (6/34, 17.4%) or CI ear (3/34, 8.8%). The diverse hearing histories of bimodal users, as characterized by PCA (**Table 4.1**), predicted changes in aural preference toward the non-implanted ear (**Figure 4.5A**); main contributors were delayed implantation and longer HA use in the deaf ear (**Figure 4.5C**). Insufficient access in the poorer ear prior to implantation (despite HA use) promoted reorganization over 2 - 3 years of asymmetric hearing which persisted despite subsequent bimodal stimulation. These findings are consistent with animal models demonstrating increasing cortical activity from the better hearing ear with earlier and longer asymmetric hearing loss in cats with congenital deafness (Kral et al., 2013a, 2013b; Tillein et al., 2016) and in rats and ferrets with temporary asymmetric hearing loss (Keating and King, 2013; Polley et al., 2013; Popescu and Polley, 2010), as explained by strengthening of crossed and uncrossed pathways from the hearing ear and reduction of ipsilateral inhibition or contralateral excitation from the deaf ear (Kral et al., 2013a, 2013b; Tillein et al., 2016). A risk of aural preference for the CI ear was found with ongoing CI use (post-CI component, **Figure 4.5B**) in bimodal users with poor residual hearing in the non-implanted ear (**Figure 4.5D**), suggesting that the HA could not provide sufficient sound for bilateral cortical representation of both ears. Taken together, measures of cortical aural preference reveal limitations of bimodal stimulation for treating asymmetric hearing loss when it is delayed (pre-implant) and/or unbalanced (post-implant).

Speech perception testing also supported the importance of early hearing experience (**Figure 4.7C,D**). Whereas cortical aural preference was sensitive to the timing of symmetric bilateral sound (**Figure 4.5C,D**), speech perception depended on access to high frequencies in each ear independently (**Figure 4.7E,F**). These two measures were not significantly correlated with one another, reflecting a vulnerability of speech perception to high-frequency hearing loss which is not captured by cortical dipoles evoked by high level broadband clicks. Thus, residual low-frequency acoustic function in the non-implanted ear maintained expected input to the auditory

cortices but was not translated into benefits for understanding speech through a HA without sufficient hearing in high frequencies.

4.5.3 Aural preference occurs rapidly with asymmetric hearing in development

There appears to be a rapid time course of cortical plasticity in response to asymmetric hearing loss in children. Bimodal users experienced a change of 7.4%/year of CI delay away from expected contralateral aural preference (**Figures 4.4, 4.5, 4.6**). A remarkably similar time course of 10%/year of inter-implant delay was shown by children who experienced the most extreme form of asymmetric hearing loss due to unilateral CI use after early onset bilateral deafness (**Figure 4.6**). Consequently, expected aural preference reversed in the ipsilateral cortex of the better stimulated ear by 3.2 years in bimodal users and 2.2 years in bilateral CI users, which indicates that the developing auditory brain rapidly responds to an imbalance in bilateral input. Importantly, the changes in both groups persisted despite chronic bilateral input through bimodal (2.4 ± 2.5 years) or bilateral CI (3.6 ± 0.8 years) use. These results indicate that timing of balanced input, regardless of modality, is important to maintaining bilateral auditory function in children.

4.5.4 Cortical response to asymmetric hearing loss is particular to early development

The auditory system is most vulnerable to preference for one ear during early development. Effects were greatest in unilateral congenital deaf cats and decreased as the age of unilateral CI stimulation increased in bilaterally deaf cats (Kral et al., 2013a, 2013b). This is consistent with evidence of increasingly abnormal aural preference despite several years of bilateral input in both bimodal and bilateral CI users in this study who had early onset asymmetric hearing that continued for years before receiving bilateral input (**Figure 4.6, Table 4.1**). Once preference for one ear occurs, restoring expected cortical organization may be challenging if unilaterally driven maturation occurs in the auditory system and more sensitive periods of synaptic plasticity are missed during development (Gordon et al., 2013a; reviewed by Kral and Sharma, 2012). It is possible, however, that some degree of cortical change occurred during bimodal use given that some children developed cortical preference for the implanted ear and expected auditory cortical organization was achieved through implantation in many bimodal users (**Figure 4.6**).

Longitudinal measures recently collected in a unique group of young children with single-sided deafness (one normal hearing and one deaf ear) confirms that abnormal aural preference can be reversed within the first 6 months of CI use following initial cortical abnormalities (Polonenko et al., 2017b). Thus, there is growing evidence that early access to bimodal input can prevent or reverse abnormal cortical aural preference for the first/better hearing ear.

4.5.5 Implications for management of children with asymmetric hearing loss

Findings in this study support early implantation of children with asymmetric hearing loss and provide evidence for changing standard candidacy criteria. Yet, it is still not clear what combination of auditory prostheses is best for these children. It is possible, for example, that some children using bimodal hearing would fare better with bilateral CIs. For children who have sufficient residual hearing in their non-implanted ear, there may be several advantages of bimodal hearing. First, bimodal hearing protects against unilaterally driven changes by promoting expected cortical organization (**Figures 4.4, 4.5, 4.6**) which could support specialization of the right versus left auditory cortices (Jiwani et al., 2016) and cortical integration of bilateral input (Easwar et al., 2017c). Second, bimodal hearing improves detection and understanding of speech in noise by providing access to sound from both sides of the head (Arndt et al., 2017, 2015; Ching et al., 2007; Polonenko et al., 2015; Thomas et al., 2017). Third, bimodal hearing preserves low-frequency acoustic hearing which works better than CI stimulation for pitch perception in music and speech (Bartov and Most, 2014; Giannantonio et al., 2015; Polonenko et al., 2017a; Shirvani et al., 2016). Alternatively, when the non-implanted ear has poor residual hearing, findings from this study suggest that bimodal hearing cannot prevent preference for the implanted ear (**Figures 4.4, 4.5**) and is insufficient for symmetric speech perception (**Figure 4.7**). Furthermore, bimodal hearing may hinder/disrupt bilateral integration/fusion of sound and binaural/spatial hearing by introducing large mismatches in cochlear place of stimulation between ears (Landsberger et al., 2015; Reiss et al., 2014a) and neural conduction in bilateral brainstem pathways (Polonenko et al., 2015; Zirn et al., 2015). These changes could distort how subtle inter-aural differences in sound are detected and integrated in the auditory system, compromising spatial hearing (reviewed by Grothe et al., 2010). Distortions to these binaural cues by signal processing strategies (Brown et al., 2016) are likely exacerbated by independent hearing devices that differ in modality and processing algorithms. In addition to the benefit of having the same type of device on both sides, bilateral

CIs may be easier to match than bimodal devices for level and timing of stimulation. In sum, bimodal hearing may be most effective for children with sufficient hearing in both low and high frequencies.

4.6 Conclusions

Bimodal hearing promotes expected cortical processing when balanced input is provided during early development. Prolonged asymmetric hearing drives cortical reorganization to prefer stimulation from the better hearing ear. This development favours the ear with more residual hearing prior to cochlear implantation and the implanted ear after implantation if hearing in the non-implanted ear is poor. Evoked by broadband click stimuli, these cortical measures do not correlate well with speech perception scores which reflect access to high frequencies in each ear independently. Thus, delays to implantation of the poorer ear should be avoided in children who could benefit from bimodal use with ongoing monitoring of the non-implanted ear. Bilateral implantation may be warranted to prevent preference for the implanted ear and/or to support speech perception in the non-implanted ear. This decision must take into account the potential loss of residual acoustic hearing.

4.7 Acknowledgements

4.8 Funding

4.9 Conflicts of Interest

None to declare.

4.10 Supplementary Material

Supplementary Table 4.1. Group mean ± SD peak amplitude and latency for each wave in the global field power (GFP) of the cortical evoked surface potentials.

Wave	Group	Ear Stimulated	Mode Stimulated	GFP Peak Amplitude (µV)	GFP Peak Latency (ms)
P1	Normal Hearing	Left	Acoustic	2.5 ± 0.9	92.7 ± 19.4
		Right	Acoustic	2.1 ± 0.6	93.3 ± 21.8
	Left CI / Right HA	Left	Electric	2.7 ± 1.1	102.1 ± 19.6
		Right	Acoustic	3.3 ± 1.0	117.7 ± 15.0
	Left HA / Right CI	Left	Acoustic	2.6 ± 1.2	111.7 ± 25.9
		Right	Electric	2.9 ± 1.5	106.4 ± 27.9
N2	Normal Hearing	Left	Acoustic	3.3 ± 1.5	241.4 ± 48.9
		Right	Acoustic	3.4 ± 1.4	232.1 ± 44.6
	Left CI / Right HA	Left	Electric	3.2 ± 1.3	231.6 ± 31.5
		Right	Acoustic	2.9 ± 1.1	245.8 ± 47.6
	Left HA / Right CI	Left	Acoustic	2.9 ± 1.2	256.6 ± 45.0
		Right	Electric	3.2 ± 1.5	240.0 ± 43.2

4.10.1 Auditory cortices respond to acoustic and electric stimulation in children during the N2 time window

Axial views of grand mean omnibus-corrected pseudo-Z maps showed regions of activation (higher pseudo-Z, in red) underlying N2 upon stimulation of the left and right ear for each group (**Supplementary Figure 4.1A**). Activity localized to both auditory cortices in all conditions and groups. Voxels within these 'hot spots' of activity containing the highest pseudo-Z values were located in similar auditory cortical areas (**Supplementary Figure 4.1B**) across groups of children ($F(2,97) = 0.04$, $p = 0.96$) and ear stimulated ($F(1,97) = 0.9$, $p = 0.33$). The centroid location of these peak voxels differed by 6.2 ± 2.0 and 5.2 ± 1.5 mm between the normal hearing group and the left CI/right HA and left HA/right CI groups respectively, and by 4.2 ± 0.3 MNI between the two bimodal groups. Variation around these centroids were similar (group: $F(2,47) = 0.3$, $p = 0.74$; ear: $F(1,47) = 0.01$, $p = 0.91$; cortex: $F(1,47) = 0.5$, $p = 0.50$).

Group mean and individual peak dipole moments (**Supplementary Figure 4.1B**) and latencies (**Supplementary Figure 4.1C**) from chosen voxels are shown for the left and right auditory cortices upon monaurally stimulating the ipsilateral and contralateral ear. Unlike P1, magnitude of peak dipoles underlying N2 differed by ear and group (ear x group: $F(2,47) = 5.4$, $p = 0.008$). Magnitude of peak dipoles tended to be larger for contralateral versus ipsilateral stimulation in children with normal hearing ($t(15) = 2.4$, $p = 0.09$), but were similar regardless of stimulated ear in bimodal users (Left CI/Right HA group: $t(17) = -1.7$, $p = 0.17$; Left HA/Right CI group: $t(17) = 0.2$, $p = 0.83$). Underlying N2, peak dipole latencies were faster in the left cortex ($F(1,47) = 6.43$, $p = 0.02$) and faster upon stimulation of the contralateral ear ($F(1,47) = 4.9$, $p = 0.03$), and these differences held for all three groups ($F(2,47) = 1.5$, $p = 0.23$).
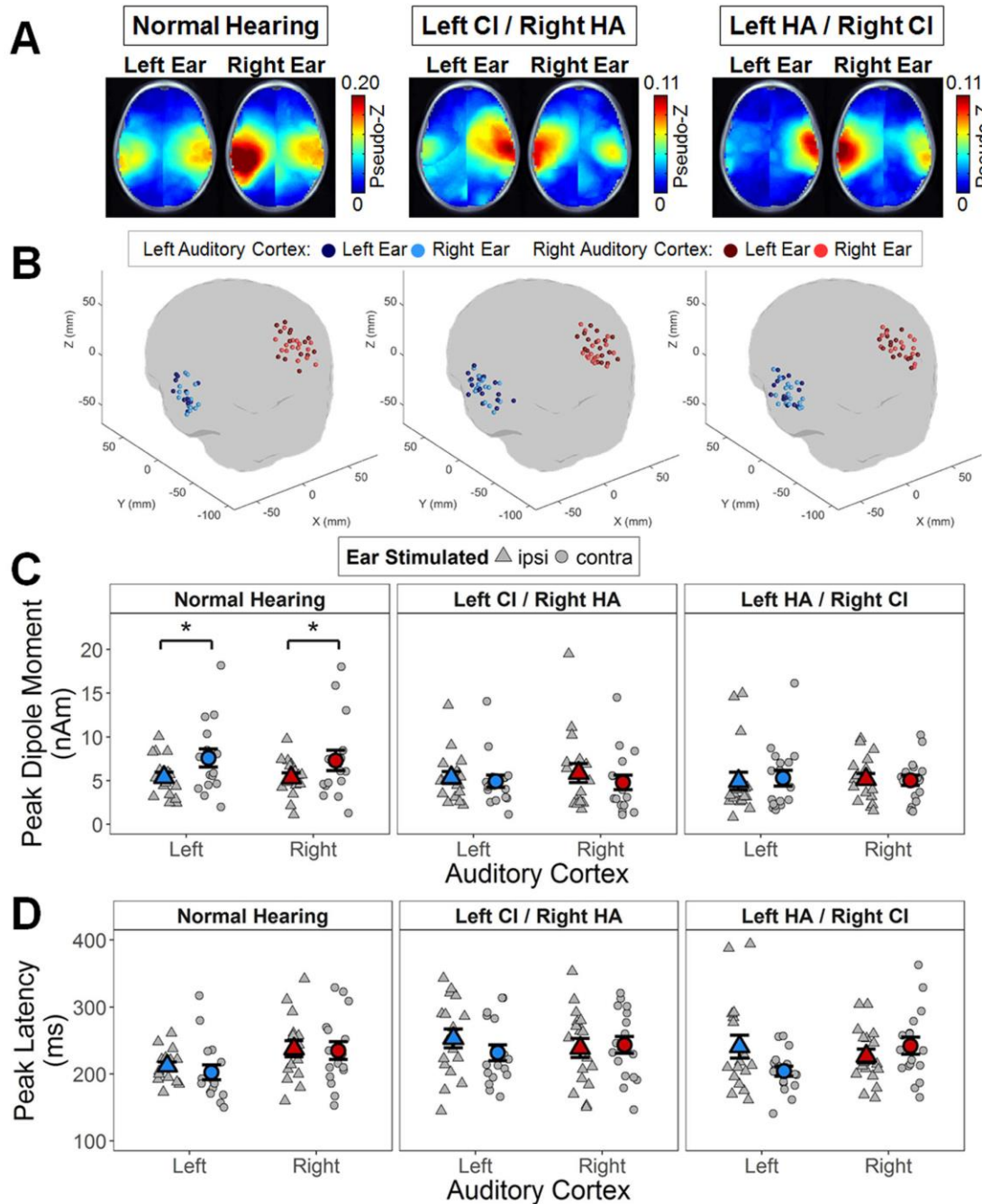
Supplementary Figure 4.1. Evoked source activity for N2.

(**A**) Axial views of each group mean omnibus-corrected pseudo-Z (higher signal-to-noise-ratio in red) maps show regions of activation during N2 upon stimulation of the left and right ears. Activity localized to both auditory cortices in all conditions and groups. (**B**) Peak dipoles in the auditory cortices were located at similar locations in the left (blue) and right (red) auditory cortices upon stimulation of the left (dark colour) and right (light colour) ear. For each group, the

mean ± SE (coloured) and individual (gray) maximum peak (**C**) dipole moments (nAm) and (**D**) latencies extracted from chosen voxels are shown for the left (blue) and right (red) auditory cortices upon stimulating the ipsilateral (ipsi; triangles) and contralateral (contra; circles) ear in each group. CI=cochlear implant; HA=hearing aid; * $p < 0.05$.

4.10.2 Some bimodal users with asymmetric hearing experience have abnormal preference for one type of stimulation

Aural preference was calculated for each cortex. On average, there were no cortex differences for N2 ($F(1,47) = 0.9$, $p = 0.35$). However, unlike P1, aural preference differed by group for N2 ($F(2,47) = 4.4$, $p = 0.02$). Specifically, when averaged across cortex, the contralateral aural preference exhibited in children with normal hearing was reduced in bimodal users, but only to a significant extent in those children with a left CI/right HA ($t(26.9) = 3.1$, $p = 0.01$), whose aural preference reversed to abnormally prefer the ipsilateral ear.

To further investigate whether the cortices of some bimodal users preferred one type of stimulation, aural preference was calculated for cortices ipsilateral to each type of device (e.g., ipsilateral to CI is the left cortex for children with a left CI) and plotted for each child in each group (**Supplementary Figure 4.2A**). Most children in the bimodal groups developed primarily contralateral aural preference in both cortices like their peers with normal hearing (**Supplementary Figure 4.2A**). However, 10 (29.4%) bimodal users developed abnormal preference in both cortices for one type of stimulation (**Supplementary Figure 4.2A**) ($n = 5$ for HA, $n = 5$ for CI). An additional two bimodal users developed abnormal ipsilateral aural preference in both cortices.

To evaluate how hearing histories impact this abnormal cortical development, multiple linear regressions were completed between aural preference and the pre- and post-implant hearing experience components identified by PCA, as well as the variables comprising these PCA components. Similar to during P1, aural preference of the cortex ipsilateral to the HA reversed to abnormally to prefer this better ear with greater pre-CI hearing experience component values (**Supplementary Figure 4.2B**), and with longer periods of asymmetric hearing prior to implantation (**Supplementary Figure 4.2D**). Although during P1 the cortex ipsilateral to the CI began to abnormally prefer the implanted ear with greater post-CI hearing experience component values and with longer implant experience, this was not significant for N2 (**Supplementary**

Figure 4.2C,E respectively). Findings were independent of which ear had the better hearing and maintained a HA (unstandardized β for bimodal group $p > 0.05$). Bivariate and partial R^2 values and the corresponding p-values are provided in **Supplemental Table 4.2**.

Supplementary Table 4.2. Multiple regression parameters for significant predictors of aural preference.

Cortex	Predictor	Bivariate		Partial		
		R^2	p-Value	R^2	p-Value	Adjusted p-Value
Ipsilateral to HA	Component: Pre-CI Hearing Experience	0.24	0.004	0.18	0.02	0.06
	Duration of Hearing Aid Use Before Implantation	0.10	0.06	0.05	0.20	0.26
Ipsilateral to CI	Component: Post-CI Hearing Experience	<0.01	0.70	0.01	0.58	0.58
	Duration of Implant Use	0.02	0.40	0.03	0.33	0.37
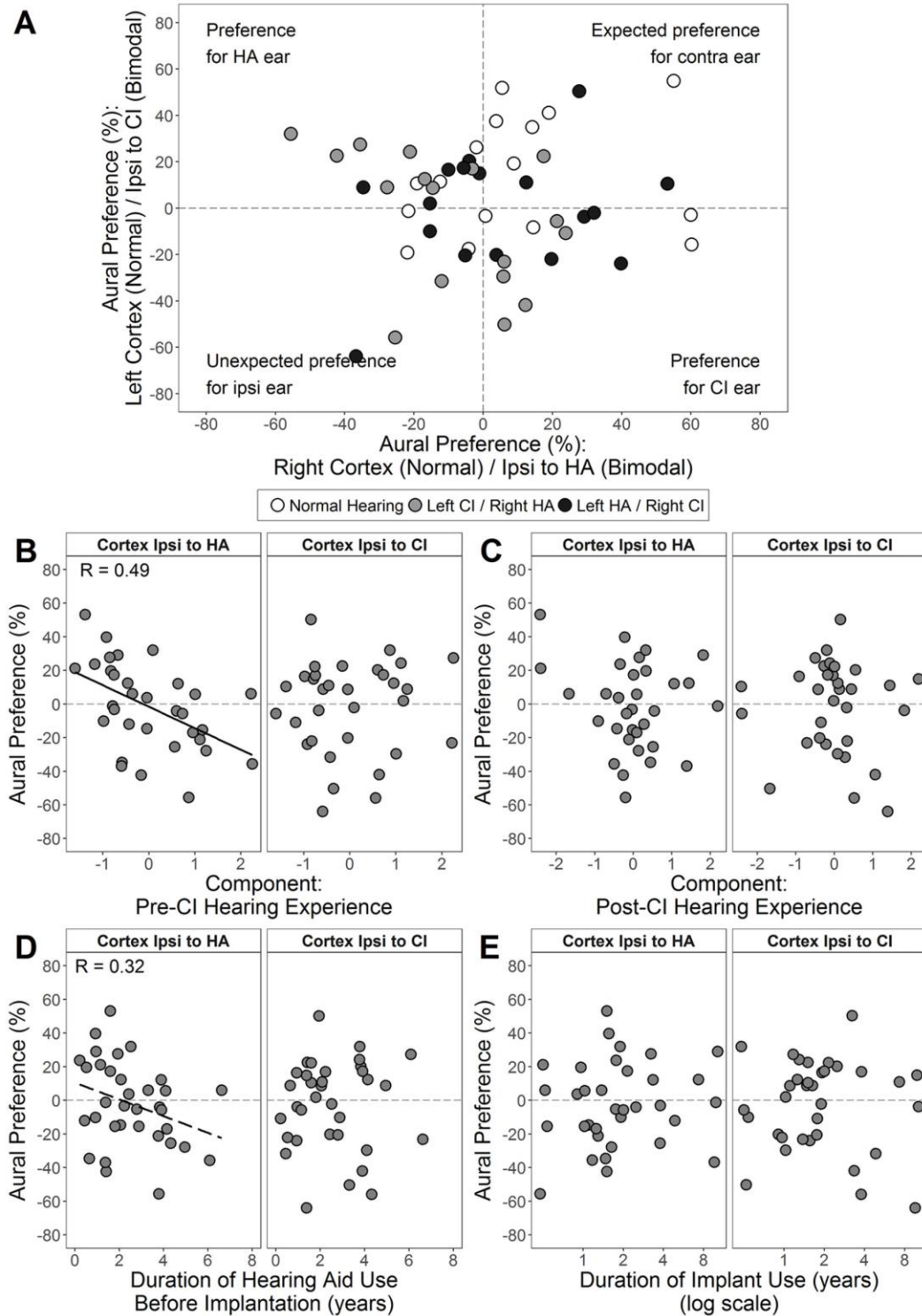
Supplementary Figure 4.2. Aural Preference for N2.

(**A**) Aural preference (%) for each auditory cortex is plotted for each child with normal hearing (white), a left cochlear implant (CI)/right hearing aid (HA) (gray), and a left HA/right CI (dark gray). For bimodal users, aural preference was calculated for cortices ipsilateral (Ipsi) to each

type of device to evaluate whether some children prefer one type of stimulation (e.g., Ipsi to CI is the left cortex for children with a left CI). Aural preference in bimodal users is then shown for the cortices ipsi to the HA and ipsi to the CI as a function of the pre- (**B**) and post- (**C**) implant hearing experience components identified by Principal Component Analyses (PCA), and as a function of (**D**) duration of HA use before implantation, and (E) duration of CI use. Positive values indicate preference for stimulation of the contralateral ear. Solid regression line: $p < 0.05$; dashed regression line: $p < 0.1$.
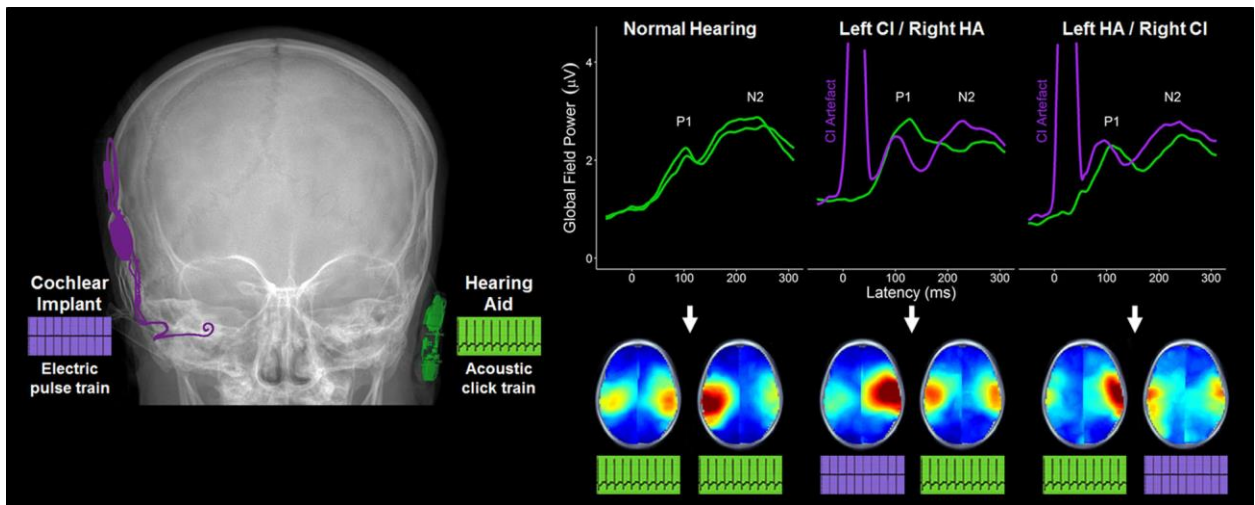
Supplemental Figure 4.3. Graphical abstract.

Cortical responses in Chapter 4 were only analyzed at one time point following a period (> 6 months) of bimodal use. Therefore, it is unclear whether abnormal cortical aural preference was initially present at time of implantation and did/could not change with bimodal use, or because the children did not wear or accept their device(s). Therefore, plasticity of the auditory cortices to bimodal stimulation was assessed in an additional two studies. In Chapter 5 plasticity of the auditory cortices to bimodal stimulation was assessed in an unusually homogeneous group of five young children (< 4 years of age) with normal right sided hearing who received a cochlear implant to treat deafness in their left ears. I was able to rule out device use/acceptance as a factor in this neuroplasticity by confirming consistent daily use through datalogging technology that was available in the external component of their cochlear implant (processors). In Chapter 6 I studied a slightly larger cohort of children with various degrees of residual hearing in their non-implanted ear.

5   Cortical Organization Restored by Cochlear Implantation in Young Children with Single Sided Deafness

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5.1   Abstract

Early treatment of single sided deafness in children has been recommended to protect from neurodevelopmental preference for the better hearing ear and from social and educational deficits. A fairly homogeneous group of five young children (≤ 3.6 years of age) with normal right sided hearing who received a cochlear implant to treat deafness in their left ears were studied. Etiology of deafness was largely cytomegalovirus ($n = 4$); one child had an enlarged vestibular aqueduct. Multi-channel electroencephalography of cortical evoked activity was

measured repeatedly over time at: 1) acute (0.5 ± 0.7 weeks); 2) early chronic (1.1 ± 0.2 months); and 3) chronic (5.8 ± 3.4 months) cochlear implant stimulation. Results indicated consistent responses from the normal right ear with marked changes in activity from the implanted left ear. Atypical distribution of peak amplitude activity from the implanted ear at acute stimulation marked abnormal lateralization of activity to the ipsilateral left auditory cortex and recruitment of extra-temporal areas including left frontal cortex. These abnormalities resolved with chronic implant use and contralateral aural preference emerged in both auditory cortices. These findings indicate that early implantation in young children with single sided deafness can rapidly restore bilateral auditory input to the cortex needed to improve binaural hearing.

5.2 Introduction

There are significant consequences of single sided deafness (SSD) in childhood on auditory development and function (Burton et al., 2012; Gordon et al., 2015; Schmithorst et al., 2014) but questions about treatment remain (Van de Heyning et al., 2016). In the present study, we examined whether cochlear implantation of the deaf ear in a fairly homogeneous group of five young children with normal or near-normal hearing in the other ear can restore expected organization of the auditory cortices.

The prevalence of childhood unilateral hearing loss is estimated to be 0.06 to 3.0% (Berninger and Westling, 2011; Bess et al., 1998), and has known developmental and educational consequences (Bess and Tharpe, 1984; Gordon et al., 2015; Lieu et al., 2010). These effects relate, in part, to poor spatial hearing (Arndt et al., 2015; Hassepass et al., 2013); indeed, unilateral listening in childhood reorganizes cortical areas involved in spatial awareness and attention (Easwar et al., 2017c; Jiwani et al., 2016; Schmithorst et al., 2014). Children with bilateral deafness who used one cochlear implant (CI) for some time prior to bilateral implantation are a unique group of single sided listeners who experience neurodevelopmental preference for the first/better hearing ear both in the brainstem (Gordon et al., 2007b, 2007c, 2012) and cortex (Gordon et al., 2013b). Similar findings are reported from kittens born with unilateral deafness (Kral et al., 2013b; Tillein et al., 2016) or experimentally induced unilateral/asymmetric hearing in young animals (Keating and King, 2013; Polley et al., 2013; Popescu and Polley, 2010). Such auditory asymmetries have consequences for processing

binaural timing and level cues (Hancock et al., 2013; Popescu and Polley, 2010) which are integral for locating and distinguishing one sound amongst many (Grothe et al., 2010). Importantly, bilateral cochlear implantation without delay protects from development of the "aural preference syndrome" (Gordon et al., 2013b). Thus, to avoid problems of single sided listening and preserve opportunities for binaural hearing, it has been recommended that hearing loss (unilateral or bilateral) be treated by providing the most appropriate device in each ear as soon as possible (Gordon et al., 2015).

Despite research-based recommendations, treatment in children with unilateral hearing loss has been inconsistent (Van de Heyning et al., 2016). In the case of SSD where an auditory nerve is present, a CI is arguably the most appropriate device to stimulate the impaired ear (Arndt et al., 2017; Tokita et al., 2014; van Zon et al., 2015) but this is not the present standard of care. Potential for success is suggested by benefits of electrical stimulation from a CI in one ear and amplified acoustic input through a hearing aid contralaterally ("bimodal" listening) in children with asymmetric hearing (Ching et al., 2007; Mok et al., 2007; Nittrouer and Chapman, 2009; Straatman et al., 2010) and from adults with SSD who were implanted to treat disruptive tinnitus in the deaf ear (Tokita et al., 2014; van Zon et al., 2015). Benefits for listening to speech in noise are realized over listening with the unimplanted ear alone and increase as the duration of deafness decreases (Arndt et al., 2017). Early studies of implantation in children with SSD show early signs of benefit (Arndt et al., 2015; Greaver et al., 2017; Hassepass et al., 2013; Rahne and Plontke, 2016; Tavora-Vieira and Rajan, 2016; Thomas et al., 2017) and one case report in an older child suggests the potential for longitudinal changes in crossmodal plasticity (Sharma et al., 2016). To understand the functional outcomes and define an optimal period for implantation in SSD, it is essential to address whether expected function in bilateral auditory pathways can be restored during early important developmental periods.

In the present study, plasticity of the neural input to auditory cortices was measured to assess whether expected representation can be restored by providing electrical stimulation from a CI in one ear with normal hearing in the other ear in early development. Results in a group of young children (≤ 3.6 years) who were deaf in their left ears from infancy demonstrate marked and rapid uptake of input from the newly implanted ear, restoring symmetric representation of both ears in the auditory brain.

5.3 Methods

5.3.1 Participants

Five children (3 male) with normal or near-normal hearing in their right ears (pure-tone average of .5, 1, 2 kHz, PTA: mean $\pm$ SD = 17.7 $\pm$ 4.8 dB HL, range = 15.0 – 25.0 dB HL) and severe to profound deafness in their left ears (PTA: 109.3 $\pm$ 18.1 dB HL, range = 78.3 – 120.0 dB HL) participated in the present study. Hearing thresholds were obtained 1.9 $\pm$ 0.9 months (range: 1.0 – 2.9 months) prior to implantation at age 2.8 $\pm$ 1.0 years (range: 1.0 - 3.4 years old) using visual reinforcement (S1, S3, S5) or play (S2, S4) audiometry with insert earphones. The decision to implant children with single-sided deafness (SSD) in our program has been a multi-stage process involving families and the multi-disciplinary cochlear implant team. A more detailed accounting of the factors involved in our population of children presenting with SSD has recently been reported (Sokolov et al., 2017). The children included in the present study were the first 5 with early onset single-sided deafness to undergo cochlear implantation in our program. Parental written informed consent was obtained for all participants according to study protocol #1000002954 approved by the Hospital for Sick Children Research Ethics Board. Four of five children were diagnosed with congenital cytomegalovirus (cCMV) based on presence of CMV DNA detected by PCR of the neonatal dried bloodspot ($n = 3$) or cCMV associated white matter changes on MRI ($n = 1$). MRI revealed an enlarged vestibular aqueduct (EVA) on the left side for the other child (S2). Four children were referred to our clinic once unilateral deafness was detected through neonatal hearing screening and upon parental concern in one child with cCMV (S3). Candidacy for cochlear implantation was determined by the multidisciplinary CI team based on protocols established in children with bilateral hearing loss (Daya et al., 1999; MacDonald et al., 2004). Implantation of the left ear occurred at 1.1 years of age in one child (S5) and between 3.3 and 3.6 years (3.4 $\pm$ 0.1 years) in the other four children.

Daily use of the CI was confirmed by datalogs available from the CI speech processor. Complete datalog data were available for four of the five children (previously reported by Polonenko et al., 2017c); datalog data was only available at one time (chronic stimulation) for S1. Because it is typically difficult to obtain or measure behavioral changes to speech during early stages of cochlear implant use in young children (Thomas et al., 2017), auditory function and plasticity were monitored using electrophysiology.

5.3.2 Electrophysiology

EEG measures were recorded at three time points: 1) acute stimulation (0.5 ± 0.7 weeks of implant use); 2) early chronic stimulation (1.1 ± 0.2 months of implant use), and 3) chronic stimulation (5.8 ± 3.4 months of implant use). Recording was missed at the second time point (early chronic stimulation) for one child (S1) due to scheduling conflicts. Stimuli were 36 ms trains of acoustic clicks (100 µs) delivered at 250 Hz via an insert earphone to normal hearing ears or electric biphasic pulses (57 µs pulse-width) delivered at 250 Hz via an L34 processor to an apical electrode (#20) of the CI. These trains of stimuli were presented at 1 Hz. Levels were confirmed by maximum auditory brainstem response (ABR) wave V/eV amplitude to ensure similar activation of both ears at the upper part of the dynamic range (loud but comfortable) (Jiwani et al., 2016; Polonenko et al., 2015). Electrical fields of cortical activity were recorded across 64 channels and common referenced. Time windows containing amplitude peaks of activity were evaluated using the time-restricted artefact and coherent source suppression (TRACS) beamforming method (Easwar et al., 2017c; Gordon et al., 2013b; Jiwani et al., 2016; Wong and Gordon, 2009). Briefly, the linearly constrained minimum variance type beamformer suppressed 97% of the CI artefact corresponding to the largest four singular vector values between -80 to 10 ms (Wong and Gordon, 2009) before localizing activity evoked by the implanted ear. Age-dependent head geometry and tissue conductivities were accounted for when calculating lead potentials for 63,307 3x3x3 mm voxels using a boundary element model mesh that was constructed from age-appropriate Montreal Neurologic Institute (MNI) head model templates generated using the Template-O-matic toolbox (Wilke et al., 2008). Activity in each hemisphere was evaluated by suppressing the other hemisphere (Dalal et al., 2006). Peak activity in both the left ($X \leq -55$ mm) and right ($X \geq 55$mm) auditory cortical areas ($-35 \leq Y \leq 5$; $-10 \leq Z \leq 20$) were analysed. Maximum dipole moment (nAm) and latency were extracted for all voxels, and the voxel with the largest signal-to-noise ratio (pseudo-Z (Vrba and Robinson, 2001)) above a statistical baseline threshold of noise (one-tailed omnibus-noise T-test (Petersson et al., 1999)) in both auditory cortical areas was chosen. Consistency of coordinates and peak dipole moments and latencies were verified in the top 10 voxels with highest pseudo-Z values in these defined regions.

5.3.3 Statistical analysis

Group surface activity was analyzed using repeated measures ANOVA. Given the progressive increase in follow up intervals, duration of CI use at testing was log-transformed. This log transformation permitted linear regression while preserving the effective non-linear relationship. As frequently used in biomedical sciences (e.g., Baayen et al., 2008; Miller et al., 2017; Polonenko et al., 2017c; Uchida et al., 2016), linear mixed effects regression (Mcculloch and Neuhaus, 2006) with random intercept and slope for each child was conducted with the *lme4* package (Bates et al., 2015) to evaluate individual changes in daily CI use and source cortical activity with log-transformed duration of CI use while controlling for repeated values from the same child. Significance of the regression was determined using a likelihood ratio test. Repeated measured ANOVA was used to analyze average daily CI use across environments with different level ranges in dB A.

5.3.4 Data availability

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

5.4   Results

All children were followed over their first six months of CI use. Daily use of the CI (mean $\pm$ SD = 7.1 $\pm$ 0.7 hours/day) was confirmed by datalogs available from the CI speech processor (**Figure 5.1A**). One child (S5) showed few hours of average daily CI use at the first 2 test times; however, this child experienced frequent disconnections between the external and internal equipment (36.2 $\pm$ 11.0 times per day), as previously reported in young CI users (Easwar et al., 2016; Polonenko et al., 2017c), accounting for an additional 5.4 $\pm$ 1.7 hours/day that the CI was worn. Daily CI use in the 4 children with complete data did not vary with CI experience ($\chi^2(1) =$ 0.3, $p = 0.61$). This time was mostly spent in environments with moderate sound levels (50 - 70 dB A) (level: $F(5,15) = 18.6$, $p < 0.001$) at all three time points (time: $F(2,6) = 0.5$, $p = 0.62$; level x time: $F(10,30) = 0.2$, $p = 1.0$) (**Figure 5.1B**), consistent with datalogging information from a cohort of seven children with SSD (Polonenko et al., 2017c).
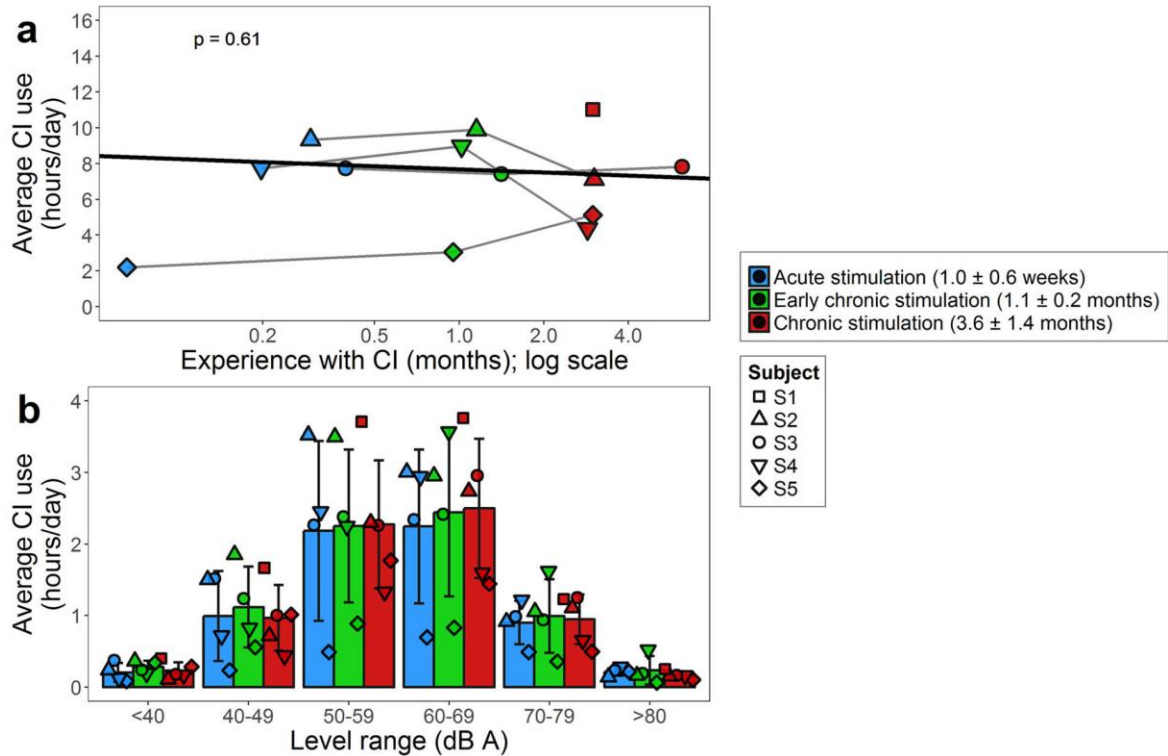
Figure 5.1. Evidence of chronic stimulation from datalogging information collected from the children's cochlear implant processors.

(**A**) The total average number of hours per day that each child used their cochlear implant (CI) is plotted against duration of CI experience (symbols connected with gray lines). Colours indicate the time points closest to the test time points that datalogs were collected, and the black line indicates the full linear mixed model based on $n = 4$ and log-transformation of CI use. (**B**) Average daily CI listening $\pm$ SD was predominantly at 50 - 69 dB A across time points. Datalogs were available for 4 children at all time points. A fifth child (S1) had one datalog at chronic stimulation ($n = 5$ at this time point). Data from four of the five children were also included in (Polonenko et al., 2017c).

