Somatosensory Cross-Modal Reorganization in Children with Cochlear Implants

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Thesis directed by Dr. Anu Sharma

**Background:** In cross-modal reorganization, a well-known phenomenon that occurs in sensory deprivation, intact sensory modalities can recruit and repurpose cortices of deprived modalities. Cross-modal reorganization has been linked to behavioral outcomes in deaf, cochlear-implanted adults. However, there have been no efforts to directly investigate these phenomena in deaf children who receive cochlear implants, even though cross-modal reorganization could potentially shed light on the variability in speech and language outcomes observed in this population.

**Purpose:** The current study included the following aims: 1) To characterize maturation of cortical somatosensory evoked potentials using high-density EEG in normal hearing children, for use in comparison with children with cochlear implants; 2) To examine somatosensory-to-auditory cross-modal reorganization using high-density EEG in children with cochlear implants; 3) To investigate possible correlations between somatosensory-to-auditory cross-modal reorganization and speech perception in children with cochlear implants. We hypothesized that high-density EEG and estimation of the sources of cortical activity would reveal somatosensory cross-modal reorganization in children with CIs, and that these findings would be correlated with behavioral outcomes in these children.

**Methods:** Cortical somatosensory evoked potentials (CSEP) were recorded in response to vibrotactile stimulation of the right index finger in 5-19 year old children with normal hearing (NH) and cochlear implants (CI). Developmental changes were investigated by comparing CSEP latency and amplitude and cortical source estimates across age. Finally, results from a measure of speech perception in noise were correlated with CSEP responses in children with cochlear implants.

**Results:** Waveform morphology and cortical activation were stable across age in the NH group, though latency and amplitude comparisons across age revealed some developmental patterns
for the NH children. CI children showed larger amplitudes and shorter latencies for some CSEP components, along with activation of auditory cortical areas in response to vibrotactile stimulation, suggestive of somatosensory cross-modal recruitment. CSEP waveform components were correlated with behavioral performance on a clinical measure of speech perception in background noise for CI children.

**Conclusions:** Overall, our data are suggestive of somatosensory cross-modal reorganization in children with cochlear implants, which may have bearing on their speech perception performance with these devices. Our findings indicate that somatosensory cross-modal reorganization may be a source of variability in CI outcomes, which deserves further investigation.
Dedication

I dedicate this work to the same people to whom I owe and dedicate my life: my incredible wife, terrific sons, and wonderful parents. I also commit this project to the individuals who might benefit from the findings contained herein. Ultimately, my hope is that this research will serve these people in needed and worthwhile ways.
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Chapter 1

Review of the Literature

1.1 Introduction

Cochlear implants (CI) are devices that restore hearing to deaf individuals via direct electrical stimulation of the auditory (VIII) nerve. These devices have proven extremely useful in restoring auditory function to many children born with hearing loss. However, many other implant recipients have had relatively little success in behavioral speech understanding with cochlear implants (Harrison et al., 2005; Nicholas & Geers, 2007; Holt & Svirksy, 2008). Only some of this variability has been explained, despite investigation into many factors (Svirsky et al, 2000; Sarant et al, 2001; Tobey et al, 2003; Geers, 2006; Geers et al, 2009). Thus, there remains a need for research that aims to discover why some pediatric CI users perform well, while others do not, in order to optimize treatment and management of these patients. One area of exploration that may be useful in providing insight into this disparity is cortical maturation and plasticity. Understanding extrinsic influences on neuronal maturation and harnessing neural plasticity for patient treatment is a recent focus in neuroscience and an important direction of future CI research (Cramer et al, 2011; Karns et el, 2012).

In this manuscript, we document the background, rationale, specific aims, and results of two separate studies designed to examine the influence of cross-modal reorganization a certain type of neural plasticity - as a factor that explains an additional portion of the variance in cochlear implantation outcomes.
1.2 Cochlear Implantation in Children

Since the first cochlear implantation in the 1970s, cochlear implants have assisted many to hear, where they were not able prior to receiving the device. According to some estimations, about 324,200 individuals adults and children throughout the world have received cochlear implants (as of 2013), with roughly 38,000 children in the United States having been implanted (NIH, NIDCD, 2013). While hearing aids are successful in many children with mild to moderate hearing loss, cochlear implants are largely used in individuals with greater degrees of hearing impairment (i.e., severe to profound). At present the U.S. Food and Drug Administration (FDA) has approved CIs in children down to one year of age.

In general, cochlear implants work to restore hearing by directly stimulating the auditory (VIII) nerve. These devices consist of both an internal and an external component. The former is made up of an electrode array, which is inserted into the cochlea and, by hugging the modiolus, innervates the spiral ganglion cells of the VIII nerve. Modern cochlear implants may have more than 20 electrodes. Moving laterally toward the portion of the skull that sits just under the skin behind the outer ear (i.e., pinna), this electrode array is attached to a radio frequency receiver. This receiver is affixed to the skull during surgery and covered over with skin, so as to be completely implanted. In its most basic form, the external portion of the device consists of one or more microphone(s), a speech processor, a power source (i.e., batteries), and a transmitter. When functional, the cochlear implant receives sound via the microphone, which is, in turn, decoded by the sound processor. That is, once transduced, the sound signal is broken down into signals that will be sent to electrodes along the array (i.e., within the cochlea). The signal that is devised by the sound processor is sent across the skin, via radio frequency, to the implanted receiver, which then sends the signal downstream to the electrode array. Specialized clinical audiologists are responsible for adjusting the settings, or map, of a cochlear implant to match a given patient's needs. For instance, each electrode along the array may have a different threshold for stimulation and unique levels at which stimulation is no longer comfortable. During mapping appointments, audiologists can fine-tune
these, and other, settings to the patients satisfaction.

In children, the development of age-appropriate speech and receptive/expressive language is of utmost importance. In fact, this concern has been a significant catalyst in the progressive decrease in age of implantation that has occurred in children. Indeed, early implantation has proven important to improved outcomes in cochlear implant recipients (e.g., Svirsky, Teoh, & Neuberger, 2004). However, a great deal of the variance in the behavioral outcomes of cochlear-implanted children has still not been explained, though a number of studies have aimed to discover the predictors of success (Svirsy et al, 2000; Sarant et al, 2001; Tobey et al, 2003; Geers, 2006; Geers et al, 2009). Many of these investigations have focused on demographic factors, such as age of implantation, household income, mothers level of education, communication mode, among others. Collectively, however, these factors have only explained approximately 30-60 percent of the variance in outcomes for CI children (Fink et al, 2007). Fewer studies have concentrated on neurophysiological contributions to cochlear implant success. The current study aims to investigate one area of neuroplasticity cross-modal reorganization that may be significant in the brains of individuals in whom sensory deprivation is a feature.

1.3 Cross-Modal Reorganization Under Conditions of Sensory Deficit

Reorganization of the cortex has a tendency to occur in people who experience sensory deficit (Bavalier & Neville, 2002; Merabet & Pascual-Leone, 2010). Hearing loss is a naturally occurring condition that causes deprivation of the auditory cortex, which provides a crucial opportunity to study cross-modal reorganization in humans. A wealth of evidence in both animals and humans supports the notion that the auditory cortex can be recruited by other sensory modalities when deprived of normal auditory input. For example, visual stimuli have been shown to activate auditory cortex in both animals and humans with hearing loss (Rebillard et al, 1977; Neville et al, 1983; Finney et al, 2003; Fine et al, 2005; Sadato et al, 2005; Doucet et al, 2006; Buckley & Tobey, 2011; Fine et al, 2011). In one example of this cross-modal activation, Neville et al (1983) showed changes in cortical visual evoked potentials (CVEP) in participants with severe to profound hearing loss,
such that peak amplitudes of visual waveform components (i.e., N1) were greater over frontal and temporal areas of the skull than those of participants with normal hearing. This finding points to greater activation of typically auditory areas of the brain by visual stimuli in congenitally deaf adults. Similarly, both auditory and somatosensory stimuli (e.g., Braille reading) activate visual cortex in blind adults (Hyvarinen et al, 1981a, 1981b; Neville et al, 1983; Uhl et al, 1991 Kujala et al, 1995; Sadato et al, 1996; Cohen et al, 1997; Hamilton & Pascual-Leone, 1998). Thus, it seems that cross-modal reorganization of deprived sensory cortices is a common finding in persons with sensory deficit.

A number of studies have highlighted the functional consequences of cross-modal reorganization. In general, it seems that the recruiting modality(s) often show enhanced functionality, while the recruited modality may present with deficits (Neimeyer and Starlinger, 1981; Neville & Lawson, 1987; Lessard et al, 1998; Rettenbach et al, 1999; Bavalier et al, 2000; Levnen & Hamdorf, 2001;). For example, Bavalier and colleagues (2000) demonstrated that the deaf participants in their study showed enhanced visual attention to peripheral visual motion, due to increased recruitment by visual cortices (of auditory areas) in these individuals. Similar sensory enhancement has also been noted in the blind, such that both auditory and somatosensory sensory processing can be enhanced (e.g., Cohen et al, 1997; Roder et al, 1999;). Additionally, Lomber et al (2010; see also Bavalier & Hirshorn, 2010) reported that congenitally deaf cats showed enhanced visual processing in the form of improved peripheral visual localization and decreased visual movement thresholds when compared with normal hearing cats. What is more, these improvements were eliminated when the auditory cortices of the deaf cats were reversibly deactivated, indicating that those auditory regions mediated visual processing enhancements. These data provide convincing evidence that auditory areas subserved visual processing.

Germane to the current proposal, cross-modal reorganization has proven to be a factor in predicting behavioral outcomes in cochlear implant recipients. For instance, Doucet et al (2006), assessing high-density (EEG) responses to a visual motion stimulus, showed that adult cochlear implant users with poor behavioral speech perception (0% mean score) exhibited activation in
visual, auditory, and multi-sensory cortical areas, which was taken as an indicator of cross-modal reorganization. In contrast, participants with good speech perception (≈73% score) presented with activation relegated to the visual cortices, which pointed to lack of cross-modal reorganization in these participants. In another study, Buckley and Tobey (2011) showed correlations between the N1 cortical visual evoked potential (CVEP) component and speech perception outcomes in adults with cochlear implants, such that increases in the amplitude of the N1 over the right temporal area (taken as an index of visual-to-auditory cross-modal reorganization) were associated with decreases in speech performance. Together, these findings seem to indicate that the extent of cross-modal reorganization may be systematically related to behavioral outcomes in CI recipients.

1.4 Somatosensory-Auditory Cross-Modal Reorganization

While reorganization between the visual and auditory modalities has been well described in both animals and humans with hearing loss, a limited literature is available that illustrates reorganization between somatosensory and auditory brain regions. However, somatosensory-to-auditory cross-modal reorganization is plausible for several reasons. First, the somatosensory and auditory cortices, anatomically, are very close in proximity and share underlying neural connections. Anatomical convergence such as thalamo-cortical and cortico-cortical connections (e.g., somatosensory activated / traced neurons in the belt area of the auditory cortex) and somatosensory processing occurring in primary and higher-order auditory cortices, has been demonstrated in animal anatomical and physiologic studies (Lindsley et al, 1999; Schroeder et al, 2001; Schroeder & Foxe, 2002; Fu et al, 2003; Brosch et al, 2005; Kayser et al, 2005; Lakatos et al, 2005, 2007; Hackett et al, 2007) and human brain imaging investigations (Foxe et al, 2000, 2002; Lutkenhoner et al, 2002; Goebbel et al, 2003; Caetano & Jousmki, 2006). For example, a recent study by Lakatos and colleagues (2007) provided evidence for physiologic interaction of the auditory and somatosensory cortices in macaque monkeys. These authors demonstrated that the somatosensory system was instrumental in resetting the phase of neural oscillations, which lead to enhancement of accompanying incoming auditory signals and suppression of unrelated signals. In addition, human behavioral studies have
revealed interactions between the auditory and somatosensory systems (Spence et al, 1998; Jousmki & Hari, 1998; Merat et al, 1999; Levnen & Hamdorf, 2001; Schurmann et al, 2004). For instance, somatosensory perception can be mediated by changing the frequency of simultaneously presented auditory stimuli. Jousmki & Hari (1998) asked participants to rub their hands together in a back and forth manner while they listened to the sound of this rubbing through headphones. These investigators reported that if they accentuated the high frequencies of the auditory component of the experiment, participants indicated that their hands felt rougher than when no alteration to the sound was made (i.e., the parchment-skin illusion). Thus, there seems to be an anatomical and physiological precedent for conjecture regarding cross-modal interaction and possibly reorganization between the somatosensory and auditory systems.

