INTER-TRIAL COHERENCE AS A MARKER OF CORTICAL DYS-SYNCHRONY IN CHILDREN WITH AUDITORY NEUROPATHY SPECTRUM DISORDER (ANSD)

by

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Inter-trial Coherence as a Marker of Cortical Dys-synchrony in Children with Auditory Neuropathy Spectrum Disorder (ANSD)

Thesis directed by Professor Anu Sharma

ABSTRACT

Background: Auditory Neuropathy Spectrum Disorder (ANSD) is a recently discovered form of hearing loss, which is characterized by a lack of neural synchrony at the brainstem. However, there is very little information on the impact of sub-cortical dys-synchrony on cortical development, functioning and behavioral outcomes in ANSD.

Purpose: Two experiments are presented. The first experiment examines auditory cortical development and phase synchrony in cortical responses in a pediatric patient with unilateral ANSD. The second experiment utilizes time-frequency analysis of single trial EEG data to examine differences in cortical phase synchrony between 91 children with auditory neuropathy spectrum disorder (ANSD), 50 children with sensorineural hearing loss, and 41 children with normal hearing.

Methods: In Experiment 1, cortical auditory evoked potentials (CAEPs), dipole and current-density analyses, independent component analyses (ICA), inter-trial coherence, and the patient's performance on measures of speech perception were compared for the ear with normal hearing (NH) and the ear with ANSD. In Experiment 2, inter-trial coherence (ITC) analyses were performed on CAEPs from each group. The peak strength of ITC and the time and frequency ranges of significant ITC were compared between groups and subgroups categorized by hearing loss, technology intervention types and cortical maturation.

Results: In Experiment 1, differences were observed between the NH ear and the ear with ANSD for all test measures. In Experiment 2, no correlation was found between test age and the ITC measures examined for the normal hearing group. Clinical diagnosis, degree of hearing loss, intervention type and cortical maturation showed significant relationships with ITC measures.

Conclusions: Children with ANSD show significant cortical deficits, which include abnormal cortical organization, high degrees of inherent cortical variability, and deficits in cortical phase synchronization to speech. Given the importance of normal cortical maturation and functioning for speech and language acquisition in children, the results suggest new evidence for behavioral outcomes associated with children with ANSD.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1

REVIEW OF THE LITERATURE

1.1. Auditory Neuropathy Spectrum Disorder

Auditory Neuropathy Spectrum Disorder (ANSD) is a recently documented disorder, which is estimated to affect 10 -15% of patients with sensorineural hearing loss (SNHL) (Talaat et al., 2009, Kirkim et al., 2008). Neural dys-synchrony is a hallmark of all patients with ANSD, and this population presents certain challenges to clinicians in quantifying and treating the sensory and perceptual losses associated with this dys-synchrony. Diagnosis of ANSD is performed clinically through the acquisition of otoacoustic emissions (OAEs) and auditory brainstem response testing (ABR); typically, ABR responses are absent or abnormal, while OAE responses remain intact. Generally, a cochlear microphonic (CM) is obtained during ABR recording in patients with ANSD, which reverses polarity upon a change in polarity of the stimulus (Starr et al., 1991, Berlin et al., 1998, Berlin et al., 2003). The absent ABR reflects the disruption in neural synchrony at the level of the eighth nerve and/or brainstem. Santarelli and Arslan (2002) found that the CM and summating potential (SP) were present at the normal threshold for the vast majority of the subjects with ANSD that they tested, which would be consistent with normal cochlear hair cell function.

Acoustic reflexes are also abnormal in patients with ANSD, providing further evidence of abnormalities in brainstem functioning in this population. In a study of 136 patients with ANSD, only three had middle ear muscle reflexes at 95 dB HL or below, and there was universal abnormality of reflexes at 1 and 2 kHz in every ear tested

(Berlin et al., 2005). This result held for both ipsilateral and contralateral conditions. Since OAEs remain robust in many individuals with ANSD, suggesting normal functioning of the outer hair cells, the site of lesion has been proposed to be at the level of the inner hair cells of the cochlea, at the synapse between the inner hair cells and the auditory nerve, along the auditory nerve itself, or at the level of the brainstem (Starr et al., 1996, Ptok, 2000, Gibson and Sanli, 2007, Rance and Aud, 2005).