Longitudinal cortical recordings were successfully completed after CI activation. Two amplitude peaks (P1, N2) were identified in the mean global field power responses (**Figure 5.2A**, mean $\pm$ 1SD latency and amplitude are indicated). Electrical artefact from the CI is clear during stimulus presentation (0 to 36 ms) in the left ear (blue) responses. There was no significant change in P1 or N2 amplitude (P1: time: $F(2,22) = 0.3$, $p = 0.74$; ear: $F(1,22) = 0.3$, $p = 0.58$; time x ear: $F(2,22) = 0.2$, $p = 0.80$; N2: time: $F(2,22) = 1.9$, $p = 0.18$; ear: $F(1,22) = 0.2$, $p = 0.67$; time x

ear: $F(2,22) = 0.6$, $p = 0.54$) or latencies (P1: time: $F(2,22) = 3.1$, $p = 0.07$; ear: $F(1,22) = 2.5$, $p = 0.13$; time x ear: $F(2,22) = 0.2$, $p = 0.84$; N2: time: $F(2,22) = 2.9$, $p = 0.08$; ear: $F(1,22) = 2.0$, $p = 0.17$; time x ear: $F(2,22) = 2.2$, $p = 0.14$) over time for either the hearing or CI ear. Opposite polarities of P1 (frontal positive) and N2 (frontal negative) are largely consistent from the normal hearing ear in topographical plots over time (**Figure 5.2B**). By contrast, the left CI evoked an abnormally frontal negative P1 and frontal positive N2 with acute stimulation, which normalized at early chronic stimulation (**Figure 5.2B**). Source activation for P1 evoked by the right normal hearing ear (**Figure 5.2C**) indicated a consistent hotspot (high pseudo-Z signal-to-noise ratio in red) in the left temporal lobe at all times. Acute CI stimulation evoked a small region of activation in the right temporal cortex with high left frontal activity. At early chronic stimulation, this latter cortical response reduced with small hotspots of activity in both temporal lobes. With chronic CI exposure, activity became focused in the contralateral right temporal lobe.
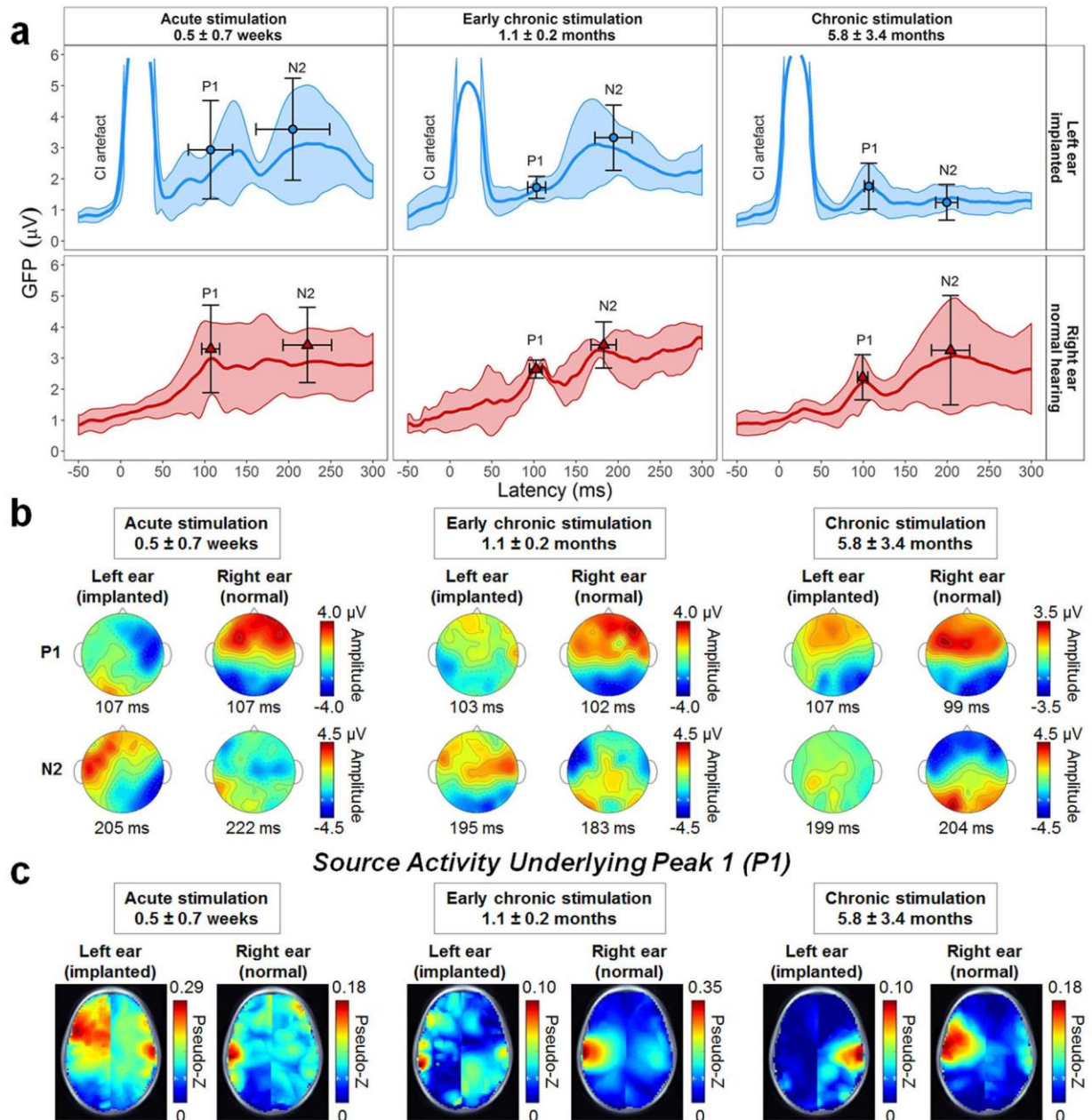
Figure 5.2. Surface recordings and source locations over time of CI stimulation: acute (initial activation week), early chronic (1 month), chronic (6 months).

(**A**) Mean (solid line) ± SD (shaded region) global field power (GFP) as a function of post-stimulus time for each ear. The cochlear implant (CI) artefact is visible during stimulation presentation (0 – 36 ms), which occurred at latencies earlier than peaks P1 and N2. Mean ± 1SD of P1 and N2 peaks identified from each child's GFP are indicated by symbols and errorbars. There were no significant changes (*p* > 0.05) in either peak amplitudes or latencies over time. (**B**) Topographical distributions of mean average-referenced surface responses at these mean peak

latencies of P1 and N2. Opposite frontal-posterior polarities for P1 and N2 are evident for stimuli presented to the right normal hearing ear in all three recordings. Responses from the left ear CI were reversed in polarity at the first recording but the subsequent two recordings revealed frontal-positive activity for both P1 and N2. (**C**) Axial views of mean source activity in each of the 63,307 3x3x3 mm voxels (higher signal-to-noise pseudo-Z ratio in red) show widespread regions of activation underlying P1 for both the implanted and normal hearing ears upon acute stimulation. Activity became localized primarily to temporal lobes with chronic CI use. Because one child (S1) had missing data for the second visit, all measures for both P1 and N2 had $n = 5$ for acute and chronic stimulation; $n = 4$ for early chronic stimulation.

Peak dipoles were measured from the voxels with the highest pseudo-Z in left and right auditory cortices (locations in **Figure 5.3A**). Chosen voxels varied around the mean location for each cortex by 15.4 ± 5.5 mm and there was no significant change in voxel location over time (ear: $F(1,7) = 0.0, p = 0.85$; time: $F(2,14) = 1.5, p = 0.25$; coordinate: $F(2,14) = 1.1, p = 0.34$; ear x time x coordinate: $F(4,28) = 0.8, p = 0.45$). Peak dipole moments did not significantly change with CI stimulation in either auditory cortex for either the normal right ear (Left Cortex: $\chi^2(1) = 0.09, p = 0.49$; Right Cortex: $\chi^2(1) = 0.007, p = 0.93$) or left CI ear (Left Cortex: $\chi^2(1) = 0.87, p = 0.35$; Right Cortex: $\chi^2(1) = 0.48, p = 0.49$).
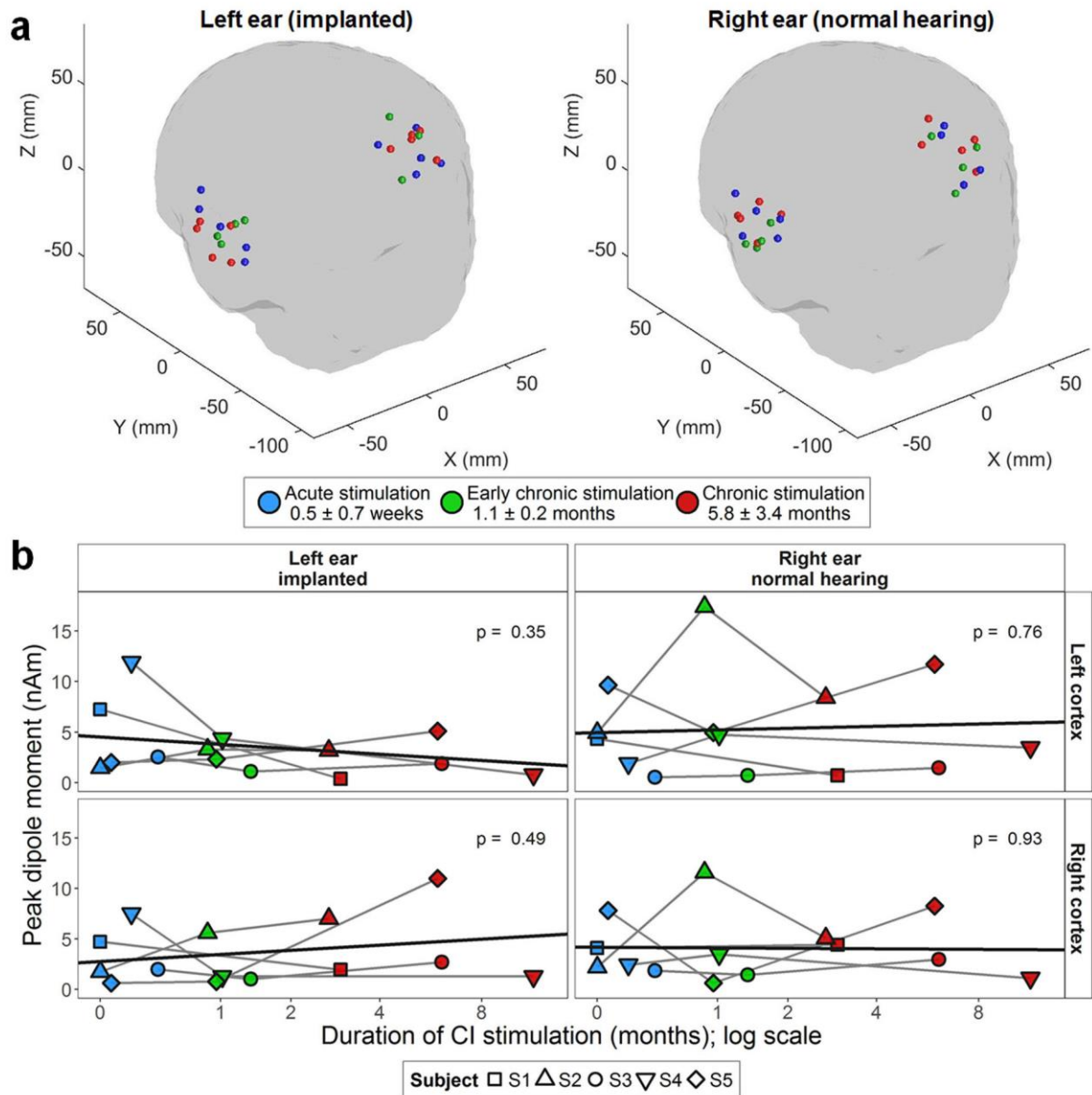
Figure 5.3. Peak dipole moments in the auditory cortices underlying P1.

(**A**) Peak dipoles were located at similar locations for both the left implanted and right normal hearing ears over time. (**B**) Peak dipole moments for each ear and cortex individually varied somewhat with CI experience but there were no overall changes for right ear stimulation or left CI stimulation ($p > 0.05$). Symbols connected by gray lines indicate individual data, and the black line indicates the full linear mixed effects model using log-transformed CI use as a predictor. Data was missing from one child (S1) at early chronic stimulation, which had $n = 4$. Both acute and chronic stimulation time points had $n = 5$. Colours indicate test visits: acute (blue), early chronic (green), and chronic (red) CI stimulation.

Differences in dipoles between the left and right auditory cortices for each ear in each child were calculated as: Cortical Lateralization = 100 x [right cortex – left cortex] / [right cortex + left cortex]. Four children exhibited an unexpectedly large ipsilateral lateralization of cortical activity in response to the new left CI at acute stimulation and with early chronic CI use (**Figure 5.4A,B**). A significant shift in lateralization to the expected contralateral right cortex was realized with chronic CI use in all children ($\chi^2(1) = 7.6$, $p = 0.006$). Lateralization from the normal right ear was initially variable for the group (contralateral left ($n = 2$), bilateral ($n = 2$), and abnormal ipsilateral ($n = 1$)) but consistent for each child over time ($\chi^2(1) = 0.003$, $p = 0.96$). Cortical lateralization from both ears, plotted for each child at initial CI use (two early time points) and after chronic CI stimulation (**Figure 5.4B**), reflects the change in distribution from abnormal to expected contralateral cortical lateralization after chronic stimulation, particularly in responses from the CI left ear.

The aural preference of each auditory cortex (Aural Preference = 100 x [contralateral ear – ipsilateral ear] / [contralateral ear + ipsilateral ear]) was variable at acute stimulation (**Figure 5.4C**) with abnormal ipsilateral preference for the CI in the left cortex for three of five children. Data plotted from both cortices in each child (**Figure 5.4D**) reveals abnormal aural preference bilaterally for either the CI or normal hearing ear at the first two time points, resolving with chronic CI use to expected contralateral aural preference in both cortices. Interestingly, three children showed an unexpected preference for the new CI ear (**Figure 5.4D**) at acute stimulation and the other two children showed a preference for the normal hearing right ear in both auditory cortices. This likely reflects the abnormal distribution of frontal negative activity initially evoked by the CI (**Figure 5.2B**) and associated ipsilateral cortical lateralization (**Figure 5.4A**). After early chronic stimulation, preference for CI stimulation reduced and a trend for aural preference for the normal hearing ear emerged ($n = 2$). After chronic CI use, a distribution of expected contralateral aural preference had been established in both auditory cortices.
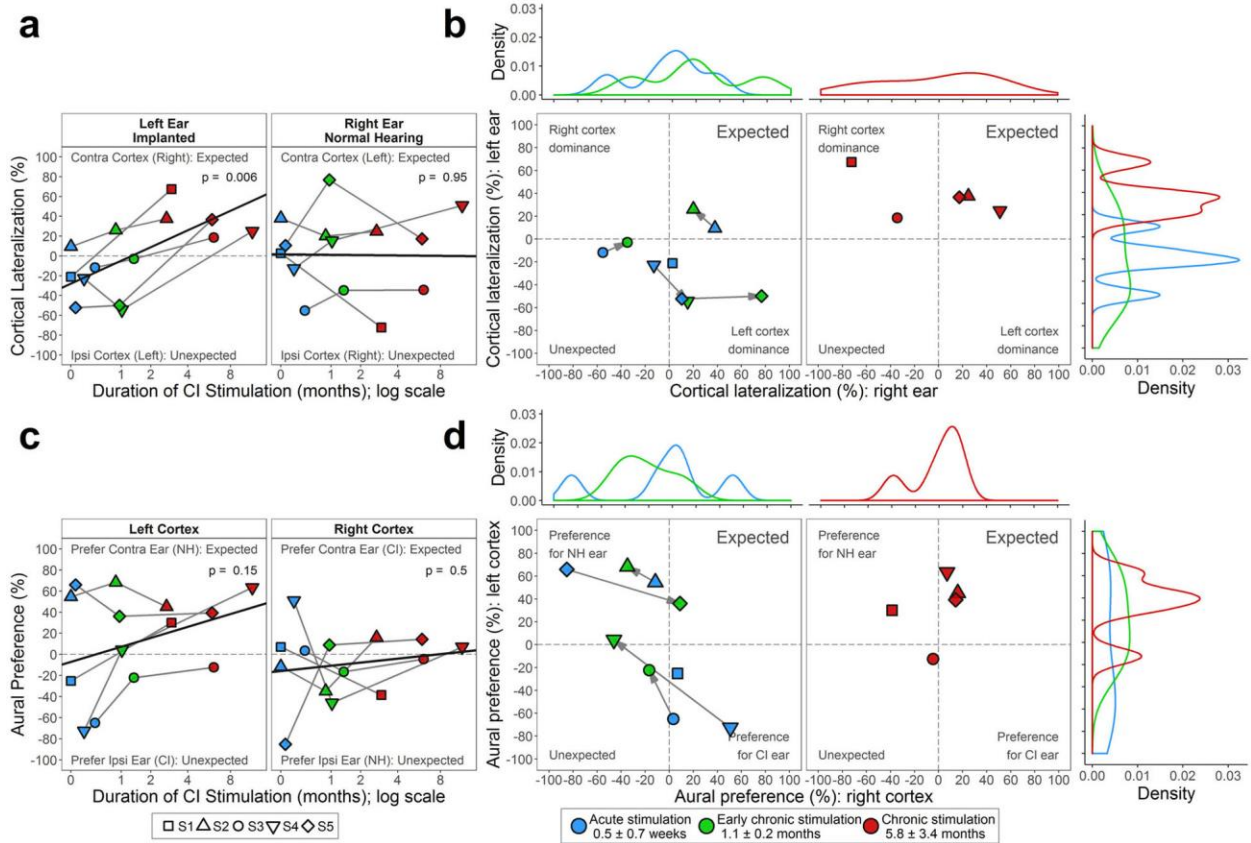
Figure 5.4. Abnormal cortical activity reverses with chronic CI stimulation.
(**A**) Stimulation of the new left implanted ear revealed abnormal cortical lateralization (weighting) to the ipsilateral (left) cortex, which reversed towards the right cortex with chronic CI stimulation ($p < 0.05$). (**B**) Stimulation of the normal hearing ear revealed expected cortical lateralization to the contralateral left cortex in three of five children, which remained consistent with time. As a result, a distribution of expected cortical lateralization from both ears to the contralateral auditory cortex emerged after ~6 months. (**C**) Each cortex abnormally preferred stimulation from the ipsilateral ear in most children with acute stimulation, but tended to reverse towards preferring contralateral stimulation with CI stimulation ($p < 0.05$). (**D**) Both cortices preferred stimulation from only one ear at early time points. Distribution of preference for the expected contralateral ear emerged in both cortices by ~6 months.

5.5 Discussion

Cortical recovery from SSD occurred rapidly in a small but relatively homogenous group of young children (≤ 3.6 years old) who consistently wore their CI for several hours daily. Unexpected cortical responses to acute CI stimulation were characterized by abnormal distribution over the surface of the head (frontal negative for P1 and positive for N2), corresponding to high activity both within the defined temporal auditory areas and beyond in areas including the left frontal cortex. The extra-temporal activity identified in these five young children is consistent with a recent case study (Sharma et al., 2016) and may reflect recruitment of the arousal and attention network (Kane and Engle, 2002) for early stage cortical processing of sound. Thus, the naiveté of the ear coupled with the atypical input delivered by the CI induced heightened cortical reactions at the initial test. With chronic CI use, responses normalized with a marked reduction in extra-temporal activity.

Auditory immaturity of the deaf ear resulted in asymmetric input to both auditory cortices at early stages of CI use. Consistent activity levels (dipoles) in auditory cortices were evoked over time but intra-subject measures indicated a shift with CI use from abnormal toward expected contralateral cortical lateralization from each ear and to expected contralateral aural preference in each auditory cortex. Thus, excitatory inputs from the deaf ear are preserved but initially reduced in number and/or strength (Tillein et al., 2016). Similar results occurred with unilateral implant use in children with bilateral deafness (Gordon et al., 2013b; Jiwani et al., 2016); importantly, those abnormalities often did not resolve despite several years of bilateral use and were associated with asymmetric speech perception (Gordon et al., 2013b). By contrast, repeated measures in the present cohort of young children reveal remarkable developmental plasticity within a 6 month period likely attributable to both the relatively early stage of cortical development, during which synaptogenesis may still be possible (Huttenlocher and Dabholkar, 1997), and the relatively short duration of unilateral deprivation to cells expecting binaural input (Hancock et al., 2013, 2010; Tillein et al., 2016).

Behavioral data in young children at such an early stage of device use were not possible to obtain but findings from children with longer term bilateral implant experience suggest that protection of bilateral pathways will promote symmetric speech perception (Gordon et al., 2013b; Gordon and Papsin, 2009). This is particularly important in light of the high incidence of cCMV and

EVA as etiologies of SSD (Arndt et al., 2015) which come with a risk of progressive loss of hearing in the normal ear (Gopen et al., 2011; Lanzieri et al., 2017). Benefits of implantation to spatial hearing have been reported in older children with SSD (Arndt et al., 2015; Hassepass et al., 2013; Thomas et al., 2017) but could be improved with better integration of bimodal input and preservation of binaural cues than presently possible (Polonenko et al., 2015; Reiss et al., 2014b, 2015; Zirn et al., 2015). Binaural disruptions by spectral cues coming from the pinna (outer ear) on only one side also need to be resolved. Importantly, the present findings demonstrate that bilateral pathways are available for these future efforts to promote binaural hearing when young children with SSD are provided with cochlear implants.

In conclusion, cochlear implantation in young children with SSD effectively treats unilateral deafness by promoting bilateral auditory development. This gives an unparalleled opportunity to advance opportunities to promote binaural hearing in children deprived of this important spatial information.

5.6   Acknowledgments

5.7   Author contributions

KG and MP wrote the main manuscript text and MP prepared the figures. MP, KG, SC, and BP reviewed and revised the manuscript.

5.8   Conflicts of interest

None to declare.

5.9   Supplemental Information
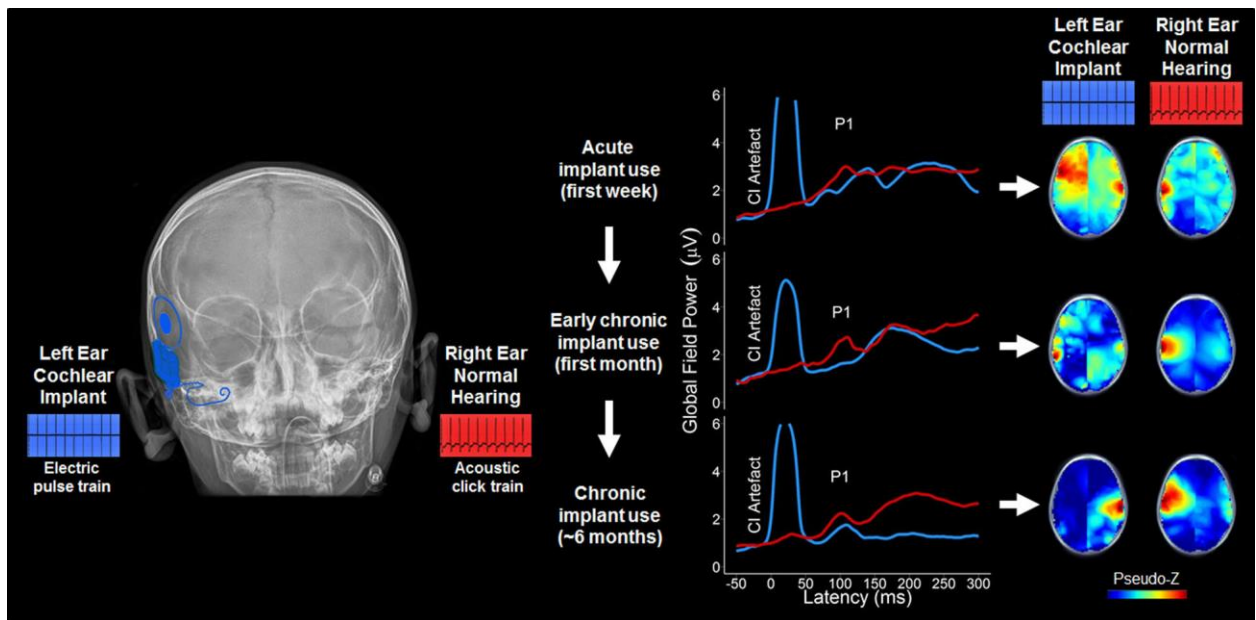
Supplemental Figure 5.1. Graphical abstract.

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Chapter 6
Paper 4

</div>

It remained unclear from Chapter 5 whether the initially abnormal cortical responses were unique to children with normal hearing in the non-implanted ear or more broadly extend to children with various degrees of asymmetric hearing loss. Therefore, in Chapter 6 I expanded our cohort to study cortical neuroplasticity in 10 children with various degrees of residual hearing in their non-implanted ear.

6 Cortical Plasticity with Bimodal Use in Children with Asymmetric Hearing loss

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Polonenko, M.J., Papsin, B.C., & Gordon, K.A. (2018). Cortical plasticity with bimodal use in children with asymmetric hearing loss. Hearing Research, 2018; in press.1-11. doi: 10.1016/j.heares.2018.02.003.

6.1 Abstract

This longitudinal study aimed to identify auditory plasticity promoted by a cochlear implant in children with asymmetric hearing loss. Participants included 10 children who experienced (mean $\pm$ SD) 3.1 ± 3.6 years of asymmetric hearing (difference of 47.2 ± 47.6 dB) before receiving an implant at age 8.7 ± 5.1 years. Multi-channel electroencephalography was measured at initial implant use (5.8 ± 3.2 days) and after 10.2 ± 4.1 months in each child. Monaurally presented stimuli consisted of 36 ms trains of 9 acoustic clicks/biphasic electric pulses at a rate of 250 Hz, repeated at 1 Hz. The time-restricted artifact and coherent source suppression (TRACS) beamformer was used to locate sources underlying peak amplitudes of cortical responses. Results indicated consistent activity from the non-implanted ear but significant implant-driven changes to the auditory cortices. Initially, the newly implanted ear evoked activity which strongly lateralized to the ipsilateral auditory cortex and contributed to a significant aural preference for implant stimulation in children with limited acoustic experience pre-implantation. Cochlear implant use reversed these abnormalities, but the resolution was limited in children with longer periods of asymmetric hearing. These findings suggest that early implantation of children with

asymmetric hearing rapidly restores hemispheric representations of bilateral auditory input in the auditory cortex. Most recorded changes were isolated to pathways stimulated by the cochlear implant, potentially reflecting an abnormal independence of the bilateral pathways with possible consequences for binaural integration in these bimodal listeners.

6.2 Introduction

Children with asymmetric hearing loss were not traditionally considered to be cochlear implant candidates in their deaf ear because they have access to sound in their better hearing ear with or without a hearing aid. Yet, without adequate hearing from one side, they do not have access to bilateral hearing, increasing their listening difficulties and putting them at risk for educational challenges (Kuppler et al., 2013; Lieu et al., 2013, 2010). In the present study, we examined auditory plasticity of bilateral input to the cortex in a cohort of children with asymmetric hearing who received a cochlear implant. Cortical changes were monitored repeatedly during the first year of implant use.

Bimodal hearing (acoustic and electrical stimulation of the auditory system) in children has been previously explored when provided in the same ear (Gantz et al., 2016; Skarzynski et al., 2014; Wolfe et al., 2017) and when provided bilaterally (acoustic input with or without a hearing aid in one ear and electrical hearing through a cochlear implant in the other ear) (Ching et al., 2007, 2005, 2001; Chmiel et al., 1995; Dettman et al., 2004; Litovsky et al., 2006; Luntz et al., 2005). Most reports have described bimodal hearing in children with severe to profound hearing loss and a few recent studies have investigated hearing abilities in children with better residual hearing in the non-implanted ear (Arndt et al., 2015, 2017; Cadieux et al., 2013; Polonenko et al., 2015, 2017b, 2018a; Ramos Macias et al., 2016). In general, even limited input provided by a hearing aid in the non-implanted ear benefits speech perception in quiet and noise, sound localization and oral communication (Ching et al., 2007; Mok et al., 2010, 2007; Nittrouer and Chapman, 2009; Straatman et al., 2010). These findings reflect the challenges of listening with one ear which are eased, however slightly, by providing some degree of bilateral hearing.

Impairments to bilateral hearing are particularly pronounced in children who are deaf in both ears and use one cochlear implant. This form of single sided hearing promotes reorganization in the auditory system during sensitive developmental periods. Pathways from the stimulated ear are strengthened in both animal models (kittens) (Kral et al., 2013a, 2013b; Tillein et al., 2016)

and children (Gordon et al., 2013b), becoming more strongly represented in both auditory cortices. Additional cortical areas are also recruited to support hearing (Jiwani et al., 2016). At the same time, deprivation of the opposite ear arrests development in ascending pathways from that side and could increase the possibility of pathways from this ear decoupling from the auditory network or connectome (Jiwani et al., 2016). These changes impair later efforts to restore typical cortical responses by stimulating the deprived ear and establish binaural hearing, as shown by persistent aural preference for the first implanted ear despite many years of bilateral cochlear implant use (Gordon et al., 2013b). Similar changes in the developing inferior colliculus and primary auditory cortices have been shown in animal models even when the unilateral hearing loss is mild and reversible (Keating and King, 2013; Polley et al., 2013; Popescu and Polley, 2010). Importantly, increased aural preference for the better hearing ear compromises binaural processing in the auditory cortex (Easwar et al., 2017c, 2017b, 2018) which could help to explain why children with bilateral cochlear implants have impaired fusion of bilateral input (Steel et al., 2015) and poor spatial hearing (e.g., Chadha et al., 2011; Ehlers et al., 2017; Gordon et al., 2014; Litovsky et al., 2010). Restricting the duration of unilateral listening to less than 2 years protects children from persistent aural preference (Gordon et al., 2013b; Polonenko et al., 2018a) but it was not clear from those data whether aural preference was recovered or had never occurred. In a recent study (Chapter 5), longitudinal recordings in a small but fairly homogenous group of young children (< 4 years old) who had single sided deafness revealed that short periods of aural preference can be reversed. A large response from the newly implanted ear quickly subsided with implant use, revealing aural preference for the normal hearing ear; with longer implant experience, more symmetric representation of input from ears was evident in cortical responses (Polonenko et al., 2017b). It remains unclear whether these initially abnormal responses are unique to children with normal hearing in the non-implanted ear or more broadly extend to children with various degrees of asymmetric hearing loss.

Children with asymmetric hearing loss are at risk for experiencing aural preference for their better ear because, despite having a profoundly deaf ear, they were not traditionally considered candidates for cochlear implantation. Recently, however, a large cohort of children with asymmetric hearing who received a cochlear implant were followed and showed typical cortical representation from both ears after ~2 years of bimodal use (Polonenko et al., 2018a). Nonetheless, aural preference for the non-implanted ear persisted in those children whose

cochlear implantation was delayed relative to the onset of their asymmetric hearing loss. Because testing was only completed after bimodal use, it was unclear whether the normal findings in the majority of children reflected normal cortical development or, rather, a reversal of aural preference for the better ear due to early cochlear implantation. Longitudinal measures completed in a similar but smaller cohort of children allowed us to address this question in the present study. Our hypotheses were that children with asymmetric hearing loss who receive a cochlear implant exhibit: 1) abnormal cortical preference for the deprived ear at initial cochlear implant activation and 2) reversal to contralateral cortical representation with chronic cochlear implant stimulation and continued acoustic hearing in the other ear (bimodal listening), dependent on the duration and extent of asymmetric hearing prior to implant.

6.3   Methods

6.3.1 Participants

Ten children with asymmetric hearing loss (mean ± SD difference = 47.2 ± 47.6 dB) were recruited who were implanted at age 8.7 ± 5.1 years after a period of 3.1 ± 3.6 years of asymmetric hearing. All but one child received an implant in the left ear. Many children had residual low frequency hearing in the implanted ear (250Hz: 53.1 ± 42.9, 500Hz: 74.5 ± 42.5 dB HL). Unaided and aided hearing thresholds are provided in **Figure 6.1**. Of 10 children, 6 had asymmetric hearing loss and 4 had good low frequency but poor high frequency hearing loss bilaterally (**Figure 6.1**). Etiologies of hearing loss included congenital cytomegalovirus ($n = 3$), genetic mutation ($n = 2$) and unknown ($n = 5$). Further demographic details are provided in **Table 6.1**. Parental written informed consent was obtained for all participants according to study protocol #1000002954 approved by the Hospital for Sick Children Research Ethics Board.
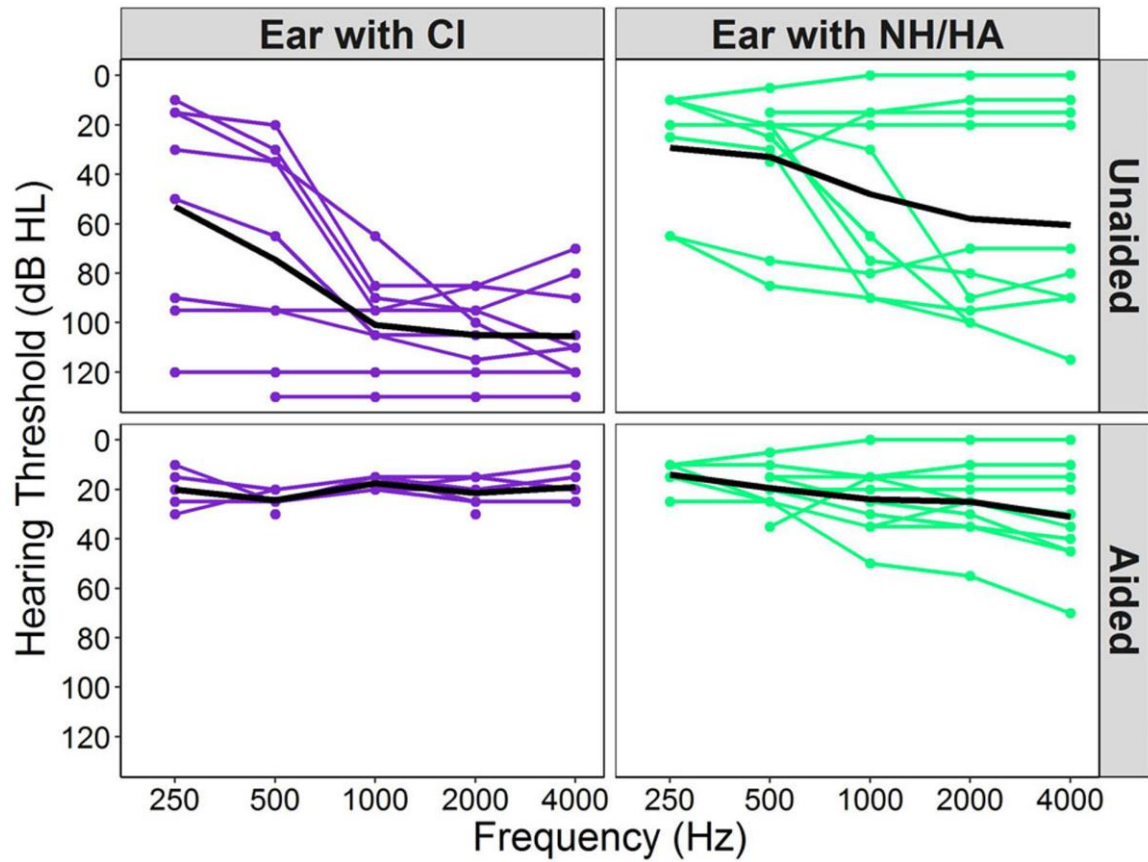
Figure 6.1. Pre- and post-implantation hearing thresholds.

Pre-implantation unaided (top row) and post-implantation aided (bottom row) hearing thresholds in the non-implanted ear (green) with normal hearing (NH) or a hearing aid (HA) and the ear with a cochlear implant (CI) (purple). Of 10 children, 6 had asymmetric hearing loss and 4 had good low frequency but poor high frequency hearing loss bilaterally. Mean thresholds are shown by the black line.

Table 6.1. Demographic information for all children.

Subject	Implanted ear	Etiology	Age (years)		Deprivation (years)		Hearing experience (years)	
			Diagnosed	Implanted	Bilateral	Unilateral	Pre-CI acoustic	Asymmetric
1	Right	Unknown	0.0	12.1	0.0	0.0	12.0	0.0
2	Left	CMV	2.2	3.3	0.0	1.2	3.3	3.3
3	Left	Genetic	0.2	9.7	1.0	4.9	8.5	8.5
4	Left	Unknown	6.0	9.4	0.0	0.1	6.4	3.4
5	Left	Unknown	12.9	14.2	0.0	0.1	12.9	1.3
6	Left	Unknown	0.2	13.6	0.0	0.1	13.5	0.0
7	Left	CMV	0.1	3.6	0.0	3.6	3.5	3.5
8	Left	Unknown	5.0	15.2	6.0	0.1	10.2	10.2
9	Left	Genetic	0.1	4.8	0.0	0.1	4.7	0.0
10	Left	CMV	0.0	1.1	0.0	1.1	1.1	1.1
Mean ± SD			3.0 ± 4.4	8.7 ± 5.1	0.8 ± 2.0	1.2 ± 1.8	7.6 ± 4.4	3.1 ± 3.6

CMV = Congenital cytomegalovirus; SD = standard deviation; CI = cochlear implant.

6.3.2 Electrophysiology

Electroencephalography (EEG) measures were recorded across 64 surface channels referenced to the right earlobe in all children at initial implant activation (5.8 ± 3.2 days) and after 10.2 ± 4.1 months of cochlear implant (CI) use. Stimuli consisted of 36 ms trains of 9 acoustic clicks (100 µs) delivered at a rate of 250 Hz via an insert earphone to non-implanted ears or 9 electric biphasic pulses (57 µs pulse-width) delivered at a rate of 250 Hz via an L34 research implant processor to an apical electrode (#20) of the internal CI electrode array. Trains were presented monaurally at 1 Hz with maximum comfortably loud levels, which were confirmed to evoke similar activation at the upper part of the dynamic range as measured by maximum wave V/eV amplitude of the auditory brainstem response (ABR) (Jiwani et al., 2016; Polonenko et al., 2015). Children sat in a sound proof booth and watched a muted movie or read a book during the recording. Responses were measured using the NeuroScan-4.5 system and Synamps-II amplifier (Compumedics USA, Inc., Charlotte, NC) with a 1000 Hz sampling rate and a 0.15 to 100 Hz bandpass filter. Continuous EEG data were separated into epochs at each stimulus presentation. Epochs were 1000 ms in duration and included a 200 ms pre-stimulus interval. At least two replications were obtained, each including at least 100 epochs. Epochs containing activity exceeding ± 100 µV in the vertex (Cz) channel were rejected, and then responses were filtered from 1 to 30 Hz and average-referenced for further analysis. Epochs were averaged together for visualization of surface waveforms in each channel (e.g., as shown for the mean responses in **Figure 6.3A**) and to plot the spatial distribution of activity across the surface of the head at peaks in the surface waveforms (i.e., across surface recording channels; shown in **Figure 6.3B**).

The Time-Restricted Artifact and Coherent source Suppression (TRACS) method (details described in Gordon et al., 2013b; Wong and Gordon, 2009) was used to localize source activity in time windows encompassing the first amplitude peak of the surface waveform (identified by the arrow in **Figure 6.3A**). Briefly, TRACS is an adaptive spatial filter (linearly constrained minimum variance type beamformer) that estimates the contribution (dipole activity) of each of the ~64,000 3x3x3 mm spaces (voxels) of the brain's volume to the recorded surface activity, and suppresses up to 97% of the CI artifact, which was estimated during stimulus presentation (-80 to 10 ms). Because both auditory cortices could have coherent activity, source activity in each hemisphere was evaluated while suppressing activity in the contralateral temporal lobe (for details see Dalal et al., 2006). Age-dependent head geometry and conductivities of the brain,

skull and scalp were accounted for by a 3-layer boundary element model that was constructed from age-appropriate Montreal Neurologic Institute (MNI) magnetic resonance imaging (MRI) templates generated with the Template-O-matic toolbox (Wilke et al., 2008). Activity in each voxel was normalized relative to the pre-stimulus baseline (-200 to -80 ms) using a pseudo-Z statistic, calculated as a ratio of the mean signal to the standard deviation of the pre-stimulus baseline (Vrba and Robinson, 2001). A one-tailed omnibus *t*-test (Petersson et al., 1999) used an average with half the trials flipped in polarity (i.e., plus-minus average which removes the time-locked activity) to determine a statistical threshold pseudo-Z of baseline brain activity (omnibus value). This omnibus value was subtracted from the pseudo-Z value in each voxel in order to identify which voxels contained activity above baseline brain activity. Maximum dipole strength and latency were extracted from the source time series for all voxels, but for further analyses the voxel with the largest pseudo-Z above the omnibus threshold was chosen in both the left (X ≤ -55 mm) and right (X ≥ 55mm) auditory cortical areas (-35 ≤ Y ≤ 5; -10 ≤ Z ≤ 20) (Easwar et al., 2017b, 2017c, 2018; Gordon et al., 2013b; Jiwani et al., 2016; Polonenko et al., 2018a). Locations of chosen voxels for each time point are shown in **Figure 6.2**.
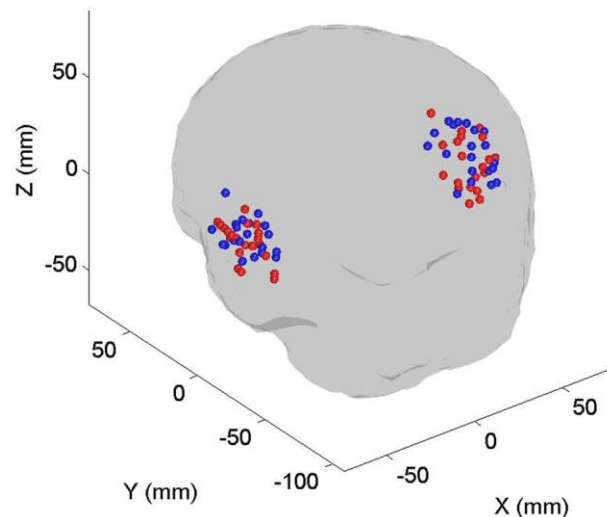
Figure 6.2. Locations of chosen voxels for further analysis.

Locations of voxels with the largest pseudo-Z above omnibus threshold in the left and right auditory cortices for responses evoked after 5.8 ± 3.2 days (blue) and 10.28 ± 4.1 months (red) of CI use.

Peak dipoles from these chosen voxels in left and right auditory areas were used to calculate hemispheric representations of source activity with two metrics. Cortical lateralization (%) characterized the difference in dipoles between the contralateral and ipsilateral auditory cortices for each ear, according to the formula: 100 x [contralateral cortex – ipsilateral cortex] / [contralateral cortex + ipsilateral cortex]. Positive cortical lateralization values indicated that stimulation of an ear resulted in greater activity in the contralateral than ipsilateral cortex and vice versa for negative scores. Aural (stimulation) preference (%) characterized the degree of activation in one auditory cortex upon stimulation of each ear, and was calculated as: 100 x [contralateral ear – ipsilateral ear] / [contralateral ear + ipsilateral ear]. Positive aural preference values indicated a preferential stimulation by the contralateral ear whereas negative values indicated an ipsilateral ear preference.

6.3.3 Statistical analyses

Differences in amplitude and latency of peak evoked surface activity (GFP) were analyzed using repeated measures ANOVA with time and ear as within-subject variables. Greenhouse-Geisser corrections for lack of sphericity were used when indicated. Changes in dipole magnitude, cortical lateralization and aural preference with duration of CI use were evaluated using the *lme4* package (Bates et al., 2015) to conduct linear mixed effects regression (Mcculloch and Neuhaus, 2006) with random intercept and slope for each child. A likelihood ratio test was used to determine significance of the regression. Pearson correlations were used to assess associations between demographic variables and cortical lateralization and aural preference.

6.4   Results

6.4.1 Auditory responses evoked by acute and chronic electric and acoustic input

Cortical responses were evoked by both electric CI and acoustic stimulation. Plots of the mean ± SE surface activity at the vertex (Cz) recording channel as well as the GFP of these responses are provided in **Figure 6.3A**. The GFP represents the spatial standard deviation of activity across all surface recording channels, and peaks represent the times of greatest change in field potential. Accordingly, latencies are provided for the GFP instead of only one surface recording channel. But because the GFP provides only positive values, polarity is described based on the common-

referenced activity at Cz (**Figure 6.3A**) and the topographic spatial distribution of activity across all channels (**Figure 6.3B**).