Further, sound and vibration represent essentially the same physical process (i.e., oscillation), although they are typically propagated through different mediasound through air and vibration through solids (Von Bksy, 1959; Levnen et al, 1998; Soto-Faraco & Deco, 2009). In contrast to the visual and auditory systems, somatosensory-auditory interaction may be more likely due to the fact that both the somatosensory and auditory systems are sensitive to physically similar classes of stimuli. In fact, Soto-Faraco & Deco (2009) argue that in a normal system, the correlation between the processing similarities likely leads to integrative interactions, as opposed to mere combination of sensory cues as might be seen in other multisensory interaction. Additionally, the auditory and somatosensory systems respond to overlapping ranges of frequencies. Because auditory and somatosensory stimuli have virtually equal temporal patterns, and because neurons in these systems respond to the same range of frequencies (i.e., 5-300 Hz; Harrington & Downs, 2001), it is reasonable to believe that the auditory subcortical and cortical neurons could appropriately encode somatosensory input (Levnen et al, 1998). Thus, presented with a dearth of auditory input in deafness, it is physically possible for the cortex to re-organize such that somatosensory stimuli could be processed in auditory cortical regions.

There is also evidence that the somatosensory system is involved in speech perception (e.g., Skipper et al, 2006; Ito et al, 2009). For instance, Ito and colleagues (2009) showed that stretch-
ing the face, and thereby stimulating the somatosensory receptors responsible for orientation and stretch of the facial skin, changed participants perception of an auditory phoneme. The above authors argued that, given the abundance of somatosensory receptors in the facial skin and the fact that this skin is systematically deformed during speech production, it is plausible to believe that somatosensory input important in control of speech articulators, may also be vital to speech perception.

The underlying mechanisms that lead to somatosensory-to-auditory cross-modal reorganization are still unknown, though several hypotheses have been offered. These conjectures include unmasking of competitive latent multisensory neural connections when one modality is deprived of input (Levnen et al, 1998, 2001; Foxe, 2000 Schroeder et al, 2001), thalamo-cortical reorganization (Sur et al, 1998; Lomber et al, 2009; Meredith et al, 2011), and attention to non-deprived modalities that may facilitate cross-modal reorganization (Levnen, 2001; McDonald et al, 2003).

Animal studies have yielded strong evidence that somatosensory-to-auditory cross-modal reorganization can occur in deafness. For example, a recent study by Meredith and Lomber (2011) enlisted cats, which underwent one ototoxic treatment near the time of auditory onset that caused partial hearing loss and then a second treatment after weaning that lead to profound hearing loss, to examine somatosensory-to-auditory cross-modal reorganization. Following these treatments, the anterior auditory fields (AAF) of both normal hearing and deafened cats were tested for responsivity to auditory, visual, and somatosensory stimuli. While control subjects showed nearly 100% responsivity to auditory stimuli, early-deafened cats AAFs were most responsive to somatosensory stimuli (78%) and less so to visual stimuli (44%). Virtually none of the neurons in the AAFs of early-deafened cats responded to auditory stimuli. Allman and colleagues (2009) carried out a similar study in ferrets. However, this investigation differed in an important way. That is, instead of deafening their subjects early in life, these researchers did so when their subjects had already reached adulthood. They found that after as little as 14 days of deafness, the auditory cortices of their subjects had begun to show somatosensory-to-auditory cross-modal reorganization. Furthermore, approximately 76 days after the onset of deafness, 84% of auditory cortical neurons showed
responsivity to somatosensory stimuli. The striking findings from these studies provide convincing evidence to support the notion that somatosensory-to-auditory cross-modal reorganization occurs in deafness, possibly more so than with other sensory modalities.

Relatively few studies have examined cross-modal reorganization between the somatosensory and auditory systems in human deafness (Levnen et al, 1998; Baldwin, 2002; Sharma et al, 2007; Auer et al, 2007; Karns et al, 2012). What is more, virtually none of these investigations have shed light on the functional consequences of such reorganization. However, while limited, the results from the above investigations provide evidence that somatosensory-to-auditory cross-modal reorganization can occur in people with hearing loss. For instance, a recent study by Karns and colleagues (2012) using EEG and functional magnetic resonance imaging (fMRI) performed in humans showed similar results to the animal data described above. That is, in congenitally deafened adult participants, a greater portion of the auditory cortex was involved in processing somatosensory stimuli than visual stimuli. In another example, Levnen and colleagues (1998) used magnetoencephalography (MEG) to show activation of the auditory cortex by vibrotactile stimuli. These investigators applied vibrotactile stimuli to participants hands through a hollow tube, which was closed at the end closest to the participants and attached to a speaker that presented 180 and 250 Hz tones (100 ms in length) during MEG recordings. All subjects showed activation of the primary somatosensory cortex (SI) contralateral to the stimulated hand, consistent with activation of the Pacinian corpuscles, which respond to vibrations between 60-300 Hz (peak sensitivity between 200-300 Hz; Harrington & Downs, 2001). In contrast, the deaf adult subject in this study exhibited strong bilateral activation of the superior temporal (ST) auditory cortices, as evidenced by both magnetic signals (i.e., similar to cortical evoked potentials) and magnetic field patterns on the scalp. Similar results were presented by Sharma et al (2007), in that vibrotactile stimuli (180 and 250 Hz) elicited activity in the somatosensory cortices of one adult with deafness and one with normal hearing. Consistent with the Levnen et al (1998) study, however, these stimuli also led to activation of the higher-order auditory, cortex (including a portion of Wernickes area) in the deaf adult. These studies establish a precedent for somatosensory-to-auditory cross-modal
reorganization in human deafness.

While the above investigations provide neurophysiologic evidence of cross-modal reorganization between the auditory and somatosensory systems in people with hearing loss, they are somewhat limited in scope. That is, to date there has been no study of somatosensory-to-auditory cross-modal reorganization in children with hearing loss, even though one study, to our knowledge, has provided evidence of somatosensory-auditory interaction in children with normal hearing (Brett-Green et al, 2008). In this study, the investigators presented auditory, somatosensory, and simultaneous auditory-somatosensory stimuli to children ages 6-13 and compared CAEPs, CSEPs, and their summed response to the cortical evoked response elicited in the simultaneous condition. They found that the response to the simultaneously presented stimuli showed larger amplitudes than the sum of the two waveforms elicited by single stimuli, indicating multisensory interaction in children that was similar to that of adults. Additionally, previous work from our group has shown that deaf children who were implanted late in childhood (i.e., > 7 years of age) showed evidence of cross-modal reorganization, such that parieto-temporal cortex was activated by auditory stimuli (Gilley et al, 2008). This area of the post-central gyrus is thought to be part of somatosensory cortex. In contrast, children with normal hearing and early implanted children presented with activation essentially confined to auditory cortex. While extremely informative, the above studies have not addressed the critical issue of the behavioral consequences of somatosensory-to-auditory cross-modal reorganization. Given the high degree of plasticity of the cortex in children, somatosensory-to-auditory cross-modal reorganization may be even more extensive than that found in adults and have significant behavioral consequences in pediatric patients with hearing loss.

1.5 Organization of Somatosensory Neural Pathways

The somatosensory system is responsible for the sensation of a number of phenomena, such as pressure, vibration, pain, temperature, stretching, and proprioception. Each of these sensations is associated with unique sensory receptor(s). For instance, vibration is processed by two separate types of receptoreach accountable for different frequency ranges. That is, Meissners corpuscles
preferentially process vibratory stimuli of very low frequency, or flutter (i.e., 30-50 Hz; Purves et al, 2001). Additionally, the Pacinian corpuscles are specialized to receive high frequency sensory information (i.e. up to 350 Hz). Both of these types of mechanoreceptor are innervated by highly myelinated large axons, which leads to swift transmission of afferent signals (Purves et al, 2001).

Once a high-frequency vibratory signal is transduced into neural impulses, it most often travels to the cerebral cortex via the lateral cervical system. That is, the first order neurons in the system enter the spinal cord via the dorsal horn of their associated vertebra and course upwards through the fasciculus cuneatus. Once they reach the cuneate nucleus, they synapse with second order neurons. Second order neurons projections ascend through the medial lemniscus and cross over the midline to the ventral posterior lateral nucleus (VPN) of the thalamus, where they synapse again (Gilman & Newman, 1992).

From the VPN, third order neuronal projections ascend to the primary somatosensory cortex (SI) in the post-central gyrus (Brodman areasBA3a, 3b, 1, and 2; Brodmann, 1909) via the posterior limb of the internal capsule and corona radiata. BA 3b receives most of the projections from the VPN, and, in turn, projects to BA 1 and 2. BAs 1 and 2 also have connections to motor cortices and parietal association regions (Jones, 1986). The primary somatosensory cortices are organized somatotopically. That is, there is a whole body representation that is organized sequentially, starting deep in the central sulcus (feet and legs) moving laterally and ventrally to the lateral fissure (head), with the trunk and upper limbs in between in each of the above BAs (Nelson et al, 1980). While each part of the body is represented in these cortical maps, areas associated with the highest peripheral sensory receptor density, such as the hands and lips, are disproportionately large compared to other areas with low receptor density (Nakamura, et al, 1998; Stowell, 1984).

Primary somatosensory areas project to secondary somatosensory cortex (SII), which is located just above the lateral (Sylvian) fissure in BA 40. Though smaller that SI, SII is also somatotopically organized (Hari et al, 1993). Though most of the incoming projections to SII probably come from SI, there are some that branch and ascend to directly innervate SII from the VPN. Furthermore, while most of the inputs to the SII are from contralateral origins, SII appears to
receive some projections from ipsilateral sources (Burton, 1986). Following SII processing, BA 7 in the parietal cortex receives projections from this area (i.e., somatosensory association cortex). In addition, some have shown evidence of connections between these higher-order association areas and multimodal regions of the frontal lobes (Huang et al, 2005).

While the above explanations focused solely on unisensory processing, multisensory processing is also relevant. Numerous reports have elucidated details regarding the interactions between the somatosensory and auditory systems in the brain. In fact, there seems to be a strong tie between these two sensory systems from subcortical to cortical levels. For instance, a number of reports have shown convergence of auditory and somatosensory processing in the auditory belt areas (i.e., caudomedial and caudolateral) of macaque monkeys (Brosch et al 2005; Fu et al 2003; Kayser et al 2005; Schroeder and Foxe 2002; Schroeder et al 2001). This convergence was later shown by Hackett and colleagues (2007) to be fed by projections from both corticocortical (i.e., retroinsular and granular insula, and other parietal, temporal, and occipital areas) and thalamic areas (i.e., medial geniculate complex, suprageniculate, posterior, limitans, and medial pulvinar). Furthermore, it is known that the first neuronal interaction of the somatosensory and auditory systems occurs in the dorsal cochlear nucleus of the brainstem (e.g., Itoh et al, 1987; Pfaller and Arvidsson, 1988; Shore et al, 2000; Zhou and Shore, 2004; Haenggeli et al, 2005; Zhan et al, 2006). These connections may even be related to findings of tonotopic organization found within the somatosensory system (Hashimoto, Mashiko, & Kimura, 1998; Harrington & Downs, 2001). Thus, connections between the somatosensory and auditory systems are seemingly rich and well established.