Characteristics of children with ANSD include a large amount of intra-individual and inter-individual variability in behavioral responses for pure tone audiometric thresholds and speech recognition scores. Hearing loss as measured with pure tone thresholds can include anything from a mild to a profound deficit (Cone-Wesson, 2004, Doyle et al., 1998, Zeng and Liu, 2006, Starr et al., 1996). Rance et al. (1999) found a fairly even distribution of hearing thresholds in the participants observed, which was confirmed with results from Starr et al. (2000), Sininger and Oba (2001), and Madden et al. (2002a). Five of the 14 children examined in the study by Rance and colleagues (1999) found significant fluctuations in threshold of about 20 dB. Gorga et al. (1995) and Starr et al. (1998) found even greater fluctuations of audiometric thresholds in patients with temperature-sensitive ANSD. Sininger and Oba (2001) and Starr (2000) report that approximately one third of the ANSD patients from their databases have fluctuating audiometric thresholds.

Researchers have noted no particular correspondence between the level of hearing loss and speech recognition performance in any given individual with ANSD (Rance and Aud, 2005, Sharma et al., 2011). Indeed, speech discrimination scores are often worse than would be expected for a given amount of hearing loss (Deltenre et al.,

1999, Rance et al., 1999, Rance et al., 2002, Rance et al., 2007b, Rapin and Gravel, 2003). Zeng et al. (2005) have described ANSD patients as differing from patients with sensorineural hearing loss, in that intensity encoding remains relatively intact within the auditory system for patients with ANSD, while coding of temporal information becomes severely distorted. This is the opposite of what happens in patients with sensorineural hearing loss and no ANSD, who tend to have reasonably good temporal encoding, but impaired processing of intensity information.

Zeng and Liu (2006) found that participants with ANSD had greater difficulty understanding speech in noise when compared to normal hearing subjects and those with cochlear impairment. They found severe temporal processing impairments in the ANSD patients they tested, and suggest that the cause for impaired speech recognition ability in ANSD is likely to be due to an inability to process temporal information in speech, rather than an inability to detect short-duration sounds. In addition, the binaural summation effect that benefited speech discrimination for ANSD patients in quiet disappeared in the noisy condition. A more recent study of speech perception in noise in patients with ANSD confirmed these results, and found that speech perception in noise for a group of listeners with ANSD was significantly impaired compared to normal hearing controls, and suggested that this deficit may be due to difficulties in processing the envelope and fine structure cues of the speech signal (Narne, 2013). Sininger and Oba (2001) reported that 69% of the ANSD patients from their database had speech discrimination scores that fell below the expected normative range (from Yellin et al., 1989).

1.2. Prevalence and Risk Factors/Etiology Considerations

Talaat and colleagues (2009) estimate the prevalence of ANSD to be 13.4% among infants and children with severe to profound hearing loss. In 86.7% of the cases they examined, the ANSD was bilateral; the other 13.3% had unilateral ANSD. Cheng et al. (2005) suggest that patients with unilateral ANSD may have a different etiology from those who present with bilateral ANSD. Specifically, Cheng and colleagues examined genetic contributors to hearing loss at a school for the deaf, and found that one child with a genetic mutation in the GJB2 gene (which encodes connexin 26) had hearing loss on both sides, but OAEs present on one side, suggesting that this etiology does not necessarily destroy all outer hair cell function. Kirkim et al. (2008) found the prevalence among the newborns they tested to be approximately 15% (10 out of 65 newborns with abnormal ABR results were found to have ANSD). Seven of these babies had hyperbilirubinemia as the major risk factor associated with their diagnosis of ANSD. Rea and Gibson (2003) note that as many as 40% of NICU babies may have ANSD, secondary to hypoxia at birth.

Other ANSD risk factors include infections, exposure to ototoxic medications, genetic and syndromic conditions, and prematurity (Kraus, 2001, Beutner et al., 2007, Dowley et al., 2009). As already mentioned, hyperbilirubinemia and anoxia at birth are the most common risk factors associated with ANSD, presenting in more than 50% of cases (Stein et al., 1996, Deltenre et al., 1999, Simmons and Beauchaine, 2000, Starr et al., 2000, Sininger and Oba, 2001, Franck et al., 2002, Madden et al., 2002b, Dunkley et al., 2003, Berlin et al., 1998). Starr and colleagues found that infectious agents were involved in approximately 10% of 67 ANSD patients they evaluated.