At initial CI stimulation, most children showed an initial broad negative peak or a slight negativity at Cz from 50 - 130 ms (mean ± SD, range, median: 107.1 ± 24.0 ms, 77 - 154 ms, 96 ms) followed by a positive peak at 173.1 ± 42.0 ms (127 - 258 ms, 158 ms). This positive peak was delayed by 54.4 ± 54.0 ms (-13 - 160 ms, 43 ms) compared to the positive peak at 118.7 ± 19.9 ms (96 - 157 ms, 117.5 ms) to input from the non-implanted ear (paired t-test: $t(9) = 3.2$, $p = 0.01$). With chronic CI stimulation, the children exhibited a positive peak for both the CI and non-implanted ears at 112.2 ± 14.4 ms (97 - 140 ms, 107.5 ms) and 112.0 ± 29.1 ms (82 - 156 ms, 100.5 ms) respectively. Besides differing polarity at the initial visit, latency and amplitude of the first GFP peak were similar across ears (latency: $F(1,9) = 0.6$, $p = 0.47$; amplitude: $F(1,9) = 4.5$, $p = 0.06$) and visit (latency: $F(1,9) = 0.02$, $p = 0.88$; amplitude: $F(1,9) = 3.1$, $p = 0.11$). Mean ± SE peak GFP amplitude and latency are shown by points overlaying the mean GFP waveform in **Figure 6.3A**.

Average-referenced topographic surface distributions of mean evoked activity across all recording channels are shown in Figure 3B for mean GFP peak latencies (~105 ms; black arrows in **Figure 6.3A**). These topographies indicated a frontal negative-posterior positive polarity oriented contralateral to the newly implanted ear (**Figure 6.3B**). This pattern resolved with CI use into a more central frontal positive-posterior negative response in both ears (and positive peak response at the vertex, where Cz is located) (**Figure 6.3B**).

Source activity underlying the surface peaks identified in **Figures 6.3A and 6.3B** was evaluated using the TRACs beamformer. In **Figure 6.3C**, axial views of grand mean source pseudo-Z across the brain reveal largest hotspots of activity in the temporal auditory areas upon stimulation of either ear. Bilateral activation stimulated by the new implant became lateralized to the contralateral auditory cortex with CI use, whereas the un-implanted ear consistently evoked contralateral activation at both visits, on average.
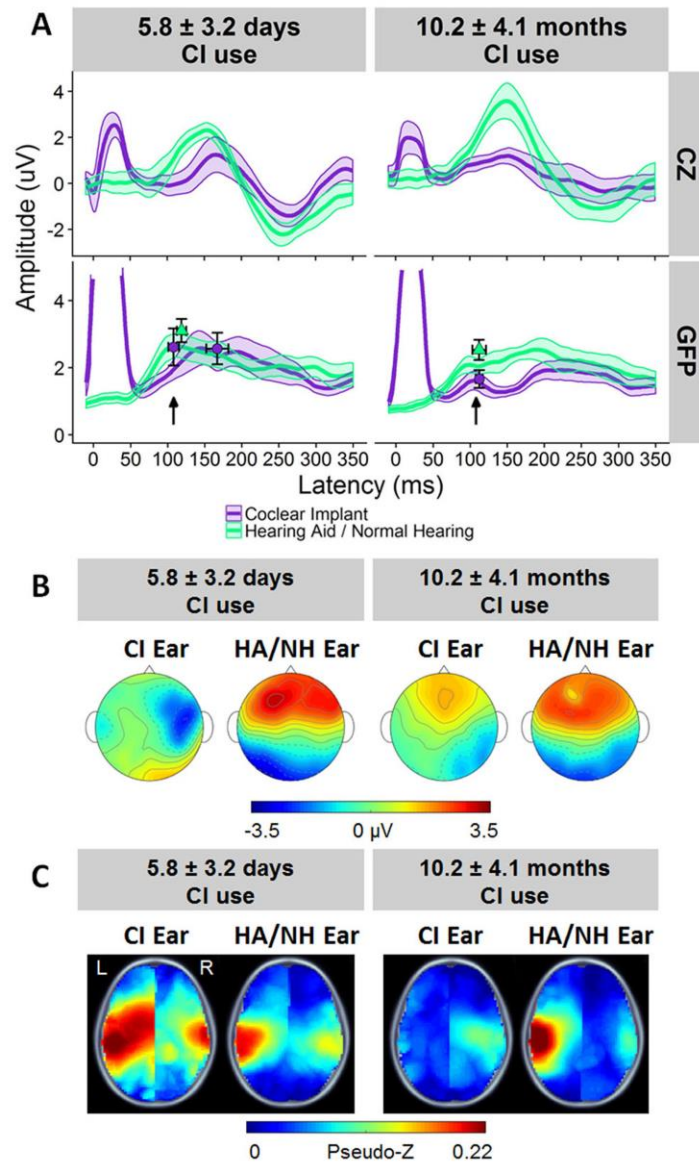
Figure 6.3. Evoked surface and source cortical activity.

(**A**) Mean (solid line) ± SE (shaded region) common-referenced *surface* evoked activity at the vertex (Cz) recording channel (top row) and the global field power (GFP; spatial standard deviation of surface potentials across electrodes) waveforms (bottom row) at initial cochlear implant (CI) activation and after > 6 months CI use. Points with error bars indicate mean ± SE GFP peaks. Black arrows indicate the peak GFP latency (105 ms) at which topographic distributions of mean average-referenced EEG activity across the *surface* of the head are shown in (**B**). (**C**) Axial view of mean evoked *source* activity (higher signal-to-noise ratio, pseudo-Z, in red) in ~64,000 voxels that were evaluated using the TRACS beamformer. CI = cochlear implant; NH = normal hearing; HA = hearing aid; GFP = global field power; L = left; R = right.

6.4.2 Abnormal ipsilateral response to initial cochlear implant resolves with chronic use

Figure 6.4 plots cortical lateralization evoked from both the CI and opposite non-implanted ear for both time points. Initial responses to cochlear implant stimulation abnormally lateralized to the ipsilateral cortex in most children (mean ± SD cortical lateralization, range, median: -9.5 ± 27.9%, -52.2 - 36.1%, -19.8%) but this normalized with chronic CI use, shifting to contralateral lateralization (29.9 ± 22.9%, 1.9 - 75.2%, 21.7%; mixed model regression: $\chi^2(1) = 4.1,\ p = 0.04$). Stimulation from the non-implanted ear showed a wide distribution at both time points (cortical lateralization at initial stimulation: -6.7 ± 34.8%, -74.2 - 40.5%, 1.7%; chronic stimulation: 2.6 ± 30.2%, -50.2 - 51.0%, 8.0%); there were no significant changes between the two test times ($\chi^2(1) = 1.0, p = 0.31$). Individual cortical lateralization measures are plotted over time of CI use in **Figure 6.5A** to further illustrate the changes in responses evoked by the CI and relatively stable responses evoked by the non-implanted ear. Changes in cortical lateralization were driven by significant decreases in ipsilateral activity (dipoles) evoked by the implant over time ($\chi^2(1) = 4.6, p = 0.03$) (**Figure 6.5B**).
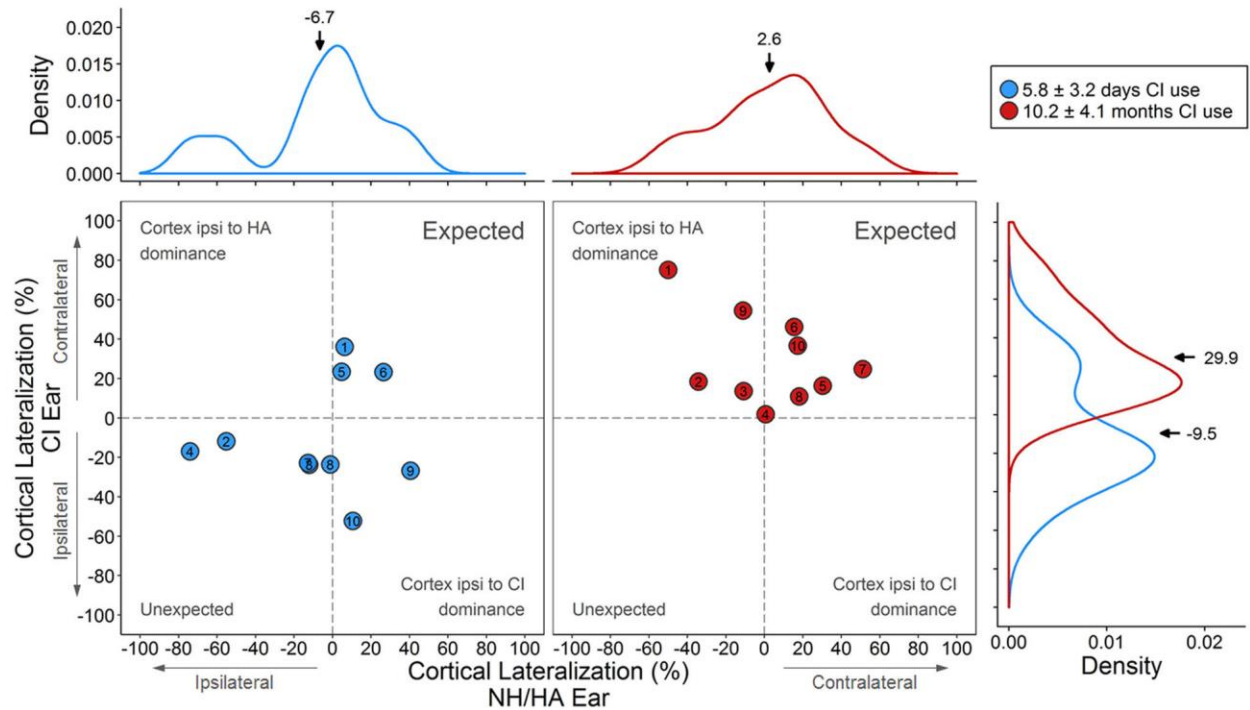
Figure 6.4. Cortical lateralization of activity evoked by each ear.

Cortical lateralization =100 x [dipole magnitude in contralateral cortex – ipsilateral cortex] / [contralateral cortex + ipsilateral cortex]. Initial responses to cochlear implant stimulation abnormally lateralized to the ipsilateral cortex (negative values) but resolved to contralateral lateralization (positive values) after chronic stimulation. No overall change in lateralization occurred from stimulation of the non-implanted ear with normal hearing (NH) or a hearing aid (HA). Black arrows mark mean values, which are indicated above the arrows. Participants are identified by their number, as listed in **Table 6.1**.
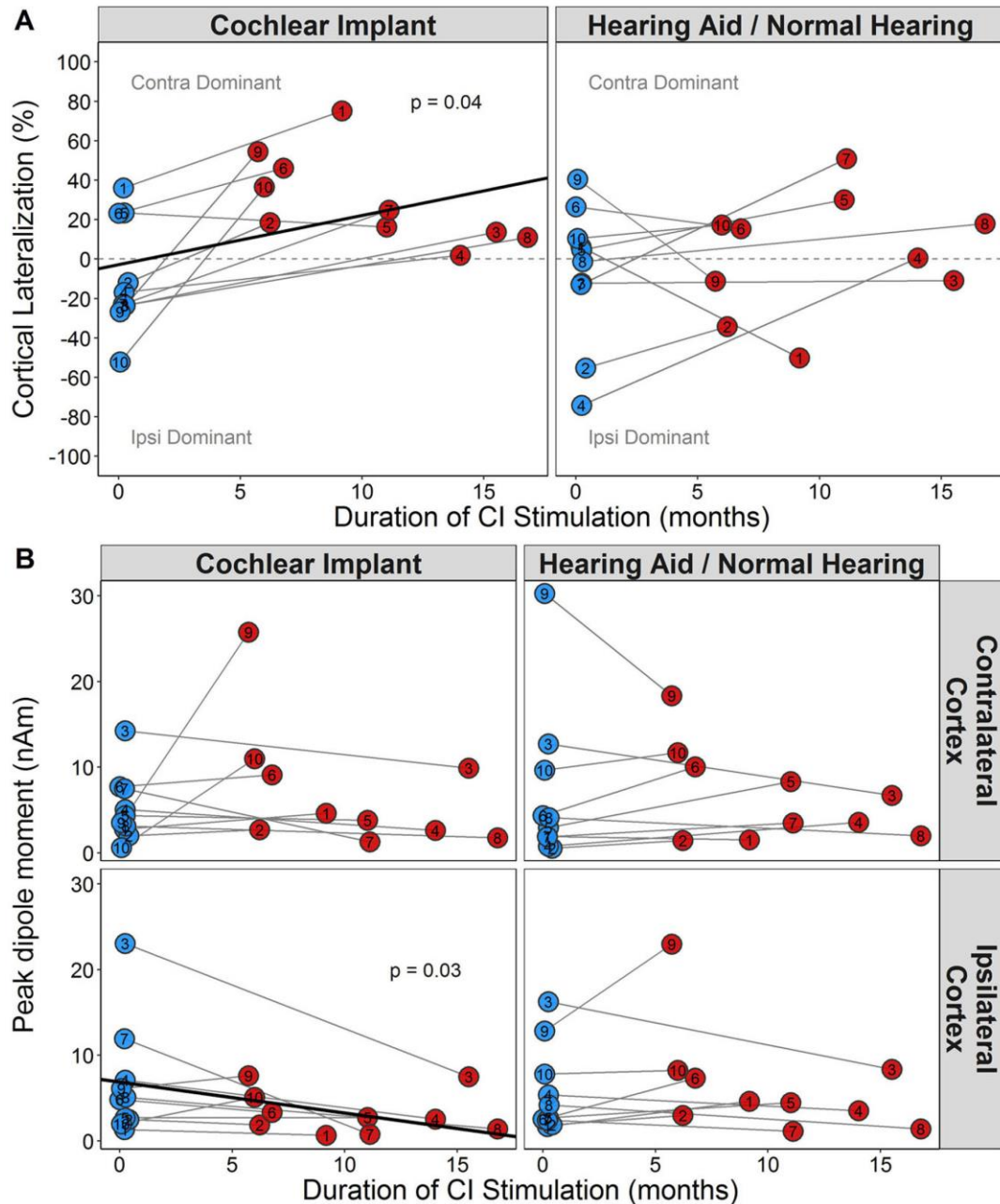
Figure 6.5. Cortical lateralization and evoked source dipole activity.

(**A**) Significant changes towards expected contralateral lateralization (positive values) response with implant use, confirmed by mixed effects linear regression ($\chi^2(1) = 4.1$, $p = 0.04$). No significant changes were found for responses from the non-implanted ear ($\chi^2(1) = 1.0$, $p = 0.31$). (**B**) Changes in cortical lateralization were driven by significant decreases in ipsilateral activity (dipoles) evoked by the implant over time ($\chi^2(1) = 4.6$, $p = 0.03$). Participants are identified by their number, as listed in **Table 6.1**. Cortical lateralization = 100 x [contralateral cortex – ipsilateral cortex] / [contralateral cortex + ipsilateral cortex].

6.4.3 Abnormal aural preference for the better hearing ear resolves with implant use

Figure 6.6 plots the aural preference in both left and right auditory cortices. Initially, a wide distribution of aural preference was present in both auditory cortices; often there was an abnormal over-representation of one ear in the auditory brain, as indicated by preference in both cortices for either the non-implanted ear or the newly implanted ear. There was high variability around the mean for both the cortex ipsilateral to the non-implanted ear (aural preference: -1.3 ± 43.5%, -85.2 - 50.9%, 0.2%) and the cortex ipsilateral to the CI (-10.7 ± 52.5%, -79.9 - 66.4%, -7.9%). With chronic stimulation, a more focused distribution of bilateral representation occurred in the cortex ipsilateral to the non-implanted ear (3.1 ± 9.4%, -14.3 - 14.3%, 6.3%) and contralateral preference emerged in the opposite cortex (30.1 ± 25.1%, -12.4 - 63.4%, 39.6%). Individual aural preference measures are plotted over time of CI use in **Figure 6.7**. Mixed effects linear regression confirmed that the CI began to have expected representation in the cortex ipsilateral to the non-implanted ear with CI use ($\chi^2(1) = 4.2$, $p = 0.04$). There were no effects of CI use on aural preference in the cortex ipsilateral to the non-implanted ear ($\chi^2(1) = 0.06$, $p = 0.81$) but the analyses confirmed a significant reduction in variability (paired t-test: $t(9) = 2.8$, $p = 0.02$).
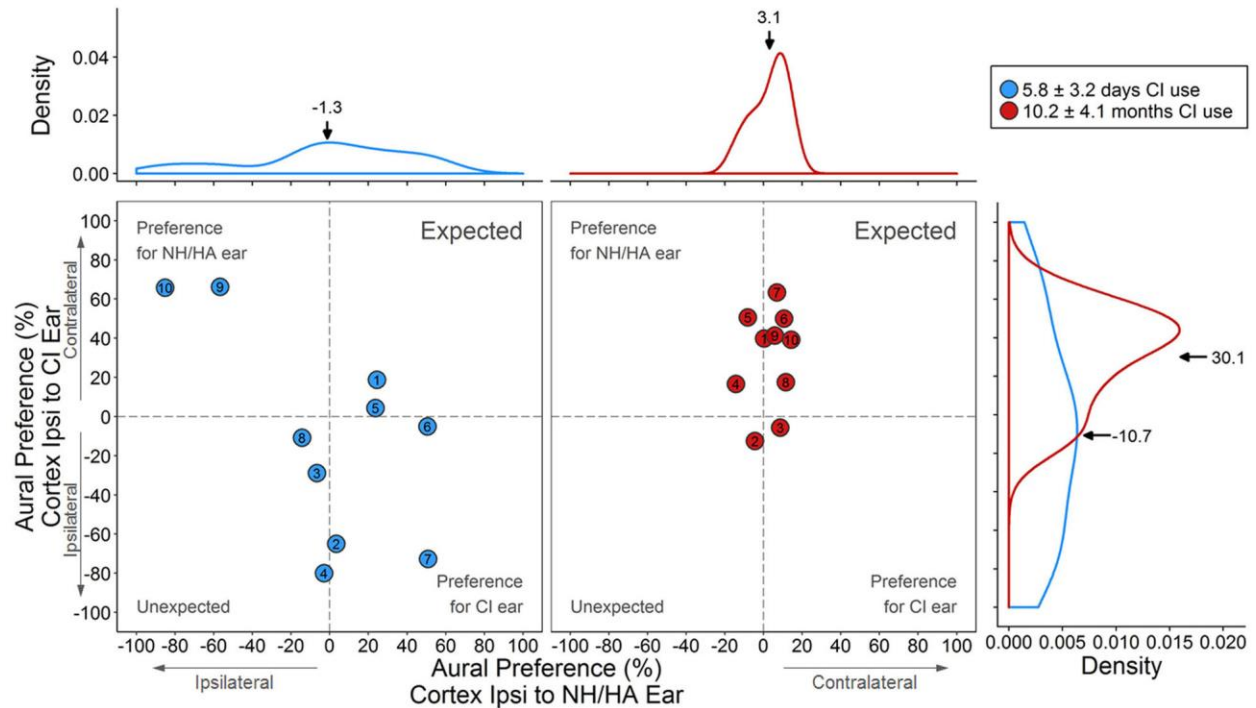
Figure 6.6. Aural preference of activity evoked in each cortex.

Aural preference in each cortex = 100 x [contralateral ear – ipsilateral ear] / [contralateral ear + ipsilateral ear]. Initial responses reveal abnormal preference for one ear in both cortices(i.e., one cortex exhibits contralateral aural preference and the other cortex exhibits ipsilateral aural preference). With chronic cochlear implant (CI) stimulation, CI input became increasingly represented in the contralateral cortex and the distribution of aural preference became more focused. Expected contralateral preference for the non-implanted ear (hearing aid (HA) or normal hearing (NH)) emerged in the opposite cortex. Black arrows mark mean values, which are indicated above the arrows. Subjects are identified by their number, as listed in **Table 6.1**.
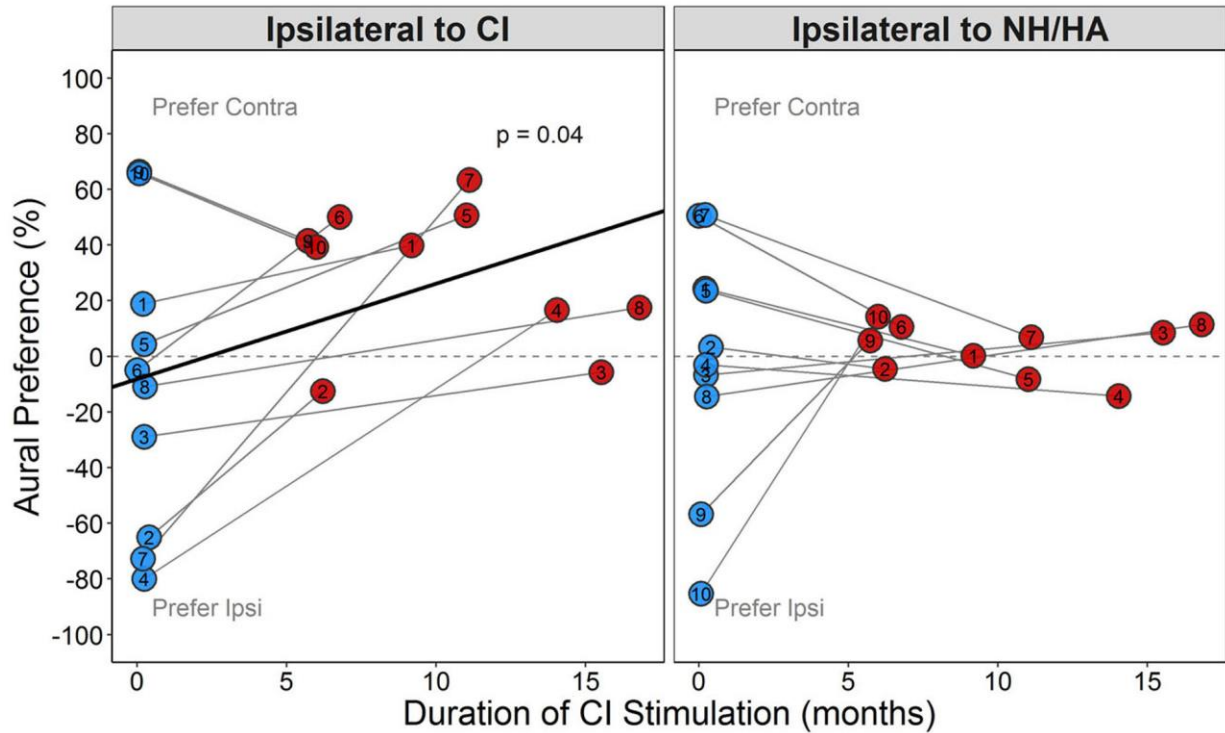
Figure 6.7. Change in aural preference with cochlear implant use.

Expected aural preference (=100 x [contralateral ear – ipsilateral ear] / [contralateral ear + ipsilateral ear]) for the contralateral (positive values) non-implanted ear (with a hearing aid (HA) or normal hearing (NH)) emerged in the cortex ipsilateral to the cochlear implant (CI) ($\chi^2(1) = 4.2$, $p = 0.04$). Mixed effects linear regression found no effects of time on aural preference in the cortex ipsilateral to the non-implanted ear ($\chi^2(1) = 0.06$, $p = 0.81$), but there was a significant reduction in variability (paired t-test: $t(9) = 2.8$, $p = 0.02$). Participants are identified by their number, as listed in **Table 6.1**.

6.4.4 Resolution

At initial CI use, cortical lateralization from the newly implanted ear was more abnormal (ipsilateral) in children with worse hearing ($R = -0.65$, $p = 0.04$) and shorter periods of acoustic experience ($R = 0.83$, $p = 0.003$) (**Figure 6.8A**). After CI experience, children with longer periods of asymmetric hearing prior to implantation were less likely to recover cortical lateralization from the implanted ear to the contralateral cortex ($R = -0.73$, $p = 0.017$) (**Figure 6.8B**) or aural preference for the acoustic input in the opposite cortex (ipsilateral to the implant) (**Figure 6.8C**) ($R = -0.57$, $p = 0.08$).
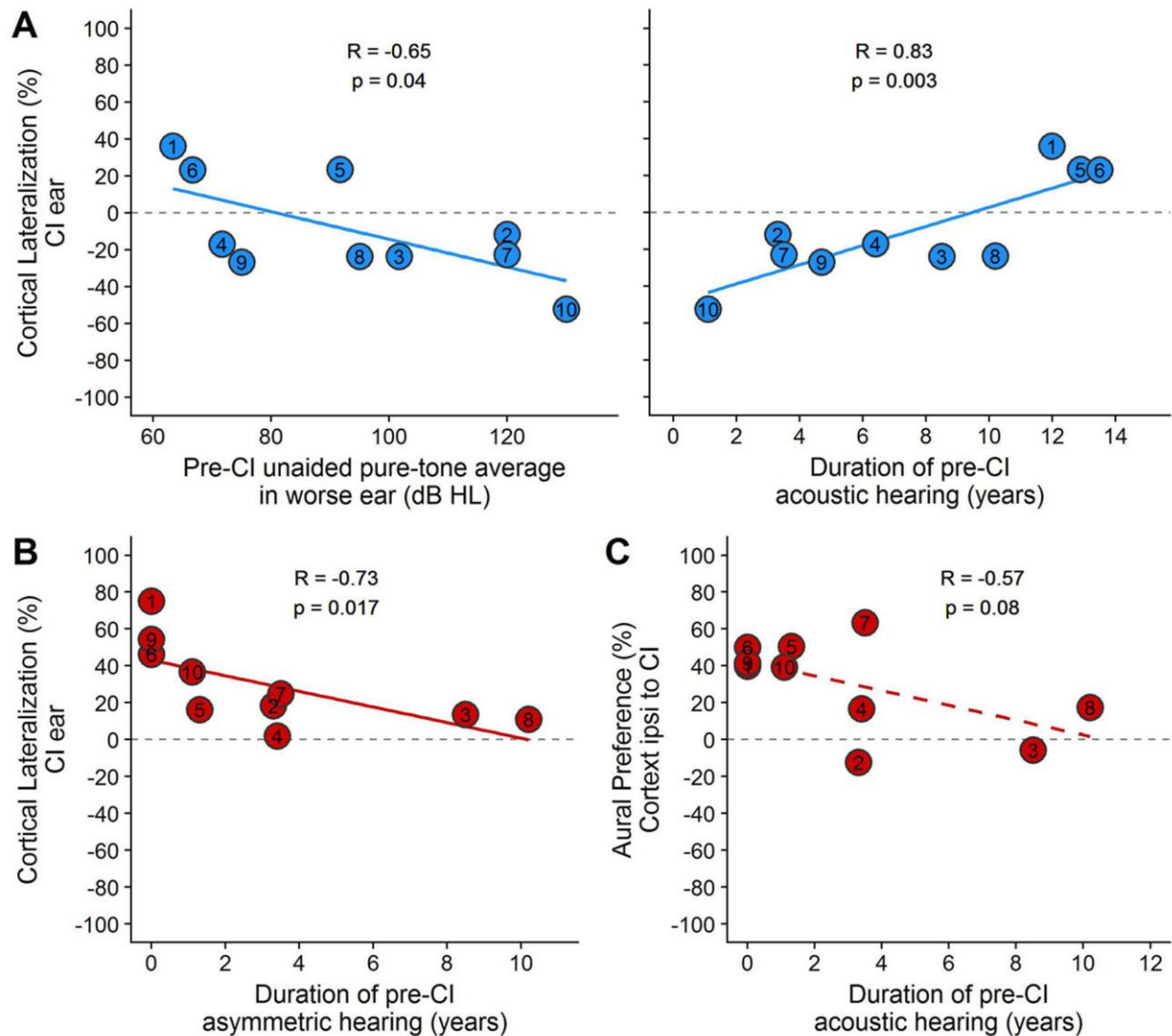
Figure 6.8. Predictors of initial and persistent abnormal cortical representation of bilateral auditory input.

(**A**) Cortical lateralization from the newly implanted ear was more abnormal (ipsilateral) in children with worse hearing and shorter periods of acoustic experience pre-implantation. Children with longer periods of asymmetric hearing prior to implantation were less likely to recover expected (**B**) cortical lateralization from the implanted ear or expected (**C**) aural preference for the contralateral un-implanted input in the cortex ipsilateral to the implant. Participants are identified by their number, as listed in **Table 6.1**.

6.5 Discussion

The present study examined effects of providing a cochlear implant in one ear in children who had some degree of residual hearing in their other ear. **Figure 6.1** and **Table 6.1** indicate the variability in hearing history. Although these children were older at the time of cochlear implantation, most did not experience bilateral auditory deprivation. Instead, many of the children (7/10) experienced periods of asymmetric hearing. The degree of hearing loss in the implanted ear and asymmetric hearing loss had significant effects on cortical representation of the CI in one ear and acoustic hearing in the other ear (bimodal hearing).

6.5.1 Abnormal surface responses suggest auditory immaturity and deprivation in the implanted ear

One of the most striking findings in the present cohort of 10 children was the abnormal response to initial CI stimulation. Responses across all 64 recording channels at initial CI use were in the same latency range for the newly implanted ear as the experienced ear albeit with a negative peak followed by a slightly delayed positive peak (~55 ms on average) (**Figure 6.3A**). Initial CI stimulation had obvious effects on the spatial distribution of surface responses and the estimated cortical source dipoles. The surface response to the new implant was strongly negative in contralateral frontal channels (**Figure 6.3B**). Many children showed this negative peak at a midline recording position (Cz), although Cz was beyond the average hot spot of negative surface potentials and was thus more likely to have variable polarity (**Figure 6.3B**). The variability of responses at Cz emphasizes the need to assess cortical responses across multiple cephalic positions to fully capture responses (Ponton et al., 2000). Multi-channel recording also enables source localization which indicated an abnormal increase in ipsilateral auditory cortex activity in response to the new implant (**Figure 6.3C**).

Responses to initial CI stimulation likely reflect immaturity and other effects of deprivation in the pathways from this newly implanted ear. Previous work examining cortical responses at Cz in preterm infants hint at abnormal surface topography given that a broad negative peak was reported in approximately the same latency range as the initial CI responses reported here (Rotteveel et al., 1987; Weitzman et al., 1967). Cz responses change with development; the negative peak changes polarity in infancy to a positive peak (Lippé et al., 2009) and then decreases slightly in latency through childhood (Ponton et al., 2002, 2000). Data from children

who are deaf in both ears and receive CIs reveal the greatest variability of responses at Cz at the first day of CI activation, suggesting heterogeneity in effects of deafness on the auditory system (Gordon et al., 2011). This could reflect different etiologies and onset of deafness in childhood. Cz responses from children whose hearing loss was associated with mutations in the GJB-2 gene were similar to one another, characterized by a negative peak at ~100 ms (Gordon et al., 2011). The negative peak in the present cohort of children shared similar latency and topography to the N1 of the mature P1-N1-P2 complex (Ponton et al., 2000; Ponton and Eggermont, 2001; Wunderlich and Cone-Wesson, 2006) but had clear distinctions. First, it had no preceding P1 peak and second, it changed into an immature positive peak typically seen in children with < 12 years of "time in sound" (Jiwani et al., 2013; Ponton et al., 2000). The positive peak decreases in latency with CI use (Ponton and Eggermont, 2001) if the period of early deprivation is limited (Sharma et al., 2007, 2005), and then matures into the P1-N1-P2 complex with 9+ years of CI experience (Jiwani et al., 2016, 2013). Speech perception can be poor when these changes in the Cz cortical response are not observed (Gordon et al., 2008a).

Changing morphology of the surface responses in children using cochlear implants suggests development of underlying cortical generators. Multiple electrode recordings not only provide comprehensive characterization of the evoked surface potentials (Ponton et al., 2000) but can also be used for estimating underlying sources. A recent study using multiple electrode recordings in young children with single sided deafness revealed a similarly negative response across frontal recording channels in response to initial stimulation of a CI in the deaf ear (Polonenko et al., 2017b). This topography corresponded to significant activity in left fronto-temporal cortical areas which was the ipsilateral cortex for most of the present cohort (9/10 implanted in left ear).

6.5.2 Abnormal response to initial CI use in ipsilateral cortex

The robust signal in left fronto-temporal cortex evoked by the CI at initial use decreased with ongoing bimodal experience in the present cohort of children (**Figure 6.3C**). This change was further examined by assessing dipoles in voxels with the highest signal to noise ratios in left and right temporal areas (**Figure 6.2**) as in previous studies (Easwar et al., 2017b, 2017c, 2018; Gordon et al., 2013b; Jiwani et al., 2016; Polonenko et al., 2018a). Most importantly, the CI initially evoked a strong response in the ipsilateral cortex. Strong activity in the ipsilateral

temporal cortex could be due to strengthening from the better hearing ear as shown in animal models (Kral et al., 2013b) and a cohort of 34 children with asymmetric hearing prior to implantation (Polonenko et al., 2018a). Cortical reorganization in response to unilateral hearing loss is particularly evident during development (Keating and King, 2013; Kral et al., 2013a, 2013b; Polley et al., 2013; Polonenko et al., 2018a; Popescu and Polley, 2010; Tillein et al., 2016). Increased representation from the hearing ear comes with an increase in neurons in the ipsilateral cortex which are excited by both ears and, by an increase in neurons in the contralateral cortex responding only to the hearing ear (Tillein et al., 2016).

It is also possible that increased activity in left cortex reflects greater attention than normal being paid to the new CI stimulation (Kane and Engle, 2002) despite the passive recording paradigm. The same strong response in left fronto-temporal cortex in young children with single sided deafness (left ear) to acute CI stimulation supports this, particularly as the frontal component in that cohort of toddlers decreased considerably by ~1 month of CI use (Polonenko et al., 2017b). Perhaps then, this activity reflects an increased awareness to the very new CI input which facilitates temporal activity in the same hemisphere and resolves with CI use because the child acclimates to the CI stimulation. This cortical area may continue to play an important role in the cortical network involved in CI hearing; adolescents with long term right unilateral CI experience also showed increased recruitment of small left frontal area during passive listening (Jiwani et al., 2016). Further analyses are needed to determine whether left frontal cortical activity in these 3 cohorts is distinct from responses in left temporal areas and to examine how these areas may be functionally connected within cortical networks by their phase and/or amplitude of oscillatory activity.

A third possibility is that the increased response in the left auditory cortex is related to hemispheric specialization for speech (Zatorre et al., 2002; Zatorre and Belin, 2001). Many of the children studied here had better hearing in their right ear which is thought to have an advantage over the left ear due to direct input to language networks in the left hemisphere (Bruneau et al., 2015; Eichele et al., 2005; Kimura, 1973, 1961; Westerhausen and Hugdahl, 2008). If so, there may be cortico-fugal or cortico-cortical connections that promote input from the newly implanted ear to this dominant auditory hemisphere. Negative surface potentials, such as those evoked by the new CI in fronto-temporal areas of the head, are thought to reflect cortico-cortical activity in the superficial levels (I-III) of the cortex, indicating re-entrant or

reciprocal intra- and inter-hemispheric connections to auditory areas (Ponton et al., 2000; Ponton and Eggermont, 2001). In this light, the cortex may be trying to interpret the new CI input as it would input from the more experienced right ear.

6.5.3 Early balanced bilateral hearing promotes cortical representation from both ears in development

With CI use, symmetric representation from both ears was established in the cohort of 10 children studied. The acoustic ear promoted cortical lateralization to the contralateral cortex in half the children at all test times and the typical pattern of contralateral lateralization was realized in response to the CI by ~10 months for most children (**Figure 6.4**). The decrease in abnormal ipsilateral lateralization to the CI over time was explained by reductions in evoked dipoles in the ipsilateral auditory cortex (**Figure 6.5**). This rapid change provides further evidence that the initial response to CI use was atypical and restricted to input from the CI side. Moreover, the relative stability in cortical lateralization and dipoles evoked by the opposite ear (**Figure 6.5**) suggests an increasing role of the deprived ear without disrupting responses to stimulation from the first ear. This is an encouraging finding which demonstrates that representation from both ears can be established in the auditory brain by providing bimodal input with limited delay (Polonenko et al., 2018a) and supports evidence of improved hearing in children using bimodal devices rather than a hearing aid alone or a CI alone (Ching et al., 2007; Mok et al., 2010, 2007; Nittrouer and Chapman, 2009; Straatman et al., 2010).

The large ipsilateral dipoles evoked by the CI at initial activation also affected aural preference. Aural preference was widely distributed in the ipsilateral cortex (**Figure 6.6**), giving the impression of preference for the CI in all but 2 of children, who, instead, showed aural preference for the better ear in both cortices. The reduction of ipsilateral dipoles after ~10 months of CI experience shifted the initial emphasis away from the implant to reveal an aural preference for the better hearing (contralateral) ear in the cortex ipsilateral to the CI and an emerging preference for the CI ear in the contralateral cortex (**Figure 6.7**). These data are very similar to normal hearing peer groups previously reported (Easwar et al., 2017b; Gordon et al., 2013b; Polonenko et al., 2018a), further confirming that cortical representation of input from both ears was established on average within a year in this cohort of children using bimodal devices.

Analyses of demographic variables in the present cohort revealed that the ipsilateral auditory cortex became more vulnerable to responding abnormally to initial CI stimulation when children had poorer hearing and less experience with acoustic hearing (**Figure 6.8A**). As the period of asymmetric deprivation lengthened, the new input became more heavily lateralized to the cortex contralateral to the hearing ear (ipsilateral to deprived ear), perhaps reflecting an increasing role of this cortex for hearing unilaterally. As discussed above, increased attention and/or language processing in this cortex may be needed by these children to process the new input to pathways from the deprived side.

Although abnormally strong dipoles in the cortex ipsilateral to the CI reduced with CI experience in most of the present cohort, the change was negatively correlated with the period of asymmetric hearing prior to implantation (**Figure 6.8B**). This means that there were long-lasting effects of listening with a better ear. This finding supports earlier work suggesting a sensitive period in development for re-establishing contralateral activation from the unilaterally deprived ear. In children with bilateral CIs, the same large response from the ipsilateral cortex was measured in response to the second CI when the delay to bilateral implantation (duration of unilateral CI use) exceeded 2 years (Gordon et al., 2013b). Again, the right ear was the first hearing ear which stimulated increased activity in the contralateral left auditory cortex. The weaker second implanted ear was able to develop if provided with input early in development. Therefore, the importance of early intervention for re-establishing symmetric cortical organization has now been shown in children receiving bilateral CIs with minimal or no delay (Gordon et al., 2013b; Polonenko et al., 2018a), young children with single sided deafness (Polonenko et al., 2017b) and the present cohort of children with moderate to profound hearing loss in their better ear. Further studies should assess how robust these changes are across larger cohorts of children using bimodal devices with a variety of hearing histories.

6.6   Summary and Conclusions

In children who had some residual hearing prior to implantation, the new cochlear implant evoked strong dipole responses in the ipsilateral auditory cortex. Strength of this atypical activation significantly correlated with the duration and degree of deprivation in the implanted ear. This atypical activity subsided with CI use more readily in children who had more bilateral

hearing prior to implantation. These findings confirm that bilateral hearing should be provided to children as early as possible in development using the most appropriate device in each ear.

6.7 Acknowledgments

Chapter 7
Paper 5

Chapters 4 to 6 identified electrophysiological evidence of a developmental aural preference with asymmetric hearing. Given the asymmetries in brainstem and cortical development, I then asked whether these neurophysiological changes were corroborated by behavioural consequences of asymmetric speech perception and compromised ability to make use of spatial hearing.

7 Limiting Asymmetric Hearing Improves Benefits of Bilateral Hearing in Children Using Cochlear Implants

This chapter has been reformatted from the manuscript in review with Scientific Reports:

Polonenko, M.J., Papsin, B.C., & Gordon, K.A. (in review). Limiting asymmetric hearing improves benefits of bilateral hearing in children using cochlear implants. Scientific Reports.

7.1 Abstract

Neurodevelopmental changes occur with asymmetric hearing loss, limiting binaural/spatial hearing and putting children at risk for social and educational challenges. These deficits may be mitigated by providing bilateral hearing in children through auditory prostheses. Effects on speech perception and spatial hearing were measured in a large cohort of > 450 children who were deaf and used bilateral cochlear implants or bimodal devices (one cochlear implant and a contralateral hearing aid). Results revealed an advantage of bilateral over unilateral device use but this advantage decreased as hearing in the two ears became increasingly asymmetric. Asymmetric hearing occurred when bilateral implantation of an ear with severe to profound deafness was delayed, creating aural preference for the better hearing ear. These findings indicate that bilateral input with the most appropriate device for each ear should be provided early and without delay during development.

7.2 Introduction

Cochlear implantation has become standard treatment for childhood deafness. One cochlear implant promotes significant gains in speech understanding (Gordon and Papsin, 2009; Sarant et al., 2001) and language development (Boons et al., 2013; Hess et al., 2014; Nicholas and Geers,

2007; Tobey et al., 2013) when provided early in development. On the other hand, access to sound in only one ear results in impaired binaural hearing (Gordon et al., 2015, 2014; Litovsky and Gordon, 2016), which is the foundation for sound localization. Without access to spatial hearing, children with asymmetric hearing are at risk for social and educational deficits (Bess and Tharpe, 1984; Gordon et al., 2015; Lieu et al., 2010). We thus sought to promote bilateral hearing development by providing the most appropriate device in each ear to our large cohort of children with deafness (Gordon et al., 2015). A cochlear implant was provided in ears with severe/profound deafness; children with bilateral deafness received two cochlear implants whereas children with better hearing in one ear received one cochlear implant and a hearing aid in the other, better hearing, ear (bimodal hearing) (Cadieux et al., 2013; Gordon et al., 2015; Gratacap et al., 2015; Polonenko et al., 2015).

Limited or distorted binaural hearing challenges development. Children spend much of their time interacting and learning in dynamic environments, such as the playground and classroom (Ching et al., 2009; Easwar et al., 2016; Polonenko et al., 2017c) in which they listen to sounds coming from multiple directions. Binaural hearing supports detection of these sounds and the ability to distinguish one sound from another by differences in their spatial locations. To do this, the auditory system largely depends on comparing the level and timing of sounds arriving at the two ears (Grothe et al., 2010). Even if this binaural coding is impaired (Easwar et al., 2017c), children can take advantage of hearing with both ears by taking advantage of the ear with the better signal-to-noise ratio. This ear has best access to the sound of interest relative to other sounds. The ear closest to the sound source is often relied upon because intensity at the further ear is attenuated by the head (head shadow). Intact binaural hearing further improves listening compared to only listening with the ear that has the better signal-to-noise ratio (binaural squelch) and provides better audibility by combining the signals from each ear (binaural summation) (Gray et al., 2009). Restoring children's access to spatial/binaural cues is thus important to aid hearing in most common situations. Spatial/binaural hearing is clinically evaluated by measuring speech recognition in difficult noise conditions (speech-in-noise) or while listening with both ears over each ear alone (binaural benefit), and measuring the ability to better detect or understand speech when noise comes from different directions than the target speech (spatial unmasking). Asymmetric hearing may distort binaural cues, rendering poorer binaural benefit for speech perception and skewed abilities to detect speech in the presence of other sounds/noise.