1.6 Maturation of Somatosensory Neural Pathways

To large degree the principles that mediate neuronal maturation in other sensory systems apply directly to the somatosensory system. For instance, there is a large body of evidence that maturation of the somatosensory cortex (i.e., somatotopic organization) is dependent on sensory experience (e.g., Nicolelis et al, 1996). Also, it has been shown that synaptic connections throughout the somatosensory system are formed and strengthened via Hebbian activity (i.e., long-term
potentiation and depression; LTP & LTD, respectively; Eggermont, 1988). Furthermore, myelo-
genetics play a role in the maturation and refinement of neural pathways in development of the
somatosensory system (Eggermont, 1988). Age-related changes in neuronal structure and function
have been studied extensively using evoked potentials (Allison et al, 1984; Fagan, Taylor, & Logan,
1987; Eggermont, 1988; George & Taylor, 1991; Taylor et al, 1996; Pihko et al, 2009; Tombini et
al, 2009). The majority of these studies have employed direct electrical stimulation of peripheral
nerves as their evoking stimulus. Additionally, most of them have investigated peripheral nerve
conduction across age as a measure of development. Overall, this type of study has consistently
found that neural conduction time decreases rapidly early in life, while peak amplitudes can increase
(Desmedt, 1973; Cadilhac et al, 1986; Eggermont, 1988). This steep decrease in neural conduc-
tion times typically slows by the age of four years, after which modest decreases in latency are seen
through adulthood (Allison et al, 1984). It should be noted that co-occurring changes in height and
length of extremities can offset neural conduction decreases in older children (Gilmore et al, 1985;
Bartel et al, 1987). However, some studies have shown noteworthy decreases in cortical inter-peak
latencies with increasing age (e.g., Allison et al, 1984; Nishimura et al, 1986). That is, when height
and extremity length are accounted for, development-related decreases in neural conduction times
have been observed. While the above studies have provided useful information regarding decreases
in neural conduction times with age, there is a conspicuous shortage of information concerning
development of evoked potentials from the cortex, beyond the initial thalamo-cortical potential.
In addition, developmental studies using stimuli other than direct electrical stimulation, which are
currently lacking, may also be of interest.

It is important to note that neural conduction times change based on the stimulation tech-
nique used. That is, somatosensory evoked potentials (SSEP) can be elicited by using either direct
electrical stimulation of a nerve or by activating sensory receptors with stimuli such as vibration.
Either way leads to neural impulses being propagated through the same pathways. However, elec-
trical stimulation tends to evoke SSEP waveforms with sharper peaks of shorter latencies than
vibrotactile stimulation (see Desmedt, 1988). While these effects may seem advantageous, elec-
trical stimulation may not be tolerated well by some. Thus, vibrotactile stimulation may prove superior in some ways to the application of direct electrical current. This notion may be especially true in children and those with electrical medical devices, such as cochlear implants. Despite their methodological differences, vibrotactile SSEPs appear very similar morphologically to those elicited with electrical stimulation, albeit occurring somewhat later in time. Vibratory stimuli have been successfully used in conjunction with both EEG, magnetoencephalography (MEG) and functional magnetic resonance imaging (fMRI) in numerous investigations to study the structure and function of the somatosensory neural pathways (e.g., Hmlinen et al, 1980; Levnen et al 1998; Baldwin, 2002; Auer et al, 2007; Sharma et al, 2007)

1.7 EEG and Cortical Source Localization Methods in the Study of Cross-modal Reorganization of the Somatosensory and Auditory Systems

Within the realm of brain imaging, there are several methods that provide useful information regarding the structure and function of the brain under a given condition. However, each of these methods has its advantages and disadvantages. In the study of cochlear-implanted individuals, EEG presents several distinct advantages over other methods, such as fMRI, due to its non-invasiveness and low cost. Most importantly, EEG can be performed in individuals with cochlear implants, whereas fMRI under typical circumstances cannot, because the highly magnetic nature of MRI leads this method to cause potential injury to participants or damage to their devices. Also, the electrical signal that is produced by a cochlear implant would likely interfere with fMRI recordings. In addition to its relative non-invasiveness and accessibility, in recent years, many have worked to devise methods to localize sources of cortical activity using high-density EEG recordings (see Pascual-Marqui, 1999 for a review). However, two major problems present obstacles to localizing cortical generators. These are termed the forward problem and the inverse problem. The former refers to the calculation of scalp potentials, given a set of neural current sources. In contrast, the inverse problem is defined as the estimation of the generators of neural activity from the distribution of scalp currents, as measured by the various electrodes in an EEG recording (Hallez
et al, 2007; Grech et al, 2008). A number of methods have been devised to overcome each of these problems. For instance, the forward problem requires accurate modeling of the head. This type of estimation calls for determination of the size, shape, and conductive properties of the various tissues involved in volume conduction of the EEG signal from its source (i.e., a group of large cortical pyramidal neurons) to the EEG electrodes (Hallez et al, 2007). One example of a commonly used head modeling method is the Boundary Element Method. This technique provides a reasonably accurate identification of the boundaries between the brain-skull, skull-scalp, and the scalp-outside of an MRI image, which allows for correct estimation of the thickness and shape of these elements. However, this method also assumes isotropic (i.e., homogenous) conduction of the neuro-electric signal through these various tissues.

The inverse problem has spurred the development of both parametric and non-parametric methods for its solution (Grech et al, 2008). There exists an ongoing debate over which of these methods is the best. That is, because there are an infinite number of solutions to the inverse problem (i.e., the solution is non-unique), there is no optimal solution. Pascual-Marqui (1999) argued that the viability of any given method hinges on its ability to correctly localize sources known a priori in simulation studies. Given this criterion, methods such as sLORETA (i.e., standardized Low Resolution Brain Electromagnetic Tomography; Pascual-Marqui, 2002), which have been shown to have zero localization error, provide accurate localization of cortical sources of activity, albeit with somewhat low spatial resolution. A number of studies have shown high similarity between cortical activity generators localized using fMRI (Mulert et al, 2004) and intra-cranial recordings (van der Loo et al, 2007), and EEG source localization methods, such as sLORETA.

While there are many ways to solve both the forward and inverse problems, based on previous investigation, our laboratory has developed a method that produces reliable cortical source localization results in both children and adults with normal hearing and those with hearing loss (see Gilley, 2008; Campbell and Sharma, 2013, 2014; Sharma, Campbell, & Cardon, 2015). This technique requires a number of steps. First, there are various steps aimed at minimizing noise within the EEG data. That is, following baseline correction, bad channel rejection (i.e., elimination of
channels that have excessive muscle, electrical, environmental, or other artifact) and broad artifact rejection (i.e., rejecting trials that contain data exceeding +/- 100 V in amplitude), EEG data are subjected to independent components analysis (ICA). This analysis serves to identify temporally independent EEG components that underlie the overall waveform and is accomplished by using the EEGLAB toolbox in MATLAB (Makeig et al, 1997; Delorme & Makeig, 2004). ICA is run on the concatenated EEG trials for each subject, so as not to risk losing data in the averaging process (Gilley, 2008; Campbell and Sharma, 2013, 2014; Sharma, Campbell, & Cardon, 2015; Debener et al, 2006, 2008). Once independent components (ICs) can be viewed, a pruning process takes place to remove unwanted ICs and retain meaningful data. That is, the CSEP waveform is used as a template to identify ICs that contain data related to the CSEP, as well as those that contain spurious data. ICs that account for a significant amount of the variance of the CSEP, and do not contain excessive amounts of unwanted noise, are kept for future analyses. Other ICs are excluded. ICA processing has been used in previous studies as an effective step in modeling deep cortical sources involved in sensory cortical activity in both normal hearing and cochlear-implanted subjects (Makeig et al., 1997, 2004; Hine and Debener, 2007; Debener et al., 2008; Gilley et al., 2008; Joos et al., 2012; Campbell and Sharma, 2013, 2014)

Following the pruning process, data are transferred and imported into the CURRY Scan 7 software suite for cortical source localization analysis (i.e., current density reconstruction; CDR). Within this software, participants CSEP data are loaded and grand averaged by groups related to age and/or hearing status. The latencies at which the groups CSEP waveform peaks occurred are noted. Data then undergo baseline correction and noise estimation, relative to the pre-stimulus interval (-100-0 ms). The signal-to-noise ratio (SNR) that is calculated by this estimation is vital to the solution of the inverse problem, as the spatial accuracy of this process is very sensitive to noise level. Because the Electrical Geodesics EEG recording system, used in this project, is a high impedance system, noise estimation and mitigation is of utmost importance. Thus, in addition to the aforementioned noise reduction and estimation methods, relative deviation of the source model is also altered during the analysis to account for low SNRs.
Solving the forward problem requires accurate modeling of the volume conduction of brain, skull, and scalp. Many advocate using participants' individual MRIs to ensure precise head modeling (Hallez et al., 2007). However, this method was not possible in the current study, because children with cochlear implants cannot undergo MRI scanning. Therefore, in CI studies, an averaged MRI must be used (MNI; Mazziotta et al., 1995; 2001). These MRIs are adjusted in terms of the white matter volume to match the ages of the participants (Wilke et al., 2006; Gilley et al., 2008; Groeschel et al., 2010). Then, using the Boundary Element Method (BEM), head models are created.

After volume conductor modeling takes place, estimation of the cortical current densities associated with somatosensory stimulation is performed using the sLORETA algorithm (Pascual-Marqui, 2002). As previously described, while there are many methods used to solve the inverse problem, sLORETA has been shown to have low localization error and has been consistently used in the literature (e.g., Wagner et al., 2004; Gilley et al., 2008; Joos et al., 2012; Sandmann et al., 2012; Campbell and Sharma, 2013, 2014; Sharma, Campbell, & Cardon, 2015). In essence, sLORETA is a statistical method that calculates the likelihood that an area of the cortex was activated during a given condition. This analysis returns current density reconstructions projected to the aforementioned head model in the form of a color gradient. Within this graded overlay, yellow represents the area of activation with the highest likelihood of activation, with increasingly darker colors signifying regions of reduced likelihood. No color suggests that there was not a significant probability of a given cortical area showing activation. The above cortical source localization methods have been employed to examine visual and somatosensory cross-modal reorganization in adults with early-stage hearing loss (Campbell & Sharma, 2014; Cardon & Sharma, in preparation), changes in resource allocation in adults with hearing loss (Campbell & Sharma, 2013), and in case studies of children with cochlear implants (Sharma, Campbell, and Cardon, 2015).

In summary, the need to further explain the variation in behavioral performance in children with cochlear implants is evident, given its wide range. In addition to the factors that have been investigated previously, neural plasticity is one possible area of research from which answers may come. Previous studies in deaf adults and animals have shown cross-modal reorganization between
the somatosensory and auditory systems. Given the extremely plastic state of children's brains, the tendency for reorganization of deprived sensory systems, the similarity between sound and vibration, the anatomical proximity and underlying interconnection between the somatosensory and auditory systems, and the physiological possibility that the auditory cortex could process somatosensory input, it is reasonable to hypothesize that cross-modal reorganization between these two sensory systems could take place in children with cochlear implants. Furthermore, it may be that the degree of cross-modal reorganization could explain some of the variance in behavioral outcome in children with cochlear implants. Thus, the current study proposed to investigate whether cross-modal reorganization of the auditory cortex by the somatosensory system occurs in children with cochlear implants, and whether it is related to speech perception outcome in these children.
Chapter 2

Specific Aims

2.1 Specific Aims

Specific Aim 1: To establish somatosensory cortical development in normal hearing children using high-density EEG, for use in comparison with cochlear-implanted children

Two methods will be used in Study 1 to ascertain developmental patterns in children with normal hearing between the ages of 5-17 years. First, 128-channel high-density EEG will be recorded as the right index finger of each participant is stimulated with a vibrotactile stimulus. These cortical somatosensory evoked potentials (CSEP) will be analyzed and latencies and amplitudes of each of the CSEP waveform components will be identified. These will subsequently be statistically compared between age groups. Additionally, sources of cortical activity responsible for these CSEPs will be determined via current density reconstruction (CDR).

Hypothesis: CSEP waveform analysis will show increased latencies and decreased amplitudes as age increases. Generators of cortical activity will be centered in the post-central gyrus of the cerebral hemisphere contralateral to the side of stimulation and will remain stable across the age span of interest.

Specific Aim 2: To examine somatosensory-to-auditory cross-modal reorganization in children with cochlear implants

Study 2 will employ two methods to examine cross-modal reorganization of the auditory cortex by the somatosensory system in children with cochlear implants. First, 128-channel high-density EEG
recordings will be elicited by vibrotactile stimulation of the index finger in these children. CSEP waveform analysis will be aimed at determining the peak latencies and amplitudes of all CSEP components for each participant. These values will be statistically compared with those found in normal hearing age-matched participants (Study 1). Furthermore, estimation of the sources of cortical activity in response to vibrotactile stimulation will be performed for the CI children. These results will be qualitatively compared with those from normal hearing children.

**Hypothesis:** Cochlear-implanted children will present with different latency and amplitude patterns across scalp ROIs compared with normal hearing children, such that shorter latencies and greater amplitudes will be observed for cochlear-implanted children. Also, current density reconstruction will show activation of the temporal cortices in children with cochlear implants, but not in children with normal hearing, though both groups of subjects will show activation of the somatosensory cortices.