Mumps and meningitis have also been implicated in etiological risk factors for ANSD (Prieve et al., 1991, Sininger et al., 1995, Rance et al., 1999). Charcot-Marie-Tooth Syndrome (I and II), a genetic disorder that involves demyelination of the axonal sheath, is found in a relatively high proportion of late-onset cases of ANSD (Sininger and Oba, 2001). Axonal loss has also been reported in Charcot-Marie-Tooth, and ABR results in this population have been reported to be abnormal (Cassandro et al., 1986, Chance and Fischbeck, 1994, Ouvrier, 1996). A neurodegenerative condition called Friedrich's ataxia has also been associated with ANSD, and four cases were described in Sininger and Oba (2001).

As mentioned, genetic etiologies such as abnormalities in the connexin 26 gene may be related to ANSD. Cheng (2005) found abnormalities in the connexin 26 gene (GJB2) in 21 out of 76 (27.6%) of children with ANSD tested at a school for the deaf. One mechanism which may cause ANSD is a synaptic disorder at the level of the inner hair cell and auditory nerve (Starr et al., 1991). Abnormalities in the gene that encodes otoferlin (DFNB9) may disrupt the production of neurotransmitters, which are required for the normal functioning of the synapse between the inner hair cells and the auditory nerve (Varga et al., 2003, Varga et al., 2006, Yasunaga et al., 1999). This mechanism may be presynaptic, which would involve the release of neurotransmitters into the synaptic space, or postsynaptic, involving the ability of receptor sites on the nerve to respond to those neurotransmitters (Starr et al., 2000). More general neuropathies may be present for patients with ANSD, as well, particularly those with an onset of symptoms after the age of 15 years. Rance and Aud (2005) report that about 80% of patients older than 15 years with late onset symptoms of ANSD also have generalized

neuropathic disorders, possibly involving a loss of myelin from the axon sheath. Sininger and Oba (2001) found that the most common etiological profile included both genetic and neonatal risk factors; in fact, 80% of the children presenting with early onset ANSD had a mixture of risk factors reported.

1.3. Synchrony in ANSD

Several models have been proposed that may explain the lack of synchrony in afferent nerve transmission for patients with ANSD. Potential contributors to the lack of synchrony could include demyelination of the afferent axonal fibers and/or axonal loss (Starr, 2001). Demyelination could cause staggered firing of the auditory nerve fibers, leading to a decrease in amplitude of the response as the signal is summed. While demyelinated fibers are capable of carrying an action potential, they do so with prolonged refractory periods, and a general inability to carry high-frequency pulse trains, both of which would interfere with neural timing (McDonald and Sears, 1970, Rasminsky and Sears, 1972, Pender and Sears, 1984). Overall conduction time is increased, and demyelination could result in a loss of propagation along neural pathways (Rasminsky and Sears, 1972). Temperature-dependent neuropathies are argued to be more likely due to a conduction block than a disruption of neural timing (Marsh, 2002).

Axonal loss would also lead to a decrease in amplitude of the response, due to a lack of fibers that would contribute to the decrease in strength of the signal. Sometimes the effects of axonal loss are similar enough to demyelination as to be difficult to distinguish etiologically (Rapin and Gravel, 2003). While there is a reduction in the total number of axons required to carry a given neural signal, in general, refractory periods

remain unaffected and the neural fibers are capable of carrying stimuli at a high frequency rate (Kuwabara et al., 1999).

Sural nerve biopsies in patients with auditory neuropathy and a concomitant peripheral neuropathy have found both demyelination of nerve fibers and axonal loss (Butinar et al., 1999, Starr, 2001). During postmortem examination of the auditory fibers in one of these patients, it was found that the auditory nerve also had neural fiber loss (although it was not as extensive as that in the sural nerve). The researchers suggest that if the pattern of neural loss followed that of the sural nerve, the large auditory fibers are likely to have been lost first. Large auditory nerve fibers are characterized by high spontaneous discharge rates, rapid conduction velocities, and low discharge thresholds (Gleich and Wilson, 1993, Liberman, 1982), and therefore their loss would be relevant to some of the defining attributes found in the ANSD population.

Some work has been performed to examine the differences in performance that might occur in demyelinating disorders versus axonal loss. In a recent study from the Rance lab (2012) it was found that comparable speech performance results can be obtained in individuals with known demyelinating disorders (Charcot-Marie Tooth type 1A) when compared to those with known axonal loss disorders (Friedreich's ataxia). However, electrophysiological test results on the ABR were able to distinguish between the disorders based upon the etiological differences involved, as the axonal loss of Friedreich's ataxia tended to produce normal conduction times in the brainstem but reduced response amplitudes, and the demyelination found in Charcot-Marie Tooth syndrome produced prolonged ABR interpeak latencies.