The timing of bilateral cochlear implantation is important. As revealed by electrophysiological and functional imaging studies, delaying access to sound in early childhood allows cortical cross-modal plasticity to reorganize auditory areas (Easwar et al., 2017b; Gordon et al., 2013b; Jiwani et al., 2016; Kral et al., 2013a, 2013b; Lee et al., 2001) as well as cortical areas involved in spatial attention and awareness (Easwar et al., 2017b; Jiwani et al., 2016; Schmithorst et al., 2014) but treating only one of two ears with hearing loss leaves the second ear deprived of sound. This creates a new problem termed the "aural preference syndrome" (Gordon et al., 2015). When hearing is asymmetric, the developing brain reorganizes to preferentially respond to the better hearing ear (Gordon et al., 2013b; Keating and King, 2013; Kral et al., 2013a, 2013b; Polley et al., 2013; Polonenko et al., 2017b, 2018a; Popescu and Polley, 2010), compromising the ability to process bilateral input (Tillein et al., 2016). This reorganization occurs within 2-3 years of unilateral hearing and persists even if bilateral input through bilateral cochlear implants or bimodal devices is provided thereafter and used for several years (Chapter 4) (Gordon et al., 2013b; Polonenko et al., 2018a). Recent studies (Chapters 5 & 6) suggest that the aural preference syndrome can be reversed if symmetric/balanced bilateral input is provided during early developmental periods (Polonenko et al., 2017b, 2018a).

In the present study, we examined whether neurophysiological support for limited delays to cochlear implantation in children is consistent with functional (behavioural) outcomes. Several groups have reported spatial hearing from small cohorts (< 20) of children who received bilateral cochlear implants sequentially after fairly limited (< 2 years) bilateral auditory experience (Chadha et al., 2011; Galvin et al., 2017; Killan et al., 2015b; Litovsky et al., 2006; Murphy et al., 2011; Peters et al., 2007; Sheffield et al., 2015; Sparreboom et al., 2011). These studies revealed better speech thresholds in noise while using two implants, but asymmetric preference for a better signal at the first implanted ear in several children who underwent sequential implantation. Studies with larger cohorts of children (≥ 50) suggest that children benefit from bilateral implants despite delays to bilateral input but longer delays impair performance in the second hearing ear, creating asymmetric abilities between the two ears for understanding speech (Gordon and Papsin, 2009; Illg et al., 2017, 2013; Kocdor et al., 2016; Strøm-Roum et al., 2012) and for spatial hearing (Ching et al., 2017; Cullington et al., 2017). One of the main problems of relating existing speech perception data to electrophysiological findings is that only a few of the behavioural studies include children with very short or no delays to bilateral implantation

(Cullington et al., 2017; Gordon and Papsin, 2009), leaving a question about the most appropriate timing of bilateral input to prevent behavioural consequences of aural preference.

Behavioural data from children using bimodal devices are also needed. Whereas electrophysiological data included children with a range of hearing in the non-implanted ear (normal to severe/profound) (Polonenko et al., 2015, 2017b, 2018a), previous studies largely focused on children who have significant (severe/profound) hearing loss in their non-implanted ear (Ching et al., 2014, 2007; Holt et al., 2005; Luntz et al., 2005; Simons-McCandless and Shelton, 2000). These studies reveal benefits of bimodal hearing over the use of a cochlear implant alone but continued challenges for listening to speech in noise. Data from some children with better hearing in the non-implanted ear also reveal bimodal improvements in speech perception and spatial hearing that depend on duration of deafness in the poorer ear and access to consistent sound in the better ear (Arndt et al., 2015; Cadieux et al., 2013; Gratacap et al., 2015; Polonenko et al., 2018a). The cohorts of bimodal users represent a very diverse population of implant users (Arndt et al., 2015; Clemmens et al., 2013; Lin et al., 2017; Polonenko et al., 2018a; Sokolov et al., 2017). Asymmetric hearing loss in children appears to have an increased incidence of auditory nerve hypoplasia, enlarged vestibular aqueducts and positive cytomegalovirus (Clemmens et al., 2013; Polonenko et al., 2018a; Sokolov et al., 2017). These etiologies are associated with acquired and/or progressive hearing loss which could mitigate some of the deleterious effects of inter-implant delay (Illg et al., 2013; Killan et al., 2015b; Kocdor et al., 2016). Accordingly, the present study aimed to characterize the pre-implantation hearing histories of all children and to use this information to predict lasting effects of the degree and duration of asymmetric hearing on speech perception and spatial hearing.

Given the importance of bilateral input during development, we asked whether providing bilateral input through bilateral cochlear implants or bimodal devices worked to promote symmetric functional outcomes in a large diverse cohort of children, thereby preventing functional aural preference. We hypothesized that the benefit of bilateral input: 1) increases with earlier access to bilateral input; 2) does not need to be restricted to one mode of stimulation/hearing and 3) related to hearing experience/demographic information. Results suggest that listening through bilateral devices is better than with one device, and the best timing for intervention is to provide bilateral devices as early as possible. Decisions regarding the type of device should consider the degree of residual hearing and asymmetry between ears.

7.3 Methods

7.3.1 Participants

All methods were performed in accordance with the study protocol #1000002954 approved by the Hospital for Sick Children's Research Ethics Board. Parental consent was obtained for all participants. All available speech detection and recognition outcomes as well as demographic information between 2001-02-25 and 2017-06-20 (16.3 years) were collected from 461 children with bilateral devices: 80 (17.4%) children who used one cochlear implant (CI) and had normal hearing or used a hearing aid (HA) in the contralateral ear ("Bimodal"); 18 (3.9%) bimodal users who received a second CI ("Bimodal Sequential"); 170 (36.9%) children who received two CIs in sequential surgeries but did not wear a HA during the delay ("Sequential"); 193 children who received two CIs in the same surgery, 154 (33.4%) before age 4 years ("Simultaneous") and 39 (8.5%) after age 4 years ("Older Simultaneous"). Most implants were from Cochlear Ltd, except for 5 children who received an Advanced Bionics array in their first implanted ear. Most children received a peri-modiolar CI24RE internal electrode array (56.0% of CI1; 73.5% of CI2); the type of array was unknown for 11 (2.4%) CI1 and 4 (1.1%) CI2 (details are provided in **Supplemental Figure 7.1**). Group demographic details regarding first implanted ear, gender and whether the hearing loss was asymmetric are described in **Table 7.1A**. Asymmetric hearing loss was defined as: 1) hearing loss better than profound in one ear; 2) asymmetry $\geq$ 10 dB HL at 3 adjacent frequencies and/or pure-tone-average (PTA) asymmetry $\geq$ 15 dB HL.

7.3.2 Etiology of deafness differs by group

The distribution of known and unknown etiologies of deafness is shown for each group in **Figure 7.1**. Genetic, radiological and medical history information was available for 441/461 children (95.7%). With this information, etiology of hearing loss was identified in at least 50% (51.0 - 66.7%) of children in each group. Etiology was unknown in 17.5 - 36.0% of children in each group. Etiological distributions partitioned bimodal device from young bilateral CI users: consistent with their congenital bilateral deafness (**Table 7.1**), children with bilateral CIs had a higher rate of genetic (e.g., *GJB2*, *MTRNR1*, *DFNB*, *MITF*, *MYO7A/15A*, *LOXHD1* mutations; $\chi^2(4) = 17.1$, FDR-adjusted $p = 0.005$) or family history ($\chi^2(3) = 22.5$ FDR-adjusted $p = 0.001$) etiology of deafness, whereas bimodal users and older simultaneous bilateral CI users had a higher rate of malformations which are often associated with progressive and/or asymmetric

hearing loss (e.g., enlarged vestibular aqueduct (EVA), incomplete partition type II (IP-II/Mondini), Cock's dysplasia (common cavity, CC) or cochlear hypoplasia connected with Pendred, CHARGE, Branchio Oto Renal (BOR), X-linked deafness with stapes gusher (Phelp's) and Klippel Feil syndromes; $\chi^2(3) = 15.7$, FDR-adjusted $p = 0.005$).
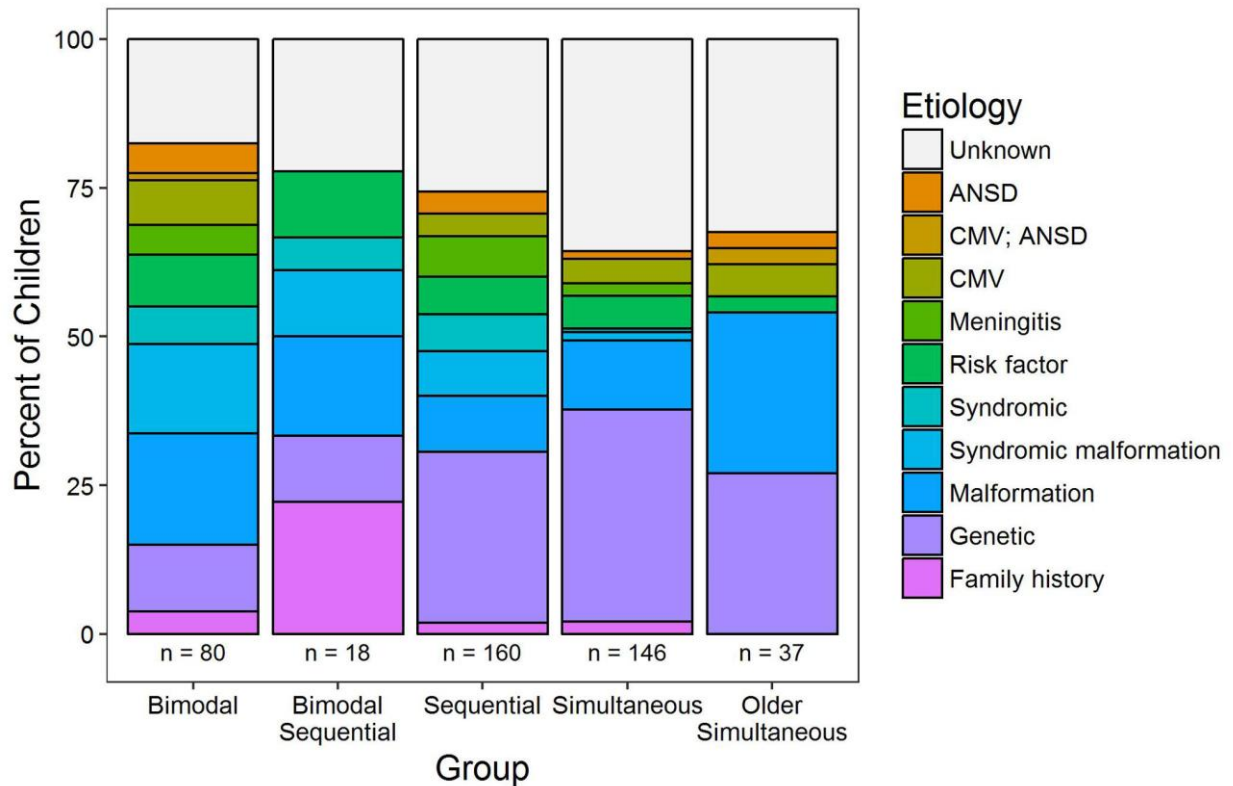
Figure 7.1. Etiology of deafness by group.

Distribution of known (coloured) and unknown (gray) etiologies of deafness in each group. Knowing family history (pink), genetic (purple) or radiological findings (blues) accounted for at least 50% of etiologies of deafness for each group. Numbers of children (*n*) in each group are provided.

7.3.3 Speech perception in quiet and co-located noise

7.3.3.1 Tests

Speech perception was evaluated in both quiet and co-located +10 dB SNR noise using words presented at 60 dB SPL through a loudspeaker at 0° azimuth in a sound-treated audiometric

booth. Speech perception tests were chosen based on language and developmental stage of the child. The following tests were used at the earliest and latest (or only) test dates, ordered by difficulty: Early Speech Perception test (earliest : latest ESP pattern/words; $n = 7:2 / 23:2$); Digit Identification (Digits; $n = 3:5$); Word Identification by Picture Identification (WIPI; $n = 20:9$); Glendonald Auditory Screening Procedure (GASP words; $n = 94:22$); Multisyllabic Lexical Neighbourhood Test (MLNT words; $n = 92:67$); and Phonemic Balanced Kindergarten test (PBK words; $n = 201:333$). Children responded by either pointing to a picture best representing the heard word from a group of pictures (closed-set: ESP, WIPI) or repeating the heard word (closed-set: Digits; open-set: GASP, MLNT, PBK). Because number of words varied across tests (12-25 words), percent correct scores were transformed to rationalized arsine units (RAU) and then corrected for guessing on closed-set tests (Sherbecoe and Studebaker, 2004; Studebaker, 1985).

7.3.3.2 Administration

All tests but the PBK were administered with monitored live voice and used speech-weighted noise. PBK tests (predominant test in available data) were administered with recorded words and the associated multi-talker noise in most cases; sometimes speech-weighted noise was used due to technical difficulties, and for some children live voice was used because of their language, developmental stage or attention abilities. Quiet and noise PBK scores from a subset of children ($n = 181$, 62.8%) were analyzed and confirmed that test administration differences did not affect speech perception in quiet (CI1, CI2/HA, bilateral), calculated asymmetry or bilateral advantage across groups (see Supplementary material, **Supplemental Table 7.1**, and **Supplemental Figure 7.2**). Significant effects of noise and presentation (recorded versus monitored live voice) were found for absolute speech perception scores in noise and thus were included as covariates in group analyses for this condition.

7.3.3.3 Conditions

In quiet, 439 children listened to words presented from the front while wearing one device at a time (unilaterally), and 374 (85.2%) of these children also listened to words while wearing both devices at the same time (bilaterally). Scores were also obtained in noise for CI1 and for the bilateral condition for 288 (65.6%) of the children. Of these, 94 (32.6%) children also had unilateral scores for both ears in noise. Repeated tests were available in quiet for both ears in

312/439 (71.1%) children and for bilateral scores in 309/374 (82.6%) children, as well as in noise for the better ear (CI1) and bilateral conditions in 272/288 (94.4%) children. Data were available for CI2 in noise for 89/94 (94.7%) children. A detailed breakdown of numbers by group, ears tested and condition is provided in **Supplemental Table 7.2A**.

To evaluate changes across repeated tests completed by the same child, scores were converted to a P̲ediatric R̲anked O̲rder S̲peech P̲erception (PROSPER) score (Trimble et al., 2008), which hierarchizes score (< 50%, ≥ 50%) and type of test into one score that could be followed over time. This accounts for a possible change in score by virtue of moving from a simpler to more challenging test. If two tests were available on a given test date, the more difficult test for that child was chosen. The number of available test dates ranged from 2 - 11, with a median of 3 tests per child (**Supplemental Table 7.2B**). Mean ± SD ages at the earliest and latest test dates were 7.3 ± 4.1 and 10.6 ± 4.1 years old respectively, for a difference of 3.3 ± 2.3 years (see **Supplemental Table 7.2C** for a breakdown by group). To evaluate speech performance in all children, scores from the latest or only available date were used, giving the greatest proportion of similar tests administered (PBK; 333/439 (75.8%)) and greatest chance for any asymmetry between ears to resolve.

7.3.4 Spatial unmasking (speech detection in co-located and separated noise)

Children wore both devices (bilateral) during testing. Speech detection thresholds (SDT) were measured as described previously (Chadha et al., 2011; Polonenko et al., 2016a). Briefly, recorded speech was presented from a loudspeaker at 0° azimuth in the presence of speech-weighted noise presented at a level of 60 dB SPL at 0° and ±90° azimuth. The speech stimulus consisted of a male talker repeatedly saying 'bup-bup-bup.' Level of the speech adaptively changed in 2 dB increments. Spatial unmasking described the benefit obtained when noise was spatially moved away from the speech and was calculated as: SDT with noise at 0°– SDT with noise at ±90°. Data were available for 171 children, 38 (22.2%) of whom performed the test more than once. Most of these children were tested on 2 occasions (**Supplemental Table 7.2**). When multiple sessions were available, the latest date was chosen for cross-sectional analyses of all children. Children were 8.4 ± 4.1 and 9.6 ± 4.3 years old at the earliest and latest tests respectively, with a difference of 1.3 ± 0.5 years.

7.3.5 Statistical Analyses

Principle component analysis (PCA) was completed on demographic variables in the hearing history rather than step-wise regression because many variables were correlated and would introduce collinearity into a multiple linear regression model. This also allowed for variables that described a similar aspect of hearing history to be combined into one component that guided correlation analyses with outcome measures.

ANOVA was used to assess group differences in a number of measures: demographic variables provided in Table 1; principle component values; asymmetry in speech perception; asymmetry in spatial unmasking; and asymmetry in speech perception across etiology. Repeated measures ANOVA was used to assess main effects and interactions for group differences (between-subject factor) where conditions were repeated (within-subject factor): bilateral speech perception scores in quiet versus in noise; bilateral advantage for speech perception over using CI1 or CI2/HA alone; bilateral advantage in quiet versus in noise; speech detection thresholds with noise directed to the front, CI1 or CI2/HA; and spatial unmasking with noise moved from the front to CI1 versus CI2/HA. Greenhouse-Geisser corrections for lack of sphericity were used when indicated by a significant Mauchly test of sphericity. Tukey's honest significant difference (HSD) post-hoc testing was completed for significant effects in the ANOVA and repeated measures ANOVA to account for family-wise error in multiple comparisons.

The asymmetry in speech perception and in spatial unmasking was assessed in order to further highlight the capabilities and challenges of bilateral device users. Asymmetry between CI1 and CI2/HA was further assessed using Lin's concordance correlation coefficient (Lin et al., 2002; Watson and Petrie, 2010), which assesses the extent to which points conform to the line of best fit (correlated) and how far that line is from the unity line (perfect agreement). This analysis quantified asymmetry in each child while accounting for the absolute accuracy of scores or unmasking in each ear, which is lost when only difference measures (i.e., the asymmetry) are provided. This complexity and richness in information is important to retain while evaluating the wide variability in outcomes in diverse groups of bilateral device users. Furthermore, Lin's coefficient accounts for differences/deviations from agreement (i.e., symmetry) (whereas Pearson correlations do not). This way, the complexity and variability of the individual data across children who had poor scores and good scores could be highlighted alongside asymmetry.

An ANOVA analysis assessed group differences in speech perception asymmetry, bilateral advantage and spatial unmasking asymmetry. The significance of these difference measures was analyzed compared to zero using independent t-tests with false-discovery rate (FDR) corrections to p-values for multiple comparisons (Benjamini and Hochberg, 1995).

Pearson correlations were used to assess the following relationships between the following outcome measures: bilateral advantage versus absolute asymmetry in speech perception; bilateral speech detection thresholds versus bilateral speech perception in noise coming from the front; and asymmetry in spatial unmasking versus asymmetry in speech perception. Correlations were also completed to identify relationships between asymmetry in speech perception and the PCA components of hearing history. These correlations guided which demographic variables were considered for regression analyses in order to predict changes in speech perception asymmetry.

Linear mixed effects regression models (Mcculloch and Neuhaus, 2006) were used to assess changes speech perception asymmetry over time, as well as the progression from easier to harder tests of speech perception (PROSPER score) with bilateral device experience. These mixed regressions were used instead of simple linear regression in order to account for repeated measures per child and to allow for individual variation in the relationship over time. To do this, random effects of both intercept and slope for each child (1+ years | subject) were added to the regression model. A likelihood ratio test was used to determine significance of predictors in the regression. The equation of the full linear mixed effects model is given below:

$$\text{score} \sim \text{years} + \text{group} + \text{years} : \text{group} + (1 + \text{years} \mid \text{subject})$$

Visual inspection of residual plots for each analysis did not reveal any obvious deviations from homoscedasticity or normality.

7.3.6 Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

7.4   Results

7.4.1 Principle component analysis of hearing history differentiates groups of children receiving bilateral devices

Group demographic details are described in **Table 7.1**. To better understand the largest sources of variation in several related demographic variables of the hearing histories in children with bilateral devices (ANOVA group comparisons for each variable, $p < 0.0001$; **Table 7.1**), a principal component (PC) analysis was completed after log-transforming and standardizing the following pre-implantation variables: age at first implantation; unaided pure-tone-average of 0.5, 1, 2 kHz (PTA) in the first and second implanted ears or ear that maintained HA use; pre-implantation unaided PTA asymmetry; post-implantation (bilateral devices) aided PTA asymmetry; and durations of asymmetric hearing loss, unilateral deafness (thresholds $\geq$ 90 dB HL), bilateral deafness and pre-implantation acoustic hearing. Mean $\pm$ SD for these variables by group are summarized in **Table 7.1B**. Complete data for all these variables, available in 361/461 (78.3%) children, were used in the PCA. Three components with eigenvalues > 1 were extracted, which together explained 69% of the variance in hearing histories. By combining several related demographic variables into components, the comprehensive hearing history could be considered when predicting behavioural outcomes.

Table 7.1. Group numbers and mean ± SD of time- and hearing-based factors used in the principal component analysis, and of the first 3 principal components.

Variable		Bimodal Devices (HA + CI) (n=80)	Bimodal Sequential BiCI (n=18)	Sequential BiCI (n=170)	Simultaneous BiCI (n=154)	Older Simultaneous BiCI (n=39)	Statistic *p < 0.05
A. Factors not in PCA							
Implanted ear: Left / Right (% Right)		40/40 (50.0%)	7/11 (61.1%)	33/137 (80.6%)	n/a	n/a	$X^2(2)$=24.8*
Gender: Female / Male (% Male)		31/49 (61.3%)	5/13 (72.2%)	79/91 (53.5%)	59/95 (61.7%)	22/17 (43.6%)	$X^2(4)$=7.3
Hearing loss: Symmetric / Asymmetric (% Asymmetric)		20/60 (75.0%)	8/10 (55.6%)	142/11 (7.2%)	139/6 (4.1%)	24/11 (34.1%)	$X^2(4)$=201.3*
Bilateral device use (years)	Speech perception test	3.2±2.9	2.0±1.4	3.8±2.8	5.1±2.2	2.5±1.8	$F(4,432)$=14.1*
	Spatial unmasking test	3.2±3.0	2.4±1.5	6.5±3.1	5.1±2.7	2.8±1.9	$F(4,164)$=10.3*
B. Factors in PCA							
Age (years)	Age at CI1	7.2±4.6	6.7±3.9	3.3±3.3	1.7±1.0	10.0±4.4	$F(4,455)$=78.4*
Duration of experience (years)	Pre-CI acoustic hearing	6.0±4.6	5.2±3.9	0.6±1.5	0.2±0.6	5.7±4.6	$F(4,413)$=91.6*
	Asymmetric hearing	2.4±3.4	1.6±3.1	0.1±0.7	0.0±0.2	0.4±1.8	$F(4,411)$=28.5*
Duration of deafness (years)	Unilateral	1.6±2.7	1.1±2.9	0.1±0.7	0.0±0.2	0.4±1.8	$F(4,411)$=17.9*
	Bilateral	0.1±0.6	0.3±0.6	1.1±1.8	0.8±0.5	1.6±2.8	$F(4,413)$=10.2*
Pre-CI unaided PTA (dB HL)	CI1 ear	93.4±18.2	94.2±19.5	107.5±13.8	104.8±14.0	95.1±13.6	$F(4,400)$=15.3*
	CI2/HA ear	67.5±22.7	84.0±7.5	107.0±14.6	104.6±14.2	99.4±12.1	$F(4,420)$=94.3*
Hearing asymmetry (dB)	Pre-CI unaided	27.9±26.9	17.9±15.7	6.9±7.5	6.6±7.4	10.0±11.8	$F(4,399)$=35.1*
	Post-CI aided	10.0±7.2	5.6±5.8	4.0±4.1	3.0±3.1	1.9±1.7	$F(4,393)$=31.8*
C. Main PCA Components (Eigenvalues >1)							
PC1: Asymmetry		-4.6±2.2	-3.2±1.8	0.3±1.3	0.7±1.1	-1.0±1.6	$F(4,356)$=168.1*
PC2: Unilateral deafness		-2.2±2.9	-1.0±2.8	-0.9±1.4	-0.7±1.1	0.9±1.2	$F(4,356)$=19.67*
PC3: Any deafness (unilateral and/or bilateral)		5.7±4.9	2.7±4.0	1.8±2.8	1.3±2.1	-0.3±1.5	$F(4,356)$=28.22*

CI = cochlear implant; HA = hearing aid; BiCI = bilateral cochlear implants; PTA = pure-tone average of .5, 1, 2 kHz hearing thresholds; PC = principal component; CI1 = first implanted ear; CI2 = second implanted ear
Note: Groups were compared using a Chi-Square test for proportion variables and ANOVA for continuous variables. The corresponding Chi-squared and F statistics are provided in the last column.

To describe what each PC encompassed, variables that contributed proportionally more to the PC than expected from equal contributions were considered (i.e., >100% / 9 variables = 11.1%). The first two components together explained 57.7% of the variance in hearing history and both included variables associated with asymmetric hearing experience prior to implantation (age at CI1, duration of asymmetric hearing, and duration of unilateral deafness). However, additional variables that differed between the two components contributed to different aspects of the asymmetric hearing experience. The first component (PC1) individually explained 42.6% of the variance in hearing history and, along with the 3 variables that were related to pre-implant asymmetric hearing experience, included variables associated with the duration and degree of residual acoustic hearing (duration of pre-acoustic hearing and unaided PTA in the CI2/HA ear).

This first component thus reflected the contribution of the better ear to the asymmetric hearing experience. The second component included the unaided PTA in the CI1 ear, reflecting the contribution of residual hearing or deafness in the poorer hearing ear to the asymmetric hearing experience. This second component explained 15.1% of the variance. A third component, explaining 11.4% of the variance, was associated with any deafness or poor residual hearing pre- or post-implantation (duration of unilateral and bilateral deafness, unaided PTA in CI2/HA ear, post-CI asymmetry in aided PTA). The relationships between components are plotted in **Figure 7.2** (**Figure 7.2A** shows PC1 and PC2 and **Figure 7.2B** shows PC1 and PC3). Also shown by arrows are the correlation coefficients (factor loadings) of the variables with each component. The factor loading matrix of the PCA is provided in **Supplemental Table 7.4**; shaded and bolded factors most contributed to each PC.

Groups were clearly identified by differences in PC scores (**Table 7.1C**, ANOVA $p < 0.001$). PC1 differentiated groups with varying degrees and durations of asymmetry: bimodal users experienced the most asymmetry (negative PC1 values) followed by bimodal sequential users (Tukey HSD post-hoc test $p = 0.008$). The older simultaneous group had significantly less asymmetric hearing than both bimodal groups (both $p < 0.001$) but significantly more than the bilateral simultaneous (all $p < 0.001$) and sequential (all $p < 0.001$) groups who both experienced very minimal asymmetry ($p = 0.17$). This is consistent with the number of children categorized as having (a)symmetric hearing loss and the mean PTA asymmetries in **Table 7.1A/B**. PC2 differentiated groups with residual or unilateral hearing: older simultaneous users experienced periods of progressive bilateral hearing loss (higher PC2 scores, all $p < 0.001$) compared to the minimal hearing experience of sequential and simultaneous bilateral CI users prior to implantation (PC2 scores around zero). This contrasts with the negative PC2 scores of bimodal groups (all $p < 0.01$) who had better residual hearing in the CI1 ear ($p < 0.001$), later implantation ($p < 0.001$), and longer durations of asymmetric hearing ($p < 0.001$) and unilateral deafness ($p < 0.001$). Although bimodal and bimodal sequential groups significantly differed by asymmetric (PC1 $p = 0.008$) but not deafness-related PC scores (PC2 $p = 0.08$; PC3 $p = 0.11$), bimodal sequential users had worse residual hearing in the ear that kept the HA while waiting to receive a second implant ($p = 0.001$), and consequently tended to have less hearing asymmetry pre-CI2 ($p = 0.069$).
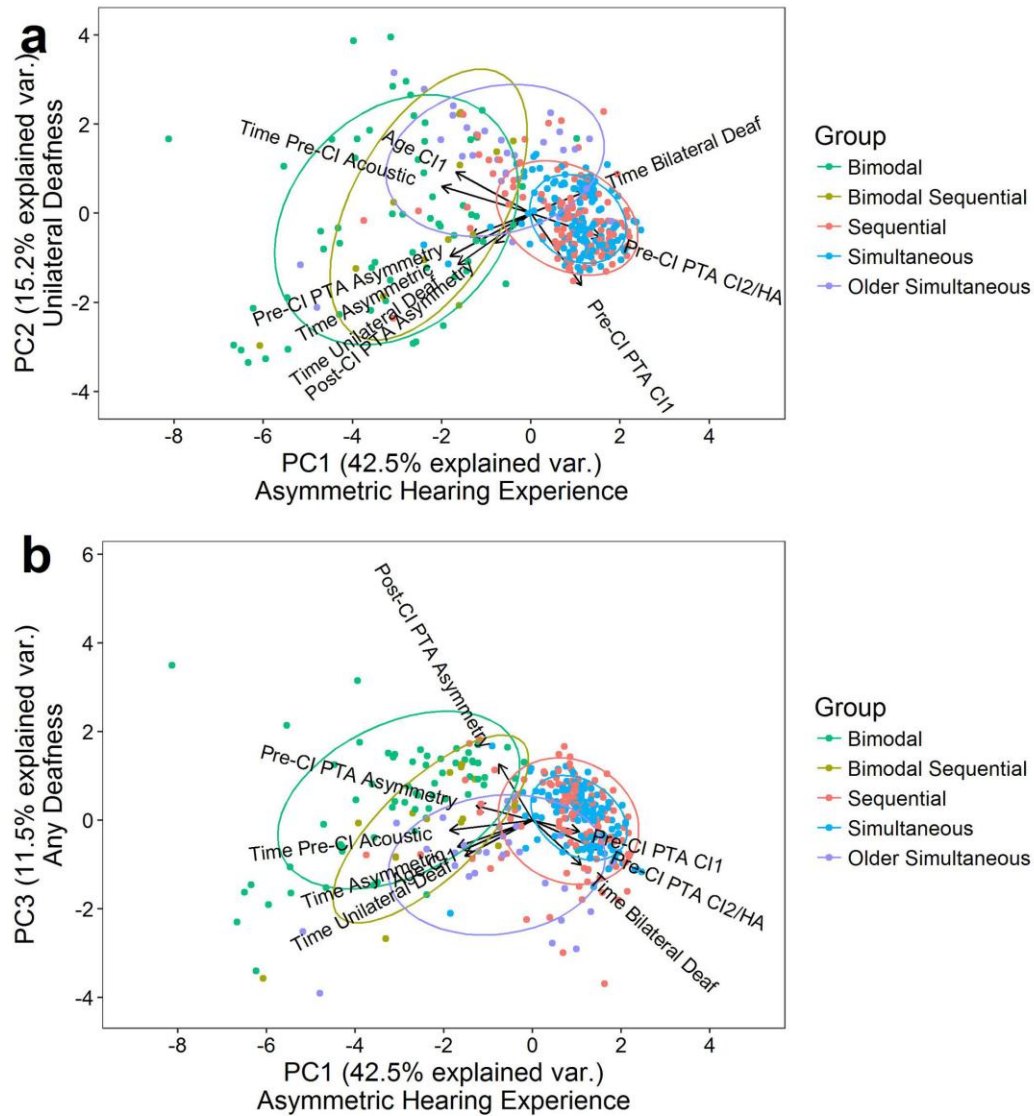
Figure 7.2. Principal component analysis of hearing histories.

Principal component (PC) scores and their loading vectors are displayed for (**A**) PC2 and (**B**) PC3 relative to PC1, which together explained 69% of the variance in the hearing histories of each group of bilateral device users. Variables contributing highly to PC1 related to the asymmetric hearing experience whereas the combination of highly contributing variables to PC2 and PC3 correspond to unilateral deafness or any type of deafness (unilateral and bilateral) respectively. Ellipses represent 68% (±1SD distributions) of the scores for each group, which are differentiated by colour.

7.4.2 Most children rapidly achieve open-set speech perception skills after bilateral/bimodal device use

The first analyses examined longitudinal changes in speech perception accuracy on standardized tests after activating bilateral input through bilateral CIs or bimodal hearing. The same test was administered to each ear in quiet and noise during a single session, so the Pediatric Ranked Order Speech Perception (PROSPER) score was similar for both ears and condition at each test time. Representative data for CI1 in quiet are plotted **Figure 7.3**. Of 307 children tested repeatedly, 186 (60.6%) children with initial scores <33 (i.e., easier tasks than the PBK) progressively improved by 4.3±0.6 PROSPER scores per year of bilateral device use (linear mixed effects regression; likelihood ratio test $\chi^2(1)$=219.4, p<0.001; **Figure 7.3A**). This means that children advanced through two tests each year. The rate of change with bilateral device experience was similar for all groups ($\chi^2(3)$=3.9, p=0.274) but the intercept varied by group ($\chi^2(3)$=63.9, *p*<0.001). Simultaneous users began their bilateral hearing with easier tasks (-4.0±1.2 PROSPER score; 2 tests) and sequential users started with a harder task (2.7±1.3 PROSPER score; 1 test) than the bimodal and older simultaneous groups, which partly reflected their older age at bilateral device use (**Figure 7.3B**). This meant that, of the children who reached the milestone of testing by PBK (133/186; 71.5%), 82% of bimodal users (9/11) and 84% of the simultaneous bilateral CI group (65/77) were under 8 years of age, whereas only approximately half of the sequential (17/35; 48.6%) and older simultaneous (5/10; 50.0%) bilateral CI groups could be tested with the PBK by 8 years of age (Fisher's Test p<0.001; **Figure 7.3B**).
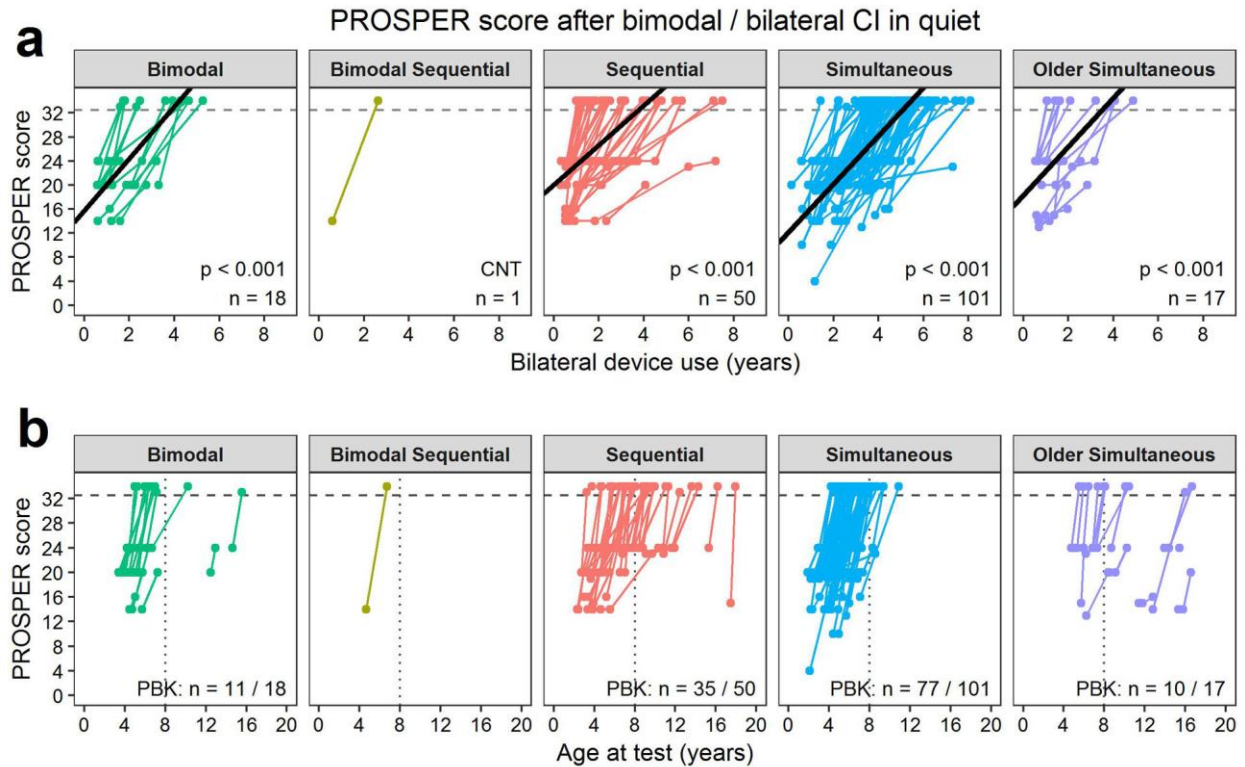
Figure 7.3. Progressive speech perception testing with time.

(**A**) The Pediatric Ranked Order Speech Perception (PROSPER) score for the CI1-quiet condition increased with bilateral device experience (linear mixed-effects regression with likelihood ratio test: $\chi^2(1) = 219.4$, $p < 0.001$; solid black lines) at a similar rate for each group ($\chi^2(3) = 3.9$, $p = 0.274$). This measure hierarchizes accuracy ($< 50\%$, $\geq 50\%$) and test from simple detection to open-set word recognition. The dashed gray line delineates scores for the most challenging PBK words test (≥ 33). Coloured lines join scores for each child across time. The bottom right corner of each panel displays the number of children (*n*) in each group for whom repeated testing was available with initial scores <33. (**B**) Most children progressed to testing with the PBK (numbers indicated at the bottom right of each panel) but this occurred after age 8 years (dotted line) in more of the sequential and older simultaneous bilateral implant users than bimodal and simultaneous users.

7.4.3 Asymmetric speech perception develops in some children

Functional aural preference was measured as asymmetric speech perception between the two ears using scores from the latest available test. Most were PBK test scores (333/439, 75.8%). The simultaneous group used bilateral devices the longest ($p < 0.001$) but all groups used both

devices for at least 2 years (**Table 7.1A**). Asymmetry in speech perception is shown in **Figure 7.4**. In **Figure 7.4A**, speech perception scores for the ear with the HA (bimodal users) or CI2 (bilateral CI users) are plotted against those of the CI1 ear. In quiet, at least 68% ($\pm$1SD) of children in all but the simultaneous group had better speech perception scores using CI1 than CI2/HA, as indicated by ellipses and data points below the unity line, and small ($< \pm 0.4$) concordance correlation coefficients. The same asymmetries were found for sequential and bimodal groups when testing in noise, although overall scores were poorer (**Figure 7.4A**), whereas speech perception continued to be symmetric between the ears in both simultaneous groups. Only a few bimodal sequential bilateral CI users were tested in noise.

Mean $\pm$ SE asymmetry (**Figure 7.4B**) favoured CI1 across groups (insufficient bimodal sequential data in noise for analyses) but the degree of asymmetry varied by group (ANOVA, quiet: $F(4,434) = 14.6$, $p < 0.001$; noise: $F(3,85) = 2.9$, $p = 0.038$). Speech perception was more asymmetric for bimodal and sequential groups than the simultaneous group in quiet (both Tukey HSD post-hoc $p < 0.001$), and for sequential compared to simultaneous bilateral CI users in noise (Tukey HSD post-hoc $p = 0.032$).

Longitudinal measures in both ears were available in 307 (69.9%) children and revealed little change in asymmetry using linear mixed effect regression (0.6 ± 0.3 RAU/year of age; $\chi^2(1) = 5.4$, $p = 0.02$; see **Supplemental Figure 7.3**). There was no significant change in slope by group (interaction: $\chi^2(4) = 5.6$, $p = 0.20$) but, consistent with **Figure 7.4**, the degree of asymmetry differed by group (intercept: $\chi^2(4) = 66.8$, $p < 0.001$): bimodal and sequential groups had the greatest asymmetry (25.7 and 22.0 RAU respectively) and simultaneous groups had the least (-1.1 - 1.3 RAU).
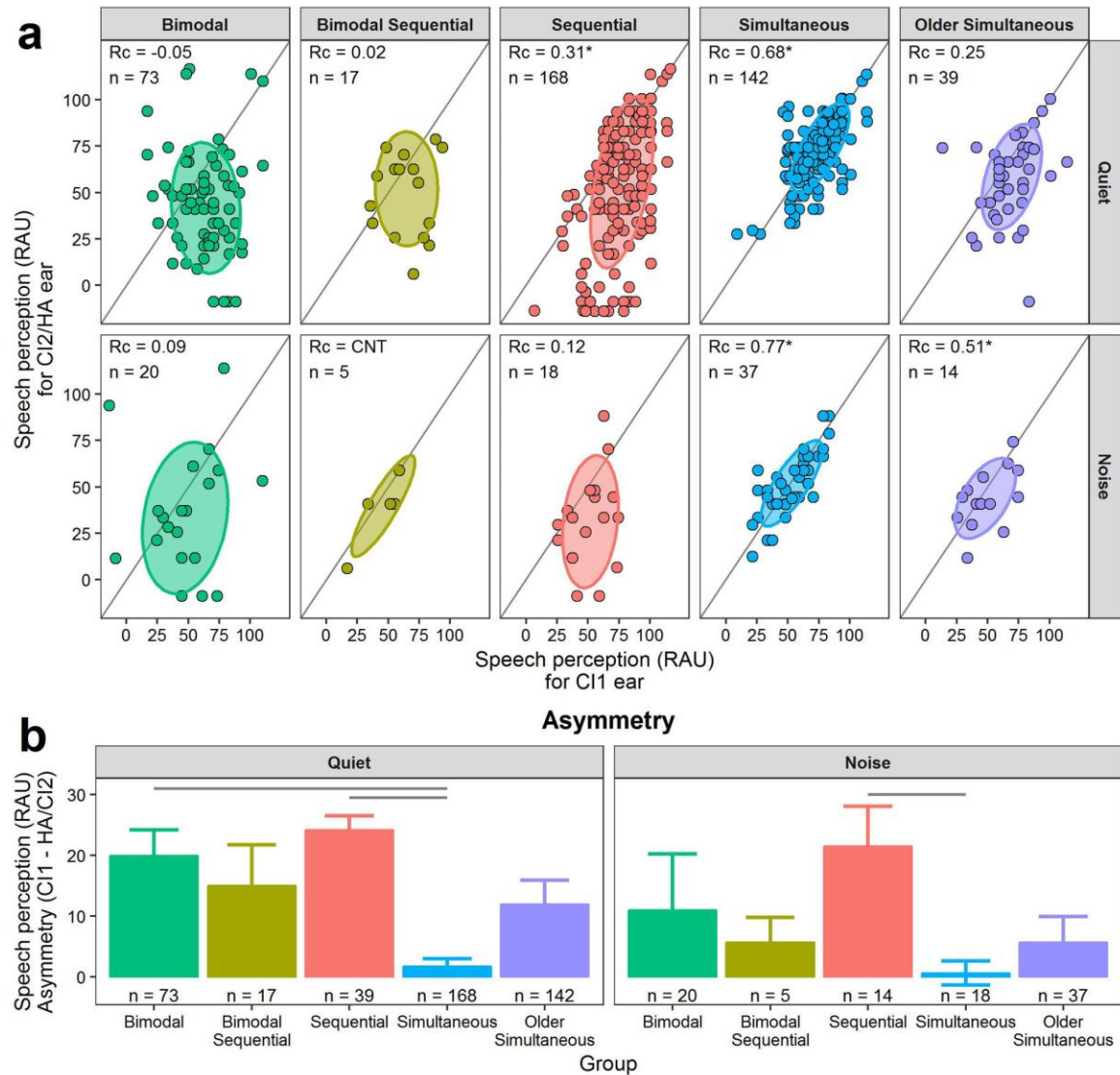
Figure 7.4. Asymmetry in speech perception between each ear tested in quiet and noise.
(**A**) Speech perception in rationalized arcsine units (RAU) of the ear with the hearing aid (HA) or second cochlear implant (CI2) was worse than that of the first implanted ear (CI1) for all but the simultaneous groups when measured in quiet or +10 dB SNR noise, as indicated by ±1 SD (68% of data) ellipses residing below the gray unity lines. Concordance correlation coefficients (*Rc*) and number of children (*n*) are provided for each group and condition; asterisks indicate when the 95% confidence interval of the *Rc* estimate does not cross zero. (**B**) Mean (± SE) asymmetry in speech perception (RAU) was greatest in bimodal and sequential bilateral CI users and smallest in young simultaneous bilateral CI users. Positive values indicate better scores for CI1. Gray lines denote Tukey HSD post-hoc comparisons with $p < 0.05$. CNT = could not test (too few children); CI = cochlear implant; HA = hearing aid.