**Specific Aim 3:** To examine possible correlations between somatosensory-to-auditory cross-modal reorganization and speech perception in children with cochlear implants

In the second part of Study 2, the relationship between cross-modal reorganization and speech perception abilities of children with cochlear implants will be examined. This association will be characterized by determining cochlear-implanted children’s scores on a measure of speech perception in background noise (Bamford-Kowal-Bench Speech Perception in Noise Test; BKB-SIN). Correlations will then be performed between these scores and latency and amplitude measures from scalp ROIs.

**Hypothesis:** Significant negative relationships will be found for CSEP peak components and speech perception in noise performance.

### 2.2 Human Subjects Assurances and Protection

This study was conducted in accordance with the requirements for the protection of human subjects under the University of Colorado at Boulder Institutional Review Board (IRB). All par-
participants provided either verbal assent or written consent according to age, and guardians signed authorized consent forms approved under protocol 0906.16.
Chapter 3

Study 1 Background

3.1 Introduction

There is a rich history of research that provides evidence that a sensory system that is deprived of its typical extrinsic input has the ability and tendency to re-organize (see Bavlier & Neville, 2002 for a review). That is, functional sensory modalities can recruit deficient sensory cortices for processing of their own incoming signals. This neuroplastic process is known as cross-modal reorganization. Given the lack of auditory and visual input to deaf and blind persons, respectively, these individuals are at risk for cross-modal reorganization of the auditory and visual cortices by other senses (Bavalier & Neville, 2002; Merabet & Pascual-Leone, 2010).

Electroencephalography (EEG) is a promising way to study cross-modal reorganization in cochlear-implanted individuals, given its high degree of temporal resolution and non-invasive nature especially when elicited via vibrotactile, and not, electrical stimuli (Spackman, 2008). However, relatively little has been done to characterize the development of the cortical somatosensory evoked potential (CSEP) in young childhood through adolescence in response to vibrotactile stimuli. Thus, the present study is aimed at being a first step in charting the development of CSEPs in response to non-invasive vibrotactile stimulation in the school age years in order to provide a benchmark from which to compare studies of cross-modal re-organization in deafness and blindness.

Both short and middle latency somatosensory evoked potentials (SSEP) have been studied a great deal and are used as indicators of the state of function of the peripheral and central somatosensory systems. For instance, median nerve stimulation and subsequent measurement of
neural conduction time is routinely used in medical settings (e.g., Hume & Cant, 1978). In contrast, later CSEPs are used less and are not as commonly described in the literature.

Evoked potentials are often described using three major features: 1) general appearance, or morphology, of the evoked potential waveform; 2) latency of the evoked potential waveform peaks; 3) amplitude of these peaks. Each of these characteristics has the potential to change throughout development. For instance, in the central auditory system, the latencies of evoked potentials decrease with age (Eggermont, 1988; Ponton & Eggermont, 1996; Sharma et al, 1997). This developmental phenomenon can be an indication of increases in neural conduction due to myelination and improved synaptic efficiency, among other factors (Eggermont, 1988). In contrast, a number of studies have found that CSEP latencies increase with age (Alison et al, 1984). This pattern of latency increase is especially prominent during the first 2 years of life, but slows after the age of approximately 4 years (e.g., Gilmore et al, 1985; Bartel et al, 1987; Pihko et al, 2009). The increase in latency observed in CSEPs can be explained by associated increases in height and extremity length that come with age (Gilmore et al, 1985; Bartel et al, 1987; Allison et al, 1984). Despite the overall increases in CSEP waveform component latency, central conduction time, as measured by inter-peak latency, does decrease as age increases through early adulthood (Allison et al, 1984). There are currently no reports in the literature that give an account of the developmental patterns of CSEP amplitude in response to vibrotactile stimulation.

The CSEP is made up of a number of waveform components. For the current study, we will focus on four primary waveform peaks: P50, N70, P100, N140 (Hari et al, 1984; Michie et al, 1987; Hmlinen et al, 1990; Hoshiyama et al, 1995). The P50 is a positive-going peak that is generated by the primary somatosensory cortex (SI) contralateral to the side of stimulation. Following the P50 is the N70, which is also generated by the primary somatosensory cortex opposite the side of stimulation. The P100, which follows the N70, has bilateral generators, although contralateral sources seem to contribute more to this component than ipsilateral ones. In contrast to earlier CSEP components, the P100 has generators in the secondary somatosensory cortex (SII). Finally, the N140, which is a broad negative-going component following the P100, likely has multiple
generators, which seem to be localized to the posterior parietal cortex mostly contralateral to the side of stimulation. While there is considerable variability in the literature regarding the naming, appearance, and latencies of these components, due to differences in stimulus type and presentation, age of participants, etc, the current study will employ the descriptions found in Hmlinen et al (1990). The nomenclature from this study will be used here, because of the similarity of the methods between it and the current study (i.e., vibrotactile stimulation to the fingertip).

The somatosensory system is responsible for various types of sensory processing each with their respective specialized sensory receptor. Vibration, for example, is sensed primarily by Merkel cells and Pacinian corpuscles. The former is preferentially sensitive to slow vibration (i.e., 5-40 Hz), while the latter is tuned to higher frequency information between 60-300 Hz (Harrington & Downs, 2001). These are both found in the glabrous skin of the palm of the hand. Once vibration is transduced into neural impulses, it is thought to travel to the cerebral cortex via both the dorsal column-medial lemniscus and lateral cervical system. It is thought that most of the nerve fibers from these pathways eventually synapse in the contralateral SI and SII (Jones & Powell, 1973). SI (Brodmann areas 3a, 3b, 2, 1) and SII (near Brodmann area 40) are both located posterior to the central sulcus (i.e., post-central gyrus). It appears that Brodmann area 3 receives the majority of thalamo-cortical projections. This area then projects to Brodmann areas 1 and 2, which have connections to motor and association cortices (Jones 1986). It should be noted that, due to the fact that most somatosensory afferents crossover the midline, CSEPs are typically observed contralateral to the side of stimulation (e.g., Hämäläinen et al, 1990).

The purpose of this study was to use high density EEG to characterize developmental changes in the CSEP to vibrotactile stimuli during the school age years by documenting latency, amplitude, and morphological dynamics. We examined the cortical sources of EEG activity in response to vibrotactile stimuli to determine the underlying generators of the CSEP components during development.
Chapter 4

Study 1 Materials and Methods

4.1 Participants

Participants for the current study were made up of 35 children and adolescents between the ages of 5 and 17 years of age (17 female). The overall group was divided into three age groups for recruiting and analysis. These groups were: 1) 5-7 year old children (n = 9; mean age = 6.95 years; SD = 0.53 years); 2) 8-10 year old children (n = 11; mean age = 9.81 years; SD = 0.97 years); 3) 11 year old and older children and adolescents (n = 15; mean age = 12.9 years; SD = 1.45 years). It should be noted that the oldest age group consisted of individuals under the age of 14, except for one 17 year old who was added for comparison with subjects in Study 2. All of these individuals had normal hearing, which was defined as auditory thresholds at or below 20 dBHL at 250, 500, 1,000, 2,000, 4,000, and 8,000 Hz. These thresholds were obtained in each participant by a certified clinical audiologist. Additionally, none of the participants had any history of neurological disorder. All subject were recruited and underwent informed consent procedures in accordance with the Institutional Review Board of the University of Colorado at Boulder.

4.2 Testing Procedures

High-density EEG was recorded from each subject using a 128-channel net (Electrical Geodesics, Inc.), which was individually fitted. During testing, participants were seated in a comfortable chair facing a television monitor in a double walled sound suite. Continuous EEG, which would later be segmented into CSEP epochs (see EEG Analysis section below), was recorded as regularly spaced
vibrotactile stimuli were presented to the right index finger of each subject. These data were recorded using Netstation 4 software (Electrical Geodesics, Inc.). EEG recordings were sampled at 1,000 Hz and underwent initial filtering using a band-pass filter set to 0.1-200 Hz.

The CSEP evoking stimulus consisted of a 250 Hz tone burst. Each stimulus was 90 ms in duration, with 10 ms onset and offset linear ramps. Stimuli were presented through a standard clinical bone oscillator (Sensory Systems d.b.a. Radioear Inc. B71 Bone Transducer), which was attached to each participant's right index finger with medical tape. The transducer was wrapped in copper mesh, which was attached to ground, to eliminate electrical artifact from reaching EEG recording electrodes. Stimuli played, timed, and triggered using E-Prime 2.0 software (Psychology Software Tools, Inc). A standard clinical audiometer (GSI 61 Clinical Two-Channel Audiometer) was used to control stimulus presentation level and masking. That is, all 250 Hz stimuli were presented at a level of 55 dBHL. This level, which resulted in approximately 0.122 g (1.2 m/s^2) of acceleration output by the oscillator, was determined in preliminary studies to reliably elicit CSEP responses without any risk of causing discomfort (see Weinstein, 1968). In addition to the 250 Hz stimuli, continuous white noise was presented via a loudspeaker inside the sound suite in order to mask any auditory artifact produced by the bone oscillator. In most cases, this noise was presented at 50 dBHL, which proved sufficient to mask bone oscillator noise. All participants reported that they could feel the stimulus, but could not hear it. Approximately 1000 stimuli were presented to each participant, which corresponded to the same number of CSEP epochs.

4.3 Data Analysis

4.3.1 EEG Processing and CSEP Waveform Analysis

Following recording, continuous EEG data were segmented into CSEP epochs, which corresponded to each stimulus. These epochs consisted of 100 ms of pre-stimulus and 595 ms of post-stimulus data for each of the 128 channels used in the recording. Next, baseline correction with respect to the pre-stimulus interval was performed and epochs containing data with ampli-
tudes of ± 100 µV within the specified eye channels were rejected. Furthermore, channels that contained excessive amount of artifact were flagged and removed. These bad channels were then replaced using a spline interpolation algorithm. The final step in the initial EEG analysis was to average the remaining epochs for each participant.

Based on review of the literature (esp. Hämäläinen et al, 1990), we determined that the temporo-parietal region of the scalp contralateral to the side of stimulation would be where the most robust CSEPs would occur. Thus, we devised a temporo-parietal ROI consisting of 24 electrodes that covered the parietal and temporal areas of the left hemisphere of the scalp. Waveforms from the designated electrodes from this ROI were averaged together to form a composite waveform. Peak latencies and peak-to-peak amplitudes for the P50, N70, P100, N140a, and N140b CSEP waveform components were then extracted from waveforms from the ROI for each participant. These were later used for statistical comparison.

4.3.2 Cortical Source Localization Analysis (Current Density Reconstruction)

In addition to CSEP waveform analysis, estimation of the sources of cortical activity was performed. Initially, data were imported into the EEGLAB toolbox (Delorme & Makeig, 2004), functioning within Matlab (The MathWorks, Inc, 2014). Once imported, data were subjected to another bad channel rejection algorithm, which rejected channels based on kurtosis. In other words, channels whose data reached a designated level of kurtosis (i.e., z-score of 5 or greater) were rejected. After this, CSEP epochs that contained artifact that exceeded +/- 100 µV in amplitude were excluded. Then, data were down-sampled from 1000 Hz to 250 Hz to aid in speed of subsequent processing. After the above pre-processing, independent components analysis (ICA) was performed on all data within EEGLAB. By separating the data into independent components, we were able to identify and then reject (i.e., prune) artifactual components, as well as components that accounted for miniscule portions of the variability of each of the CSEP components.

Source estimation began by importing the above data into the Curry Scan 7 Neuroimaging suite (Compumedics Neuroscan). Initially, grand averaging of the subjects in each age group took
place. Next, a second ICA was run on these data to determine which independent components accounted for the largest portion of the variance (i.e., which components to include in CDR). A head model was then constructed via the Boundary Element Method (BEM), using a standard MNI brain (Montreal Neurological Institute), which was adjusted to account for the white matter volume observed in children and adolescents of the age range included in the current study (Wilke et al, 2006; Groeschel et al, 2010). CDR was then carried out by subjecting data to Standardized Low-Resolution Brian Electromagnetic Tomography (sLORETA; Pasqual-Marqui, 2002). This analysis has been shown to provide reasonably accurate estimations of the sources of cortical activity in response to a given stimulus (Pascual-Marqui, 2007). These estimations are presented as areas of graded color, which are projected onto the aforementioned head model. This color gradient represents the probable strength of cortical activity.