While it is natural to focus upon central lesions in ANSD, inner ear disorders may also contribute to ANSD in some individuals, and animal studies of inner hair cell dysfunction have provided insights into these possible mechanisms behind ANSD (Harrison, 1998). Chinchillas treated with carboplatin have produced selective inner hair cell lesions, which caused auditory brainstem response disruption in these animals. The abnormal ABR was thought to be due to a reduced number of firing neurons, contributing to the overall potential, rather than an increase in the threshold required for neurons to fire (as evidenced by normal firing thresholds in single-units from the inferior colliculus).

Histologic examinations of the inner hair cells from 3 non-surviving NICU babies would seem to confirm that selective inner hair cell disorders exist in humans with ANSD (Amatuzzi et al., 2001). These babies had no response to screening ABRs prior to their deaths, and postmortem evaluation found that they had inner hair cell loss without concomitant outer cell loss or auditory nerve damage. Results from this small sample suggest that the abnormalities found in their ABR responses were primarily due only to inner hair cell loss.

The implication that the auditory nerve and/or brainstem is always impaired in patients with ANSD was part of the reason that *auditory dys-synchrony* was suggested as a more correct term for the condition (Berlin et al., 2001). For many years, the condition was referred to as auditory neuropathy/dys-synchrony (AN/AD). At the 2008 NHS meeting in Italy a consensus statement suggested that the condition be referred to as auditory neuropathy spectrum disorder (ANSD), as the term "spectrum" emphasized the variable nature of the disorder.

1.4. Treatment of ANSD

Hearing aids are not consistently beneficial for patients with ANSD. Rance and colleagues (2002) have reported that hearing aids are effective in approximately 50% of pediatric ANSD patients. Approximately half of the 15 children studied showed an improvement in speech recognition post-fitting. In contrast, Starr et al. (1996) reported that amplification with hearing aids was of no benefit to adults with ANSD that were studied, and in some cases were the cause of unwanted effects. At the House Ear Institute, more than half of the ANSD patients sampled were nonusers or past users of hearing aids, and only 10% received fair to good benefit from amplification (as measured through audiometric thresholds and speech recognition improvement). Another 17% showed improvement in audiometric thresholds, but no improvement in speech perception (Cone-Wesson et al., 2001). Sharma et al. (2011) also showed hearing aids were not always beneficial: they were only successful in approximately 1/3 of the ANSD sample described. One clinical concern with the use of hearing aids in children with ANSD and normal outer hair cell function is that the high-intensity output of amplification may introduce a sensory component to ANSD-related hearing loss, as outer hair cells may be affected by exposure to loud sound (Macrae, 1991, Macrae, 1995). Rance and Aud (2005) note that while increases in intensity have produced increases in phase locking and synchrony for normally hearing subjects, similar effects have not yet been described in subjects with auditory pathway abnormalities.

Cochlear implants are often considered as the next intervention step after hearing aids have been tried. In general, clinical management of patients with ANSD has shifted towards cochlear implantation in recent years (Berlin et al., 2003, Peterson

et al., 2003). A preponderance of patients with ANSD have thresholds in the severe-to-profound range, which places them within the usual candidacy requirements for a cochlear implant (Sininger, 2001). Recent research has indicated that patients with ANSD who demonstrate limited auditory skills development with conventional amplification generally do benefit from cochlear implantation, and develop auditory skills post-implantation (Pelosi et al., 2013). One potential benefit of cochlear implantation is the possibility that the precise electrical stimulation delivered via an implant would introduce synchrony into a previously dys-synchronous neural system.

Given the possible auditory nerve pathology in ANSD as described in section 1.3, such as axonal loss and demyelination, it is possible that cochlear implantation would not be successful for some patients with these mechanisms underlying their disorder. However, there is research to support implantation even with auditory nerve dysfunction. For instance, Zhou et al. (1995) reported that synchronous ABRs could be recorded with electrical stimulation of the nerve fibers in mice, even with peripheral auditory nerve demyelination. Shallop and colleagues (2004) utilized auditory evoked potentials in several ANSD patients who were implanted, and found evidence supporting the restoration of synchrony in implanted ANSD patients. If synchrony and normal neural firing patterns can indeed be restored with a cochlear implant, the hope is that it would lead to improved speech discrimination performance as well.