7.4.4 Bilateral advantage in quiet and noise for all groups

Mean ± SE bilateral speech perception scores in quiet and in noise are presented in **Figure 7.5A**. For each group, mean accuracy was ≥75 RAU in quiet but <75 RAU in noise. While accounting for the significant effect of stimulus delivery method (see **Supplemental Figure 7.2**) in a repeated measures ANOVA, bilateral scores differed by group ($F(4,299) = 5.4$, $p < 0.001$) and condition ($F(1,299) = 349.9$, $p < 0.001$) but there was no interaction between group and condition ($F(4,299) = 1.3$, $p = 0.26$). Bilateral accuracy was 8.8 ± 2.4 RAU greater for quiet than noise (Tukey HSD post-hoc $z = 3.6$, $p < 0.001$), and simultaneous bilateral CI users were 10.7 ± 3.5 RAU more accurate than bimodal users ($z = 3.1$, $p = 0.017$).

The potential advantage of bilateral CI and bimodal device use relative to each ear was examined. As shown in **Figure 7.5B**, all groups demonstrated a significant advantage of bilateral device use over listening with one ear alone (independent t-test $\mu = 0$, $p < 0.05$) but the degree of benefit significantly differed by ear and group (repeated measures ANOVA: $F(4,369) = 14.7$, $p < 0.001$). In simultaneous and bimodal sequential groups, the bilateral advantage was equal regardless of which ear was the unilateral reference (Tukey HSD post-hoc $p > 0.05$). Conversely, bilateral benefit was asymmetric with more benefit relative to the overall poorer ear alone for bimodal (the HA: Tukey HSD post-hoc $z = 5.6$, $p < 0.01$) and sequential bilateral CI users (the CI2: Tukey HSD post-hoc $z = 12.5$, $p < 0.01$). **Figure 7.5C** shows the mean ± SE bilateral advantage over listening with CI1 (often the stronger ear) alone in both quiet and noise. Irrespective of group (repeated measures ANOVA $F(4,278) = 1.8$, $p = 0.13$), bilateral advantage was 4.2 ± 1.7 RAU greater in noise than in quiet (repeated measures ANOVA $F(1,278) = 6.3$, $p = 0.013$), which highlights the importance of bilateral input in challenging acoustic conditions. Bilateral advantage over CI2/HA in noise is plotted in **Supplemental Figure 7.4**.
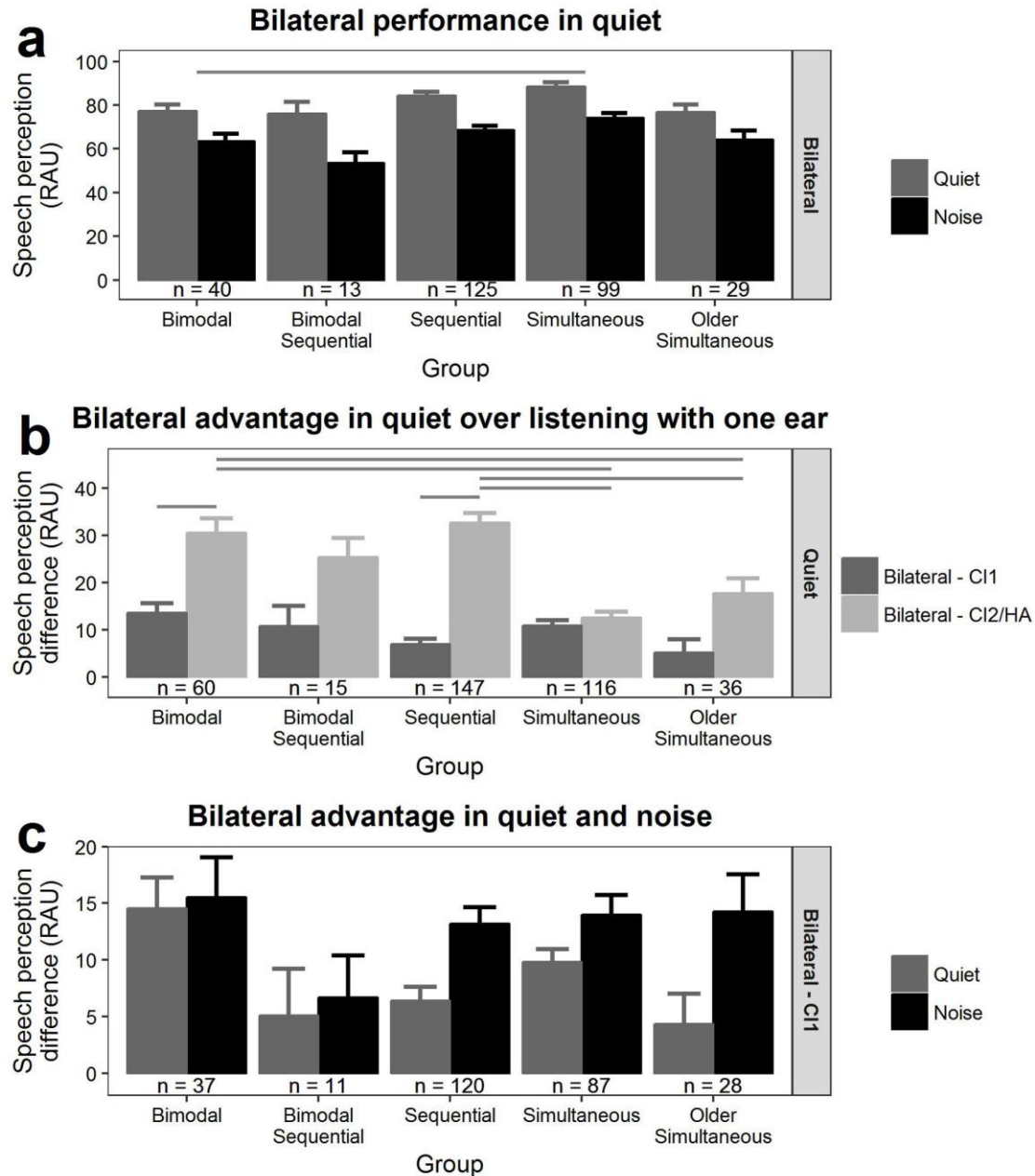
Figure 7.5. Bilateral advantage for speech perception.

(**A**) Mean ± SE bilateral speech perception accuracy was greater in quiet than in noise for all groups. Simultaneous bilateral cochlear implant (CI) users were more accurate than bimodal users (Tukey HSD post-hoc comparison $p < 0.05$). (B) Bilateral advantage was calculated as: bilateral - unilateral speech perception. Mean ± SE bilateral advantage is provided. In quiet, all groups experienced bilateral benefit over listening with only one ear. There was a group x ear interaction in bilateral advantage. The bilateral advantage to speech perception was greater compared with HA/CI2 alone versus CI1 alone for bimodal and sequential users. The bilateral

advantage over HA/CI2 was greater for bimodal and sequential users than both simultaneous and older simultaneous groups. Gray lines indicate significant post-hoc Tukey HSD comparisons (*p* < 0.05). (**C**) The bilateral advantage over listening with only CI1 was greater in noise than quiet across groups (main effect of condition only).

7.4.5 Symmetric speech perception is needed for greatest advantage of bilateral hearing

Figure 7.6 shows the advantage of bilateral input for speech perception over listening with the best performing ear alone. Regression lines indicate a decreasing bilateral benefit as absolute asymmetry between the two ears increases (R = -0.34 to -0.73, $p < 0.05$). A similarly negative relationship was found between the advantage of adding bilateral hearing to hearing with CI1 alone and asymmetry in speech perception (**Supplemental Figure 7.5**). There was no relationship between absolute bilateral speech perception accuracy and asymmetry in speech perception, or with principle components or hearing history variables comprising the principle components ($p > 0.05$).
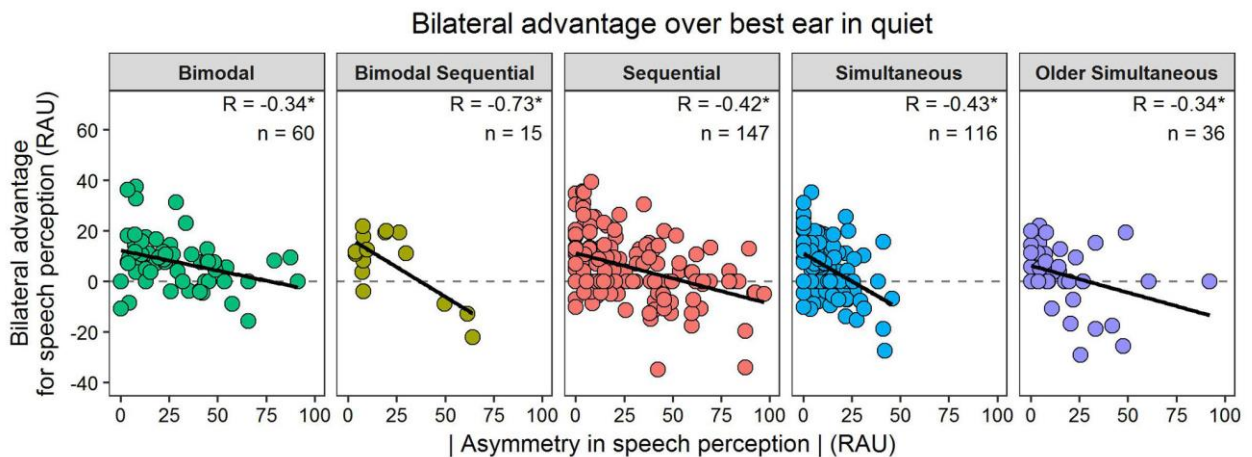
Figure 7.6. Asymmetry and bilateral advantage for speech perception are related.
For each group the advantage of bilateral input over the best performing ear alone decreased as the absolute asymmetry in speech perception in quiet increased. Correlation coefficients (*R*) and number of children (*n*) are provided for each group and condition. Asterisks indicate correlations with *p* < 0.05.

7.4.6 Children with bilateral/bimodal devices benefit from spatial hearing

Mean ± SE detection thresholds for speech in noise are presented in **Figure 7.7A**. Age at test differed by group (ANOVA $F(4,166) = 41.4$, $p < 0.001$): simultaneous users were younger than bimodal users (Tukey HSD post-hoc $p < 0.001$), and both of these groups were younger than the other three groups ($p < 0.05$). Furthermore, simultaneous and sequential groups had longer bilateral device use than the other groups (all $p < 0.05$; **Table 7.1A**). Because younger children are expected to have worse speech thresholds in noise (Chadha et al., 2011; Garadat and Litovsky, 2007; Schafer et al., 2012), age was added as a covariate to subsequent analyses. Speech detection thresholds were affected by direction of noise (repeated measures ANOVA $F(2,328) = 9.3$, $p < 0.001$) but not group ($F(4,164) = 2.2$, $p = 0.07$) or age ($F(1,164) = 3.3$, $p = 0.07$). Speech detection thresholds improved (more negative) when noise was spatially separated from the speech (spatial unmasking) (Tukey HSD post-hoc $z < -3$, $p < 0.001$) and was best when noise was directed towards CI2/HA ($z = -2.6$, $p = 0.031$).

To further explore these differences, the degree of spatial unmasking (thresholds with collocated - spatially separated speech and noise) was calculated for each noise direction (**Figure 7.7B**). Most children had positive (improved) spatial unmasking values. The ±1SD distribution ellipses (68% of data) and data points above the unity line for the bimodal and sequential groups suggest these groups tended to derive more spatial unmasking when noise was directed to CI2/HA. Accordingly, concordance correlation coefficients were small ($< ±0.4$) or insignificant. Bimodal sequential and both simultaneous groups had ±1SD distributions along the unity line indicating overall symmetric spatial hearing. Age did not impact spatial unmasking (covariate in repeated measures ANOVA $F(1,164) = 0.01$, $p = 0.92$) but there was a significant interaction between group and direction of noise ($F(4,164) = 2.6$, $p = 0.035$), whereby bimodal users experienced (mean ± SD) $2.5 ± 0.6$ dB greater spatial unmasking with noise directed to the HA than CI1 (Tukey HSD post-hoc $z = 3.9$, $p < 0.01$). Overall, the groups experienced $3.3 ± 3.6$ dB (bimodal group) to $3.9 ± 2.1$ dB (older simultaneous group) spatial unmasking.

Asymmetric spatial unmasking between the two sides could relate to aural preference. As shown in **Figure 7.7C**, asymmetric spatial unmasking differed across groups (ANOVA $F(4,14) = 2.5$, $p = 0.041$) regardless of age ($F(1,164) = 0.5$, $p = 0.48$). Bimodal ($2.5 ± 0.6$ dB, independent t-test $t(35) = -3.9$, FDR-adjusted $p = 0.002$) and sequential bilateral CI users ($1.2 ± 0.6$ dB, $t(33) = -$

2.2, $p = 0.088$) had notable asymmetries. Asymmetry in the bimodal group, in particular, was greater than the test step-size of 2 dB and greater than the asymmetry in simultaneous users (difference: 2.3 ± 0.2 dB; Tukey HSD post-hoc $p = 0.026$). This preference for a better signal-to-noise ratio in CI1 occurred in the sequential users despite similar access to sound in each ear as measured by aided pure-tone average thresholds; the difference between the two CIs in this group was 4.1 ± 4.1 dB which was less than the test step-size of 5 dB (Table 1B). The asymmetric use of spatial separation in bimodal users could partly reflect the 10.0 ± 7.2 dB better audibility provided by the CI1 relative to HA which is a difference of 2 test step-sizes (**Table 7.1B**).
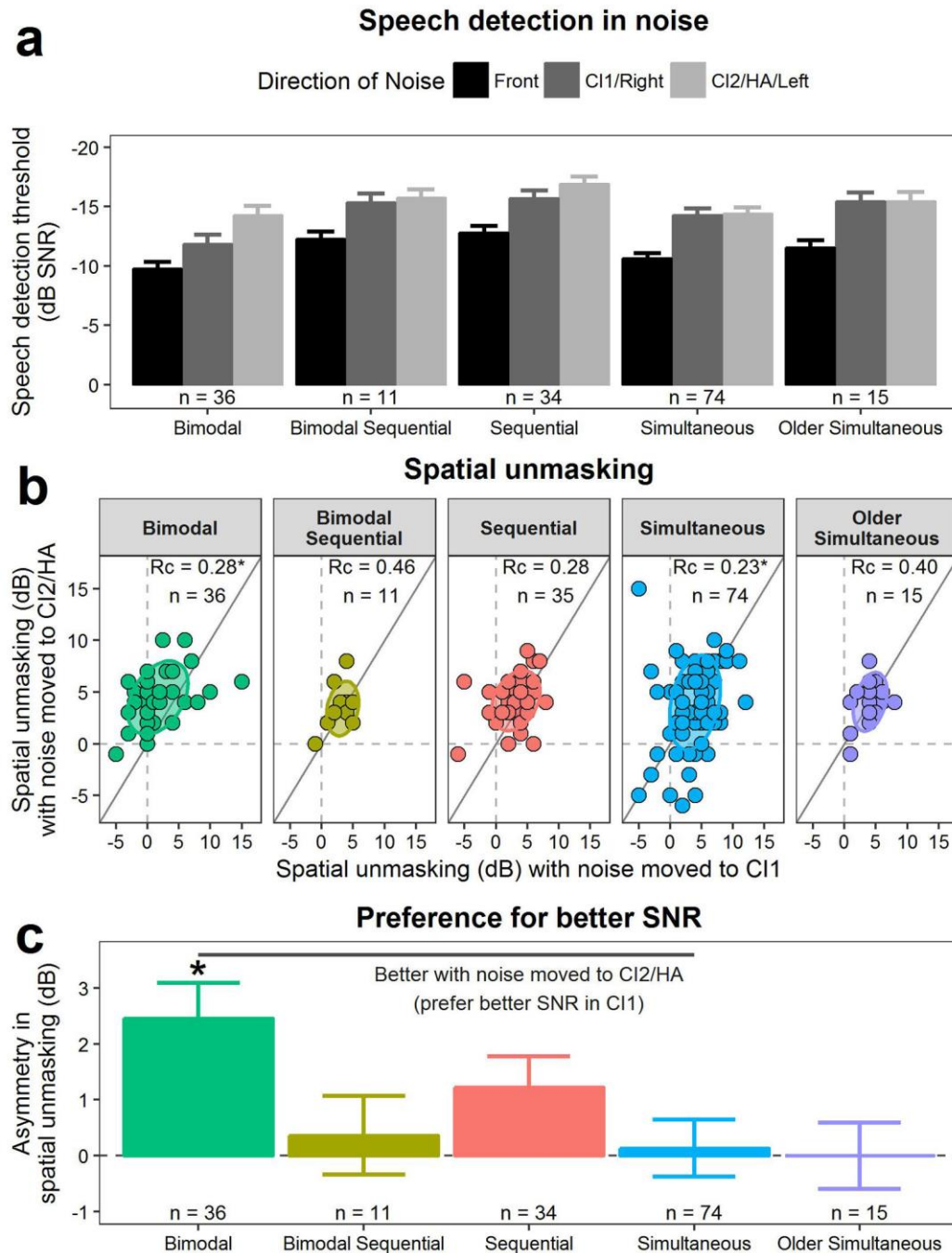
Figure 7.7. Speech detection and spatial unmasking in noise.

(**A**) Mean ± SE speech detection thresholds with speech-weighted noise to the side of the first implanted ear (CI1; dark gray) or to the side of ear with the second cochlear implant (CI2) or hearing aid (HA) (light gray) were better (more negative) than with noise coming from the front (black). Note the reversed scale; better (negative) scores are shown going upwards. (**B**) Most children benefited from spatial unmasking (values > 0) from when noise was moved from the

front to the side of CI2/HA versus from the front to the side of CI1. Gray lines denote unity, ellipses represent the ±1SD (68%) distribution of response in each group. The concordance correlation coefficient (*Rc*) is given for each group, with an asterisk identifying when the 95% confidence interval does not cross zero. (**C**) Mean ± SE difference in spatial unmasking between moving noise from front to either side (asymmetry). The asterisk indicates a significant difference from zero (FDR-corrected $p < 0.05$) based on independent *t*-tests and the gray line denotes significant difference between groups based on ANOVA ($p < 0.05$).

7.4.7 Aural preference is revealed by both speech detection and perception

Of the 439 children with speech perception data, 148 (33.7%) also underwent spatial unmasking testing. Each test was completed within 4.7 ± 13.5 months of each other. Outcomes for each test are compared in **Figure 7.8**. Bilateral speech perception scores in co-located noise at front did not correlate with speech detection thresholds in co-located noise at front ($p > 0.05$; **Figure 7.8A**) and asymmetry in speech perception tested in quiet or noise did not correlate with asymmetry in spatial unmasking (p > 0.05, except $p = 0.01$ for bimodal sequential users for speech perception asymmetry in quiet). Yet, both measures revealed consistent preference for CI1 (**Figure 7.8B**) in bimodal and sequential bilateral CI users. The ±1SD (68% of children) distributions fall in the quadrant indicating a preference for CI1 in both measures; they had better speech perception scores when using CI1 and more benefit from spatially separating speech and noise when CI1 had the better signal-to-noise ratio (**Figure 7.8B**). In contrast, the two simultaneous group distributions did not cluster in one quadrant, indicating no overall preference for one ear on either measure.
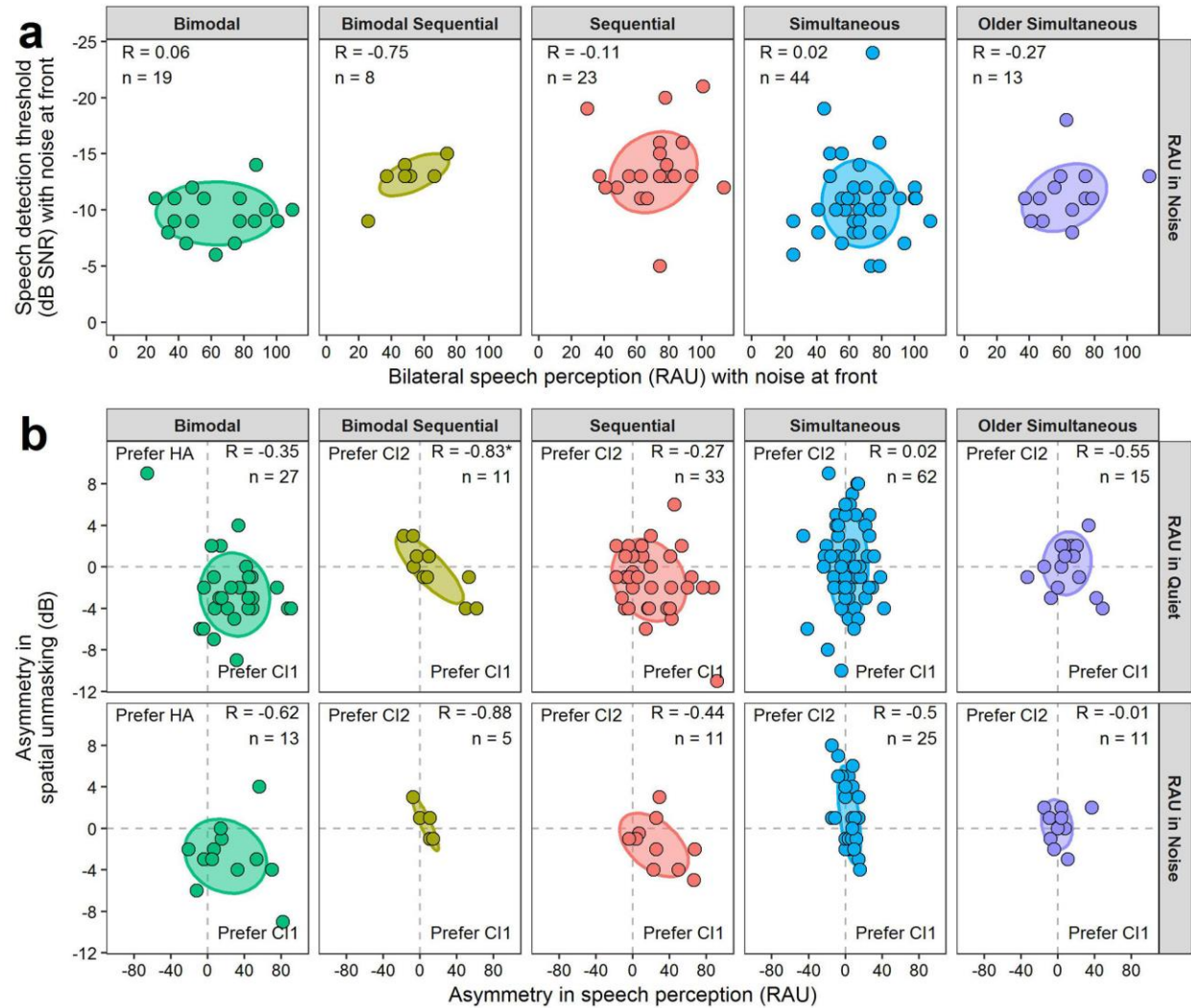
Figure 7.8. Relationship between speech detection and speech perception.

(**A**) There was no relationship between speech detection thresholds in co-located noise (at front) and bilateral speech perception in co-located noise. (**B**) The relationship between asymmetry in spatial unmasking and asymmetry in speech perception tested in quiet and noise. For bimodal and sequential bilateral cochlear implant (CI) users, asymmetries in both measures favoured better performance with CI1 (bottom right quadrant). Pearson correlation coefficients (*R*) and number of children (*n*) are provided in each panel. * *p* < 0.05.

7.4.8 Asymmetry increases with delayed or poor access to bilateral sound

Etiology did not predict speech perception asymmetry (ANOVA: $F(4,419) = 0.7$, $p = 0.58$) or spatial unmasking asymmetry ($F(4,158) = 0.2$, $p = 0.94$) (see **Supplemental Figure 7.6**). Rather, asymmetry was predicted by the time- and hearing-based variables in the children's diverse hearing histories. Correlations were first completed to identify associations between speech perception asymmetry and PCA components, as they captured different aspects of bilateral device users' pre-implantation hearing. In quiet, speech perception asymmetry increased with lower PC2 scores (more unilateral deafness) ($R = -0.19$, $p < 0.001$, $n = 350$) and higher PC3 scores (any deafness) ($R = 0.16$, $p < 0.001$, $n = 350$). Effects of individual variables comprising significant PCA associations were then assessed, along with the following variables not included in the PCA: delay to bimodal/bilateral implantation and bilateral device use at time of testing. Considering all children irrespective of group, speech perception asymmetry increased with delay to bimodal/bilateral implantation ($R = 0.32$, $p < 0.001$, $n = 431$) and unaided hearing thresholds (worse residual hearing) in the HA/CI2 ear ($R = 0.12$, $p = 0.011$, $n = 408$).

These relationships were particularly strong in sequential bilateral CI users and bimodal users respectively. Bivariate regressions in each group suggested that asymmetry increased by 3.9 RAU/year delay to bilateral implantation in sequential bilateral CI users (**Figure 7.9A**; $F(1,166) = 41.2$, $p < 0.001$, $R^2_{adjusted} = 0.20$), and increased by 9.5 RAU/10 dB worsening of hearing thresholds in the HA ear of bimodal users (**Figure 7.9B**; $F(1,71) = 25.6$, $p < 0.001$, $R^2_{adjusted} = 0.26$). This means that bimodal users had similar symmetry to simultaneous users ($\pm 1SD = \pm 15$ RAU) when they had mild to moderately-severe hearing loss in the non-implanted ear (35 - 65 dB HL unaided PTA). Otherwise, they showed aural preference for CI1 when the non-implanted ear had severe/profound loss (PTA > 70 dB HL) or aural preference for the HA ear when that ear had near-normal hearing (PTA < 35 dB HL). Sequential bilateral CI users developed an asymmetry > 15 RAU when delay to bilateral implantation exceeded 3.5 years.
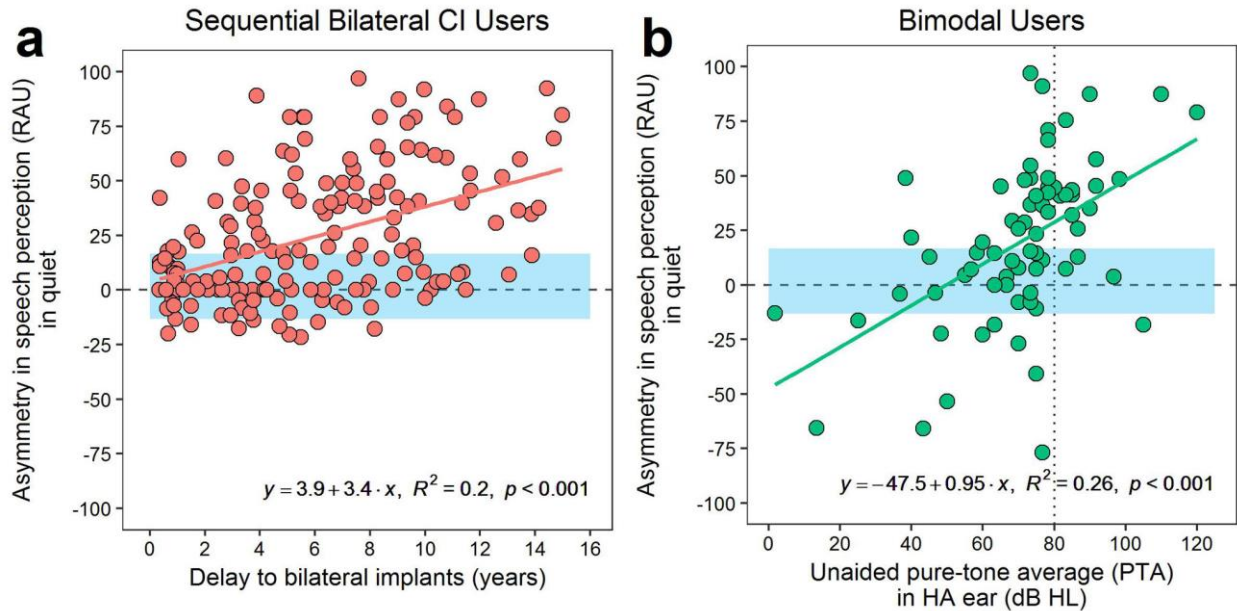
Figure 7.9. Changes in speech perception asymmetry in quiet.

Asymmetry in speech perception tested in quiet increases as a function of (**A**) delay to bilateral implantation in sequential bilateral cochlear implant (CI) users, and (**B**) unaided pure-tone average (PTA) of hearing thresholds for 0.5, 1, and 2 kHz in the non-implanted ear with the hearing aid (HA) of bimodal users. The dotted vertical line in (**B**) indicates a severe-to-profound hearing loss (80 dB HL). Blue shaded regions indicate ±1SD asymmetry of the simultaneous group for comparison. CI = cochlear implant; RAU = rationalized arcsine unit.

7.5   Discussion

This study evaluated effectiveness, timing, and asymmetry of bilateral input in a large, diverse, and inclusive cohort of children who hear with bimodal devices or bilateral cochlear implants. Results demonstrated that: 1) speech recognition is better with bilateral than unilateral hearing; 2) bilateral hearing does not need to be restricted to one modality; and 3) asymmetric hearing creates functional aural preference for the better/first ear, limiting bilateral/spatial hearing. These findings are consistent with electrophysiological evidence of aural preference and support the recommendation to avoid this developmental change by providing access to sound with the most appropriate device in each ear as soon as possible.

Regardless of hearing history, most children recognized speech better (by 9.2 ± 14.0 RAU) when listening with two devices over one ear alone (**Figures 7.5, 7.6**) even when this involved adding their poorer performing ear. This bilateral advantage is consistent with the 10 - 15% advantage reported in smaller cohorts of bilateral implant users with simultaneous (Gordon and Papsin, 2009) or short (< 2 year) inter-implant delays (Gordon and Papsin, 2009; Illg et al., 2017), but is larger than the 0 - 10% reported for children with longer (> 2 years) inter-implant delays (Gordon and Papsin, 2009; Illg et al., 2013; Strøm-Roum et al., 2012) or who use bimodal devices (Ching et al., 2007). Including more children with limited auditory deprivation and better residual hearing likely contributed to the greater bilateral benefit exhibited by the present cohorts of sequential bilateral CI and bimodal users. It is also worthwhile noting that the bilateral advantage was further pronounced in noise (**Figure 7.5C**), highlighting the utility of bilateral hearing in challenging listening situations.

Bilateral device users also adeptly detected speech when noise levels exceeded those of speech (**Figure 7.7A**). Similar detection thresholds of -10 to -15 dB speech-to-noise ratio (SNR) were observed in peers with normal hearing (Chadha et al., 2011; Murphy et al., 2011) or bilateral CIs (Chadha et al., 2011; Galvin et al., 2017; Murphy et al., 2011). Measures of speech detection allowed testing of children with wide ranges of age, native language, and developmental ability but detection is an easier task than speech recognition. This explains the lower SNR levels in this study compared to the -9 to +7 dB SNR speech recognition thresholds reported for children with normal hearing (Garadat and Litovsky, 2007; Schafer et al., 2012) or CIs (Ching et al., 2017; Cullington et al., 2017; Killan et al., 2015a; Sparreboom et al., 2011). The ability to detect and understand speech in noisy conditions improves with age (Chadha et al., 2011; Garadat and Litovsky, 2007; Schafer et al., 2012) as the auditory system matures. Changes continue into adulthood (Murphy et al., 2011) with the largest changes occurring over the first 5 years (Garadat and Litovsky, 2007; Schafer et al., 2012). In the present cohort, detection thresholds did not change with age when accounting for group, perhaps because most children were older than 5 years and had early access to sound (**Table 7.1; Supplemental Table 7.3**).

The advantage of bilateral hearing existed for both bimodal and bilateral CI hearing. This suggests that the auditory system can integrate, at least to some extent, two very different auditory signals to facilitate listening in quiet and noisy situations. Indeed, even limited input from a HA can work with a CI to help bimodal users perceive speech and develop language

(Ching et al., 2007; Moberly et al., 2016; Mok et al., 2010, 2007; Nittrouer and Chapman, 2009; Straatman et al., 2010). By having better residual hearing and access to sound than previous bimodal users (Ching et al., 2007), the present cohort of bimodal users exhibited improvement in speech perception and detection on par with their peers using two CIs (**Figures 7.5B, 7.7A**). Like bilateral CIs, bimodal devices adequately stimulate the bilateral auditory pathways to promote symmetric brainstem development (Polonenko et al., 2015) and typical hemispheric representation of sound (Polonenko et al., 2017b, 2018a) when provided with limited delay to children with sufficient residual hearing. For the deaf ear, a CI outperforms a HA: the 30.5 ± 23.8 RAU bilateral benefit over listening with a HA alone (**Figure 7.5B**) supports expanding implantation criteria to allow bimodal hearing in children with some residual hearing. This, along with asymmetric speech perception (**Figure 7.9B**), also suggests that bimodal users with poor residual hearing in their non-implanted ears may fare better with bilateral implants. Remaining residual low-frequency hearing has delayed implantation so that temporal fine structure for music and emotion perception, not available through CI use (McDermott, 2004), can be maintained (Ching et al., 2007; Scorpecci et al., 2016; Shirvani et al., 2016). However, children using bimodal devices with little residual hearing (PTA > 80 dB HL) do not perceive music or emotion better than their peers with bilateral implants (Bartov and Most, 2014; Giannantonio et al., 2015; Polonenko et al., 2017a). The greatest bilateral advantage may be derived through the most appropriate bilateral devices for the hearing loss in each ear, regardless of modality.

Although there was clear benefit of listening bilaterally rather than unilaterally with bilateral CIs and bimodal hearing, most children developed asymmetric function which limited this advantage (**Figure 7.6**). This was particularly evident in children who experienced asymmetric hearing or unilateral deprivation (**Figure 7.9**) and consequently developed aural preference for the better/first hearing ear (**Figures 7.4, 7.7, 7.8**). Moreover, this preference persisted despite several years of bilateral device use (**Table 7.1A**). These lasting deleterious effects of asymmetric hearing in development are consistent with neurophysiological findings including persistent asymmetries in brainstem development (Gordon et al., 2012) and increased cortical representation from the better than poorer hearing ear (Gordon et al., 2013b; Jiwani et al., 2016; Polonenko et al., 2018a).

For most children, asymmetric speech perception reflected poorer performance in the second or non-implanted ear relative to the first implanted ear. Whereas scores consistently exceeded 50

RAU for the first implanted ear, scores when listening with the other ear varied from 0 to 100 RAU (**Figure 7.4**). The resulting range of asymmetries was similar to previous reports (~20 - 40% asymmetry in sequentially implanted children (Gordon and Papsin, 2009; Illg et al., 2017; Strøm-Roum et al., 2012) and 0 - 5% (Gordon and Papsin, 2009) asymmetry or 0.9-1.1 CI2/CI1 ratio (Kocdor et al., 2016) in simultaneously implanted children). Also consistent with previous studies (Gordon and Papsin, 2009; Kocdor et al., 2016), delay to bilateral input contributed to asymmetric speech perception (**Figures 7.4, 7.6, 7.9**). Asymmetric speech perception leaves children with limited bilateral hearing (**Figure 7.6**) during sensitive periods in development. Although consistent daily implant use can improve speech perception in both ears (Easwar et al., 2017a; Sarant et al., 2001), asymmetry did not correlate with bilateral device use in this study. Rather, delaying sufficient access to sound during development created asymmetric hearing with prolonged consequences of deteriorated speech perception and limited benefit of bilateral input.

Aural preference also affected spatial hearing. All groups showed ~3 - 4 dB spatial unmasking which was poorer than the normal range of 5 - 10 dB (Garadat and Litovsky, 2007; Gordon and Papsin, 2009; Killan et al., 2015b; Murphy et al., 2011; Schafer et al., 2012), but within the 2-4 dB range reported for sequential bilateral CI and bimodal users (Chadha et al., 2011; Ching et al., 2017; Cullington et al., 2017; Killan et al., 2015b; Litovsky et al., 2006; Murphy et al., 2011). More importantly, simultaneous groups took similar advantage of spatial unmasking when noise moved to either side (**Figure 7.7**) (Gordon and Papsin, 2009) whereas children who had asymmetric speech perception detected speech 1.2 - 2.5 dB better when noise moved towards the poorer/second ear than the better/first ear (**Figures 7.7, 7.8**). This asymmetric use of spatial separation in bimodal and sequential groups falls within the lower range of previously reported 1.8 - 4 dB asymmetries favouring a better signal to the first implanted ear (Chadha et al., 2011; Cullington et al., 2017; Litovsky et al., 2006; Murphy et al., 2011). The degree of asymmetry measured may have implications for everyday function. Even an improvement of 1-2 dB in spatial unmasking can reduce self-rated difficulties in situations containing background noise and reverberation (Polonenko et al., 2016a), and small increases in SNR can improve speech intelligibility (Wong et al., 2012). Poorer (reduced) SNR on one side signals a potential for reduced speech perception in the condition when the "preferred" or better ear is masked by noise. Although asymmetries in spatial hearing can decrease after 3 years of bilateral input as the

second ear's performance improves (Cullington et al., 2017), the present cohort used their bilateral devices for 3 - 6 years, suggesting that these aural asymmetries are long-lasting.

Bilateral implants provided similar audibility from each device for all children (**Table 7.1B**) but only sequentially implanted children exhibited asymmetric spatial unmasking. This suggests that the aural preference for their first implanted ear is not simply a function of audibility in each ear but includes ignoring/neglecting information from the worse ear. By contrast, bimodal users had poorer hearing thresholds when using the HA than when using the CI and thus experienced both periods of asymmetric hearing and asymmetric audibility in each ear (**Table 7.1B**). The asymmetric access to sound with the two different types of hearing devices may exacerbate the asymmetry in spatial hearing, potentially explaining why bimodal users exhibited the largest spatial unmasking asymmetry.

This study is the first to directly compare asymmetries measured by two different measures of speech perception. Children exhibiting asymmetric speech perception also showed asymmetric spatial hearing that favoured the first implanted ear (**Figure 7.8B**). This agreement between the two behavioural measures suggests an underlying functional/behavioural aural preference. Notably, electrophysiological measures similarly assert an underlying premise for aural preference that emphasizes the importance of minimizing delay to bilateral hearing in bimodal and bilateral implant users. Extensive reorganization of auditory pathways occurs with asymmetric hearing during development, leading to an over-representation of the better ear (Gordon et al., 2012, 2013b; Keating and King, 2013; Kral et al., 2013a, 2013b; Polley et al., 2013; Polonenko et al., 2015, 2017b, 2018a; Popescu and Polley, 2010). Brainstem asymmetries (Gordon et al., 2012) and cortical aural preference (Gordon et al., 2013b; Polonenko et al., 2018a) favouring the first hearing/implanted ear occur within 2-3 years of asymmetric input. Years of subsequent bilateral input cannot simply reverse aural preference (Gordon et al., 2013b; Polonenko et al., 2018a), unless bilateral input is provided quickly and at early ages (Gordon et al., 2013b; Polonenko et al., 2017b). Similarly, stronger aural preference occurs with reduced age of unilateral hearing in deaf white kittens (Kral et al., 2013a, 2013b) and with temporary asymmetric hearing in ferrets and rats (Keating and King, 2013; Polley et al., 2013; Popescu and Polley, 2010). Persistently asymmetric speech perception occurs when bilateral input is delayed for ~3.5 - 4 years as shown in **Figure 7.9a** and in previous studies (Cullington et al., 2017; Gordon and Papsin, 2009; Illg et al., 2017, 2013; Kocdor et al., 2016; Strøm-Roum et al., 2012).

The slightly staggered timelines suggest that underlying neurophysiological changes develop rapidly and take ~1 - 2 years longer to translate into measurable and consistent functional changes. This could reflect increasing complexity of speech perception, which requires temporal and spectral processing, relative to responses in temporal (auditory) cortices evoked by brief broadband click/pulse stimuli (Polonenko et al., 2018a).