4.4 Statistical Analysis

CSEP waveform analysis results, including peak latency and peak-to-peak amplitude, were each subjected to one-way ANOVA with age group as a between subjects factor to assess possible differences between the aforementioned age groups for each of these factors. Additionally, Bonferroni post-hoc tests were performed in conjunction with the ANOVAs to determine any pairwise differences in the above waveform characteristics between age groups.
Chapter 5

Study 1 Results

5.1 CSEP Waveform Analysis Findings

Plots of the grand average CSEP waveforms for each of the age groups (i.e., 5-7, 8-10, and 11-17 year olds) from the temporo-parietal ROI are shown in Figure 5.1. Across all ages, all of the components of the CSEP (i.e., P50, N70, P100, N140) can be reliably identified. In the majority of subjects, regardless of their age, the N140 appeared as a bifid negative going peak. Given this pattern, we classified the first of the N140 peaks as the N140a, while the second was called the N140b. Thus, CSEP waveform morphology appears to be stable (with respect to presence of peak components) across the age range examined in this study. These findings are consistent with reports that claim that the morphology of somatosensory evoked potentials shows developmental changes up to the age of approximately 5-6 years of age, but then becomes adult-like after this time window (Fagan, Taylor, & Logan, 1987; Pihko et al, 2009).

In order to determine more detailed differences between the age groups CSEP waveforms, both peak latency and peak-to-peak amplitude results from the aforementioned ROI were subjected to statistical comparison. Several latency and amplitude differences were found. For example, the youngest group showed significantly shorter latencies for the N70 (p = 0.037; F = 3.69) compared with the oldest group and the N140a (p = 0.002; F = 8.06) compared with both older groups. The 5-7 year old children also exhibited significantly larger CSEP amplitudes for the N70 (p = 0.003; F = 7.26), P100 (p = 0.004; F = 6.66), and N140b (p = 0.002; F = 7.483) CSEP components relative to the two older groups. The findings related to latency are reflective of expected developmental
patterns and consistent with previous findings for latency (e.g., Allison et al, 1984; Sitzgolou & Fotiou, 1985 Pihko et al, 2009). However, there appears to be no information about the maturation of peak-to-peak amplitude of CSEPs recorded to vibrotactile stimuli in the literature.

5.2 Cortical Source Localization Results (sLORETA)

Results from cortical source localization analysis are shown in Figure 5.2. Initially, sources were computed for each age group separately. However, it was found that all groups source estimations were comparable. Thus, all participants were combined for final cortical source analysis. Visual inspection and computer-aided determination of the areas of significant activation yielded by sLORETA analysis revealed the following: 1) the P50, N70, and P100 CSEP waveform components presented with virtually the same areas of activation of the left hemisphere. These included, post-central gyrus (BA 2, 3, 5, 40), pre-central gyrus (BA 4, 6), Inferior parietal lobule (BA 40), and superior parietal lobule (BA 7); 2) the N140a and N140b generators were also very similar. In addition to all of the previously mentioned activated areas (i.e., for the P50-P100 CSEP components), medial and superior frontal gyri were also activated for the N140a and N140b. These results appear to be consistent with previous reports of the generators of activity resulting from stimulation of the right hand (Hämäläinen et al, 1990). As expected, due to crossed activation in the somatosensory system, all of these activations were located contralateral to the side of stimulation.
Figure 5.1: **CSEP waveforms for children 5-7, 8-10, and 11-17 years old**
CSEP waveforms from the temporo-parietal ROI for each of the three age groups of children with normal hearing in the study: 1) 5-7 year old children (top); 2) 8-10 year old children (middle); 3) 11-17 year old children (bottom). Each waveform shows all CSEP waveform components of interest: P50, N70, P100, N140a, and N140b.
Figure 5.2: **Current density reconstructions (CDR) for CSEP waveform components in children with normal hearing**

A. Cortical activations in response to vibrotactile stimulation of the right index finger in children with normal hearing. Activations are organized in rows corresponding to each CSEP waveform component. Sagittal (left) and coronal (right) slices are presented for each of these components. Three-dimensional Montreal Neurological Institute (MNI) coordinates for each activation are listed below each row of slices. The F-distribution scale presents the color gradient associated with the maximum (yellow) through the minimum (black) likelihood for activation as calculated by sLORETA. B. A table listing all areas of significant activation for each CSEP waveform component.
The goal of the current study was to examine developmental characteristics in somatosensory evoked potentials from the cortex, elicited by vibrotactile stimulation of the right index fingers of children with normal hearing. This project was also of interest as a first step toward studying cross-modal reorganization between the somatosensory and auditory cortices in children with cochlear implants.

The main findings of the study were: (i) CSEP peak waveform components were present across the age range of the current investigation; (ii) expected developmental patterns of CSEP latency and amplitude were present in the data; (iii) Estimations of cortical generators of the recorded activity were stable across age for all CSEP components. That is, cortical activity was localized to the post-central gyrus, association cortices of the parietal lobe, and pre-central gyrus contralateral to the side of stimulation across the age span. In addition to these areas, later components (i.e., N140a and N140b) also showed activation in frontal cortices.

6.1 Cortical somatosensory evoked potentials

The morphological aspects of the participants CSEP data (Figure 5.1) were consistent with previous reports. For instance, in one study Hmlinen et al (1990) used vibrotactile stimuli applied to the middle finger to evoke potentials from the primary and secondary somatosensory cortex. The morphology of the waveforms presented in this study included the P50, N70, P100, and N140 CSEP components, similar to Hämäläinen et al., (1990). The CSEP waveform consistently showed
all peak components across the wide age range. This pattern of stability of peak components across age differs from the developmental progression observed in cortical evoked potentials recorded to visual and auditory stimuli. Morphology of evoked potentials recorded in the visual and auditory modalities changes significantly with respect to presence of peak components throughout the age range studied here (e.g., Ponton et al, 2000; Gilley et al, 2005; Campbell & Sharma, in preparation). The Hämäläinen et al (1990) study, which also used vibrotactile stimulation, had subjects that were all around 20 years of age. The majority of children in the oldest age group in the current study were between the ages of 11-14, however, one subject was 17 years of age. His CSEP waveform resembled those of the younger children in our study. Furthermore, we have observed, in unpublished data, that the CSEP waveforms of adults (ranging in age from 21 to 71) are morphologically comparable to the CSEP waveforms presented in the current study (Cardon & Sharma, in preparation). Thus, it appears that the CSEP may be unique across modalities, in that major peak components are present and remain constant from school age through adulthood.

We observed some expected age-related differences in CSEP latencies and amplitudes from the aforementioned ROI, such that the latencies of the N70 and N140a were significantly shorter and the N70, P100, and N140b amplitudes were significantly larger in the youngest group, relative to older children. In every case, these differences occurred between the youngest and either one or both of the older two groups. This pattern is consistent with previous studies that state that the major developmental changes seen in CSEP components are typically completed by age 4, and afterward slow considerably (e.g., Desmedt, Brunko, & Debecker, 1976; Allison et al, 1984; Sitzgolou & Fotiou, 1985; Fagan, Taylor, & Logan, 1987 Eggermont, 1988; Pihko et al, 2009). Given the age range of the current study, the participants may have been too mature for observation of more robust developmental effects.

6.2 Current Density Reconstruction

Current density reconstructions yielded results that matched both our hypothesis and previously reported findings. Numerous investigations have outlined the generators of the various CSEP
components. For instance, previous studies have found that the P50 CSEP component is generated in the post-central gyrus of the cerebral hemisphere contralateral to the side of stimulation (e.g., Mauguière et al, 1983). More specifically, P50 seems to originate from SI. The N70 also appears to be generated in contralateral SI (Michie et al, 1987). Hmlinen et al (1990) proposed, based on both animal and human studies (e.g., Hari et al, 1983, 1984; Hämäläinen et al, 1988), that the P100 originates from a combination of ipsi- and contralateral SII cortex. The N140 CSEP component seems to have a number of generators, which are likely distributed throughout the posterior parietal regions of the cortex, with the strongest contributions coming from cortices contralateral to the stimuli.

Specifically, some have proposed that the N140 is influenced by generators in contralateral SII (Hari et al, 1983, 1984, 1993) and also contains activity from Brodmann are 46 and other frontal cortices (Desmedt and Tomberg, 1989; Hämäläinen et al, 1990). The current results mirror these reports descriptions of the sources of cortical activity that contribute to the CSEP. That is, all CSEP components from the current study were localized to the primary, secondary, and association somatosensory cortices (BA 3, 2, 1, 5, & 7) in the hemisphere contralateral to the side of stimulation (See Figure 5.2). In addition, pre-central gyrus was activated in the current density reconstructions for each of the CSEP components. This activity may be mediated by connections between the pre- and post-central gyrus (e.g., Pandya & Kuypers, 1969). Finally, it may be interesting to note that the N140a and N140b CSEP components show activation of medial and superior frontal cortices (i.e., Brodmann area 6), which is consistent with the characterization of the generators for these components offered by Hämäläinen et al, (1990) that indicate frontal cortex involvement in the generation of the N140 CSEP.
Chapter 7

Study 1 Summary and Conclusions

7.1 Summary

Analysis of CSEP waveform morphology revealed present and consistent CSEP peak components across younger and older school aged children. Peak component latency and amplitude from CSEPs recorded from the left parietal scalp region showed expected developmental patterns. Finally, current density reconstructions showed stable activation of the somatosensory cortices across the 5-17 year old age range.

7.2 Conclusion

Vibrotactile stimulation of the right index fingers of children with normal hearing between the ages of 5-17 years lead to reliably recorded CSEPs from and localized to the somatosensory areas of the contralateral hemisphere. Some developmental patterns were observed in CSEP peak latency and amplitude. Future studies may employ these techniques in clinical populations to examine possible cross-modal reorganization from the somatosensory modality.
Chapter 8

Study 2 Background

Despite ongoing improvement in cochlear implantation from devices to management there remains a high degree of variability in the behavioral outcomes (e.g., speech and language development) of children with cochlear implants (CI; Svirsky et al., 2000; Sarant et al., 2001; Tobey et al., 2003; Harrison et al., 2005; Geers, 2006; Nicholas & Geers, 2007; Holt & Svirsky, 2008; Geers et al., 2009). Given this variability, it is difficult to predict the level of benefit an implant will provide a given patient. Recent investigation has been aimed at discovering the underlying factors associated with this variability (Svirsky et al., 2000; Sarant et al., 2001; Tobey et al., 2003; Geers, 2006; Geers et al., 2009). However, despite these efforts, only partial determination of these factors has been achieved (i.e., approximately 35-62%; Fink et al., 2007).

The behavioral outcomes of children with CIs range from age-appropriate to poor (e.g., Geers et al., 2009). A number of factors have been shown to contribute to this wide range of variability. These underlying predictors include age at implantation, residual hearing prior to implantation, duration of deafness, parent-child interaction, socioeconomic status, performance IQ, working memory capacity, communication mode, family size (Geers 2004; Harrison et al., 2005; Fink et al., 2007; Nicholas & Geers, 2007; Holt & Svirsky, 2008; Lin et al., 2008; Wang et al., 2008; Chang et al., 2010; Niparko et al., 2010; Buckley & Tobey, 2011; Kral & Sharma, 2012; Dettman et al., 2013). Of all of these factors, one that seems to stand out is age at implantation. Earlier implantation appears to lead to greater chances for favorable outcome (Geers et al., 2009; Sharma et al., 2002a, b; Svirsky, Teoh, & Neuberger, 2004; Geers, 2006; Niparko et al., 2010).
It is likely that cortical development and neuroplasticity play an important role in outcomes for children with implants. For example, the sensitive period or time window of heightened neural plasticity for optimal auditory cortical maturation is approximately 3.5 years of age (Huttenlocher & Dabholkar, 1997; Sharma et al., 2002a, b, c). Children who receive CIs within this time period (best before 2 years of age) are far more likely to show progress in auditory cortical development (Sharma et al., 2002, 2005; Kral and Sharma, 2012). Investigation into additional aspects of cortical neuroplasticity may provide additional insight regarding the variability in CI outcome.