In general, implantation has provided improved speech perception ability to many ANSD patients, often with comparable results to implantees with sensorineural loss (Trautwein et al., 2000, Shallop et al., 2001, Trautwein et al., 2001, Madden et al., 2002a, Shallop, 2002, Mason et al., 2003, Peterson et al., 2003). In a recent study,

Budenz and colleagues (2013) examined cochlear implantation outcomes in 17 children with ANSD as compared to a similar group of children with cochlear hearing loss. They found that children with ANSD and those without ANSD performed similarly on measures of speech perception (the IT-MAIS and the MAIS). However, outcomes tended to be poorer in children with ANSD who had concomitant developmental or cognitive delays. These results were consistent with a study by Breneman et al. (2012), who found that children with ANSD achieved similar speech perception results to their peers with sensorineural hearing loss after implantation.

The benefits of implantation have carried over to speech production development as well for patients with ANSD, with gains that are comparable to matched groups of patients with sensorineural hearing loss and cochlear implants (Buss et al., 2002). In addition to providing increased audibility to patients with ANSD, cochlear implants may provide a better means of stimulating the central auditory pathways, as evidenced by the ability to record evoked responses such as the ABR (Shallop et al., 2001, Trautwein et al., 2001, Buss et al., 2002). The mechanism behind the improvement in the implanted population could be due to increased synchrony (phase coherence) in existing fibers, or an increase in the population of neural fibers that are being stimulated by sound.

Age of intervention is also an important consideration for any child with hearing loss, not only those with ANSD. Studies from Yoshinaga-Itano and colleagues (1998) and Moeller (2000) indicate that intervention with amplification that is received by the age of 6 months has a much greater likelihood of producing the best outcomes. The Sharma lab (2007, 2002a, 2002b, 2002c, 2005) has also produced numerous studies

that indicate that the central auditory system develops best when intervention with electrical stimulation is received during an early sensitive period of approximately 3 years. A new study from the Sharma lab indicates that the sensitive period for children with ANSD may be closer to 2 years (Cardon and Sharma, accepted).

1.5. Cortical Development and ANSD

The ABR is high-frequency and biphasic, and represents the summation of action potentials produced by neurons in the eighth nerve. In contrast, cortical auditory evoked potentials (CAEPs) have dendritic sources, and are slow, low frequency potentials that occur over tens to hundreds of milliseconds, and are therefore more resistant to jitter (on the order of milliseconds) caused by underlying disruptions in dys-synchrony (Kraus et al., 2000). Evidence of the forgiving nature of longer latency potentials is described in Michalewski et al. (1986), who reported a standard deviation of around 20 milliseconds for late-latency cortical potentials, which is far greater than the ABR responses which are separated by only 1-2 milliseconds.

CAEPs have been used to investigate cortical maturation in children with ANSD. Cortical maturation is a predictor of speech and language development in children in general (Eggermont and Ponton, 2003, Moore, 2002, Sharma and Dorman, 2006), and it is likely to be an important predictor in children with ANSD as well. Only a few studies have examined cortical development in children with ANSD, but all have indicated that measures of cortical development are predictors of appropriate speech and language development.

Sharma and colleagues (2011) examined the P1 central auditory evoked potential responses (CAEPs) in 21 children with ANSD. The P1 is a component of the

cortical auditory response, and its latency is considered a biomarker of maturation of the auditory cortex (Sharma et al., 2002b, Sharma et al., 2009). Children with ANSD were divided into three groups: ANSD children with normal P1 latencies, ANSD children with delayed P1 latencies, and ANSD children with grossly abnormal P1 waveform morphology (no latency was identified for the latter group). It was found that the P1 waveform latency and morphology corresponded very well to speech performance as measured by the Infant-Toddler Meaningful Auditory Integration Scale (IT-MAIS), suggesting that the P1 CAEP is a good predictor of outcome for ANSD children. Further case study presentations by Cardon et al. (2012) and Campbell et al. (2011) illustrated the use of CAEPs as a clinical tool for assessing the cortical maturation of children with ANSD. Since pure tone audiometry often does not correspond well to speech measures in these patients, the P1 CAEP may provide very valuable information in the ANSD population as a predictor of outcomes, and therefore may assist in clinical decision-making.

Consistent with results from the Sharma group described above, in a recent study of 14 children with ANSD who had received cochlear implants, researchers examined the relationship between speech perception performance and the duration of sensory deprivation pre-implant with the P1 component of the CAEP (Alvarenga et al., 2012). The P1 was identified in 12 of the 14 children studied, and speech perception measures and the duration of sensory deprivation were found to correlate with the P1 latency.