By including children with short or no delays to bilateral implantation, this study is one of few to directly provide behavioural evidence that corroborates electrophysiological findings about the most appropriate timing of bilateral input. Simultaneous bilateral cochlear implantation can be performed safely in young children who are bilaterally deaf (Das Purkayastha et al., 2011) without increased risk for complications or cumulative costs (Grainger et al., 2012; Merdad et al., 2014; Ramsden et al., 2009). Moreover, simultaneous bilateral implant users develop symmetric representations of each ear in the auditory cortex (Easwar et al., 2017b; Gordon et al., 2013b), symmetric speech perception (**Figure 7.4**) (Gordon and Papsin, 2009), equal bilateral advantage over either ear (**Figure 7.5**), and equal spatial unmasking when noise moves to either ear (**Figure 7.7**) (Chadha et al., 2011). Yet, as with any clinical population, individual variability exists and some asymmetries could occur even when early bilateral input is provided simultaneously (**Figure 7.8A**). Contributing factors may include ear differences in: hearing loss progression, cochlear shape, insertion and position of the electrode array, neural integrity, stimulation consistency due to external device malfunctions, or pitch mismatches that may affect binaural fusion into one auditory image. Despite these potential sources of variability, the present data assert that providing early simultaneous bilateral input will give children the best chance of developing speech perception (reaching open-set word identification at a younger age shown in **Figure 7.3**) and avoiding aural preference.

In summary, the present study contributes behavioural corroboration to electrophysiological evidence of an "aural preference syndrome" that develops with both unilateral and asymmetric bilateral hearing during childhood. To avoid these deteriorations in hearing, our findings show that bilateral devices appropriate for the hearing loss in each ear should be provided early and without delay. Although children were not randomly assigned to treatment groups, the evidence presented here is consistent with several other studies of functional outcomes and underlying neurophysiological changes. A randomized control trial is unlikely to yield findings that would markedly change the clinical recommendations suggested here. Promoting early bilateral

auditory development as soon as possible maximizes the opportunity for children to develop symmetric speech perception and spatial hearing; skills that are not only important for listening and navigating in complex environments (Litovsky and Gordon, 2016) but also for academic and social success (Borton et al., 2010; Lieu et al., 2010; Sangen et al., 2017; van Wieringen et al., 2018).

7.6   Acknowledgements

7.7   Competing interests

The authors declare no competing financial or non-financial interests.

7.8   Supplemental Material

7.8.1 Demographic information
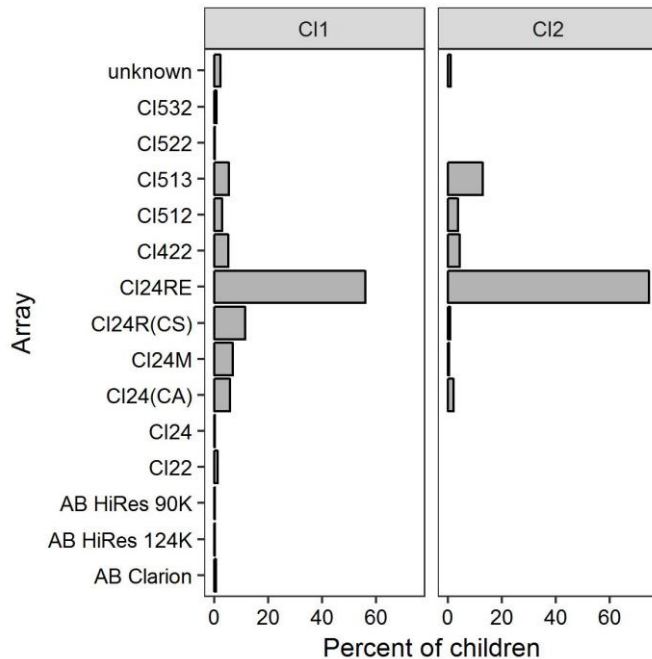
Supplemental Figure 7.1. Distribution of internal arrays for each implanted ear.
Percentage of children with each type of internal array implanted in each ear (CI1:CI2 $n =$
461:375). Most implants were from Cochlear Ltd, except for 5 children who received an
Advanced Bionics (AB) array in their first implanted ear. Most children received a CI24RE in
both ears. The type of array was unknown for 11 (2.4%) CI1 and 4 (1.1%) CI2.

7.8.2 Test delivery affects speech perception scores in noise but not measures of asymmetry or bilateral advantage

To determine the effect of test delivery on speech perception measures, repeated measures
ANOVA was completed on a subset of children (181/288 = 62.8%) who were tested in both
quiet and noise with the most common and challenging test (PBK), using ear (bilateral, CI1,
CI2/HA) or difference (asymmetry, bilateral advantage over CI1, bilateral advantage over
CI2/HA) as a within-subject factor, method (monitored-live voice, recorded) and group as
between-subject factors, and age as a covariate. Recorded speech stimuli were used in 123/181
(68.0%) children tested in quiet and 100/141 (70.9%) children tested in noise. Speech-weighted
noise was used with monitored-live voice delivery and when multi-talker noise could not be used

with recorded stimuli due to technical difficulties. However, most of the time multi-talker noise was used with recorded PBK delivery. The number of children by group, condition, ear(s) tested and delivery method are provided in **Supplemental Table 7.1**.

Supplemental Table 7.1. Number of children tested in each group and condition.

Condition	Group	Ear tested	Stimulus Delivery Live Voice	Stimulus Delivery Recorded	Total
Quiet	Bimodal	CI1, Bilateral	14	17	31
		CI2/HA	14	17	31
	Bimodal Sequential	CI1, Bilateral	4	7	11
		CI2/HA	4	7	11
	Sequential	CI1, Bilateral	14	42	56
		CI2/HA	14	42	56
	Simultaneous	CI1, Bilateral	20	41	61
		CI2/HA	20	41	61
	Older Simultaneous	CI1, Bilateral	6	16	22
		CI2/HA	6	16	22
Noise	Bimodal	CI1, Bilateral	10	13	23
		CI2/HA	5	9	14
	Bimodal Sequential	CI1, Bilateral	2	7	9
		CI2/HA	1	4	5
	Sequential	CI1, Bilateral	9	37	46
		CI2/HA	3	11	14
	Simultaneous	CI1, Bilateral	15	30	45
		CI2/HA	12	23	35
	Older Simultaneous	CI1, Bilateral	5	13	18
		CI2/HA	3	10	13

Speech perception scores and difference measures are shown in **Supplemental Figure 7.2**. In quiet, method of stimulus delivery did not significantly affect speech perception scores ($F(1,170) = 3.0$, $p = 0.08$) or difference measures ($F(1,170) = 0.0$, $p = 0.88$), and there were no interactions between method and ear tested (scores: $F(2,340) = 1.5$, $p = 0.23$; differences: $F(2,340) = 2.6$, $p = 0.10$) or group (scores: $F(4,170) = 0.4$, $p = 0.84$; differences: $F(4,170) = 0.1$, $p = 0.97$). Although speech perception scores in noise were better for live voice than for recorded stimuli ($F(1,70) = 10.7$, $p = 0.002$), this effect was consistent for each ear ($F(2,140) = 0.8$, $p = 0.43$) and group ($F(4,70) = 0.0$, $p = 0.99$). Consequently, stimulus delivery did not affect asymmetry or bilateral advantage (difference scores) in noise (main effect: $F(1,70) = 0.2$, $p = 0.62$, method x group: $F(4,70) = 0.3$, $p = 0.84$; method x difference score: $F(2,140) = 1.3$, $p = 0.26$).
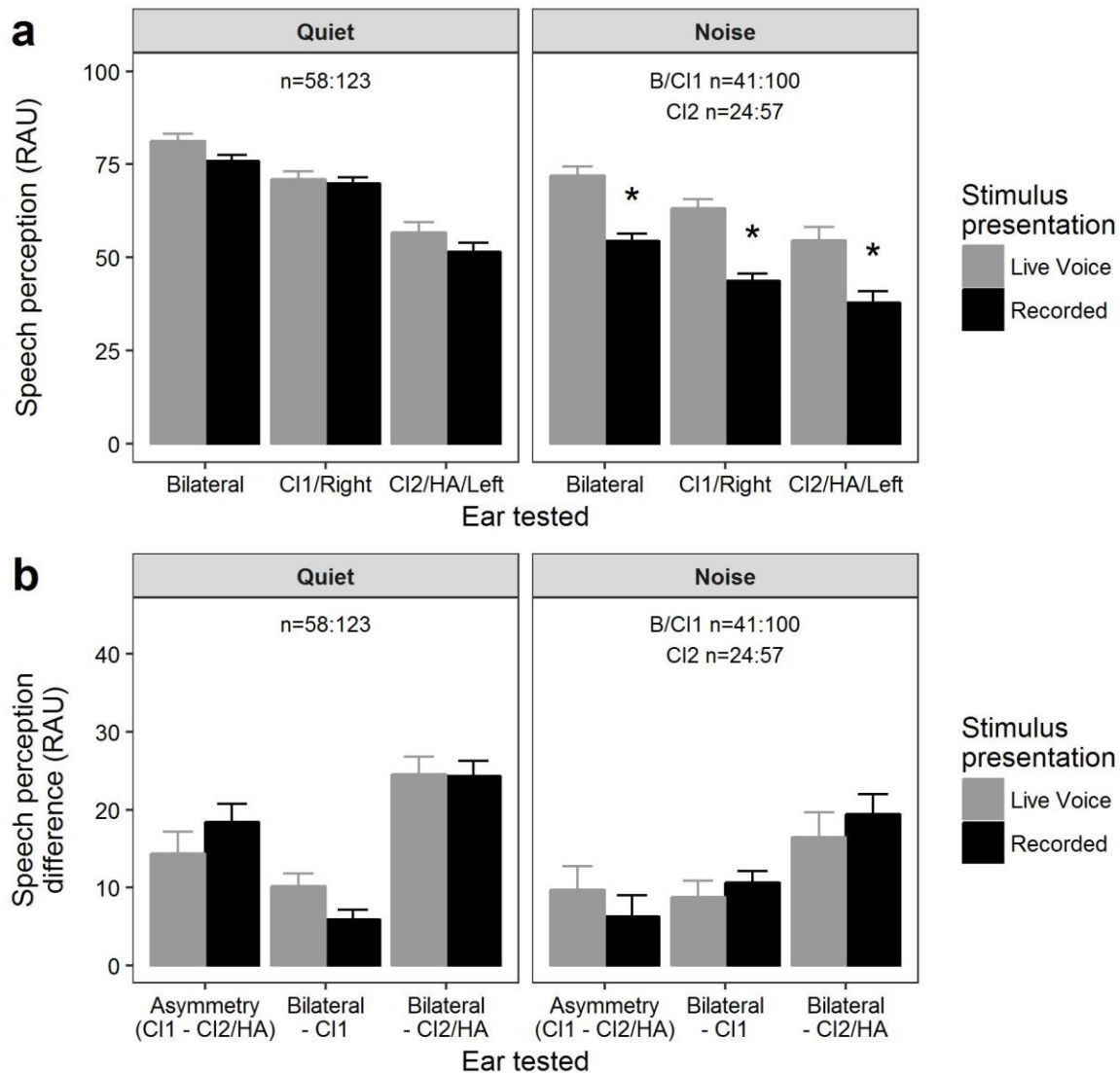
Supplemental Figure 7.2. Effect of stimulus delivery method on speech perception outcomes.

Mean ± SE speech recognition scores for (**A**) each ear(s) tested and (**B**) the resulting differences between ears are shown for children who were tested in quiet and noise with speech delivered either by monitored live voice (gray) or with recorded stimuli (black). For the noise condition, speech-weighted noise was used with monitored-live voice presentation and sometimes with recorded stimuli when technical difficulties precluded the typical multi-talker babble noise. Most children were tested with recorded stimuli; numbers of children tested are provided for live voice:recorded stimulus presentation. Delivery method only affected the absolute score in noise; there was no effect on measures of asymmetry or bilateral advantage. * $p < 0.05$; B = bilateral; CI = cochlear implant; HA = hearing aid.

7.8.3 Numbers of children with available data

Supplemental Table 7.2. Number of children and test dates with available speech perception scores.

A. Number of children

Group	Cross-sectional data: n(%) Quiet		Cross-sectional data: n(%) Noise		Longitudinal data: n(%) Quiet		Longitudinal data: n(%) Noise	
	CI1 & CI2/HA	Bilateral, CI1 & CI2/HA	CI1 & CI2/HA	Bilateral & CI1	CI1 & CI2/HA	Bilateral, CI1 & CI2/HA	CI1 & CI2/HA	Bilateral & CI1
Bimodal	73	61 (83.6)	20 (27.4)	39 (53.4)	38 (52.1)	28 (45.9)	0 (0.0)	12 (30.8)
Bimodal Sequential	17	14 (82.4)	5 (29.4)	10 (58.8)	14 (82.4)	13 (92.9)	3 (60.0)	8 (80.0)
Sequential	168	147 (87.5)	18 (10.7)	121 (72.6)	123 (73.2)	118 (80.3)	2 (11.1)	108 (88.5)
Simultaneous	142	116 (81.7)	37 (26.1)	90 (62.7)	108 (76.1)	93 (80.2)	15 (40.5)	73 (82.0)
Older Simultaneous	39	36 (92.3)	14 (35.9)	28 (71.8)	29 (74.4)	27 (75.0)	2 (14.3)	21 (75.0)
Total	439	374 (85.2)	94 (21.4)	288 (65.6)	307 (69.9)	279 (74.6)	22 (23.4)	223 (77.4)

B. Number of tests in longitudinal data | **C. Age at earliest and latest tests**

Group	Longitudinal data: Range (median) Quiet		Longitudinal data: Range (median) Noise		Longitudinal data: age at test Mean ± SD (years)		Longitudinal data: age at test Range (years)	
	CI1 & CI2/HA	Bilateral, CI1 & CI2/HA	CI1 & CI2/HA	Bilateral & CI1	Earliest test	Latest test	Earliest test	Latest test
Bimodal	2-4 (2)	2-4 (2)	n/a	2-3 (2)	8.2±4.1	9.9±4.2	3.4-16.9	4.4-17.9
Bimodal Sequential	2-6 (3)	2-6 (3)	2-3 (2)	2-5 (2.5)	10.2±3.2	13.3±2.4	4.7-16.1	9.3-17.3
Sequential	2-11 (3)	2-10 (3)	2-3 (2.5)	2-10 (3)	8.8±4.1	12.7±4.0	2.3-17.5	4.2-18.0
Simultaneous	2-8 (3)	2-7 (3)	2-3 (2)	2-7 (3)	4.1±1.2	7.5±1.9	1.9-7.3	2.9-12.2
Older Simultaneous	2-10 (3)	2-10 (3)	2-3 (2.5)	2-10 (3)	10.3±4.1	12.3±4.1	4.7-17.1	5.9-18.6
Total	2-11 (3)	2-10 (3)	2-3 (2)	2-10 (3)	7.3±4.1	10.6±4.1	1.9-17.5	2.9-18.6

Supplemental Table 7.3. Number of children and tests with available spatial unmasking scores.

Group	N(%) of children Cross-sectional	N(%) of children Longitudinal	No. of tests Range (median)	Mean ± SD age (years) Earliest test	Mean ± SD age (years) Latest test	Age range (years) Earliest test	Age range (years) Latest test
Bimodal	35	7 (20.0)	2-3 (2)	6.5±3.8	7.4±3.8	4.1-14.8	4.6-15.5
Bimodal Sequential	12	6 (50.0)	2-2 (2)	12.2±1.3	13.5±1.6	10.3-13.9	11.3-15.6
Sequential	35	8 (22.9)	2-3 (2)	13.2±1.6	14.6±1.9	11.1-15.5	11.8-17.1
Simultaneous	74	16 (21.6)	2-3 (2)	5.6±2.5	6.9±2.6	1.5-9.2	2.1-10.8
Older Simultaneous	15	1 (6.7)	2-2 (2)	5.9	6.9	5.9	6.9
Total	171	38 (22.2)	2-3 (2)	8.4±4.1	9.6±4.3	1.5-15.5	2.1-17.1

7.8.4 Principal component analysis on variables in hearing history

Supplemental Table 7.4. Factor loading matrix for principal component analysis (PCA) of demographic variables of hearing history.

Component description:	Asymmetric hearing experience	Unilateral deafness	Any deafness	Bilateral deafness	Asymmetry with poor hearing	Residual hearing	Hearing asymmetry	Asymmetry versus unilateral deaf	Early intervention
Variable:	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9
Age received CI1	**-0.73**	**0.40**	-0.33	**0.33**	-0.03	0.19	-0.14	0.00	**-0.19**
Time: pre-CI acoustic hearing	**-0.87**	0.26	-0.10	0.13	**-0.21**	0.19	-0.16	0.01	**0.23**
Time: asymmetric hearing	**-0.79**	**-0.42**	-0.28	-0.03	-0.05	-0.18	0.12	**-0.28**	0.00
Time: unilateral deafness	**-0.71**	**-0.50**	**-0.37**	-0.05	-0.06	-0.15	0.12	**0.26**	-0.01
Time: bilateral deafness	0.51	0.20	**-0.47**	**0.42**	**0.51**	-0.14	0.10	0.00	**0.08**
Pre-CI unaided PTA: CI1 ear	0.49	**-0.70**	-0.12	0.19	0.03	0.10	**-0.46**	-0.02	0.00
Pre-CI unaided PTA: CI2/HA ear	**0.68**	-0.23	**-0.31**	0.11	**-0.31**	**0.43**	**0.31**	-0.02	0.01
Asymmetric hearing: pre-CI	-0.59	-0.23	0.15	**-0.25**	**0.61**	**0.38**	0.06	0.00	0.00
Asymmetric hearing: post-CI	-0.34	-0.29	**0.59**	**0.65**	-0.01	-0.02	0.16	0.02	0.00
PCA summary:									
Eigenvalue	**3.83**	**1.36**	**1.03**	0.83	0.78	0.49	0.42	0.15	0.10
Proportion of variance	0.43	0.15	0.11	0.09	0.09	0.05	0.05	0.02	0.01
Cumulative proportion	0.43	0.58	0.69	0.78	0.87	0.93	0.97	0.99	1.00

Factor loadings are bolded and shaded for variables which contributed proportionally more to the principal component than what would be expect
HA = hearing aid; PC = principal component; PCA = principal component analysis

7.8.5 Longitudinal changes in asymmetry in speech perception
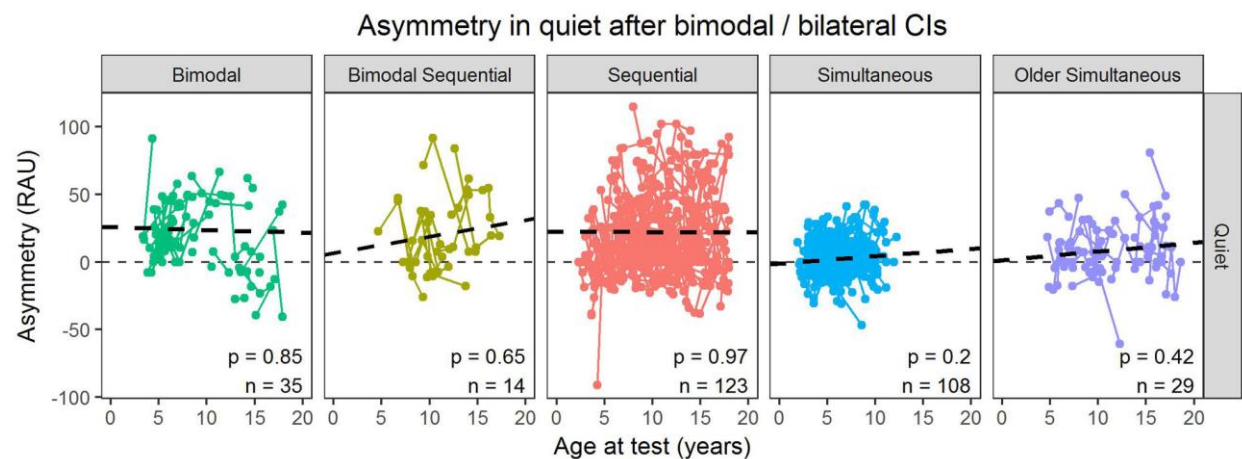
Supplemental Figure 7.3. Longitudinal changes in speech perception asymmetry with age. The difference in speech perception (asymmetry) in quiet between the first implanted ear and second implanted or hearing aid ear did not change with age at test. Coloured lines join repeated results for each child; dashed black lines indicate non-significant ($p < 0.05$) group changes in asymmetry with age based on linear mixed-effects regression. The number of children (n) is provided for each group.

7.8.6 Bilateral advantage of speech perception

Bilateral advantage over listening with one ear in noise is shown in **Supplemental Figure 7.4A**, and over listening with CI2/HA alone in both quiet and noise is shown in **Supplemental Figure 7.4B**. Bilateral advantage over listening with only the HA/CI2 was greater than over listening with CI1 alone ($F(1,87) = 7.8$, $p = 0.007$) and there was no interaction with group ($F(4,87) = 2.1$, $p = 0.09$), reflecting overall asymmetry between unilateral conditions. There was a main effect of group ($F(4,87) = 3.5$, $p = 0.011$), whereby average bilateral benefit for simultaneous users was 12.2 ± 4.2 RAU less than sequential users ($z = -2.9$, $p = 0.026$) and 12.6 ± 3.9 RAU less than bimodal users ($z = -3.2$, $p = 0.011$). The bilateral advantage over listening with HA/CI2 was not different in quiet versus noise ($F(1,95) = 0.0$, $p = 0.82$), but there remained a significant effect of group ($F(4,95) = 3.4$, $p = 0.011$). Average bilateral advantage over CI2 (left ear) alone for simultaneous users was 13.5 ± 4.6 RAU less than sequential users ($z = -3.0$, $p = 0.025$) and 14.1 ± 4.4 RAU less than the bilateral advantage over the HA alone of bimodal users ($z = -3.2$, $p = 0.012$).

Supplemental Figure 7.5 shows the advantage of bilateral input to speech perception over listening with only CI1. As the asymmetry between unilateral scores increasingly favoured CI1 (positive asymmetry values), the advantage of adding HA/CI2 decreased (all FDR-corrected $p < 0.05$). For sequential and some older simultaneous users who had large asymmetries favouring CI1, adding CI2 decreased speech perception accuracy. On the other hand, for bimodal and some simultaneous users who had asymmetries favouring the HA/CI2 (left CI for simultaneous group), the bilateral advantage was greatest because the better perceiving ear was given access to sound. This negative correlation between asymmetry and bilateral advantage also occurs when considering bilateral advantage over the best performing ear: advantage to providing bilateral input decreased as absolute asymmetry increased ($p < 0.05$ for all groups; **Supplemental Figure 7.3**).

a Bilateral advantage in noise over listening with one ear

b Bilateral advantage in noise
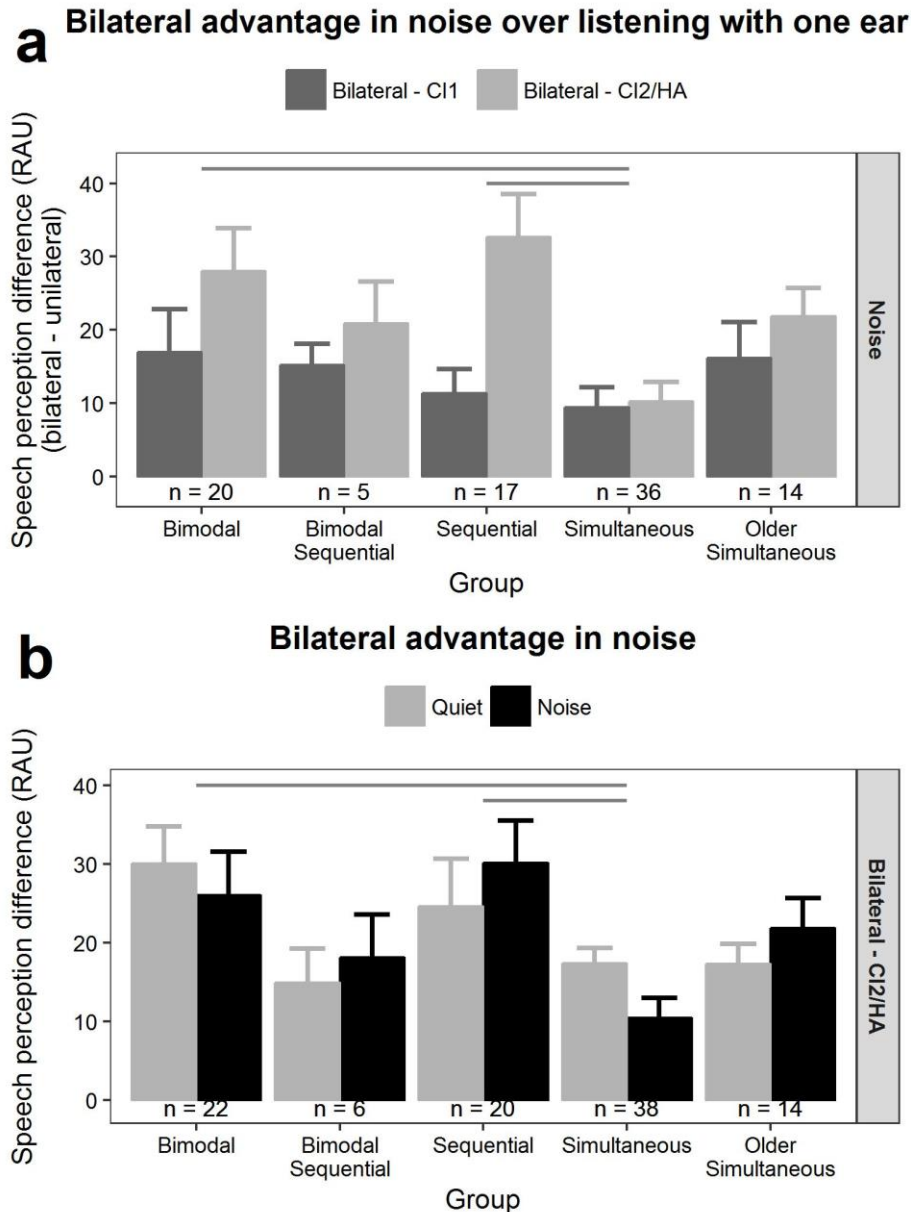
Supplemental Figure 7.4. Bilateral advantage for speech perception in noise.

(**A**) The difference in speech perception in rationalized arcsine units (RAU) while testing in noise for the bilateral condition over listening with each ear alone. Bilateral advantage over listening with only the HA/CI2 was greater than over listening with CI1 alone. Average bilateral benefit for simultaneous users was less than sequential and bimodal users. (**B**) Bilateral advantage over listening with HA/CI2 alone in both quiet and noise. Bilateral advantage differed by group but not by whether there was noise present. Average bilateral advantage over CI2 alone for simultaneous users was less than sequential users and less than the bilateral advantage over the HA alone of bimodal users.

Bilateral advantage over CI1 in quiet
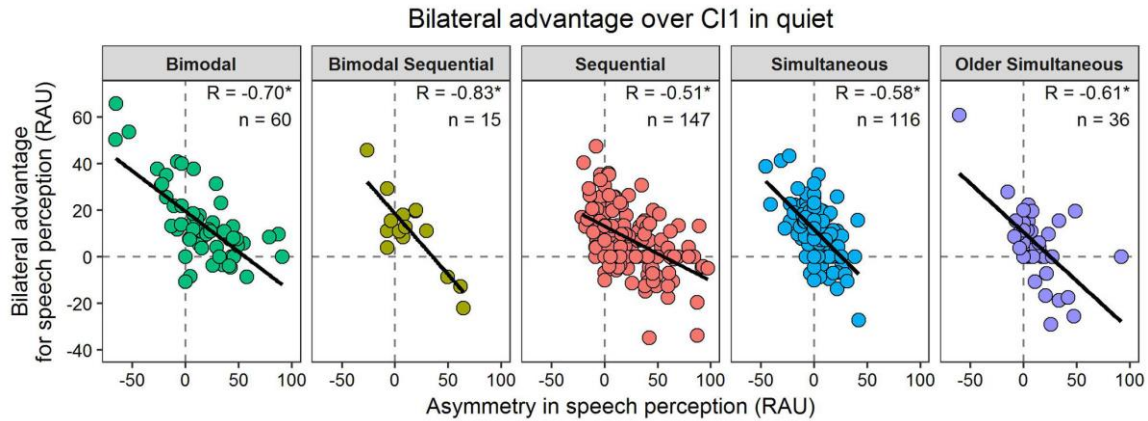
Supplemental Figure 7.5. Best advantage to bilateral input with symmetric hearing.
The advantage to speech perception in quiet was calculated as the difference between scores with bilateral input and the first implanted ear. This bilateral advantage decreased as the absolute value of the asymmetry in speech perception between ears increased. Asterisks indicate significant correlation after FDR corrections for multiple comparisons ($p < 0.05$).

7.8.7 Etiology alone does not predict speech perception asymmetry in quiet
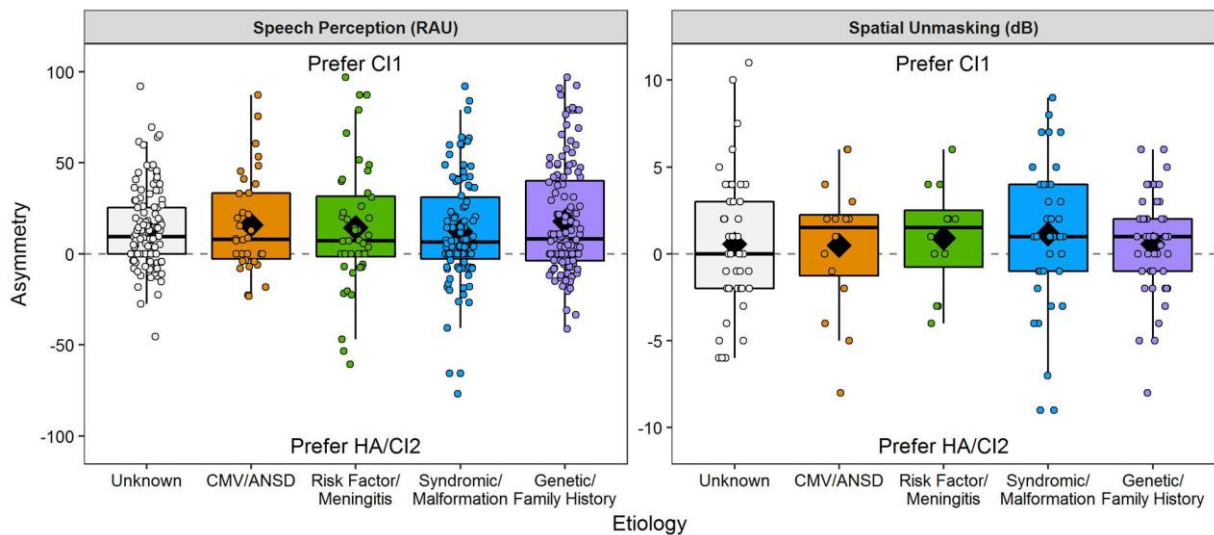
Supplemental Figure 7.6. Asymmetry in speech perception and spatial unmasking by etiology.
Asymmetries in speech perception in quiet and spatial unmasking were similar across etiology of deafness. Means are shown by the black diamonds. Values for spatial unmasking were multiplied by -1 (i.e., flipped) so that all positive values indicate a preference for the first implanted ear (CI1). CI = cochlear implant; HA = hearing aid; CMV=congenital cytomegalovirus; ANSD=auditory neuropathy spectrum disorder; RAU=rationalized arcsine unit.

Chapter 8

8 General Discussion

More children are being identified with asymmetric hearing loss through screening and early intervention programs, yet limited information exists to guide clinicians in how to remediate binaural hearing in this heterogeneous group. Binaural hearing is essential to listening and navigating in everyday acoustic environments, as well as for social and academic functioning. By comprehensively assessing auditory neurophysiology, plasticity, function, and hearing experience in children using bimodal devices, this thesis contributed to the understanding of asymmetric hearing-driven changes to the auditory system, as well as the optimal timing for providing bilateral input during development. The focus of this thesis was to determine whether treating children who have asymmetric hearing loss with bimodal hearing can promote symmetric bilateral auditory development and bilateral hearing abilities. The following section briefly summarizes the main findings of this thesis in relation to our main questions and hypotheses. Then a general discussion ensues regarding the: 1) ability of bimodal hearing to promote symmetric bilateral development and function; 2) limitations of bimodal hearing for preventing or reversing asymmetric-driven reorganization following delays to balanced bilateral input; and 3) remaining challenges faced by children using bimodal hearing.

8.1 Summary of findings

The first study of this thesis examined whether bimodal hearing preserves and protects bilateral symmetry in the auditory brainstem, as well as promotes binaural hearing. We hypothesized that differences in stimulus conduction time and neural synchrony evoked by electrical and acoustic stimuli will introduce peripheral delays in absolute peak latencies, but promote symmetric neural conduction through brainstem pathways for children with better residual hearing in the non-implanted ear. Indeed, by measuring evoked electrophysiological auditory brainstem responses, we found that the electrical cochlear implant rapidly stimulates the brainstem pathways on average ~2 ms faster than the acoustic stimulation, which likely contributed to the children's inability to perceive inter-aural timing cues. However, correcting for these peripheral delays revealed that neural conduction in the bilateral brainstem pathways can be preserved for children

who have better residual hearing or limited durations of deprivation. For these children, symmetric bilateral brainstem pathways are available for future efforts to promote binaural processing by correcting for the peripheral electrical-acoustic timing delays.

In studies two, three and four, we focused on determining whether bimodal hearing promotes symmetric representation of each ear in the auditory cortex. We hypothesized that bimodal stimulation limits cortical reorganization in children with asymmetric hearing loss by providing bilateral access to sound with the most appropriate hearing device for each ear; however, the protective ability of bimodal hearing will depend on the duration and extent of asymmetric hearing prior to implantation. Using the TRACS beamforming method on multi-channel electrophysiological recordings, we were able to measure the relative activation of each auditory cortex in response to stimulation of either ear. The second study revealed that restricting the duration of asymmetric hearing experience prior to implantation promoted symmetric cortical development. However, delaying provision of bimodal hearing resulted in persistent cortical aural preference for the better hearing ear and compromised speech perception. Because these children experienced ~2 years of bimodal use, it was unclear whether early implantation prevented aural preference from occurring in the first place or reversed asymmetric-driven reorganization. Therefore, studies three and four employed longitudinal measures of evoked cortical activity to assess asymmetric hearing-driven changes and cortical plasticity with bimodal hearing. Study three revealed that even short periods of asymmetric hearing drive abnormal cortical development, which can be rescued by early implantation and provision of bimodal hearing. Short periods of cortical aural preference and abnormal cortical activity from the deprived ear rapidly reversed with bimodal hearing in children with normal hearing in the non-implanted ear. Study four confirmed that the initial abnormalities with asymmetric hearing and the reversing effects of bimodal stimulation more broadly extended to children with various degrees of asymmetric hearing loss. These studies highlighted the importance of providing bilateral input with limited delay to alter the trajectory of asymmetric-driven cortical development.

The fifth study corroborated the electrophysiological data from the previous four studies by measuring whether children with bimodal devices and bilateral cochlear implants developed perceptual aural preference for perceiving speech and for spatial hearing. We quantified the diverse hearing histories of all bilateral device users to elucidate which factors were most

predictive of persistent perceptual asymmetries. We hypothesized that promptly giving the most appropriate device for the hearing loss in each ear will promote symmetric speech perception and use of spatial hearing. We found an advantage to bilateral hearing over listening with either device alone in all groups of children, suggesting that the auditory system can make use of auditory input delivered in the same or different modality to facilitate listening in quiet and noisy environments. However, longer durations and greater degrees of asymmetric hearing limited this advantage and best predicted development of functional aural preference for auditory input from the better hearing ear. The behavioural results from this fifth study extensively demonstrated the importance of providing appropriate bilateral auditory input without delay in order to maximize the opportunity for children to develop symmetric hearing abilities that are important for listening, navigating, learning and functioning in complex daily environments.

Therefore, even though electrical and acoustic hearing are unique and stimulate the auditory system in different ways, symmetric neural conduction in bilateral brainstem pathways and expected cortical aural preference for contralateral stimulation were achieved in many children. Moreover, most children experienced a bilateral advantage for speech perception over wearing either device alone. They also benefited from spatial hearing and were able to detect changes in binaural inter-aural level cues. Our findings also demonstrate, however, that prolonged experience with asymmetric hearing during development extensively reorganizes the auditory system, limiting future efforts to restore bilateral and spatial hearing with bimodal devices. These findings are highly relevant to clinical treatment of asymmetric hearing loss and support the recommendation to provide the most appropriate bilateral auditory prostheses as soon as possible to children who have significant hearing loss.

8.2 Bimodal hearing protects symmetric auditory development and function if provided early and to children with better residual hearing

Symmetric representation of contralateral auditory input typically marks early brainstem and cortical development, which is shaped by hearing experience through a balance of excitation and inhibition (Chapter 2). Deleterious effects of bilateral and unilateral deafness on the bilateral auditory pathways can be mitigated by providing bilateral electrical stimulation through two cochlear implants with limited delay (Cullington et al., 2017; Gordon et al., 2015, 2013b, 2012;

Gordon and Papsin, 2009). However, until now, it has remained unknown whether this normal-like developmental trajectory is also possible for children who have asymmetric hearing loss and receive bilateral input in two different modalities. The findings from each chapter of this thesis demonstrate that symmetric auditory development and function are indeed possible with bimodal devices when they are provided with limited delay. The developing auditory system integrates electrical and acoustic information, at least to some extent, to facilitate symmetric brainstem neural conduction (**Figure 3.2C**), cortical preference for contralateral stimulation (**Figure 4.4**, **Figure 4.6**, **Figure 5.4D**, **Figure 6.6**), symmetric speech perception (**Figure 4.7B**, **Figure 7.4A**, **Figure 7.9B**), advantage to listening in quiet and in noise with both devices over either device alone (**Figure 7.5**, **Figure 7.6**), spatial hearing abilities (**Figure 7.7**), and detection of inter-aural level cues (**Figure 3.3B**) in several of the children who have better residual hearing in their non-implanted ear. In fact, we show for the first time a strikingly similar sensitive period during which bilateral electrical or bimodal input should be provided to promote expected development and function (**Figure 4.6B**). This suggests that the auditory system is sensitive to both the timing and balance of bilateral input during development irrespective of stimulation mode to each ear. Furthermore, our findings support the recommendation to provide early intervention with the most appropriate devices for the hearing loss in each ear (Gordon et al., 2015).

8.2.1 Bimodal hearing promotes representation of the poorer ear

In agreement with previous studies examining the effects of unilateral deafness on the developing auditory pathways (Gordon et al., 2015, 2013b, 2012, 2007a; Kral et al., 2013a), a period of asymmetric hearing loss weakened, but did not eliminate, representation of the poorer hearing ear. Acute electrical stimulation revealed abnormal cortical responses from the deprived ear (**Figure 5.2**, **Figure 5.4**, **Figure 6.3**, **Figure 6.5A**), suggesting that bimodal hearing provided a restorative rather than preventative function in these children. However, within ~2 years of bimodal hearing, electrical stimulation promoted brainstem latencies within the electrical normative range (**Figure 3.2B**) and cortical responses with similar surface morphology (**Figure 4.2A**), underlying sources (**Figure 4.3A,B**), and strength of cortical activation (**Figure 4.3C**) to those of the non-implanted ear and to peers with normal hearing. Moreover, electrical stimulation activated the contralateral auditory cortex to a greater extent than the ipsilateral cortex (**Figure 4.3C**, **Figure 5.4A**, **Figure 6.5A**). Cortical representation of the implanted ear rapidly increased with electrical stimulation without compromising activity evoked by acoustic

stimulation of the other better hearing ear (**Figure 5.4A,C**, **Figure 6.5**, **Figure 6.7**). This suggests that electrical stimulation of the deprived ear promoted axonal myelination and synaptic development through the brainstem and into the cortex, and re-established a contralateral (crossed) dominant pathway that is consistent with previous studies (Gordon et al., 2013b; Kral et al., 2013b; Tiihonen et al., 1989).

As with typical development (Eggermont and Ponton, 2003), these underlying neurophysiological changes were also reflected in the ability of children to use the electrical stimulation for speech perception (**Figure 4.7A,B**, **Figure 7.4A**). Consistent with other studies showing improved perception with implant use (Cullington et al., 2017; Easwar et al., 2017a; Sarant et al., 2001), children progressed through standardized tests of increasing difficulty (**Figure 7.3**) and most of the children achieved good speech perception scores with their cochlear implant (**Figure 4.7A**, **Figure 7.4A**). Moreover, wearing the cochlear implant contributed to significantly better speech perception over listening with only the hearing aid (**Figure 7.5B**), indicating benefit to providing bilateral input and supporting the recommendation to implant a deaf ear irrespective of the degree of residual hearing in the other ear.

8.2.2 Early bilateral input across modalities promotes bilateral development

In line with studies of bilateral implantation (Easwar et al., 2017b; Gordon et al., 2007b, 2012, 2013b), restricting the period of deprivation and asymmetric hearing mitigated the deleterious effects of unilateral deprivation by promoting symmetric brainstem and cortical development. For the children with minimal delay to implantation, electrical and acoustic hearing were sufficient to work together to re-establish bilateral pathways. Despite peripheral delays due to differences in electrical and acoustic stimulation, bimodal hearing promoted symmetric neural conduction through brainstem pathways of the children who had limited periods of deprivation prior to implantation (the "symmetric" group in Chapter 3). This indicates that providing early bilateral input promoted myelination and synaptic efficiency in the brainstem, which potentially helped restore the balance of excitation and inhibition necessary for bilateral development. Therefore, bimodal hearing potentially mitigated the development of abnormal cortical aural preference by arresting or reversing the strengthening of crossed and uncrossed pathways from the better hearing ear that occurs with asymmetric hearing (Kitzes et al., 1995; Kral et al., 2013a, 2013b; Moore and Kitzes, 1985; Moore and Kowalchuk, 1988; Nordeen et al., 1983; Reale et al.,

1987; Vale et al., 2004; Vale and Sanes, 2002). Indeed, children who had limited periods of asymmetric hearing developed symmetric representation of each ear in the auditory cortex (**Figure 4.5**, **Figure 6.8B,C**), which was similar to the contralateral representation of sound exhibited by children who received bilateral cochlear implants with minimal or no delay (**Figure 4.6**) (Easwar et al., 2017b; Gordon et al., 2013b) and children with normal hearing (**Figure 4.4**, **Figure 4.6**) (Easwar et al., 2017b; Gordon et al., 2013b; Yamazaki et al., 2018). These neurophysiological findings were also supported by the symmetric speech perception in many of the bimodal users (**Figure 4.7B**) and the bilateral benefit obtained over using either device alone for both bimodal and bilateral devices users studied in Chapter 7 and in previous studies (Ching et al., 2007; Cullington et al., 2017; Illg et al., 2013; Mok et al., 2010, 2007; Straatman et al., 2010; Strøm-Roum et al., 2012). Also in agreement with other studies of bimodal users (Arndt et al., 2015; Cadieux et al., 2013; Gratacap et al., 2015; Greaver et al., 2017; Hassepass et al., 2013; Rahne and Plontke, 2016; Tavora-Vieira and Rajan, 2016; Thomas et al., 2017), children were able to benefit from spatial cues for improved speech detection in noise (**Figure 7.7A,B**).