A well-known feature of neuroplasticity is cross-modal reorganization or the recruitment of deprived sensory cortices for processing of the input to intact sensory modalities (see Bavelier & Neville, 2002; Merabet & Pascual-Leone, 2010 for reviews). Though most of the work that characterizes this type of plastic change has examined visual-to-auditory cross-modal reorganization (e.g., Rebillard et al., 1977; Neville et al., 1983; Finney et al., 2001, 2003; Fine et al., 2005; Sadato et al., 2005; Doucet et al., 2006; Bavelier and Hirshorn, 2010; Lomber et al., 2010; Meredith et al., 2011; Campbell & Sharma, 2014; Clemo et al., 2014; Kok et al., 2014; Scott et al., 2014), a number of studies has also shown evidence of cross-modal reorganization between the somatosensory and auditory cortices in both animals and humans (Levnen et al., 1998; Baldwin, 2002; Auer et al., 2007; Sharma et al., 2007; Meredith & Lomber, 2011; Karns et al., 2012). Additionally, while cross-modal plasticity may have evolved as a compensatory mechanism in those suffering from sensory deprivation, it is possible that it may hinder optimal restoration of sensory capability, after input is re-initiated to the deprived modality (e.g., after cochlear implantation.) That is, if the auditory cortex is recruited for processing of other sensory input, it may be less available for auditory processing, once auditory function is re-introduced via a cochlear implant (Buckley and Tobey, 2011; Doucet et al., 2006; Lazard et al., 2013a, b; Sandmann et al., 2012; Strelnikov et al., 2013). This notion has been borne out by the literature in congenitally deaf adult cochlear implant users, in which the extent of cross-modal reorganization has been shown to be negatively related to behavioral abilities, such as speech perception (Doucet et al., 2006; Buckley and Tobey, 2011; Sandmann et al., 2012; Lazard et al., 2013a, b; Strelnikov et al., 2013).
While various investigations have presented evidence of somatosensory-to-auditory cross-modal reorganization in deaf animals and human adults, to our knowledge, no study has been undertaken to examine this process in pediatric cochlear implant recipients. Thus, the purpose of the current study was to characterize possible cross-modal reorganization between the somatosensory and auditory systems in children with cochlear implants and its relationship to behavioral speech perception. To this end, we recorded high-density EEG to vibrotactile stimulation of the index fingers of cochlear-implanted children and normal hearing controls. These data were analyzed with the goal of determining the cortical regions activated by these stimuli. In addition, we correlated these activations to scores on a measure of speech perception in background noise.
Chapter 9

Study 2 Materials and Methods

9.1 Participants

Participants for the current study consisted of two groups of children between the ages of 5-19 years: 1) children with cochlear implants (CI group; n = 13; mean age at test = 12.38 years; S.D. = ± 4.16 years); 2) children with normal hearing (NH group; n = 35; mean age at test = 10.54 years; S.D. = ± 2.69 years). One child in the CI group presented with a diagnosis of Auditory Neuropathy Spectrum Disorder (ANSD) and was consequently not included in the study, due to probable differences in neurological processing. This resulted in the number of CI participants being decreased to 12 (mean age at test = 12.42 years; S.D. = ± 4.16 years). Statistical comparison using an Independent-Samples Mann Whitney U test of the ages of these two groups confirmed that they were not significantly different (p > 0.05). Ten out of 12 CI participants were bilaterally implanted, while the remaining two subjects had unilateral CIs. All bilateral CI recipients were implanted sequentially; seven of ten received their first implant in the right ear. The mean age of first implantation for the CI group as a whole was 3.90 years (S.D. = ± 4.03 years), while the average age of second implantation for bilaterally implanted children was 7.33 years (S.D. = ± 4.47 years). The average duration of CI use at the time of testing (i.e., time between first CI fitting and testing) was 8.51 years (S.D. = ± 3.92 years). Aside from the one case mentioned above, none of the participants' families reported any history of neurological involvement in any of the current subjects. All participants were recruited and tested in accordance with the Institutional Review Board of the University of Colorado at Boulder.
9.2 Stimuli

250 Hz tones, each 90 ms in duration, with 10 ms linear ramps at onset and offset, were used to elicit CSEPs. These stimuli were presented to each participant via a standard clinical bone oscillator (Sensory Systems d.b.a. Radioear Inc. B71 Bone Transducer), which was electrically shielded with copper mesh so that any electrical noise produced by the device would not be registered by the EEG electrodes. During testing this transducer was temporarily affixed to the participants right or left index finger using medical tape. Stimulus presentation timing was controlled by E-Prime 2.0 software (Psychology Software Tools, Inc), while level was mediated by using a standard clinical audiometer (GSI 61 Clincial Two-Channel Audiometer). All stimuli were presented at a level of 55 dBHL, which resulted in vibrotactile sensation in all participants (approximately 0.122 g or 1.2 m/s\(^2\) of acceleration output) that was sufficient to elicit CSEPs, but never uncomfortable (Weinstein, 1998). For all CI participants, CIs were turned off during CSEP recording to ensure that the vibrotactile stimuli were only felt and not heard. Continuous white noise was played via a loudspeaker at a level of 50 dBHL on the side of stimulation in order to mask any auditory artifact of vibrotactile stimulation for all participants. All participants reported that they could feel, but not hear, the stimulus.

9.3 EEG Recording and Analysis

For testing, each participant was seated in a comfortable chair situated in a sound treated room. They were fitted with a 128-channel EEG recording net (Electrical Geodesics, Inc.) that had been soaked in a solution of water, baby shampoo, and sodium chloride. Children in the CI group were asked to remove the external portion of their CI prior to net application and throughout somatosensory testing. EEG recordings were sampled at 1 kHz and band-pass filtered online between 0.1-200 Hz.

Following recording, EEG data were initially high-pass filtered offline at 1 Hz. These data were then segmented into epochs associated with each stimulus presentation, with 100 ms pre- and
495 ms post-stimulus intervals. Then, data were exported for further analysis in the EEGLAB toolbox (Delorme & Makeig, 2004) running within the Matlab software package (The MathWorks, Inc, 2014). Once imported, channels containing excessive amounts of noise were rejected. Then, epochs that presented with data exceeding ±100 µV in amplitude were also eliminated. The sampling rate of the data was then changed to 250 Hz to allow for subsequent processing efficiency. Data then underwent re-referencing to a common average reference. Finally, rejected channels data were replaced via spherical interpolation.

In order to observe the possible effects of activity from the auditory cortices on CSEP recordings in CI children, we averaged CSEP data from 24 electrodes in the temporal and parietal regions of the left hemisphere termed the temporo-parietal region of interest (ROI; as in Study 1). We also divided the temporo-parietal ROI into three smaller ROIs for more discreet CSEP waveform analysis based on relevant findings in the literature (Hämäläinen et al, 1990; Levnen et al, 1998; Huang et al, 2003). These ROIs were: 1) Midline ROI (EGI electrodes 55 & 62); 2) Parietal (EGI electrodes 52, 53, 54, 60, 61); 3) Temporal (EGI electrodes 39, 40, 44, 45, 50). Averaged CSEPs from each of these electrodes were averaged together to form an ROI grand average for each of the above ROIs, in each subject. Following averaging, the peak latencies and amplitudes for the P50, N70, P100, N140a, and N140b CSEP waveform components were noted for each subject’s ROIs. Subsequent calculation of peak-to-peak amplitudes for the aforementioned CSEP waveform components was carried out. Additionally, given stable neurophysiological patterns found in CSEP responses the NH group (Study 1), grand average waveforms were computed for each group (NH and CI) and all waveforms were low-pass filtered at 30 Hz, once all analysis had taken place.

9.4 Current Density Reconstruction

In preparation for current density reconstruction, each subject’s data epochs were concatenated and subjected to independent components analysis (ICA). This statistical procedure serves to detect spatially fixed, but temporally independent components that contribute to the overall evoked potential waveform (Makeig et al, 1997). ICA has been proven as a first step in the cortical
current density reconstruction process, including that performed in cochlear implant users (Makeig et al., 1997, 2004; Hine and Debener, 2007; Debener et al., 2008; Gilley et al., 2008; Campbell and Sharma, 2013, 2014; Sharma, Campbell, & Cardon, 2015). One application of ICA is artifact rejection. Thus, in the current study, independent components (ICs) containing eye blinks or movement, electrical noise, or muscle artifact were removed from the each participants dataset. After ICA artifact rejection, ICs that accounted for the highest portion of the variance around each peak of the CSEP were saved for inclusion in current density reconstruction.

Data were then transferred to the Curry® Scan 7 Neuroimaging suite (Compumedics Neuroscan™) for cortical source estimation. Initial processing steps toward current density reconstruction included baseline correction, noise estimation using the pre-stimulus interval, averaging of participants individual CSEP waveforms to for grand average waveforms, and additional ICA. This final ICA was used as a means to determine the ICs computed from the grand average that accounted for the majority of the variance for each of the CSEP waveform components preceding cortical source modeling.

Modeling of the head was accomplished using the Boundary Element Method (BEM), which is aimed at solving the forward problem by determining the boundaries between and conductance of the brain and skull, skull and scalp, and scalp (e.g., Fuchs et al, 2002; Hallez et al, 2007). Within this head model, white matter volumes were adjusted to match age-related values (Wilke et al, 2007; Gilley et al, 2008). Following head modeling, current density reconstructions (CDR) were performed for each of the CSEP waveform components using the sLORETA algorithm (Pascual-Marqui, 2002). This statistical method of determining the sources of cortical activity provides one solution to the inverse problem that has been shown to have zero localization error, albeit with relatively low resolution (see Grech et al, 2008 for a review). The results of this method appear as color gradients that represent the F-distribution of the data, which are overlaid onto representations of the brain, such as MRI images. In the current study, yellow colored areas represent the most probable area of activation, with increasingly darker areas representing decreasing probability of activation. Areas that have no color at all are taken as cortical regions with no trace of activation.
The Montreal Neurologic Institute (MNI) average brain was used as a backdrop for CDR results. Coronal slices were selected to present CDR findings.

9.5 Speech Perception in Noise

Speech perception ability was assessed in each participant in the CI group using the BKB-SIN test (Bench et al., 1979; Etymotic Research, 2005). During this testing, participants sat facing a loudspeaker at 0° azimuth with his or her CI on and functioning as it normally would. Sentence two lists of six sentences each were then presented to the participant via the loudspeaker at 65 dBA. As the sentences progressed, background noise (multi-talker babble) level was increased with each sentence. This noise increase occurred in five steps, each of 5 dB increments, or from 25 dB SNR (least challenging) to 0 dB SNR (most challenging). The participant was asked to repeat the words of the sentence he or she heard. As the tester listened to these responses, key words from each sentence were marked as correct or incorrect, and a score was given for each list based on the number of words repeated correctly. Participants received an SNR score, representing the level at which they could perceive and repeat 50% of key words. Thus, in the case of the BKB-SIN, lower scores indicate better performance (i.e., ability to perceive speech in noise under more challenging conditions). Scores from the two presented lists were then averaged together to obtain a composite BKB-SIN score for each participant. In addition, age corrections were applied to participants' composite scores to normalize results for comparison across subjects (Etymotic Research, 2005). Finally, BKB-SIN scores were correlated with latency and amplitude values from each ROI.
Chapter 10

Study 2 Results

10.1 Cortical Somatosensory Evoked Potentials

Due to the constancy in peak CSEP components and current density reconstructions (CDR) across the 5-17 year old age range found in Study 1 and to increase power for this study, we grouped all CI participants CSEP data for analysis and comparison against NH children.

Grand averages of CSEP data from the temporo-parietal ROI are shown for the CI and NH groups in Figure 10.1. Visual inspection of grand averaged CSEPs for this ROI in the CI group revealed that this group presented with similar CSEP waveform morphology as the NH group. Comparison of CSEP waveform component peak latency and peak-to-peak amplitude via Independent-Samples Mann-Whitney U tests yielded two significant differences between the CI and NH groups from the midline ROI. That is, the N140a latency was significantly shorter for the CI group as compared to the NH group (U = 134.5; Z = -2.06: p = 0.039; Figure 10.1B), while the P50 amplitude was larger for the CI group (U = 307; Z = 2.05: p = 0.041; Figure 10.1C). There were no significant differences in CSEP waveform components in the temporal or parietal ROIs (p>0.05). These findings are in keeping with the decreased latencies and increased amplitudes of cortical evoked potentials in CI patients compared to NH subjects reported in previous studies suggestive of cross-modal re-organization from the visual system in deafness (e.g., Doucet et al, 2006; Buckley & Tobey, 2010).
Figure 10.1: **Grand averaged CSEP waveforms from the temporo-parietal ROI in CI and NH children**

Grand averaged CSEP waveforms for both CI (solid line) and NH (dashed line) groups from the temporo-parietal ROI are overlaid for visual comparison. Amplitude (microvolts) is depicted on the vertical axis, while time (milliseconds) is represented on the horizontal axis.
10.2 Current Density Reconstructions

CDRs were performed for each of the CSEP waveform components. Figure 10.2 shows CDR results for vibrotactile stimulation of the right finger in both the CI group and NH group. In addition to the CDRs projected onto MRI coronal slices, the MNI coordinates of the activation are listed, as well as the F-distribution (color scale).