Rance et al. (2002) also found that speech perception performance in children with ANSD corresponded with cortical auditory evoked potential (CAEP) test results. In

15 children with ANSD who were examined, approximately half of the sample of children presented with normal CAEP latency, amplitude, and morphology. The children with normal CAEPs also had reasonable speech perception ability (comparable to their peers with sensorineural hearing loss), and those without normal CAEPs had very poor speech perception scores by contrast.

It has been described that normal cortical development relies upon a combination of internal and external factors. A neural system that has been formed with specific genetic and molecular capabilities is shaped by the input it receives (Pallas, 2001). A cortex that receives signals other than those that are typical or normal will not develop to exhibit normal qualities (Kral and Eggermont, 2007, Sur, 1988). For example, Sur and colleagues (1988) found that stimulation of the auditory cortex with visual inputs in animals resulted in the auditory cortex taking on characteristics that resembled the visual cortex, thus showing that subcortical afferent input greatly impacts cortical development. Stimulus processing at the level of the auditory cortex is affected by dys-synchrony at the level of the brainstem (Eggermont, 2007, Japaridze et al., 2002, Robinson and Rudge, 1980, Arrondo et al., 2009). Dys-synchrony at the subcortical level in patients with ANSD is likely to follow a similar pattern, and result in abnormal cortical maturation and development, which can be measured with EEG (Sharma et al., 2011, Rance et al., 2002).

As described above, neural dys-synchrony may be the main factor affecting the ANSD clinical population (Sharma et al., 2011, Rance et al., 2002). Measures that are indicators of cortical maturation, such as the P1 central auditory evoked potential (CAEP), may be very useful with the ANSD population to demonstrate the extent to

which dys-synchronous sub-cortical input has affected cortical development necessary for normal speech and language acquisition. Use of the P1 CAEP does not require a behavioral response from the child being tested, and the longer latencies of cortical waveforms do not require the precise synchrony of brainstem responses such as the ABR.

Since cortical synchrony is important for speech perception and cognition (see section 1.7), the effects of dys-synchrony are important to quantify and measure. As such, cortical responses could provide an objective tool to measure of the degree of dys-synchrony within the peripheral and central auditory systems, which in turn could predict clinical outcomes.

The studies of cortical maturation described above did not measure cortical synchrony directly, as they used averaged CAEP responses where information about the responses underlying the average is not considered. A more direct measure of cortical synchrony would involve evaluation of whether the responses underlying the aggregate are coherent or synchronous with respect to each other. New time-frequency analyses of EEG, including measures such as inter-trial coherence (ITC), allow for the direct examination of cortical phase synchrony of single trials (Makeig et al., 2004).

1.6. Inter-trial Coherence (ITC) as a Measure of Cortical Synchrony

Cortical oscillations are an integral part of many sensory and cognitive processes (Buzsaki and Draguhn, 2004, Donner and Siegel, 2011, Wang, 2010), and coherence of these oscillations is a means for distant but related groups of cortical neurons to communicate with each other (Fries, 2005). These oscillations are measurable with EEG, and patterns of EEG activity can be examined for their relationships with specific

stimuli (such as speech). Indeed, phase synchrony in cortical oscillations is proposed to be the mechanism behind our ability to temporally process and understand the complexities of the speech signal (Giraud and Poeppel, 2012).

Spontaneous EEG is composed of a combination of synchronous neural processes that include rapid phase shifts (30-80 ms) followed by longer periods of phase locking (100-800 ms) of groups of neurons, which then shift from one cluster of phase-locked neurons to other neuron clusters (Freeman and Rogers, 2002, Freeman, 2003). With the introduction of a stimulus event, the even distribution of EEG phase becomes lopsided, and the signal can become "phase-locked" to an event (Makeig et al., 2004). Inter-trial coherence (ITC) is a measure of this phase-locked EEG activity. It reflects the temporal and spectral synchronization at particular times and frequencies within the EEG recording relative to the baseline period. Tallon-Baudry et al. (1996) referred to this as a "phase locking factor." Synchronization of brain oscillations within and between cortical areas is a fundamental mechanism for combining related information, and this phase synchrony is modulated by cognitive demands (Tass et al., 1998, Palva et al., 2005).

Amplitude in the averaged P1 CAEP is theorized to result from one of two mechanisms: the addition of an evoked response to the random oscillations within the cortex, or a phase resetting of these random oscillations (Klimesch et al., 2004, Sauseng et al., 2007, Fuentemilla et al., 2006). If the additive response is assumed to be due to an increase in the number of neurons firing, it is possible that the phase synchrony (and therefore, ITC) would not change, regardless of the amplitude noted in the averaged waveform. If, however, phase synchrony (as measured by ITC) changes,

amplitude can be assumed to be due to a phase resetting of the random oscillations in the cortex.