A major contribution of this thesis to the literature on children with significant hearing loss is the demonstration that bilateral input in different modalities can be processed and used to facilitate symmetric auditory development and function. Furthermore, the data from Chapters 4-6 suggest that bimodal hearing is effective at preventing persistent aural preference for a variety of hearing losses, including single sided deafness, asymmetric hearing loss, steeply sloping mid- to high-frequency hearing loss, and in some children with severe hearing loss in the non-implanted ear. Importantly, not only do these findings reinforce the importance of providing early bilateral input, but they give testament to the remarkable plasticity and adaptability of the auditory system to use the input that it receives. This is particularly evident when bimodal hearing is provided during early stages of development (**Figure 4.5C**, **Figure 6.8B,C**, Chapter 5), corresponding to periods of high synaptic plasticity (Huttenlocher and Dabholkar, 1997; Kral and Sharma, 2012). Our data suggest that appropriate/sufficient bilateral experience is more important than the modality for driving bilateral development. The auditory system was capable of using the electrical and acoustic input to establish bilateral pathways, creating the foundation and capacity for binaural processing to occur.

8.2.3 Potential benefits of bilateral development in bimodal listeners

By promoting expected brainstem and cortical organization, bimodal hearing may alleviate some of the other changes and demands of unilateral listening and deafness. Expected cortical organization may support specialization of the right and left auditory cortices (Giraud and Poeppel, 2012; Poeppel et al., 2012; Zatorre et al., 2002; Zatorre and Belin, 2001), which are otherwise compromised with unilateral electrical stimulation (Jiwani et al., 2016). Bimodal hearing can facilitate better language acquisition than bilateral cochlear implants (Moberly et al., 2016; Nittrouer and Chapman, 2009). Also, expected organization may promote less extensive changes to extra-auditory areas and reduce the maladaptive recruitment of other areas to support listening, as exhibited by children with unilateral deafness (Propst et al., 2010; Schmithorst et al., 2005; Tibbetts et al., 2011; Wang et al., 2014; Yang et al., 2014; Zhang et al., 2015). Encouragingly, children who received simultaneous bilateral cochlear implants exhibited typical cortical development and very similar activation patterns to their peers with normal hearing, with the exception of abnormal recruitment of small areas involved in attention, visual processing and sensory integration (Easwar et al., 2017b). Continued recruitment of these areas may reflect persistent changes from early deafness or continued compensation for listening with deprived signals through electrical stimulation (Easwar et al., 2017b). Bimodal hearing, on the other hand, provides complementary acoustic information that may provide an advantage over bilateral electrical hearing. Indeed, the complementary low-frequency temporo-spectral information provided by bimodal hearing helped children react more quickly than their bilaterally implanted peers when discriminating music (Polonenko et al., 2017a) and deciding emotion conveyed by music (Giannantonio et al., 2015). Faster judgments suggest fewer mental resources were allocated to completing the task, thereby freeing up cognitive resources for other important processes (Pichora-Fuller et al., 2016; Wingfield, 2016). A frontal-temporal area associated with attention and awareness (Kane and Engle, 2002) was abnormally activated upon initial electrical stimulation of the deprived ear in long-term unilateral implant users (Jiwani et al., 2016), in one case study of single sided deafness (Sharma et al., 2016) and in our cohorts of children with single sided deafness (Chapter 5) and asymmetric hearing loss (Chapter 6). This activity decreased within months of bimodal use, while at the same time, expected cortical organization emerged (Chapters 5 and 6). Perhaps this preliminary data reflects acclimation to the new input and/or a decreased need for extra cognitive resources to support listening once each ear becomes

more equally represented in the cortex. However, further analyses are required to assess the exact nature of extra-auditory recruitment and connectivity of these areas within broader default, attention and cognitive networks.

By providing adequate auditory stimulation to each ear during early sensitive periods, bimodal hearing may also promote typical neurodevelopment and maturation through adolescence. The data in this thesis mainly included younger children in earlier stages of development, as reflected by their immature cortical surface responses that were characterized by an early frontal-positive/posterior-negative peak (Easwar et al., 2017b; Gordon et al., 2013b; Ponton et al., 2000, 2002; Yamazaki et al., 2018). During normal auditory development, polarity and morphology of surface evoked cortical responses follows neurofilament maturation within layers of the auditory cortex (e.g., Ponton et al., 2002, 2000). This positive peak reflects maturation in layer I and the deep layers IV-VI. As superficial layers III and II develop during adolescence (Moore and Guan, 2001), a surface negative peak (N1) emerges. As the cortical response changes into a polyphasic P1-N1-P2 waveform, behavioural perception of sound becomes more elaborate (described in Section 2.1.3). Deafness prevents this from occurring and decreases activity in deep layers (Kral et al., 2000), impairing the cortico-cortical and cortico-fugal connections that are important for the development of more complex perception (Kral et al., 2005).

The data from Chapters 4-6 suggest that bimodal hearing prevented this deprived trajectory from progressing and promoted typical cortical responses, at least for early development. Furthermore, data from Chapter 7 suggest that children with bilateral input progressed through tests of increasing difficulty (**Figure 7.3**) and developed the ability to make use of spatial cues (**Figure 7.7A,C**). Previous studies suggest bimodal hearing can facilitate acquisition of more complex language skills (Moberly et al., 2016; Nittrouer and Chapman, 2009). Progression in neurophysiological and behavioural development provides a promising foundation for future maturation of superficial layers and further development of more complex auditory abilities. Perhaps this in turn will prevent children with asymmetric hearing loss from developing poorer linguistic skills (Sangen et al., 2017) and lower receptive and expressive language scores (Lieu et al., 2010; Ruben and Schwartz, 1999), or allow their language scores to improve (Lieu et al., 2012) and catch up to their peers with normal hearing into adolescence. Hopefully, the expected bilateral cortical development, as well as bilateral and spatial hearing abilities achieved with early bimodal hearing, will also help mitigate the social and educational challenges faced by

children with asymmetric hearing loss (Bess and Tharpe, 1986; Borton et al., 2010; Kuppler et al., 2013; Lieu et al., 2010; reviewed by van Wieringen et al., 2018). Future studies that track cortical development and spatial hearing abilities of bimodal users as they progress through adolescence are required to confirm whether early provision of bimodal hearing can promote typical maturational trajectories in electro-acoustically stimulated bilateral pathways and maturation of more complex hearing abilities that support language, education and social function.

8.3 Longer periods of asymmetric hearing drive persistent aural preference and limits bilateral hearing with bimodal devices

8.3.1 Bimodal hearing reverses effects of asymmetric hearing

Although early intervention of asymmetric hearing loss with bimodal devices could promote symmetric auditory development and function in some children, initial cochlear implant stimulation revealed that abnormal cortical development had already occurred with both single sided deafness (Chapter 5) and various degrees of asymmetric hearing (Chapter 6). This abnormal development was characterized by a negative peak in the surface potentials at a similar latency as the typical positive peak evoked from the better hearing non-implanted ear (**Figure 5.2A**, **Figure 6.3A**), reversed frontal-negative/posterior-positive distribution of activity across the surface of the head (**Figure 5.2B**, **Figure 6.3B**), greater ipsilateral neural activation in the auditory cortex (**Figure 5.4A**, **Figure 6.5A,C**), and widespread neural activation across the cortex with particular activation in frontal-temporal areas (**Figure 5.2C**, **Figure 6.3C**). The abnormal neural activity underlying this abnormal negative peak also disrupted cortical aural preference (**Figure 5.4C,D**, **Figure 6.6**, **Figure 6.7**).

Presence of this negative peak may suggest immaturity and deprivation in the pathways from this newly implanted ear. Abnormal cortical responses with negative peaks within a similar latency range and with a similar surface topography have also been observed in premature infants with normal hearing (Rotteveel et al., 1987; Weitzman et al., 1967), and in children with congenital deafness who were implanted late (Sharma et al., 2002b) or who received cochlear implants after minimal auditory stimulation due to mutations in the GJB2 gene (Gordon et al., 2011). Larger (more abnormal) negative peaks were evoked upon initial activation of the long-deprived ear of adolescents who listened for over 10 years with only one cochlear implant (Jiwani et al., 2016).

While this negative peak may appear to correspond to the N1 of the mature polyphasic P1-N1-P2 cortical response (Ponton et al., 2000; Ponton and Eggermont, 2001; Wunderlich and Cone-Wesson, 2006), there are several differences that suggest this negative peak is indeed different from the mature N1. First, there is no preceding P1 peak in the waveform. With subsequent electrical stimulation, morphology rapidly changes into an immature positive peak (**Figure 5.2**, **Figure 6.3**) that is typically seen in children with less than 12 years of auditory experience (Easwar et al., 2017b; Jiwani et al., 2013; Ponton et al., 2000; Yamazaki et al., 2018). When auditory deprivation is limited (Sharma et al., 2007, 2005), this immature positive peak decreases in latency (Ponton and Eggermont, 2001) and matures into a P1-N1-P2 response (Jiwani et al., 2016, 2013) that resembles the normal evoked responses in adolescents and adults (Eggermont and Ponton, 2003; Jiwani et al., 2016; Yamazaki et al., 2018). Second, when the negative peak persists and the developmental morphological changes do not occur, speech perception remains significantly impaired (Gordon et al., 2005b, 2008a; Jiwani et al., 2016). In contrast, emergence of the mature N1 is associated with the development of more complex hearing abilities and better hearing outcomes (reviewed by Eggermont and Ponton, 2003). Third, as shown by the children in **Figure 5.4A,B** and **Figure 6.5**, as well as in adolescents with a similar but larger abnormal negative peak (Jiwani et al., 2016), underlying neural activation increases to the ipsilateral left auditory cortex with acute stimulation of a deprived left ear. This disrupts the typical contralateral cortical lateralization for the immature positive peak and the mature N1 typically evoked by left ear stimulation in peers with normal hearing (Jiwani et al., 2016; Yamazaki et al., 2018). Fourth, neural activity is more widespread across the cortex (**Figure 5.2C**, **Figure 6.3C**) (Jiwani et al., 2016). Activity extending beyond the auditory cortex into frontal-temporal areas may reflect greater attention to the novel stimulation by recruitment of attention networks (Kane and Engle, 2002). Fifth, negative peaks in surface potentials are thought to reflect cortico-cortical activity from intra- and inter-hemispheric connections in the superficial (I-III) layers of the cortex (Ponton et al., 2000; Ponton and Eggermont, 2001), which do not emerge or mature until after 9-12 years old (Moore and Guan, 2001). Given that most of the cohorts exhibiting abnormal negative peaks are much younger than this (i.e., <12 years old), it is unlikely that activity derives from mature superficial axons. Rather, the negative potentials may reflect immature activity in these layers or possibly indirect or non-primary cortico-cortical and cortico-fugal connections from the newly stimulated ear to the left cortex. Therefore, the negative peak likely reflects immaturity or deprived pathways rather than the mature N1.

Given that the negative peak likely reflects immaturity or deprivation, it is not entirely unexpected that the children with congenital single sided deafness in Chapter 5 initially exhibited this abnormal waveform and source activation. These children were implanted at 3.5 years old, after a period of time during which several subcortical and cortical changes occur with deafness (described in Section 2.2.4) (reviewed by Kral and Sharma, 2012). However, it was surprising that the cohort with asymmetric hearing loss also exhibited this abnormal response to initial stimulation. Unlike the children with single sided deafness in Chapter 5, many of the children included in Chapter 6 experienced some periods of acoustic experience, albeit often limited and impaired. All children exhibited a negative waveform, but those with worse hearing and less acoustic experience (i.e., congenital versus progressive asymmetric hearing loss) were more likely to have a greater amplitude to the negative peak and a greater activation of the ipsilateral cortex (**Figure 6.8A**). With longer periods of deprivation, this response may become even more abnormal: even larger (abnormal) negative surface responses and greater source abnormalities were evoked from acute electrical stimulation of long-deprived ears in adolescents who listened with only one cochlear implant for over 10 years (Jiwani et al., 2016). This larger negative peak also showed widespread activity but also de-synchronized neural oscillations in the theta and gamma frequency bands, which may reflect unfamiliarity and abnormal representation of the new input (Jiwani, 2015; Jiwani et al., 2016). Therefore, the degree of abnormality to the response may reflect degree and/or length of deprivation.

Alternatively, perhaps this negative peak represents not only a biomarker for immaturity and deprivation, but also for disrupted bilateral pathways from unilateral deafness and asymmetric hearing. The imbalance in excitation and inhibition coming from each ear during periods of asymmetric hearing may exacerbate the effects of deprivation on the pathways from this ear. Indeed, animal models of unilateral deafness and moderate asymmetric hearing loss reveal pervasive structural and synaptic changes in the brainstem and cortex that weaken representation of the worse ear and strengthen representation of the stimulated ear (Blatchley et al., 1983; Kral et al., 2013a, 2013b; Moore and Kowalchuk, 1988; Nordeen et al., 1983; Polley et al., 2013; Popescu and Polley, 2010; Potashner et al., 2000; Russell and Moore, 1995, 1999, 2002; Sanes et al., 1992; Tillein et al., 2016; Webster, 1983; Webster and Webster, 1979). Reorganization is often more dramatic with unilateral deafness than bilateral deafness (Clements and Kelly, 1978; Gordon et al., 2015; Keating and King, 2013; Keuroghlian and Knudsen, 2007; Kral et al.,

2013b; Silverman and Clopton, 1977). Perhaps then, asymmetric hearing exacerbated the effects of limited input from an ear with poor residual hearing, putting pathways from the worse ear at a competitive disadvantage and increasing the vulnerability of the ipsilateral cortex to responding abnormally to new stimulation from an implant.

Unlike the adolescents who underwent maturation with unilateral electrical stimulation (Jiwani et al., 2016), the children included in this thesis were provided with bimodal hearing within less than 8 years (most less than 4 years) of asymmetric hearing. Instead of larger negative peaks as exhibited in children with long-term unilateral cochlear implant use (Jiwani et al., 2016), bimodal users developed the typical surface morphology within at least 6 months (**Figure 4.2**, **Figure 5.2**, **Figure 6.3**). By providing earlier bilateral input, bimodal hearing may have prevented further disorganization or maladaptive changes and could rapidly register the electrical input as auditory input. Changing morphology of the surface waveforms and topography from the newly implanted ear suggests development of underlying neural generators, which was supported by the decrease in ipsilaterally evoked dipole moments (**Figure 6.5B**), emergence of expected contralateral cortical lateralization (**Figure 5.4A**, **Figure 6.5A**), and decrease in aural preference for this newly stimulated ear (**Figure 5.4C**, **Figure 6.7**). Further support comes from the better speech perception outcomes in bimodal users (**Figure 4.7**, **Figure 7.4A**) than previously exhibited in cohorts that developed persistent negative peaks (Gordon et al., 2008a, 2011). Furthermore, most children were able to benefit from bimodal input for improved speech perception and listening in noise (**Figure 7.5**, **Figure 7.7**).

8.3.2 Prolonged asymmetric hearing limits the ability of bimodal hearing to reverse abnormalities

Although providing bimodal devices was enough to reverse abnormal cortical response morphology in all children, the delay to implantation was too long for some children to promote symmetric cortical and functional representation of each ear. Longer periods of asymmetric hearing limited recovery of underlying cortical representation of each ear (**Figure 4.4**, **Figure 4.5A,C**, **Figure 4.6**, **Figure 6.8B,C**) and greater asymmetry in hearing resulted in persistent asymmetric speech perception (**Figure 7.9**). Providing bimodal hearing after longer periods of asymmetric hearing may be sufficient to stimulate the bilateral pathways to prevent further extensive unilaterally-driven changes from occurring while enabling some increased representation of the deprived ear. But this subsequent development is not sufficient to reverse

cortical reorganization that occurs over longer periods of asymmetric hearing, resulting in persistent over-representation of the better hearing ear in the auditory cortex (**Figure 4.4**, **Figure 4.5**) and functional aural preference for the better ear (**Figure 7.8B**). This abnormal neurophysiological and behavioural aural preference persisted despite at least 2 years of bimodal hearing. These findings are consistent with those from children who have bilateral deafness and received two cochlear implants in sequential surgeries. Although typical surface morphology was achieved with bilateral electrical hearing in all children irrespective of the period of unilateral cochlear implant use, underlying cortical lateralization and aural preference remained abnormal for children with longer delays to bilateral input but not those with limited periods of unilateral hearing (Gordon et al., 2013b). Therefore, although delayed bilateral input can promote some development, or prevent further abnormal development, restricting the period of asymmetric hearing is necessary to maximize the capabilities of future bilateral input to promote expected auditory development.

The findings from the studies in this thesis agree with, and extend, the current understanding of abnormal auditory development with an imbalance in auditory input by demonstrating that longer periods of any degree of asymmetry will result in persistent reorganization of the auditory system. Consistent with studies in children (Cullington et al., 2017; Gordon et al., 2013b; Gordon and Papsin, 2009; Illg et al., 2017) and animals (Blatchley et al., 1983; Kral et al., 2013a, 2013b; Moore and Kowalchuk, 1988; Nordeen et al., 1983; Polley et al., 2013; Popescu and Polley, 2010; Potashner et al., 2000; Russell and Moore, 1995, 1999, 2002; Sanes et al., 1992; Tillein et al., 2016; Webster, 1983; Webster and Webster, 1979) with unilateral deafness, delaying implantation for children with asymmetric hearing limited the ability of bimodal bilateral input to rescue the auditory system from persistent aural preference (**Figure 4.4**, **Figure 4.5**), which contributed to functional aural preference (**Figure 7.8**) and limited the bilateral advantage to speech perception (**Figure 7.6**). Such similar findings from extreme examples of asymmetric hearing (i.e., unilateral deafness), various degrees of asymmetric hearing with one deaf ear (Chapters 3-7) and moderate asymmetric hearing loss with one normal hearing ear suggest that as long as asymmetric input is delivered to the brainstem and cortex, the developing auditory system will abnormally reorganize and become more resilient to future efforts to reverse abnormalities with longer periods of asymmetric hearing. Furthermore, this suggests that any degree of asymmetry during development has deleterious effects on the auditory system.

Both the degree and trajectory of abnormal aural preference for the first or better hearing ear were strikingly similar for children with asymmetric hearing and unilateral cochlear implant listening (**Figure 4.6**) (Gordon et al., 2013b). Accordingly, duration of deprivation and asymmetric hearing consistently predicted persistent abnormal auditory development in children using bimodal devices. Children with dramatically prolonged (>4 ms) delays through the brainstem experienced longer periods of deprivation (Chapter 3). Children who experienced longer periods of asymmetric hearing before they were implanted developed cortical aural preference for the better ear that persisted despite over 2 years of bilateral experience (Chapter 4). Duration of asymmetric hearing prior to implantation also predicted the degree and ability to recover cortical representation of each ear (Chapter 6). Asymmetry in speech perception favouring the first or better hearing ear increased with delayed or poor access to bilateral sound in children with bimodal and bilateral cochlear implants (Chapter 7). Even the children who had poorer hearing in the non-implanted ear exhibited abnormal development that resembled unilateral-like changes rather than the changes that occur with bilateral deafness. In animal models, these unilateral-driven changes involve neurophysiological changes to cell size (i.e., atrophy) (Blatchley et al., 1983; Moore and Kowalchuk, 1988; Sanes et al., 1992; Webster, 1983; Webster and Webster, 1979), dendritic structure (Russell and Moore, 2002, 1999; Sanes et al., 1992), number of projections (Moore and Kowalchuk, 1988; Nordeen et al., 1983) and response properties of neurons in the brainstem and midbrain (Clopton and Silverman, 1977; Moore and Irvine, 1981; Popescu and Polley, 2010; Silverman and Clopton, 1977). These changes in turn strengthen cortical responses to both crossed and uncrossed pathways from the better hearing ear and reduce the ipsilateral inhibition or contralateral excitation from the poorer hearing ear (Keating and King, 2013; Kral et al., 2013a, 2013b; Polley et al., 2013; Popescu and Polley, 2010; Tillein et al., 2016). These changes contribute to an over-representation of the first or better hearing ear. This aural preference is consistent with the persistent abnormal changes in bimodal users who had prolonged asymmetric experience. Taken together, these findings suggest that any degree of asymmetry that distorts or disrupts the balance of excitation and inhibition is sufficient to evoke some degree of unilaterally-driven changes if left asymmetric for long enough during key developmental periods.

8.3.3 Sufficient residual hearing is necessary to stimulate bilateral pathways and avoid asymmetric-driven changes

Although any asymmetry for prolonged periods of time will result in persistent aural preference, having a significantly impaired ear contributing the asymmetry may dictate the extent of abnormality and is important to consider. Animal models of moderate asymmetric hearing loss and one normal hearing ear show unilateral-driven changes, but the changes were less extensive (Polley et al., 2013; Popescu and Polley, 2010) than the changes observed in animal models of unilateral deafness (Kral et al., 2013a, 2013b; Tillein et al., 2016). In our cohorts of children who had one significantly impaired (or deaf) ear contributing to the pre-implantation asymmetric hearing, the degree of aural preference resembled that of children who experienced unilateral stimulation with a deaf ear (**Figure 4.6**). In these cases, asymmetric hearing with one deaf ear resulted in similar reorganization. Children with worse hearing in the implanted ear were more likely to show abnormal cortical responses (**Figure 6.8A**), and waiting to save the severe/profound residual hearing in this poorer hearing ear by delaying implantation limited future speech perception abilities with the implant (**Figure 4.7D,F**).

Post-implantation degree of residual hearing in the non-implanted ear also contributed to abnormal development. For some of the children who had limited residual hearing, this created a new type of asymmetric hearing with bimodal devices, whereby the non-implanted ear had limited stimulation. Consequently, these children were more likely to develop abnormally prolonged neural conduction through the brainstem (**Figure 3.2C**), cortical aural preference for the better hearing implanted ear (**Figure 4.5B,D**), poor speech perception with the hearing aid (**Figure 4.7C,E**), and functional aural preference for the implanted ear that limited bilateral benefit and the ability to detect speech when noise was directed to the cochlear implant compared to the hearing aid (**Figure 7.4B**, **Figure 7.7C**, **Figure 7.8B**, **Figure 7.9**). Therefore, limited residual hearing in the non-implanted ear did not provide sufficient auditory stimulation to prevent asymmetric-driven changes from occurring while children used bimodal devices. Moreover, using a hearing aid with limited residual hearing does not improve accuracy of music or emotion perception for bimodal users over that of bilateral cochlear implant users, as initially anticipated (Bartov and Most, 2014; Giannantonio et al., 2015; Polonenko et al., 2017a; Shirvani et al., 2016). This suggests that children with limited residual hearing may fare better with bilateral cochlear implants. Waiting for bilateral implantation to preserve any temporal fine

structure leaves the non-implanted ear compromised and vulnerable relative to pathways from the implanted ear, promoting asymmetric-driven reorganization without the significant anticipated benefits from the limited acoustic hearing.

8.3.4 Aural preference develops within a similar timeframe for asymmetric and unilateral hearing

Asymmetric hearing promoted neurophysiological and functional aural preference within a relatively rapid time frame. Remarkably, cortical plasticity occurred at a similar rate for asymmetric hearing and for unilateral cochlear implant use (**Figure 4.6**), suggesting that the developing auditory system responds rapidly and similarly to various degrees of imbalanced bilateral input. Perhaps there is a common sensitive period to most degrees of asymmetric hearing. Cortical representation of each ear became abnormal within 2-3 years of asymmetric hearing, which resembles the 1.5 year sensitive period for providing bilateral cochlear implants to prevent asymmetric brainstem (Gordon et al., 2012) and cortical development (Gordon et al., 2013b; Kral et al., 2013a, 2013b). Moreover, this sensitive period corresponds to periods of highest synaptic plasticity, when the auditory system is most vulnerable to developing preference for one ear (Gordon et al., 2015; Huttenlocher and Dabholkar, 1997; Kral and Sharma, 2012). In support, stronger aural preference occurred when deaf kittens were provided with unilateral electrical stimulation at younger ages (Kral et al., 2013a, 2013b). The greatest reorganization with asymmetric hearing, and least amount of later plasticity with bimodal input, occurred in the cortex ipsilateral to the first or better hearing ear. This may reflect the greater vulnerability and shorter sensitive period of this ipsilateral cortex compared to the contralateral cortex (Kral et al., 2013a).

Some stimulation with asymmetric hearing over no input during periods of unilateral hearing may create some flexibility in the time course for reorganization. The one-year extension to the sensitive period for asymmetric hearing compared to the extreme case of unilateral hearing may result from some auditory input being delivered from each ear. An extra year may also be afforded in the presence of progressive hearing loss, which is associated with the more common etiologies of hearing loss in bimodal users (**Figure 4.1**, **Figure 7.1**). In accordance with previous studies (Gordon et al., 2013b; Polley et al., 2013), the asymmetric-driven changes persisted after years of subsequent bilateral hearing with bimodal devices if provided beyond this sensitive period, but reversed when the period of asymmetric hearing was restricted. Plasticity also

occurred with asymmetric bimodal hearing post-implantation. Brainstem and cortical preference for the implanted ear developed within approximately 2 years of bimodal hearing in some children who had limited residual hearing in the non-implanted ear (**Figure 3.2C**, **Figure 3.5B,D**). These children with poorer residual hearing also developed asymmetric speech perception favouring the cochlear implant (**Figure 7.9**) and better speech detection in noise when the implanted ear had a better signal to noise ratio (**Figure 7.8B**). Together, these findings reflect the importance of balanced bilateral experience to bilateral auditory development and the limitations of bimodal hearing for treating asymmetric hearing loss when it is delayed (pre-implantation) or unbalanced (post-implantation).

Development of functional aural preference also followed a similar, but slightly longer, time course as the neurophysiological changes (**Figure 7.9A**). Consistent with previous studies (Cullington et al., 2017; Gordon and Papsin, 2009; Illg et al., 2017, 2017; Kocdor et al., 2016; Strøm-Roum et al., 2012), delaying bilateral input by 3.5-4 years resulted in persistently asymmetric speech perception. The extra 1-2 years for functional changes compared with neurophysiological changes may reflect the complex nature of speech perception and listening in noise, as well as the more elaborate development that must occur for these hearing abilities to emerge and improve. As discussed in Section 2.1.3, emergence and refinement of complex hearing abilities parallel the morphological changes to evoked potentials and the underlying axonal maturation in cortical layers (reviewed by Eggermont and Ponton, 2003; Moore and Guan, 2001). Between 5 and 12 years of age, axons begin to mature in superficial cortical layers (Moore and Guan, 2001), and children develop the ability to perceive binaural cues (Litovsky, 1997; Van Deun et al., 2009), make use of spatial hearing (Chadha et al., 2011; Garadat and Litovsky, 2007; Schafer et al., 2012), and perceive degraded speech or speech in challenging listening conditions (Eisenberg et al., 2000; Elliott, 1979). Therefore, perhaps asymmetric-driven cortical changes take longer to translate into consistent and measurable changes to these more complex functional outcomes.

It is important to keep in mind that children who were provided with bilateral input past these sensitive periods could still derive benefit for bilateral and spatial hearing (Chapter 7). However, neurophysiological and functional aural preference limits this benefit (**Figure 7.6**), which may impact daily living. Improving spatial hearing by even small amounts can significantly alleviate self-rated difficulties in reverberant and noisy situations (Polonenko et al., 2016a) that children

often experience (Crukley et al., 2011; Easwar et al., 2016; Polonenko et al., 2017c). Providing early intervention maximizes outcomes (Ching et al., 2014; Cullington et al., 2017; Harrison et al., 2005) and gives children the opportunity to develop symmetric hearing abilities that are important for listening, navigating, learning and socializing in complex acoustic environments (reviews by: Litovsky and Gordon, 2016; van Wieringen et al., 2018).

8.4 Clinical implications for treating children with asymmetric hearing loss

Data from Chapters 3-7 of this thesis support early implantation of children with asymmetric hearing loss to provide balanced auditory input with the most appropriate devices given the hearing loss in each ear (Gordon et al., 2015). Balanced bilateral input should be provided with limited delay and as early in development as possible to avoid the deleterious effects of asymmetric hearing. This means providing a cochlear implant to ears with significant hearing loss and a hearing aid to ears with sufficient residual hearing. Residual hearing should be considered within the context of behavioural outcomes and duration of significant hearing impairment when deciding whether a child should receive bilateral hearing aids, bimodal devices or bilateral cochlear implants.

What constitutes as sufficient and useable residual hearing for bimodal hearing is not clearly demarcated because of the variable outcomes and hearing histories across individuals. However, the principal component analysis in Chapter 7 characterized the heterogeneous hearing histories of bimodal and bilateral implant users into three main components of asymmetric hearing, unilateral deafness and any (unilateral and bilateral) deafness, which predicted outcomes. For bimodal users, these components specifically relate to pre-implantation asymmetric hearing and unilateral deafness and post-implantation asymmetric hearing (Chapter 5). A combination of these time- and hearing-based factors consistently predicted cortical plasticity (Chapter 5), speech perception accuracy in each ear (Chapter 5) and development of asymmetric speech perception (Chapter 7). Guided by these principal components, data from **Figure 4.2C**, **Figure 5.7E**, and **Figure 7.9** suggest better neurophysiological and behavioural outcomes are achieved when bimodal hearing is provided 1) without delay (i.e., restrict asymmetric hearing) and 2) with balanced input from acoustic and electric hearing. This input is balanced when bimodal hearing is provided to children with normal hearing to a moderately-severe hearing loss in the non-

implanted ear, whereas poorer outcomes are more likely once hearing thresholds worsen past 70-80 dB HL in the non-implanted ear. Whether balanced electrical-acoustic input can be accomplished with bimodal devices for more significant hearing losses (i.e., >70-80 dB HL PTA) may depend on factors not fully captured by the hearing thresholds alone. These factors may include, but are not limited to, etiology, hair cell and neural survival, frequency resolution, and consistency of stimulation. To determine whether bilateral implantation might be warranted over bimodal devices, performance of the non-implanted ear must be considered in conjunction with hearing thresholds, hearing loss configuration, asymmetry in speech perception, and the length of time hearing and performance have been limited.

Effective early stimulation can be provided through bimodal devices for children with normal (i.e., single sided deafness) to severe hearing loss (<70-80 dB HL) in the non-implanted ear (middle group and some of the bottom group in **Figure 1.1**). For these children, bimodal hearing rapidly reversed abnormal cortical responses from the deprived ear (Chapters 5 and 6), promoted symmetric brainstem development (Chapter 3) and promoted development of expected cortical preference for contralateral stimulation (Chapter 4). Many of these children achieved similarly good or similarly poor (i.e., symmetric) speech perception with each device (**Figure 4.7B**, **Figure 7.4A**), significant bilateral advantage to adding the implant which was pronounced in noise (**Figure 7.5**) and could use spatial cues for improved speech detection in noise (**Figure 7.7**). These findings agree with the positive preliminary benefits for listening to speech in noise in children with single sided deafness or good residual hearing (Arndt et al., 2015; Cadieux et al., 2013; Gratacap et al., 2015; Greaver et al., 2017; Hassepass et al., 2013; Rahne and Plontke, 2016; Tavora-Vieira and Rajan, 2016; Thomas et al., 2017). A few of these children with normal or minimal hearing loss exhibited asymmetric speech perception favouring the non-implanted ear (**Figure 7.9B**). This could be due to the rich temporal fine structure delivered by good acoustic hearing compared to the abnormal electrical input and/or leaving the poorer ear deprived of input prior to implantation, which can limit speech perception accuracy following implantation (**Figure 4.7F**). Despite this, children with good residual hearing benefited from bilateral and spatial hearing and continued to wear their implants in a variety of environments (**Figure 3.1**) for an age-appropriate number of hours per day (Easwar et al., 2016; Polonenko et al., 2016a).

Effectiveness of bimodal hearing is less clear for the children who have bilateral steeply sloping hearing loss, with good low-frequency but poor high-frequency hearing (bottom group of **Figure**

1.1). These children were clearly experiencing difficulties with bilateral hearing aids given their desire for consideration to receive an implant. This may be due to the limited ability of hearing aids to adequately amplify sound for such poor high-frequency hearing loss (Stelmachowicz et al., 2004), which can limit speech perception (**Figure 4.7E**). Providing one cochlear implant improves speech perception on one side while retaining temporal fine structure information in the low-frequency hearing of the non-implanted ear, which could potentially be used for improved pitch, music and emotion perception. However, bimodal hearing may create post-implantation asymmetries which could compromise binaural hearing. Initial results in some of the children included in this thesis suggest that providing a cochlear implant to the slightly poorer ear promoted expected cortical development (Chapter 6) and symmetric speech perception (Chapter 7) in some children, but asymmetric speech perception favouring the implant when better thresholds were only obtained in lower frequencies (i.e., PTA >70-80 dB HL). This is consistent with the findings in the broader group of children with normal to severe hearing loss, as described above. However, further work is required to determine whether these outcomes broadly extend to this unique group of bimodal users, and whether they continue to derive acoustic advantages with their unilateral low-frequency hearing.

Evolution of implant design and surgical technique is making it possible for low frequency hearing preservation. By potentially providing access to inter-aural timing differences and temporal fine structure, bilateral acoustic low frequency hearing could benefit spatial hearing in children who have some residual hearing in the implanted ear, particularly children with sloping hearing losses. With continued advances in hearing preservation surgeries, children with sloping losses may eventually become candidates for bilateral cochlear implantation and bilateral combined electric-acoustic stimulation. However, further work is required to determine whether hearing preservation is possible for longer periods of time (>9 months) in children, who are at risk of progressive loss over the course of childhood. Moreover, a significant proportion of children (30%; see **Figure 1.1, Figure 4.1, Figure 7.1**) with residual hearing have etiologies associated with cochleovestibular abnormalities (e.g., enlarged vestibular aqueduct), which may limit hearing preservation capabilities. Therefore, future work will guide recommendations and timelines for bimodal devices versus bilateral cochlear implantation with hearing preservation in these children.

For all bimodal users, performance of the non-implanted ear should be continuously monitored due to the higher prevalence of etiologies associated with progressive hearing loss (**Figure 4.1**, **Figure 7.1**) (Lin et al., 2017; Paul et al., 2017; Sokolov et al., 2017). Ongoing monitoring is particularly important for those children with severe hearing loss close to 70-80 dB HL because delaying bilateral implantation too long without enough acoustic stimulation increases the likelihood of developing significantly delayed neural transmission through the brainstem ('asymmetric' group in Chapter 3, **Figure 3.2C,D**), aural preference for implanted ear (**Figure 4.5B,D**), poorer speech perception (**Figure 4.7C,E**), and functional aural preference for the implant (asymmetric speech perception; **Figure 7.9B**). There may be a grace period to remaining with bimodal devices prior to bilateral implantation, especially when the hearing loss is progressive (Illg et al., 2013, 2017; Killan et al., 2015b). Some acoustic experience with bimodal hearing can promote better perception of phonemic structure (relating sounds within words) (Moberly et al., 2016), complex language acquisition (Nittrouer and Chapman, 2009), and perception of music after bilateral implantation (Hopyan et al., 2012). But performance of the non-implanted ear should be monitored to avoid depriving the auditory system of effective balanced input for too long. Otherwise, ineffective bimodal hearing will promote lasting aural preference for the first implanted ear, and potentially limit future abilities with the second implant (**Figure 4.7F**). Speech perception in the ear that used a hearing aid can improve after implantation (Dhondt et al., 2017), but some children may continue to experience asymmetric speech perception following bilateral implantation (bimodal sequential users in Chapter 7; **Figure 7.4**, **Figure 7.5**). Thus, bilateral implantation may be warranted sooner rather than later to limit abnormally prolonged brainstem development and cortical aural preference for the implanted ear, as well as support speech perception in both ears. The click-evoked auditory brainstem responses (ABR) at high levels may be a useful and clinically feasible tool to aid this decision for children who cannot perform behavioural testing. Latencies of wave V and the III-V inter-wave interval differentiated children with persistent brainstem immaturities with their severe hearing losses in the non-implanted ear (**Figure 3.2C,D**). The decision to proceed to bilateral cochlear implantation must consider useable residual hearing and weigh the potential benefits from this limited hearing with the asymmetric behavioural performance and time course of asymmetric hearing, which may limit bilateral implant outcomes.

Bilateral implantation may be delayed in the children with poor residual hearing because of the potential benefits of acoustic stimulation over the abnormal electrical input. Acoustic hearing in the non-implanted ear provides greater spectro-temporal structure (representation of frequency over time) that is not adequately conveyed by cochlear implants but which is required for accurate perception of emotion and complex sounds such as music (Looi and Radford, 2011). Indeed, low-frequency acoustic hearing in bimodal users works better than electrical stimulation for perceiving music (Bartov and Most, 2014; Giannantonio et al., 2015; Polonenko et al., 2017a; Shirvani et al., 2016). The complementary information provided by the hearing aid can help children using bimodal devices react more quickly when discriminating music (Polonenko et al., 2017a) and deciding the emotion conveyed by music (Giannantonio et al., 2015). Faster judgments suggest fewer mental resources were allocated to completing the task, thereby freeing up cognitive resources for other important processes (Pichora-Fuller et al., 2016; Wingfield, 2016). Moreover, bimodal users could utilize both tempo (rhythm) and mode (pitch) cues to judge the emotion conveyed in music rather than relying mainly on tempo cues like their peers with bilateral cochlear implants (Giannantonio et al., 2015). However, this protective effect against reliance on tempo decreased with as the severity of hearing loss increased. Surprisingly, whatever pitch cues that were available with the amplified residual hearing were not sufficient to significantly improve bimodal users' perception of music relative to their peers with bilateral CIs (although they performed just as well). However, bimodal advantages to music perception, especially for accuracy, are not as great as expected and are limited for individuals with poor residual hearing in the non-implanted ear (Bartov and Most, 2014; El Fata et al., 2009; Jeong et al., 2015; Polonenko et al., 2017a). Once residual hearing in the non-implanted ear reaches the severe/profound range (>70-80 dB HL), children may no longer receive enough bimodal advantage for perceiving spoken emotion and music to warrant delaying bilateral implantation. While bimodal hearing can improve reaction time and access to multiple cues for music perception, benefits are modest. Distinctions between bimodal and bilateral cochlear implant users were limited by the fairly poor residual hearing in the non-implanted ear of bimodal users, highlighting that these children continue to experience difficulties related to their hearing loss, development, and/or device limitations.

As with any clinical populations there will be variability even if symmetric bilateral input is provided simultaneously (Chapter 7). Children who received bilateral cochlear implants

simultaneously exhibited some asymmetries favouring either ear. Some contributing factors may include differences in hearing loss progression, neural survival, cochlear shape, insertion and depth of internal array, stimulation consistency, and interaural pitch mismatches. As described in Section 2.3.2 and illustrated in **Figure 2.7**, additional sources of variability unique to bimodal users include electrical-acoustic differences in stimulation sites, modalities, and evoked synchrony, as well as the higher variability in hearing histories. Despite these potential sources of variability, the data in this thesis assert that providing effective balanced bilateral input with minimal delay will give children the best chance of avoiding neurophysiological and functional aural preference.

Therefore, as a rough guide, effective bimodal hearing can be achieved when provided early to children with hearing thresholds <70-80 dB HL in the non-implanted ear. After careful monitoring of the non-implanted ear and outcome assessment of bimodal hearing, bilateral implantation may provide more effective and balanced input for children with bilateral severe/profound hearing loss (>70-80 dB HL). Regardless, early intervention and restricted periods of asymmetric hearing are important for maximizing bilateral development and creating the capacity for binaural and spatial hearing.

Candidacy of children for bimodal devices should consider speech perception asymmetry in addition to hearing loss severity and configuration, as well as brainstem development when possible. Based on the findings from this thesis, the following recommendations are proposed for the bimodal groups characterized in **Figure 1.1**:

1. Bilateral cochlear implants without delay for "Traditional" bimodal users who have relatively flat severe hearing loss bilaterally (>70 dB HL) bilaterally. Otherwise, with bimodal hearing these children develop persistent brainstem immaturity for pathways from the non-implanted ear, poor speech perception, cortical aural preference for the implant, and asymmetric speech perception (>25-30 RAU) that limits bilateral advantage.

2. Bimodal hearing without delay for "Non-Traditional Asymmetric" bimodal users with better hearing in the non-implanted ear (<70 dB HL in one ear), including single sided deafness. Bimodal hearing promotes expected brainstem development, contralateral activation of both auditory cortices (i.e., no cortical aural preference), symmetric speech perception and bilateral advantage to speech perception. However, delaying implantation

beyond the sensitive period of 2-3 years after the onset of asymmetric hearing promotes reorganization of bilateral auditory pathways, which limits subsequent bimodal benefit.

3. More work is required to determine the best combination of devices for "Non-Traditional Sloping" bimodal users who have bilaterally good (<50 dB HL) low-frequency hearing but severe/profound high-frequency hearing loss. Bimodal devices improve speech perception in the implanted ear, promote expected cortical development (Chapter 6), and retain low-frequency hearing in the non-implanted ear with potential benefits for auditory tasks requiring pitch. However, for children with steeply sloping hearing loss and poorer low-frequency thresholds, bimodal devices may create asymmetric hearing that limits speech perception in the non-implanted ear. Future work will help determine whether bilateral implantation with long-term hearing preservation is possible in children, and whether bilateral electric-acoustic hearing improves outcomes over bimodal devices in this group of children with sloping losses.

8.5 Children with bimodal hearing experience remaining challenges with binaural processing

Providing bilateral input through bimodal devices and bilateral cochlear implants improves hearing abilities and promotes bilateral auditory development with restricted durations of asymmetric hearing. However, this development does not necessarily re-establish true binaural hearing for these children.

Impaired binaural processing is reflected in the continued challenges experienced by children using bimodal devices and bilateral cochlear implants for sound localization and listening in noise compared to their peers with normal hearing (Ching et al., 2001, 2004, 2005, 2007; Choi et al., 2017; Gordon et al., 2014; Grieco-Calub and Litovsky, 2010; Litovsky et al., 2006; Litovsky and Gordon, 2016; Luntz et al., 2005; Simons-McCandless and Shelton, 2000). Even adults with prior binaural acoustic experience struggle to perceive interaural timing and level differences with bimodal devices (Francart et al., 2008a, 2008b, 2011). Bilateral cochlear implants and bimodal devices often use default frequency allocations across electrodes. Because insertion depths and neural survival may differ in each cochlea and individual, mismatched cochlear places of stimulation can therefore be introduced (Landsberger et al., 2015; Reiss et al., 2014b; Svirsky et al., 2015; Vermeire et al., 2015), which affect perception of bilateral input as a fused

sound image (Reiss et al., 2011, 2014a, 2016), as well the integration (Gordon et al., 2012; Hu and Dietz, 2015; Smith and Delgutte, 2007) and perception (Bernstein et al., 2018; Kan et al., 2015) of binaural cues. Binaural cues are further distorted in bimodal users by the introduction of large mismatches in timing into brainstem (**Figure 3.2**) due to peripheral delays (**Figure 2.7**) (Zirn et al., 2015) and differing degrees of evoked neural synchrony (Rubinstein and Hong, 2003; Zeng, 2004). Therefore, binaural cues reach the binaural processing circuitry in the brainstem in very different ways and with very different timing. This lack of co-incidence likely affects how these cues are first processed and integrated in the brainstem and then subsequently transmitted to, and processed within the cortex.