CI children, as a group, show clear activation of the left (i.e., contralateral to the side of stimulation) somatosensory cortices (i.e., post-central gyrus; BA 3, 2, 5), as well as pre-central gyrus (BA 4, 6), inferior and superior parietal lobules (BA 40 & 7), respectively. Contralateral activations in these areas were expected (i.e., due to the crossover of ascending somatosensory pathways) and consistent with those calculated for the NH group. However, the CI group also showed robust activation of the left temporal cortex: superior temporal gyrus (BA 29, 41, 42); transverse temporal gyrus (BA 41, 42); supramarginal gyrus (BA 40); Angular gyrus (BA 39); superior frontal gyrus (BA 6); paracentral lobule (BA 6); and insula (BA 13). This pattern of activation was consistent for the P50, N70, and P100 CSEP waveform components (Figure 10.2A, B, C). Many of these areas are largely associated with auditory (BA 29, 41, 42) and speech and language (BA 39, 40) processing. Therefore, these findings are suggestive of cross-modal reorganization of the auditory cortex by the somatosensory system in CI children.

Both the N140a and N140b presented with CDRs that matched the above CSEP components. However, in addition, frontal cortices contributed to these later components in the CI group. CDR analysis showed that another portion of the superior frontal gyrus contributed to these components (i.e., BA 10; see Figure 10.2D & E), which is consistent with previous findings regarding the generators of these later CSEP components (Desmedt & Tomberg, 1989; Hmlinen et al, 1990). Overall, the activation of somatosensory cortical regions was similar between the NH and CI groups. However, the activation of temporal areas in the CI, but not the NH, group was an apparent difference, which reflects somatosensory-to-auditory cross-modal reorganization consistent with previous studies in deaf adults (Levnen et al, 1998; Baldwin et al, 2002; Auer et al, 2007; Sharma et al, 2007).
Figure 10.2: Current density reconstructions (CDR) for cortical somatosensory evoked potentials (CSEP) in normal hearing and cochlear-implanted children

A. Cortical activations in response to vibrotactile stimulation of the right index finger in children with normal hearing (NH; n = 35) and cochlear implants (CI; n = 12). Activations are organized in rows corresponding to each CSEP waveform component (P50, N70, P100, N140a, N140b). Current density reconstructions are presented on coronal slices for each of these components. Three-dimensional Montreal Neurological Institute (MNI) coordinates for each activation are listed below each MRI slice. The F-distribution scale (bottom) presents the color gradient associated with the maximum (yellow) through the minimum (black) likelihood for activation as calculated by sLORETA. B. A table listing all areas of significant activation for each CSEP waveform component.
In a subset of CI participants (n = 6), the left index finger was stimulated in addition to the right (separate conditions). All of these children received implants in their right ears first (RCI1; mean age at first implantation = 2.89 years; S.D. = ± 2.67 years). Five out of six of these participants were also implanted in the left ear at a later date (mean age at second implantation = 7.47 years; S.D. = ± 2.91 years). Figure 10.3 shows the CDR for the right and left index finger stimulation in these children.

Stimulation of the right index finger in the RCI1 group lead to activation of both somatosensory and auditory cortical areaspost-central gyrus (3, 5), pre-central gyrus (4), and paracentral lobule (6) for all CSEP components; superior temporal gyrus (39, 22); middle temporal gyrus (19, 39); inferior temporal gyrus (20) of the left hemisphere in the N70, N140a, and N140b CSEP components. Of these areas, BAs 39 and 22 are highly involved in auditory processing. This pattern of activation was expected, based on CDR results shown in the CI group as a whole (Figure 10.3). Activity in the left temporal cortical region is reflective of somatosensory cross-modal reorganization of the auditory cortex contralateral to the side of implantation in the RCI1 group.

Interestingly, the cortical activations to the left finger stimulation in the RCI1 group appeared to be centered primarily in auditory cortical areas, with some activity evident in known somatosensory cortical regions. These activated areas included: Superior temporal gyrus (39, 22); Middle temporal gyrus (39, 22); Post-central gyrus (3, 5, 7); Pre-central gyrus (4, 6); Inferior parietal lobule (40); Superior parietal lobule (7); Angular gyrus (39); Supramarginal gyrus (40). These areas of activation were largely found in the right hemisphere, though in the P100 and N140b CSEP components, post-central gyrus (i.e., somatosensory cortex) activations were partially located in the left hemisphere. Activation of auditory processing areas (BA 39, 22) in response to vibrotactile stimulation of the left finger suggests additional cross-modal reorganization of the auditory cortex ipsilateral to the side of first implantation. This finding is in accordance with previous studies reporting that the auditory cortex ipsilateral to the first CI is at a disadvantage in terms of auditory stimulation with unilateral input (Kral, 2002; Gordon et al, 2013).
Figure 10.3: Current density reconstructions (CDR) for cortical somatosensory evoked potentials (CSEP) recorded to left and right finger stimulation in cochlear-implanted children who were sequentially bilaterally implanted in the right ear first

A. Cortical activations in response to vibrotactile stimulation of the left (left panel) and right (right panel) index finger in a subset of children with bilateral cochlear implants who received their first implant in the right ear (n = 6). Activations are organized in rows corresponding to each CSEP waveform component (P50, N70, P100, N140a, N140b). Current density reconstructions are presented on coronal slices for each of these components. Three-dimensional Montreal Neurological Institute (MNI) coordinates for each activation are listed below each MRI slice. The F-distribution scale (bottom) presents the color gradient associated with the maximum (yellow) through the minimum (black) likelihood for activation as calculated by sLORETA. B. A table listing all areas of significant activation for each CSEP waveform component.
10.3  Speech Perception in Noise

Speech perception abilities in noise were measured using the BKB-SIN test (Bench et al, 1979; Etymotic Research, 2005). This test yields a signal-to-noise threshold score. In other words, each participant received a score that indicates how intense speech must be above background noise in order for a given participant to perceive 50% of words correctly. Thus, lower scores were associated with better speech perception in noise abilities.

On average, children in the CI group differed significantly in their speech perception in noise abilities from those in the NH group (U = 284.00; z = 4.35; p < 0.001), such that the CI presented with higher (worse) scores than NH children. These results can be seen in Figure 10.4A and are in keeping with previous reports of speech perception in noise findings in CI children (Gifford et al, 2011; Caldwell & Nitrouer, 2013).

In order to examine the relationship between behavioral performance and cross-modal reorganization, correlations were calculated for CSEP peak latency and peak-to-peak amplitude values and BKB-SIN scores in the CI group. This analysis revealed that the N140a latency from the Parietal ROI and the P100 amplitude from the Temporal ROI were significantly negatively correlated with BKB-SIN score (r = -0.62; p = 0.03 and r = 0.64; p = 0.03, respectively; see Figure 4B & C) providing evidence of significant negative correlation between behavioral performance and somatosensory responses. Overall, these data suggest that cross-modal reorganization, as evidenced by decreased CSEP latency and increased CSEP amplitude, results in decreased speech perception performance in noise.
Figure 10.4: Speech perception performance in background noise and cross-modal reorganization, indexed by CSEP responses, in cochlear-implanted children

A. Mean speech perception in background noise (BKB-SIN) scores for CI (white) and NH (black) children. Error bars represent standard error and significant difference is indicated with asterisks (** - p < 0.001). B. & C. Scatter plots illustrating the correlation between BKB-SIN score (lower is better) and N140a peak latency from the parietal ROI (r = -0.623; p = 0.03) and P100 peak-to-peak amplitude from the temporal ROI (r = 0.54; p = 0.03), respectively, in the CI group (n = 12).
The objective of the current study was to determine whether cochlear-implanted children would show evidence of cross-modal reorganization of the auditory cortex by the somatosensory system, and if this reorganization would be correlated with behavioral outcomes in these children. Using high-density EEG recorded in response to vibrotactile stimulation of the right and left index finger, we found the following main results: (i) CSEP morphology was consistent between CI and NH children. However, CI children showed larger amplitudes for the P50 and earlier latencies for the N140a in the midline ROI; (ii) CDR of right finger vibrotactile stimulation revealed expected activation of the left somatosensory cortices in both NH and CI children. In addition, CI participants showed activation of auditory processing areas in the left temporal and parietal association cortex by vibrotactile stimulation; (iii) decreased latency of the N140a CSEP component and increased amplitude of the P100 CSEP component were negatively correlated with speech perception in noise performance in the CI group. (iv) Finally, in a subset of children with right ear first implants, we saw significant cross-modal activation in the right hemisphere, suggesting that the cortex ipsilateral to the first cochlear implant (i.e., the cortex less activated by the first implant) is highly susceptible to cross-modal activation.

11.1 Somatosensory evoked potential evidence of cross-modal reorganization

CSEP analysis revealed waveforms with comparable morphology in the CI group, relative to the NH group (see Figure 1). However, further analysis showed some significant differences
in latency and amplitude. The finding of a larger P50 CSEP amplitude and shorter N140a CSEP latency in the midline ROI is in line with previous data presented in deaf adults which took decreases in visual cortical evoked potential latency and increases in cortical evoked potential amplitude as indices of cross-modal reorganization (e.g., Neville, Schmidt, & Kutas, 1983, Doucet et al, 2006; Buckley & Tobey, 2010; Campbell and Sharma, 2014). These authors postulated that enlargement of visual evoked potential amplitudes at the Cz electrode site in deafness was likely due to the addition of auditory cortical activity to visual processing in deaf, but not hearing, individuals. Additionally, decreased evoked potential latencies as an index of cross-modal reorganization have also been shown previously (Campbell & Sharma, 2014). Clemo et al (2014) reported that this type of neurophysiological difference is likely subserved by synaptic mechanisms, such as increased number of dendritic spines in early deafened individuals (see also Kok et al, 2013), leading to increased synaptic efficiency. Previous studies have also considered larger amplitudes and decrease latencies exhibited by deaf individuals, as indications of cross-modal reorganization, especially when these results were recorded over areas of the scalp associated with the deprived modality (e.g., Doucet et al, 2006; Buckley & Tobey, 2010; Campbell and Sharma, 2014). The midline ROI in the current study encompasses a scalp site that has been widely used for auditory evoked potential recordings (i.e., vertex or Cz; Wolpaw & Penry, 1975; Goff et al, 1977; Ponton et al, 2000). As such, an evoked response to vibrotactile stimuli (CSEP) recorded from this site may have increased potential to show auditory involvement in cross-modal reorganization. Therefore, the decreased latency of the N140a component and the increased amplitude of the P50 component from the midline ROI in CI children, having followed the previously established patterns of cross-modal reorganization described above, may be suggestive of cross-modal reorganization

11.2 Cortical source localization evidence of somatosensory cross-modal reorganization

In CI children, we saw expected activation of the somatosensory cortex including pre-and post central gyrus in response to vibrotactile stimuli. In addition, these children presented with
activation in auditory processing areas in superior and transverse temporal cortices, as well as
cortical regions important to language processing (i.e., parts of Wernickes area), in response to
these same stimuli (see Figure 2). A number of previous studies have reported cortical source
localization results that are consistent with this finding (Levnen et al, 1998; Baldwin, 2002; Auer et
al, 2007; Sharma et al, 2007; Karns et al, 2012). Most notably, the current CI participants presented
with robust activity to right finger stimulation in the left superior and transverse temporal gyri
(BA 41, 42). These areas comprise both primary and secondary auditory cortices. While some
have cross-modal reorganization primarily in higher order auditory cortices in deaf individuals
(Kral, 2007), there is a precedent for primary auditory cortical reorganization. That is, Auer and
colleagues (2007) presented evidence of activity arising from primary auditory cortices in response
to vibrotactile stimulation in six deaf young adults using fMRI. Additionally, MEG source analysis
performed by Levnen et al (1998) showed bilateral activation of superior temporal gyrus (STG)
in one adult with congenital deafness. It is possible that normally unisensory areas are taken
over by other sensory modalities (Auer et al, 2007). Subcortical pathways and connections, whose
dominant sensory modality is altered by sensory deprivation, may mediate this mechanism (e.g.,
cochlear nucleus and inferior colliculus, in the case of deafness). This driving force may occur as
the subcortically modified sensory signal ascends into the cortex, changing the cortical areas to
which it is propagated (Sur et al, 1988; Shore et al, 2008). Numerous studies have established
a precedent for both intracortical, thalamocortical, and subcortical anatomical (e.g., Foxe et al,
2000; Schroeder et al, 2001; Gobbel et al, 2003; Kayser et al, 2005; Caetano, 2007; Hackett, et
al, 2007), as well as functional (Jousmki & Hari, 1998; Lakatos et al, 2007; Brett-Green et al,
2008), connections between the somatosensory and auditory systems. Thus, subcortically driven
cross-modal reorganization of the primary and secondary auditory cortices appears to be a distinct
possibility, especially in congenitally deafened individuals whose deprivation was a factor during
the development of subcortical-cortical pathways.