Thus, differences in ITC between groups may illuminate differences in the mechanisms at work in the cortex that would not be apparent within the averaged ERP waveform. While the amplitude of the averaged EEG signal correlates with synchrony (Uhlhaas and Singer, 2006), amplitude does not capture the underlying phase synchrony for a given individual. As described above, the average amplitude (and latency) for a given EEG waveform peak may be generated by more or less synchronous neuronal firing in individual trials, depending on the number of neurons and the patterns of activity involved. Amplitude has never been considered to be a direct measure of synchrony, and amplitude alone cannot describe the frequency components within a signal, nor the phase-locking of those frequency components at a given time. For these reasons, it is desirable to employ a method other than amplitude to determine the level of synchrony for a given population of interest. Differences in phase synchrony for children with hearing loss, with or without ANSD, may reflect differences in the neuronal populations ability to respond to auditory stimuli, and/or the cognitive load that auditory processing requires for this population.

Inter-trial coherence (ITC) is a method that permits determination of synchrony, particularly when examining the overall time and frequency range of phase coherence (Lachaux et al., 1999, Tass et al., 1998, Zeitler et al., 2006). The phase-locking statistics used for ITC calculations, as described by Lachaux et al. (1999), specifically separate the amplitude component from the phase component within the overall EEG signal, since ITC reflects the phase-resetting mechanism specifically. Thus, ITC

describes the phase-locking characteristics of each frequency within an EEG signal, at specific time points post-stimulus, without regard to the averaged amplitude of a particular peak.

Makeig et al. (2004) suggest that a combination of high density EEG with independent component analysis (ICA) and time-frequency analysis (including ITC) may provide valuable information about brain dynamics. The use of ICA minimizes the loss of resolution due to volume conduction, and provides information about the spatially and temporally distinct sources of EEG activity that underlie the averaged ERP response. Using time-frequency analysis on the separated sources produced through ICA may provide an ideal way to avoid the cancellation of positive and negative voltages across the scalp, or the misallocation of activity that is recorded from distant sources.

The inter-trial coherence method that will be used as part of this study is part of the EEGLAB toolbox, a toolbox for use with the MATLAB program (Delorme and Makeig, 2004). Time-frequency analysis with this toolbox may include event-related spectral perturbation (ERSP) for a given channel or component, event-related cross-coherence (ERCOH) between channels or components, and/or inter-trial coherence for a given channel or component (ITC). The focus for the current study will be upon the last of these: inter-trial coherence.

The formula that Delorme and Makeig (2004) have used to define inter-trial phase coherence within the EEGLAB toolbox is the following:

$$ITPC(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{\left|F_k(f,t)\right|}$$

For n trials, $F_k\ (f, t)$ is the spectral estimate of trial k at frequency f and time t where || is the complex norm.

Thus, while ITC is a well-regarded measure of cortical phase synchrony, it has not been applied so far to the ANSD population where a lack of synchrony in the central auditory system is a hallmark of the disorder. In the current study, the utility of ITC as a marker of dys-synchrony in a large group of children with ANSD will be examined.

1.7. Phase Synchrony in Normal Development and Clinical Populations

Increased phase synchrony in EEG recordings has been examined in normal populations as well as specific clinical populations of interest. To understand the role of synchrony in children with ANSD, it is first helpful to understand how synchrony works in the normal-hearing brain, and how it works in children with sensorineural hearing loss who do not have ANSD. Synchronized neural oscillations are important for the maturation of cortical networks, and are the foundation of coordinated processing within the brain (Uhlhaas et al., 2010). Coordinated oscillations in the beta and gamma frequency ranges are thought to be responsible for attentional processes, as well as coordination of sensory processing and task planning. Synchronization in these frequency ranges relies upon intra-cortical connections that link neurons both within cortical areas and to more distant areas of the brain (Engel et al., 1991, Lowel and Singer, 1992). The frequency, amplitude, and temporal precision of cortical oscillations change as a part of natural growth and development, including changes in the characteristics of GABAergic neurotransmission and the myelination of axonal tracts (Hashimoto et al., 2009, Doischer et al., 2008, Ashtari et al., 2007, Perrin et al., 2009).