Children with bilateral devices learn to use interaural level differences (ILD) (Gordon et al., 2014; Salloum et al., 2010), even when they have significantly prolonged acoustic delays from wearing bimodal devices (**Figure 3.3B**). On the other hand, perception of interaural timing differences (ITD) takes longer to develop and remains poorer than normal and poorer than ILD perception (Gordon et al., 2014). Given the large peripheral delays, it is not surprising that children with bimodal devices cannot detect even large ITDs (**Figure 3.3A**). The integrative mechanisms of ILD processing in the LSO may be more resilient to peripheral delays (Finlayson and Caspary, 1991) than the binaural circuitry of ITD processing in the MSO, which heavily relies on fine-tuned excitation and inhibition, and faithful transmission of phase and timing from each ear (Brand et al., 2002; Couchman et al., 2012, 2010; Grothe, 2003; Grothe and Sanes, 1994, 1993; Jercog et al., 2010; McAlpine and Grothe, 2003; Myoga et al., 2014; Riedel and Kollmeier, 2002; Werthat et al., 2008). Therefore, like bilateral implant users (Gordon et al., 2014; Grantham et al., 2008, 2007; Laback et al., 2004; Salloum et al., 2010; Seeber and Fastl, 2008; van Hoesel and Tyler, 2003), bimodal users may depend on ILD rather than ITD detection for sound localization and listening in noise. Further evidence of poor binaural hearing comes from the inability of bilateral device users to benefit from binaural squelch (Misurelli and Litovsky, 2012; Van Deun et al., 2010, 2009), which is the improved hearing that comes from listening with both ears over listening with only the ear with the better signal-to-noise ratio. Therefore, bilateral advantages for spatial hearing in children with bilateral devices may primarily come from overcoming the monaural head shadow effect instead of binaural integration. As suggested by studies of individuals with single sided deafness (Agterberg et al., 2012; Kumpik et al., 2010; Newton, 1983; Slattery and Middlebrooks, 1994; Van Wanrooij and

Van Opstal, 2004), bimodal users could potentially make use of some monaural cues available through their acoustic input for improved sound localization. However, these pitch-related cues may be disrupted through hearing aid processing, microphone location effects (above pinna, thereby losing important spectro-temporal filtering from the pinna), and impaired frequency resolution that comes with hearing loss.

Underlying these continued challenges with binaural hearing may be the development of bilateral pathways that remain independent or require a longer time course to restore binaural sensitivity and processing. Data from Chapters 5 and 6 indicate that the cochlear implant drove cortical plasticity, whereas minimal changes occurred in the pathways stimulated by the non-implanted ear. While these findings are encouraging in the sense that the electrical stimulation from the cochlear implant did not interfere with pathways from the non-implanted ear, they also indicate that the pathways may remain independent for a period of time following restoration of bilateral input. This may limit or delay binaural integration of the bilateral input. Furthermore, unilateral deafness decreases the number of binaurally responsive neurons in the inferior colliculus and cortex, especially in the structures ipsilateral to hearing ear (Polley et al., 2013; Tillein et al., 2016). The cortex ipsilateral to the hearing ear also has a shorter sensitive period for cortical reorganization than the cortex contralateral to the stimulated ear (Kral et al., 2002). Effective bilateral input through bimodal devices can stimulate the bilateral auditory pathways to reverse abnormal hemispheric representations of each ear, but more time may be required for this bilateral input to restore or promote development of binaural responsivity and processing in ascending pathways.

Binaural integration of bilateral input may develop but potentially involves additional or alternative mechanisms than normal. The auditory brainstem shows potential for processing binaural cues delivered through bilateral cochlear implants despite periods of unilateral deprivation (Gordon et al., 2007c, 2008b, 2012). However, even for children who receive their cochlear implants with no delay (i.e., simultaneous surgeries) this bilateral input is not necessarily perceived as fused (Steel et al., 2015), nor processed normally at the level of the cortex (Easwar et al., 2017b, 2017c, 2018). Normally, each auditory cortex preferentially responds to bilateral input that is louder or leads in time from the contralateral side (Johnson and Hautus, 2010; Krumbholz et al., 2005; Lee and Middlebrooks, 2011; McEvoy et al., 1993; Werner-Reiss and Groh, 2008). However, no such distinction exists in the auditory cortices for

either ILDs or ITDs in simultaneous bilaterally implanted children, despite their ability to detect ILDs (Easwar et al., 2017b, 2017c, 2018). Moreover, deficits in binaural processing extend beyond the auditory cortices, with bilateral implant users activating parieto-occipital areas to a lesser extent than normal in response to ILDs, ITDs and unilateral stimulation (Easwar et al., 2017c, 2017b, 2018; Jiwani et al., 2016). The abnormal recruitment of other cortical areas may indicate problems with spatial coding, multi-sensory processing/integration, visual attention, and suggests that children use other mechanisms to process what binaural cues they can detect (Easwar et al., 2017c, 2018).

These remaining challenges for binaural processing may be exacerbated by current limitations in auditory device processing strategies. Higher stimulation rates are required for accurately perceiving speech through electrical hearing, but these rates compromise ITD perception (reviewed by Kan and Litovsky, 2015). ITD lateralization is best at electrical stimulation rates lower than 200 pulses per second (pps) but even at lower rates, larger than physiological ITDs are required for bilateral cochlear implant users to fully lateralize sound (Baumgärtel et al., 2017). Even at the rate of 200 pps, implant users are more sensitive to the ITDs delivered at the maximum rather than rising section of the modulated stream of pulses, which is more obscured by reflections and reverberation in more realistic environments (Hu et al., 2017). These envelope ITDs are also more perceptible for bimodal users than ITDs carried by un-modulated low frequency sounds (Lenssen et al., 2011).

Moreover, both devices of bimodal and bilateral cochlear implant users are not linked. Even when bilateral input is delivered within the same modality (i.e., two hearing aids or two cochlear implants), the processing strategies employed by each device operate independently from each other. These issues apply to bimodal users, with the additional variability introduced by different companies with different algorithms and strategies being applied to process and deliver auditory input. Independently operating processing strategies employed by each device may further distort binaural cues and/or provide inconsistent cues over time. These inconsistencies or distortions occur in bilateral hearing aids with automatic gain control (Wiggins and Seeber, 2013, 2012, 2011), as well as adaptive directionality and non-linear frequency compression processing (Brown et al., 2016). Preliminary findings in a model of uncoordinated bilateral cochlear implants confirm that ILDs are also distorted by independently operating automatic gain control and selection of which amplitude peaks to deliver via electrical stimulation (Ausili and Dietz,

2018). Therefore, even the ILD cues that bimodal and bilateral cochlear implant users rely upon for spatial hearing are distorted by the clinical devices that are provided to them. Therefore, current device limitations in hearing aids and cochlear implants smear the spatial representation of sound, further compounding the challenges of binaural integration that these children experience.

In summary, early bilateral input with bimodal devices or bilateral cochlear implants promotes symmetric auditory development, which lays the foundation for future efforts to promote binaural hearing. Children continue to experience difficulties with binaural hearing, which may be a combined function of underlying effects of asymmetric hearing during development as well as the limitations of current technology to provide consistent and faithful representations of binaural cues. By restricting asymmetric hearing, bimodal hearing maximizes the potential for children to develop bilateral and spatial hearing. Future programming efforts should attempt to minimize distortions to binaural cues.

Chapter 9

9 Current and Future Directions

Several questions and new lines of investigation arise from the data presented in this thesis, which can be organized into these main themes: 1) developmental and maturational trajectory with bimodal hearing; 2) binaural processing capabilities with bimodal hearing; and 3) effects of asymmetric hearing and bimodal hearing on other sensory systems.

9.1 Developmental and maturational trajectory of bimodal users

9.1.1 Can a period of bimodal hearing protect the auditory system for later bilateral cochlear implant use in children with poor residual hearing?

Data from Chapters 3, 4 and 7 demonstrate that children with poor residual hearing in their non-implanted ear develop persistently prolonged acoustic delays in the brainstem, cortical aural preference for the implanted ear, and poorer speech perception in the non-implanted ear within a few years of bimodal use. As discussed in Section 8.4, these children may fare better with bilateral cochlear implants. Although there was no clear bimodal advantage in this cohort who had poor residual hearing, a question arises whether a shorter period of bimodal hearing can prime the bilateral system for later bilateral cochlear implant use by stimulating pathways from each ear, while at the same time providing the auditory system with acoustic information that may provide later advantages for language and music perception (Hopyan et al., 2012; Moberly et al., 2016; Nittrouer and Chapman, 2009). Furthermore, can the bimodally-driven asymmetries be reversed with bilateral cochlear implant use? Evaluating the persistent consequences and benefits to a period of bimodal hearing prior to bilateral cochlear implantation is important to guide our understanding of what might be the optimal timing of providing bilateral devices.

Several of these "traditional" bimodal users went on to receive a second cochlear implant, either because their residual hearing declined into the candidacy hearing range or because they were receiving little benefit from their hearing aid. This provided a unique opportunity to ask whether a period of bimodal use in the presence of significant hearing loss was functionally beneficial and protected/primed the bilateral pathways for bilateral cochlear implant use. I hypothesized that in children with poor residual hearing: (1) bilateral cochlear implants provide better access

to high-frequencies than bimodal stimulation as measured by more symmetric speech perception; and (2) bimodal hearing stimulates bilateral auditory pathways, thereby promoting the recovery of bilateral symmetry with bilateral cochlear implants. Smaller evoked brainstem wave eV and inter-wave asymmetries are expected in this cohort of children who received bilateral cochlear implants after bimodal listening compared to their peers who used only unilateral implants before bilateral implantation.

In this follow-up study, I followed 19 bimodal users who received a second cochlear implant over the first 6-9 months of bilateral cochlear implant use. They received their first cochlear implant (left ear n = 13, right ear n = 6) at (mean ± SD) age 5.5 ± 3.9 years and had used bimodal hearing for 4.5 ± 3.7 years. Average pure tone hearing thresholds in their first and second implanted ears were 97.2 ± 11.3 and 88.6 ± 11.5 dB HL respectively. Speech perception for each ear was collected at 1.0 ± 1.0 years before and 0.9 ± 1.4 years after bilateral implantation. The same EEG measures from Chapter 3 were used to record brainstem responses during bimodal and early bilateral cochlear implant use. Stimuli were presented monaurally and binaurally with no timing or level difference (levels were judged as balanced). These responses will be compared to previously described cohorts of bilateral cochlear implant users who had different inter-implant delays (Gordon et al., 2008b).

Preliminary results indicate significantly asymmetric speech perception in favour of the first cochlear implant while the children wore bimodal devices (33.9 ± 9.1 RAU, p<0.01) which reduced within 0.9 ± 1.4 years with bilateral cochlear implants (12.4 ± 9.1 RAU, p=0.94). Brainstem wave eV latencies at initial activation of the second implant were variable (range -.5 to .75ms) but on average 0.15 ± 0.1 ms longer for second than first cochlear implant (p = 0.18). Linear mixed effect regression analyses of responses following activation will reveal whether responses become symmetric and exhibit integration, as evidenced by the presence and latency of binaural difference measures. Furthermore, comparison to other bilateral cochlear implant cohorts will demonstrate whether a bimodal advantage for brainstem function exists. Analyses regarding the contributions of residual hearing, age and duration of acoustic, bimodal and bilateral cochlear implant experience will give further insight into bilateral development and inform timing of bimodal to bilateral implantation.

9.1.2 When should children with steeply sloping high-frequency hearing loss receive bimodal devices or bilateral cochlear implants?

Many of the children using bimodal devices have worse hearing thresholds in the high frequencies, particularly those with steeply sloping hearing loss (bottom group of **Figure 1.1**). Many of the hearing aids fitted to pediatric bimodal users contain non-linear frequency compression, which serves to compress higher frequency information into a lower frequency region. This allows improved speech perception by giving audibility to the sounds important for speech perception that would otherwise be unaidable and inaccessible, given the degree of high-frequency hearing loss (Glista et al., 2009; McCreery et al., 2014). But this compression may come at a cost of consistent binaural cues (Brown et al., 2016) and integration in the brainstem (Klauke et al., 2015), particularly when combined with a contralateral cochlear implant. Activating this technology for bimodal users variably influences speech perception, with most neutral or positive reports corresponding to restricted parameters so that less aggressive compression occurs (Davidson et al., 2015; Park et al., 2012; Perreau et al., 2013). Further work is required to understand how these bimodal devices deliver binaural cues across the frequency range. For some children with only low-frequency hearing (very poor mid- to high-frequency hearing loss), more aggressive frequency compression settings may be required to provide sufficient audibility for speech perception. In this case, bilateral cochlear implants might provide better long-term stimulation that also may encourage balanced bilateral input, but at a cost of losing the remaining low-frequency hearing. On the other hand, the complementary information provided by the low-frequency hearing in one ear may ease listening and provide an acoustic advantage for tasks requiring pitch perception. Preliminary trends in bimodal and bilateral cochlear implant users suggest that better low-frequency hearing can improve response time (one metric of effort) when judging differences in music (Polonenko et al., 2017a), and prevent bimodal users from relying on tempo more than pitch cues when deciding the emotion conveyed through music (Giannantonio et al., 2015). There likely is an overlapping candidacy in fitting strategies for children with steeply sloping mid- to high-frequency hearing loss. More studies using a battery of tests of speech perception, binaural hearing and pitch perception are required to elucidate what the candidacy criteria would involve for the transition between bilateral hearing aids, bimodal and bilateral cochlear implants for treating children with steeply sloping hearing loss.

9.1.3 Can children with bimodal hearing develop hemispheric specialization and typical maturation?

Chapters 4-6 suggest that early provision of bimodal hearing can promote typical cortical representation of each ear. As discussed in section 8.2.3, it is reasonable to expect that this typical bilateral development potentially enables the auditory system to follow expected maturational trajectories and encourage hemispheric specialization. Future studies could track the cortical development and complex listening abilities of bimodal users as they progress through adolescence. This would confirm whether early provision of bimodal hearing can promote typical maturational trajectories in electro-acoustically stimulated bilateral pathways and maturation of more complex hearing abilities that support language, educational and social function. Evidence that electrical hearing can support cortical maturation comes from long-term unilateral cochlear implant users (Jiwani et al., 2016). These adolescents exhibit the mature poly-phasic P1-N1-P2 surface response, but underlying cortical activity remains abnormal. By providing bilateral input, bimodal hearing may encourage more typical maturation of underlying neural activity. Maintaining acoustic hearing in one ear may further support maturation and hemispheric specialization by providing complementary information in temporal fine structure that is not currently available through the electrical hearing.

To explore cortical maturation and hemispheric specialization, the same multi-channel EEG methods and beamforming techniques can be used, as well as adding time-frequency analyses of oscillatory activity. However, to explore hemispheric specialization, I would expand the repertoire of stimuli beyond broadband acoustic clicks to include speech and music, or stimuli with differing temporal gaps or pitch intervals. This would require further refinement or use of other neuroimaging techniques to ensure longer durations of cochlear implant artifact can be adequately removed or suppressed without compromising estimates of the underlying cortical activity. These electrophysiological measures would be corroborated with behavioural measures to determine whether bimodal users can accurately perceive these stimuli. I would expect speech and temporal gap stimuli to preferentially activate left auditory areas but music and pitch-related stimuli to preferentially activate auditory areas in the right hemisphere (Giraud and Poeppel, 2012; Johnsrude et al., 2000; Schonwiesner et al., 2005; Zatorre et al., 2002; Zatorre and Belin, 2001), especially for the children who have good residual hearing in their non-implanted ear. Future studies could also examine whether cortical maturation and hemispheric specialization

follow a similar trajectory in the children who experience longer periods of bilateral acoustic hearing before their hearing loss progresses to become asymmetric, and who therefore are provided with bimodal devices at an older age. I expect these children to show similar development as their peers with normal hearing, given their early experience with bilateral acoustic hearing and restricted period of asymmetric hearing by the early intervention with bimodal devices.

9.1.4 Do bimodal users abnormally recruit extra-auditory areas to support listening?

Hearing develops along with other sensory and motor systems. In this thesis I focused on auditory development and perception. But neuroimaging studies in children with cochlear implants consistently show abnormal recruitment of parietal-occipital and frontal-temporal regions during unilateral and bilateral presentation of auditory input (Easwar et al., 2017c, 2017b, 2018; Jiwani et al., 2016). This could reflect differences in sound processing, spatial hearing, sensory integration, spatial processing, and visual attention. Abnormal recruitment of extra-auditory areas could also reflect more generic processing deficits or changes within the default mode network. Does asymmetric hearing loss also drive abnormal recruitment of these areas during passive and active listening? Can bimodal hearing prevent or reverse these changes from occurring? Activation of frontal-parietal areas upon initial cochlear implant stimulation in bimodal users suggests that extra-auditory areas are recruited, but this activity quickly subsides with bimodal use (Chapters 5 and 6). Extra-auditory activity could be further explored using different analyses of the same multi-channel EEG data used in Chapters 4-6. Instead of focusing on the dipoles in each auditory cortex, dipole strength in each voxel could be compared using between-group permutation analyses, which would further highlight what areas are differentially recruited in bimodal users compared to normal when passively listening to acoustic and electric sound. This analysis allows significant detection of differentially recruited areas other than those areas most activated in response to sound (i.e., temporal areas). Second, functional connectivity analyses could be performed to determine whether different networks are involved with bimodal listening, or whether the same networks are activated but to a different extent. Furthermore, these analyses could evaluate whether oscillatory activity in different frequency bands differs from normal for bimodal users. I speculate that bimodal users will show abnormal activation patterns to their peers with normal hearing with initial bimodal use, but these patterns will become more

similar with longer durations of bimodal experience. Bimodal hearing may still recruit small areas involved in multi-sensory and spatial processing, given their remaining challenges in binaural processing.

9.1.5 Does bimodal hearing prevent abnormal connectivity within and between cortical networks and resting-state activity?

Conversely, are extra cortical areas required for processing bimodal sound, leading to more effortful listening? Unilateral deprivation reorganizes cortical networks involved in attention, memory formation, and executive functioning (Schmithorst et al., 2014; Tibbetts et al., 2011; Wang et al., 2014; Yang et al., 2014; Zhang et al., 2015), suggesting extra cognitive demands are required to listen with input from only one ear. By providing bilateral hearing and promoting symmetric cortical development, bimodal hearing may alleviate these difficulties and reduce the abnormal activation of structures within the default mode network and other cortical networks. To explore this, I measured resting-state EEG activity in bimodal users and peers with normal hearing controls. Functional connectivity will be measured and compared to determine whether functional networks differ between children with bimodal and normal hearing. I expect that bimodal hearing will prevent the extensive reorganization in other cortical networks that are demonstrated in children with unilateral hearing. However, there may be remaining differences in activation of the default mode network than normal, reflecting the greater effort that may still be required to process sound given the remaining challenges to binaural hearing in children with bimodal devices.

9.1.6 Social and educational progression in children with bimodal hearing

The ultimate goal of treating hearing loss is to promote as typical development and function as possible. Providing early effective bilateral hearing to children with asymmetric hearing loss is expeted to alleviate the challenges of unilateral hearing and to reduce the risks of social and educational difficulties (Bess and Tharpe, 1986; Borton et al., 2010; Culbertson and Gilbert, 1986; Kuppler et al., 2013; Lieu et al., 2010; reviewed by van Wieringen et al., 2018). Most of the bimodal users studied in this thesis derived bilateral advantages for speech perception in quiet and noisy situations, developed spatial hearing abilities and could detect interaural level differences. Future studies can provide insight into whether these bimodal benefits extend to daily functioning and development, by assessing how their expressive and receptive language

scores (Lieu et al., 2010; Ruben and Schwartz, 1999), verbal IQ and working memory indices (Jensen et al., 2013; Lieu et al., 2010; Niedzielski et al., 2006), academic progression and use of academic resources (Culbertson and Gilbert, 1986; Kuppler et al., 2013; Lieu et al., 2010) compare to their peers and siblings with normal hearing.

9.2   Binaural processing capabilities in bimodal users

9.2.1 Can the auditory brainstem integrate electrical-acoustic interaural timing cues?

While providing bimodal hearing stimulates the bilateral auditory pathways, delivering sound through two independent devices with substantially different timing delays to the auditory system (Chapter 3) may impede binaural processing in the brainstem and compromise binaural hearing development. Even bilateral cochlear implant users who have much smaller, but still significant brainstem asymmetries struggle to detect ITDs (Gordon et al., 2014) and may require ITDs larger than the physiologic range to fully lateralize binaural sound (Baumgärtel et al., 2017). Given the significant inter-device delays for bimodal users (Chapter 3), I expect abnormalities in brainstem processing of interaural timing differences in children using bimodal devices. I hypothesize that binaural processing will occur at a shifted range of ITDs in bimodal users, accounting for the delayed responses from the ear with acoustic hearing and hearing loss relative to the implanted ear. Therefore, binaural brainstem processing and behavioural detection of ITDs are expected to only occur at large ITDs (beyond the physiologic range of ± 1 ms, as tested in Chapter 3) lead by the slower non-implanted ear. Another question arose from this thesis about whether bilateral brainstem responses can be used to define a physiologic range of ITDs and fusion of bilateral input for bimodal users, which may inform whether customized correction of peripheral electrical-acoustic timing mismatches may help improve binaural hearing capabilities in these children. If so, then perhaps this can be programmed into the clinical bimodal devices to help improve sound localization. To test this hypothesis, I recruited 28 children with normal hearing (mean $\pm$ SD age 13.3 $\pm$ 3.1 years) and 50 bimodal users (9.3 $\pm$ 4.6 years) who received their cochlear implant (left: right ear n = 29:21) at age 6.8 $\pm$ 5.0 years and had used bimodal hearing for 2.4 $\pm$ 2.3 years. Electrophysiological measures of brainstem activity were evoked in the implanted ear by biphasic electrical pulses and in all non-implanted ears by broad-band clicks using the same procedures as described in Chapter 3. Stimuli were presented unilaterally and bilaterally at ITDs ranging from 0 to 3 ms leading from both ears.

Preliminary analyses indicate that for children with normal hearing, multiple peak brainstem responses were observed at ITDs beyond the physiological limit (≥1ms) for bilateral stimuli leading from either ear. For bimodal users, responses to bilateral stimuli contained multiple peaks at most ITDs that correspond to the latencies of wave V in the unilaterally evoked responses. Latencies of these peaks in the unilateral and bilateral brainstem responses will be evaluated. To assess binaural integration, the single and multi-peak bilateral responses can be compared with the sum of the unilateral responses (binaural difference, BD) across ITDs. In both animals and humans, BD amplitude and latency changes as a function of binaural cue and therefore, has been proposed as an indicator that some binaural processing or transformation has occurred (Ferber et al., 2016; Furst et al., 1985, 1990; Goksoy et al., 2005; Gordon et al., 2008b, 2012; Ito et al., 1988; Jones and Van der Poel, 1990; reviewed by Laumen et al., 2016; Levine, 1981; Levine and Davis, 1991; Riedel and Kollmeier, 2002). BD amplitude and latency measures will be compared with behavioural ITD detection assessed through binary logistic functions. Future studies will investigate whether correcting for large delays, introduced by the combination of internal delays and external processing delays, can permit binaural integration in the brainstem, promote a fused image of bilateral input, and allow perception of ITDs leading from either ear.

9.2.2 How are binaural electrical-acoustic interaural timing differences processed in the cortex?

Binaural processing begins in the brainstem but continues in the auditory cortex. Despite peripheral timing delays for bimodal auditory input, does the auditory cortex remain responsive in some way to binaural cues? Can stimulation of bilateral pathways and development of contralateral representation of sound create the capacity for binaural processing to occur at the level of the cortex? Normally the auditory cortex responds to a greater extent to sound leading in time from the contralateral ear (Easwar et al., 2017c; Johnson and Hautus, 2010; Krumbholz et al., 2005; McEvoy et al., 1993). Unfortunately, recent studies suggest that cortical processing of binaural cues remains impaired for children who received bilateral cochlear implants simultaneously at a young age (Easwar et al., 2017c, 2018). There was no change in the activation to different ITDs and ILDs, and other cortical areas were abnormally recruited. Is a similar fate destined for bimodal users, or can prior acoustic experience and continued bimodal hearing promote some distinctions of very large ITDs? Are parietal-occipital areas are also

abnormally activated in response to bimodal binaural cues? It would be reasonable to expect that multi-sensory integration and spatial processing may be abnormal for bimodal users. Using beamforming analyses, we will explore how the cortex responds to ITDs in the multi-channel cortical responses that I have already measured in response to ITDs ranging from 0 to 3 ms leading from either ear in a group of bimodal users and age-matched peers with normal hearing.

9.3 What are the effects of bimodal hearing and asymmetric hearing on other sensory systems?

9.3.1 Does impaired binaural processing enhance or impair visual and auditory-visual spatial processing?

Binaural processing remains impaired in bimodal users. How does this auditory impairment affect spatial perception in the visual and auditory-visual modalities? Do the auditory impairments also impair visual perception through abnormal multi-sensory processing, as suggested by the reorganization in other cortical areas? Or is visual perception enhanced through compensatory mechanisms for the impaired binaural processing? In deaf cats, cross-modal plasticity occurs to support vision. Auditory areas typically involved in sound localization and motion perception are recruited by the visual system to support visual localization and visual movement (Lomber et al., 2010; Meredith et al., 2011; Meredith and Lomber, 2011). Likewise, children with long-term deafness do not show the same cortical hypo-metabolism in auditory areas as younger children with deafness, suggesting that these areas have been recruited for other purposes (Lee et al., 2001, 2005). Perhaps by having some stimulation, bimodal users will not show the cross-modal plasticity and vision enhancement, but rather may show challenges for multi-sensory processing and spatial awareness in general. In support, young adults with developmental asymmetric vision (amblyopia) show deficits in vision localization, as expected, but also in auditory and auditory-visual localization (Richards et al., 2018). This suggests that an imbalance in one sensory modality may extend deleterious effects to other modalities. Therefore, one hypothesis is that children who use bimodal devices and have impaired sound localization will also show impaired visual and auditory-visual localization. Future studies could test this hypothesis by assessing sound localization to auditory-only, visual-only and auditory-visual stimuli in bimodal users.

9.3.2 Are children with asymmetric hearing loss at risk for vestibular and balance problems?

As discovered in Chapters 4 and 7 of this thesis, children with asymmetric hearing loss are more likely than children with bilateral deafness to have cochlear-vestibular abnormalities as the etiology of deafness. Other studies of children who have unilateral hearing loss or single sided deafness also report a 10% to 35% incidence of cochlear-vestibular abnormalities as the etiology of deafness (Arndt et al., 2015; Fitzpatrick et al., 2017; Lin et al., 2017; Sokolov et al., 2017). Even across etiologies, about 20-70% of children with sensorineural hearing loss also experience vestibular impairment (Buchman et al., 2004; Cushing et al., 2013, 2008; Licameli et al., 2009; Selz et al., 1996). Given the higher prevalence of anatomical abnormalities, are children with asymmetric hearing loss at a higher risk for vestibular impairments and balance problems? If so, do they experience asymmetric vestibular problems and does this pose a greater problem for balance? One recent study demonstrated that half of the children with single sided deafness experienced vestibular impairments, and balance function was on average poorer than normal (Sokolov et al., 2018). This raises the question whether these impairments are also seen in the broader group of children with various degrees of asymmetric hearing loss. Furthermore, does an asymmetric hearing loss and difficulty in binaural hearing affect the ability to navigate in space? If more cognitive resources are required for spatial hearing, does this impact the ability to walk and listen at the same time? Future studies could assess vestibular and balance function in the range of children with asymmetric hearing loss, to gain further insight into how asymmetric hearing loss affects development and of other sensory systems. Further studies could also gain insight into how these systems integrate together to allow navigation and function in the complex environments experienced in real-life situations.

Chapter 10

10   Conclusions

The studies in this thesis included neuroimaging measures of auditory development and plasticity using bimodal (electrical and acoustic) auditory input, which were corroborated with behavioural measures of hearing function in children with asymmetric hearing. As hypothesized, bimodal hearing promotes symmetric bilateral auditory development of the brainstem and cortex and provides benefits for bilateral speech perception and spatial hearing in children who have asymmetric hearing loss. Importantly, this occurs if bimodal hearing is provided without delay in early stages of development, and to children who have sufficient residual hearing in their non-implanted ear. Longitudinal measures of cortical activity demonstrate that abnormal development occurs with even limited periods of asymmetric hearing, but bimodal input rapidly reverses these changes when provided quickly. These findings suggest that bilateral hearing does not need to be restricted to one modality and that the auditory system can integrate electrical and acoustic hearing to some extent.

However, there are limitations of bimodal hearing to preventing persistent asymmetrically-driven reorganization of the auditory system with longer periods of asymmetric hearing pre- or post-implantation. Neurophysiological and functional (behavioural) aural preference for the better hearing ear persists despite years of subsequent bimodal device use, limiting bilateral advantages for speech perception in quiet and noisy environments and affecting spatial hearing. Bimodal hearing can re-establish bilateral hearing but there are remaining challenges for binaural hearing. Bimodal users cannot detect inter-aural timing differences, which is not surprising given the large mismatches in inter-aural place of stimulation and neural conduction in bilateral brainstem pathways. These mismatches may be further distorted by independent processing of sound by their two separate devices. Advances in device programming are required to correct for these peripheral and processing differences, thereby optimizing capacity for binaural processing.

This thesis demonstrates that any degree of asymmetric hearing during early development promotes abnormal strengthening of responses from the better hearing ear within a relatively short time frame. Sufficiently symmetric bilateral experience during early developmental periods

is more important than modality for driving bilateral auditory development. Early intervention and restricted periods of asymmetric hearing are important for maximizing bilateral development and creating the capacity for binaural and spatial hearing. Bilateral input can be effectively delivered through two different modalities when provided without delay and to children with sufficient residual hearing. These findings testify to the remarkable plasticity and adaptability of the auditory system to use whatever input it receives to help process and interpret the complex cacophony of sounds that exist in daily life.

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Polonenko, M.J., Papsin, B.C., & Gordon, K.A. (2015). The effects of asymmetric hearing on bilateral brainstem function: findings in children with bimodal (electric and acoustic) hearing. Audiology & Neuro-Otology, 20 Suppl, 13-20. https://doi.org/10.1159/000380743.

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Polonenko, M.J.*, Gordon, K.A.* (*co-first authors), Cushing, S.L., & Papsin, B.C. (2017). Cortical organization restored by cochlear implantation in young children with

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Articles In Revision:

Chapter 7 has been submitted for publication in Scientific Reports and is in revision:

Polonenko, M.J., Papsin, B.C., & Gordon, K.A. (in revision). Limiting asymmetric hearing improves benefits of bilateral hearing in children using cochlear implants.

Other Published Articles During Doctoral Studies

Papers other than from this thesis that were completed during my doctoral studies have been published in the following journals:

(Giannantonio et al., 2015; Gordon et al., 2017; Polonenko et al., 2016b, 2016a, 2017a, 2017c; Sokolov et al., 2017, 2018; Yamazaki et al., 2018)

1. Sokolov M., Gordon K.A., Polonenko M.J., Blaser S.I., Papsin B.C., & Cushing S.L. Vestibular and balance function is often impaired in children with profound unilateral sensorineural hearing loss. Hearing Research, 2018 [Epub ahead of print]. doi: 10.1016/j.heares.2018.03.032.
2. Yamazaki H., Easwar V., Polonenko M.J., Jiwani S., Wong D.D.E., Papsin B.C., & Gordon K.A. Cortical hemispheric asymmetries are present at young ages and further develop into adolescence. Human Brain Mapping, 2018; 39(2):941-954. doi: 10.1002/hbm.23893.
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7. <u>Polonenko M.J.</u>, Carinci L., Gordon K.A., Papsin B.C., & Cushing S.L. Hearing benefit and rated satisfaction in children with unilateral conductive hearing loss using a transcutaneous magnetic coupled bone conduction hearing aid. Journal of the American Academy of Audiology, 2016; 27(10): 790-804. doi: 10.3766/jaaa.15092.

8. <u>Polonenko M.J.</u>, Cushing S.L., Gordon K.A., Allemang B., Jewell S., & Papsin B.C. Stimulation parameters differ between current anti- and peri-modiolar electrode arrays implanted within the same child. Journal of Laryngology and Otology, 2016; 130(11): 1007-1021. doi:10.1017/S0022215116009026

9. Giannantonio S.*, <u>Polonenko M.J.</u>* (*co-first authors), Papsin B.C., Paludetti G., & Gordon K. Experience changes how emotion in music is judged: evidence from children listening with bilateral cochlear implants, bimodal devices, and normal hearing. Plos ONE, 2015; 10(8):e0136685. doi:10.1371/journal.pone.0136685.

Peer-Reviewed Presentations

Papers deriving from this thesis have been presented at the following conferences:

Invited Presentations

1. <u>Polonenko MJ</u>. Electrophysiological measures of auditory development in children using bimodal devices. Conference on Implantable Auditory Prostheses (CIAP), July 21, 2017. Lake Tahoe, CA.

2. <u>Polonenko MJ</u>, Papsin BC. Management of children with asymmetric hearing loss panel: Underlying physiology of binaural stimulation and the effects of asymmetric hearing loss. 42nd annual meeting of the Society of Ear, Nose and Throat Advances in Children (SENTAC), December 4-6, 2015. San Antonio, USA.

3. <u>Polonenko MJ</u>, Gordon KA. Pre-Conference Workshop: Cochlear Implants – Emerging Advances in Clinical and Research Audiology. Canadian Academy of Audiology 2015 Annual Conference and Exhibition, October 21, 2015. Niagara Falls, Canada.

Podium Presentations

1. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Spatial hearing abilities in children using bimodal devices and bilateral cochlear implants. 44th annual meeting of the Society of Ear, Nose and Throat Advances in Children (SENTAC). December 2, 2017, Toronto, ON, Canada. <u>First and second place for highest rated abstracts.</u>

2. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Early access to high frequencies promotes symmetric speech perception in bimodal and bilateral cochlear implant users. 44th annual meeting of the Society of Ear, Nose and Throat Advances in Children (SENTAC). December 2, 2017, Toronto, ON, Canada. <u>Second place for highest rated abstracts.</u>

3. <u>Polonenko MJ</u>, Papsin B, Gordon K. Cortical development requires symmetric access to sound in each ear: evidence from children with bilateral cochlear implants and bimodal auditory prostheses. Gordon Research Seminar and Conference: Auditory and Vestibular Systems: Periphery to Perception, July 10, 2016. Lewiston, MN, USA.

4. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Pediatric bimodal users: who are they? 14th International Conference on Cochlear Implants, May 12, 2016. Toronto, ON, Canada.

5. <u>Polonenko MJ</u>, McKnight CL, Gordon KA. Can bimodal hearing protect bilateral auditory development? Evidence from NIC2 recordings. Invited presentation at NIC Workshop at the 2015 Conference on Implantable Auditory Prostheses. July 14, 2015. Lake Tahoe, CA, USA.

6. <u>Polonenko MJ</u>, Jiwani S, Papsin B, Gordon K. Cortical benefits of bimodal hearing in children with asymmetric hearing loss. 14th Symposium on Cochlear Implant sin Children. December 12, 2014. Nashville, TN, USA.

7. <u>Polonenko MJ</u>, Papsin B, Gordon KA. Asymmetric auditory brainstem development and function in children with bimodal (electric and acoustic) hearing. 8th International Symposium on Objective Measures in Auditory Implants, October 17, 2014. Toronto, Canada. <u>Award winner.</u>

8. <u>Polonenko MJ</u>, Jiwani S, Papsin B, Gordon KA. Can we preserve bilateral symmetry in the developing auditory cortex with electric and acoustic (bimodal) hearing? 8th International

Symposium on Objective Measures in Auditory Implants, October 18, 2014. Toronto, Canada.

9. Polonenko MJ, Giannantonio S. A tale of two ears (and two cities). March 19, 2014. Cochlear Implant Research Noon Rounds, Toronto, Canada.

10. Polonenko MJ. Is there a mismatch in auditory brainstem development with combined electric and acoustic hearing in children? June 19, 2013. Cochlear Implant Research Noon Rounds, Toronto, Canada.

Poster Presentations

1. Polonenko MJ, Papsin BC, Gordon KA. Cortical plasticity with bimodal use in children with asymmetric hearing loss. 6th International Conference on Auditory Cortex (ICAC), September 10-15, 2017. Banff, AB, Canada.

2. Polonenko MJ, Lavallee C, Papsin B, Gordon K. Does bimodal hearing provide an advantage to bilateral brainstem development? Conference on Implantable Auditory Prostheses (CIAP), July 18, 2017. Lake Tahoe, CA, USA.

3. Polonenko MJ, Papsin BC, Gordon KA. Cortical Activity in Children with Single Sided Deafness Pre- and Post-Implantation. Association for Research in Otolaryngology 40th MidWinter Meeting, February 14, 2017. Baltimore, MD, USA.

4. Polonenko MJ, Papsin BC, Gordon KA. Cortical development requires symmetric access to sound in each ear: evidence from children with bilateral cochlear implants and bimodal auditory prostheses. Gordon Research Seminar and Conference: The Plastic and Dynamic Auditory System, July 11-15, 2016. Lewiston, MN, USA.

5. Polonenko MJ, Papsin B, Gordon K. Developmental protection of aural preference in children with asymmetric hearing loss through bimodal hearing. 2015 Conference on Implantable Auditory Prostheses. July 13, 2015. Lake Tahoe, CA, USA.

6. Polonenko MJ, Papsin BC, Gordon KA. Protecting auditory cortical development in children with asymmetric hearing loss through bimodal hearing. Collaborative Program in Neuroscience (CPIN) Annual Research Day, June 19, 2015. Toronto, Canada.

7. Polonenko MJ, Papsin BC, Gordon KA. Auditory brainstem development with combined acoustic and electric hearing in children with asymmetric hearing loss. Collaborative Program in Neuroscience (CPIN) Annual Research Day, June 10, 2013. Toronto, Canada.

8. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Is there a mismatch in auditory brainstem development with combined acoustic and electric hearing in children who have asymmetric hearing loss? Institute of Medical Science (IMS) Annual Research Day, May 28, 2013. Toronto, Canada.

Other Podium Presentations

Papers other than from this thesis that were completed during doctoral studies have been presented at the following conferences:

1. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Bimodal hearing disrupts normal brainstem ITD processing in children. Association for Research in Otolaryngology 41st MidWinter Meeting, February 11, 2018. San Deigo, CA, USA. <u>Selected for poster blitz presentation – First place.</u>
2. <u>Polonenko MJ</u>, Giannantonio S, Papsin BC, Gordon KA. Music training improves music perception in children using bilateral cochlear implants or bimodal devices. 33rd World Congress of Audiology, September 21, 2016. Vancouver, BC, Canada.
3. <u>Polonenko MJ</u>, Giannantonio S, Papsin BC, Gordon KA. Music training improves perception of emotion and music in children using bilateral cochlear implants or bimodal devices. 14th International Conference on Cochlear Implants, May 12, 2016. Toronto, ON, Canada.
4. <u>Polonenko MJ</u>, Giannantonio S, Papsin BC, Gordon KA. Residual hearing helps children with cochlear implants rely less on tempo cues to judge emotion in music. 2015 Annual Conference and Exhibition of the Canadian Academy of Audiology, October 23, 2015. Niagara Falls, ON, Canada.
5. <u>Polonenko MJ</u>, Jewell SJ. Auditory brainstem development and MAP parameters in children receiving 422 and Freedom electrode arrays in a simultaneous bilateral implant procedure. Cochlear Implant Research Noon Rounds, December 17, 2014, Toronto, Canada.
6. <u>Polonenko MJ</u>, Papsin BC, Cushing SL, Jewell S, Gordon KA. Electrophysiological predictions of map parameters using the 422 and Freedom electrode arrays. 14th Symposium on Cochlear Implant sin Children. December 13, 2014. Nashville, TN, USA.
7. <u>Polonenko MJ</u>, Carinci L, Cushing S, Gordon KA, Papsin BC. Functional outcomes in children who were implanted with a new transcutaneous bone conduction device. 23rd Percy Ireland Academic Day, May 9, 2014. Toronto, Canada.

8. <u>Polonenko MJ</u>, Gordon KA, Cushing SL, Papsin BC. Can the new 422 cochlear implant electrode array preserve hearing while working as efficiently as the Freedom array? 41st annual meeting of the Society of Ear, Nose and Throat Advances in Children (SENTAC), December 7, 2014. Long Beach, USA.

9. <u>Polonenko MJ</u>, Gordon KA, Papsin BC. Can the new 422 cochlear implant electrode array preserve hearing while working as efficiently as the Freedom array? 22nd Percy Ireland Academic Day, May 10, 2013. Toronto, Canada.

Other Poster Presentations

1. <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Bimodal hearing disrupts normal brainstem ITD processing in children. Association for Research in Otolaryngology 41st MidWinter Meeting, February 13, 2018. San Deigo, CA, USA. <u>Selected as one of the top 16 abstracts of trainees and early investigators (Henderson award)</u>.

2. <u>Polonenko MJ</u>, Deighton MR, Abbasalipour P, Papsin BC, Gordon KA. Perception of binaural level and timing cues in children with early bimodal use compared to bilaterally implanted children. Association for Research in Otolaryngology 39th MidWinter Meeting, February 22, 2016. San Diego, CA, USA.

3. <u>Polonenko MJ</u>, Cushing SL, Gordon KA, Allemang B, Papsin BC. Are stimulation parameters equivalent for the Freedom and 422 electrode arrays? 14th Symposium on Cochlear Implant sin Children. December 11, 2014. Nashville, TN, USA.

4. Morrison Steel, <u>Polonenko MJ</u>, Papsin BC, Gordon KA. Listening advantages of early intervention for bilateral deafness in children. 8th International Symposium on Objective Measures in Auditory Implants (no. 5415), October 16, 2014. Toronto, Canada. <u>First place award winner</u>.

5. <u>Polonenko MJ</u>, Carinci L, Cushing SL, Gordon KA, Papsin BC. Clinical benefit to implanting a new transcutaneous bone conduction device in children. 41st annual meeting of the Society of Ear, Nose and Throat Advances in Children (SENTAC), December 6, 2013. Long Beach, USA. <u>First Place Award Winner</u>.