In this study we observed cortical activation in parietal association areas to vibrotactile stim-
ulation. These areas included Supramarginal and angular gyri (BA 40, 39, respectively). These
areas make up part of Wernickes area, important in language processing. This finding is in agreement with previous data from MEG recordings performed by our group (Sharma et al, 2007), which showed auditory and multimodal association (i.e., Wernickes area) activity in response to vibrotactile stimulation of the hands in one deaf adult. In addition to subcortical contributions, given the multimodal nature of these areas, it is possible that unmasking and enhancement of latent multisensory connections when one modality is deprived may contribute to cross-modal reorganization in these cortical regions (Levnen et al, 1998; Auer et al, 2007).

One study in the literature appears to present conflicting evidence to the present results. That is, Hicock et al, (1997) used MEG to study possible cross-modal reorganization in one deaf young adult. These investigators reported that they found no evidence of somatosensory-to-auditory cross-modal reorganization in this subject. However, these investigators used a tapping stimulus applied to the finger, instead of a vibrotactile stimulus. Because of the similarity between sound and vibration, the auditory cortex may be better suited to process vibrotactile input, while this may not be the case with other types of stimuli (i.e., tapping). Thus, the Hickock et al (1997) study may not be directly comparable to this, and other, studies that do show evidence of somatosensory cross-modal reorganization. Overall, the majority of studies in the literature submit that cross-modal reorganization of the auditory cortex by the somatosensory system can occur in deaf individuals. We add our evidence as another piece of converging evidence that supports this notion in cochlear implanted children.

It may be interesting to note that in all of the previous studies examining cross-modal reorganization in deaf individuals, the duration of deafness was extensive (i.e., into adulthood). For example, the subject recruited for study in Levnen et al (1990) was 77 years of age and had been deaf for all or most of his life. Though the duration of deafness in the current participants was lower than many of the previous studies, the average age of implantation of children in the current study was 3.9 years; it was beyond the sensitive period for auditory cortical development (i.e., 3.5 years; Sharma et al, 2002 a, b). Given that many more children receive their implants around the FDA approved age of one year currently, future studies should investigate cross-modal reorganization in
children who were fitted with cochlear implants at early ages in order to determine if cross-modal reorganization takes place when the duration of deafness is very short in childhood.

11.3 Bilateral Implantation and somatosensory cross-modal reorganization

In the current results, children who received their CIs in the right ear first (RCI1), and who later received a second sequential CI in the left ear showed differing patterns of cortical activation between the right and left cortical hemispheres in response to somatosensory stimulation of the right and left index fingers. Stimulation of the right index finger lead to activity patterns that, for the most part, were consistent with typical somatosensory responses (post- and pre-central gyri (BA 3, 5; and 4, respectively) and activation of auditory areas (BA 39, 22) (consistent with our overall finding of cross-modal recruitment for the CI group as a whole). Results from the stimulation of the left finger were, however, quite distinct. That is, instead of the most robust activations being localized to pre- and post-central gyri, cortical generators were estimated to be in the right temporal areas, especially for the P50 and N70 CSEP components. This finding is suggestive of a higher degree of cross-modal reorganization. Our results are in agreement with the results of a study performed by Kral and colleagues (2002) in congenitally deaf white cats. These investigators reported that cats who had received their implants late (i.e., ñ 5 months) showed decreased activations in the auditory cortex ipsilateral to the implanted ear, while responses coming from the contralateral auditory cortex did not show the same pattern. Additionally, Gordon and Papsin (2009) reported that longer durations of unilateral CI use in humans (i.e., ñ 2 years) lead to abnormally high lateralization of EEG signals to the auditory cortex contralateral to the CI. In contrast, the auditory cortex ipsilateral to the implant showed very low activation (Gordon et al, 2013). The participants from the RCI1 group were fitted with their first implant around the age of 2.89 years (+/- 2.67 years), which is under the sensitive period for auditory cortical maturation (i.e., 3.5 years) reported by Sharma et al (2002 a, b). Consistent stimulation of the left auditory cortex via a cochlear implant placed in the right ear during the sensitive period may have contributed to the results from right finger stimulation that suggest near normal somatosensory activation in RCI1
children and some activation of auditory areas (Figure 4, right panel). In contrast to the right, left finger stimulation lead to robust activation of right auditory cortices in these children (Figure 4, left panel) suggesting that the weaker ipsilateral cortex is highly amenable to cross-modal recruitment by the somatosensory modality. Overall, these children spent years without optimal auditory input to the right auditory cortices, which may have allowed cross-modal reorganization of these cortical areas in the cortex ipsilateral to the CI.

It is unfortunate that we were not able to collect data from left finger stimulation of all participants in the current study. These data would have afforded us the opportunity to more systematically investigate cross-modal reorganization in cortices both ipsilateral and contralateral to participants CIs. However, from the data that we were able to collect, it seems that, in general, because ascending somatosensory information generally crosses over the midline to the cortex contralateral to the side of stimulation, it is plausible that cross-modal reorganization by this system would occur in contralateral auditory cortices as in the results of the combined CI group. However, it is also evident that the weaker (ipsilateral) cortex shows very robust cross-modal reorganization in CI recipients. Future studies should more closely examine differences in cortical responses to left vs. right finger stimulation in sequentially vs. simultaneously implanted children to determine differences in cross-modal reorganization as a function of age of second implant.

11.4 Connections between somatosensory cross-modal reorganization in CI children and speech perception

In this study we saw that decreased CSEP latency of the N140a CSEP component and increased CSEP amplitude of the P100 CSEP component were correlated with a clinical test of speech perception in noise (Figure 5). Previous studies have use decreased cortical evoked potential latency and increased cortical evoked potential amplitude as indices of cross modal reorganization (e.g., Doucet et al, 2006; Buckley & Tobey, 2010). In the present study, as cross-modal reorganization increased as measured by these indices speech perception in noise performance got worse in CI individuals. These results are consistent with previous results describing visual cross-modal plasticity
There are numerous reports in the literature that advocate the notion of the somatosensory system being involved in speech perception. For instance, Ito and colleagues (2009) showed evidence that stretching the facial skin affected the perception of an auditory phoneme. They reasoned that, since the somatosensory receptors responsible for stretching and orientation of the skin are constantly and systematically being activated during speech production, somatosensory input may also be a vital part of speech perception. Additionally, the motor theory of speech perception (Liberman et al, 1967; Liberman & Mattingly, 1985) states that perceiving speech is perceiving vocal tract gestures (Galantucci, Fowler, & Turvey, 2006). Skipper et al (2007) reported that brain areas associated with speech production (i.e., motor and somatosensory) played a significant role in mediating audio-visual speech perception (see also Watkins et al, 2003; Meister et al, 2007). These studies suggest that the somatosensory system plays a significant role in decoding what is seen, which may occur by comparing this input to intrinsic concepts of speech phonemes that are formed in the somatosensory system as speech is produced. In addition, it is reasonable to believe that CI users may rely on vibrotactile input to improve understanding (Gick & Derrick, 2009), especially under challenging listening conditions, such as speech presented in background noise. In all, the above notions present a plausible neurophysiological basis for the relationship between the somatosensory system and speech perception and for the notion that cross-modal plasticity from the somatosensory system may occur as a compensatory plasticity in deafness.
Chapter 12

Study 2 Summary and Conclusion

The current study provides evidence of cross-modal reorganization between the somatosensory and auditory systems in children with cochlear implants. Results from CSEP recordings showed significant differences between the waveforms of NH and CI children, which likely reflect differences in cortical activation patterns between these groups. Current density reconstructions secondary to stimulation of the right index finger revealed cortical activation in somatosensory cortices in both NH and CI groups, while the CI group also presented with cortical activity localized within auditory cortices. This finding offers evidence of cross-modal reorganization of the auditory cortex by the somatosensory system in the combined group of children with CIs. Our results also suggest that the cortex ipsilateral to the first implanted ear is highly susceptible to cross-modal reorganization. Finally, the degree of somatosensory-to-auditory cross-modal reorganization was negatively correlated with behavioral speech perception in noise outcomes in the CI group.

We conclude that somatosensory-to-auditory cross-modal reorganization can occur in children with CIs and that it can have adverse affects on behavioral speech and language abilities. Overall, our results suggest that some of the variability in behavioral outcome in CI children may be explained by somatosensory cross-modal reorganization of the auditory cortices in children with CIs. Future studies are needed to elucidate the details surrounding factors such as the time course, prevention and reversibility, and implications for prognoses of cross-modal reorganization in this population.
Chapter 13

Overall Summary and Conclusion

Our first specific aim was to understand the development of CSEPs in normal hearing children using high-density EEG for use in comparison with cochlear-implanted children. We hypothesized that CSEP waveform analysis would show increased latencies and decreased amplitudes as age increased. We also hypothesized that generators of cortical activity would be centered in the post-central gyrus of the cerebral hemisphere contralateral to the side of stimulation and will remain constant across the age span of interest. These hypotheses regarding developmental patterns in cortical somatosensory function were supported by the results of Study 1. First, CSEP peak latency and peak-to-peak amplitude comparisons between age groups yielded some (but not many) significant differences as a function of age, though these were only between the youngest (ages 5-7) and two older age groups (8-10 & 11-17 years of age). CSEP morphology with respect to presence of peak components was constant across the age span tested. In addition, current density reconstructions following vibrotactile stimulation of the right index finger revealed activation that remained stable for all age groups. This activity was centered in the post-central gyrus, which radiated out to the pre-central gyrus, superior and inferior parietal lobules, and frontal areas in the case of the later CSEP components. The location and constancy of these cortical source estimations supported our hypothesis. These data together provided a baseline against which we were able to compare similar measures in children with cochlear implants, in order to investigate somatosensory cross-modal reorganization of the auditory cortex, in Study 2.

In Study 2 we aimed to examine somatosensory-to-auditory cross-modal reorganization in
children with cochlear implants and its effect on behavioral speech perception abilities. We hypothesized that cochlear-implanted children would present with different latency and amplitude patterns across scalp ROIs compared with normal hearing children, such that shorter latencies and greater amplitudes would be observed for cochlear-implanted children. We also hypothesized that current density reconstruction would show activation of the temporal cortices in children with cochlear implants, but not in children with normal hearing, though both groups of subjects would show activation of the somatosensory cortices. We also projected that we would see significant negative relationships between CSEP peak components and speech perception in noise performance in children with CIs. The findings presented in Study 2 support the hypothesis contained in Specific Aim 2. That is, we found significant differences in CSEP waveform component latency between the NH and CI groups. Additionally, estimates of the sources of cortical activity also supported our hypotheses. That is, right finger vibrotactile stimulation lead to activation of the left primary and secondary somatosensory cortices, including post-central gyrus, pre-central gyrus, and parietal association areas in both NH and CI children. In contrast, the CI group also showed activation of auditory and speech and language processing areas of the temporal cortical regions, such as transverse and superior temporal gyri (BA 29, 41, 42), and other areas often associate with auditory and speech and language processing angular gyrus (39) and supramarginal gyrus (40).

Finally, our hypothesis of negative correlation between cross-modal reorganization and speech perception was supported. That is, we found negative correlations performed between a measure of speech perception in noise and the N140a CSEP latency from the temporal ROI and P100 CSEP amplitude from the parietal ROI. In other words, it appears that the degree of cross-modal reorganization is systematically related to behavioral outcome in children with CIs.

In conclusion, the findings from this study have uncovered evidence suggesting that somatosensory cross-modal reorganization may be an underlying influence on the variability in behavioral performance in cochlear-implanted children. Future studies should examine somatosensory cross-modal reorganization in CI children in more detail to better understand its impact on performance outcomes and rehabilitation.
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