Bishop and colleagues (2011a) used the ITC measure to examine auditory cortical development in children from 7 to 11 years of age measured at two different time points. Sixty-two seven-year-olds and 43 nine-year-olds were tested with 40-channel EEG caps in two sessions, spaced two years apart, with pure tone stimuli. While there was no significant difference found between sessions or groups, an interaction effect was found between session and the electrode used. In further exploring this interaction effect, ITC was found to change with age depending on the electrode being used. Specifically, fronto-central electrodes showed increases in ITC with age, particularly in the higher frequencies, while temporal electrodes showed no change or a decrease in ITC. The same research group found a significant (although somewhat smaller) change in ITC with age in an earlier study that looked at the representation of auditory discrimination in children, adolescents, and adults (Bishop et al., 2011b). Age changes were significant from 0-300 ms, but not significant from 300-600 ms in this study. The researchers say that these results support those of Ponton et al. (2002), which states that auditory maturation is not a unified process, but rather a complex interaction of different parts of the cortex maturing at different rates.

Cortical phase patterns have been described as one mechanism that allows for accurate speech discrimination - specifically, the intelligibility of syllabic patterns. Howard and Poeppel (2010) examined phase synchrony patterns in six subjects with magnetoencephalographic (MEG) recordings to speech sentence stimuli. The researchers in this study found that a difference in phase synchrony in the theta range (3-7 Hz) was sufficient to distinguish between intelligible and non-intelligible (time-reversed) spoken sentence stimuli. The results of this study supported previous work

from this research group (Luo and Poeppel, 2007), which postulated that cortical phase synchrony in the theta range during the first 200 ms post-stimulus tracks the acoustic intelligibility of spoken sentences.

The mechanisms behind speech discrimination at the cortical level are still not completely understood. Cortical processing of the speech signal may occur on multiple timescales (Poeppel, 2003, Luo and Poeppel, 2012). It is believed that phase synchronization of brain oscillations in the 20-80 ms scale may relate to short duration acoustic features of speech, and phase synchronization in the 150-300 ms time scale may correspond to syllabic processing (Poeppel, 2003, Luo and Poeppel, 2012). Phase synchronization occurs when the ongoing rhythmic activity in the cortex is interrupted by a stimulus, which prompts a phase reset (and phase alignment) in resting state oscillations (Makeig et al., 2004). Phase synchrony of oscillatory cortical activity in the theta band (3-8 Hz) may relate to broad speech envelope processing, and synchrony in the low gamma band may relate to processing of more rapidly changing information (Ghitza, 2011, Giraud and Poeppel, 2012, Poeppel, 2003). In MEG studies that explored the link between the modulation spectrum of speech signals and cortical oscillations (Luo et al., 2010, Luo and Poeppel, 2007), it was found that the phase in the theta band was useful for tracking the details of the speech signal, and was linked to intelligibility of that signal. The modulation spectrum of speech was also linked to the synchronization of neural oscillations in the theta band in another study which examined cross-modal phase modulation (Luo et al., 2010). In general, studies examining the relationship between cortical phase synchrony and speech processing are fairly new, and further research is required before these mechanisms can be accurately described.

Basic auditory discrimination ability is reflected in the mismatch negativity response, which requires subtracting the EEG waveforms obtained during an infrequent (oddball) stimulus from that obtained during a frequent stimulus. Ko et al. (2012) studied 13 adult, normal hearing participants, and found that an increase in power of cortical oscillations in the theta frequency range and an increase in ITC strength around 250 ms corresponded to the discrimination of deviant tones in the MMN response. These studies suggest that phase synchronization may be a fundamental mechanism for the perception, and perhaps the interpretation, of sound. However, there is very little information about how hearing loss can disrupt neural phase synchrony.

Some studies have explored animal models of how hearing loss affects the synchrony of random cortical oscillations, although these have primarily been limited to noise-induced hearing loss as it relates to tinnitus. Researchers found that there is increased spontaneous neural firing and spontaneous neural synchrony in the regions of the cat brain that have been recently damaged by noise-induced hearing loss, and that the tonotopic arrangement of neurons reorganizes so that cells that were previously tuned to higher frequencies retune to respond to frequencies that are near the edge of the hearing loss (Seki and Eggermont, 2003, Eggermont and Komiya, 2000, Eggermont, 2003). This increase in spontaneous synchrony is believed to be related to the perception of tinnitus; specifically, that this pathological increase of synchrony is sufficient to lead to the perception of a ringing or roaring sound. In a study that utilized magnetoencephalography (MEG) in 3 patients with chronic tinnitus, Bowyer and colleagues (2008) found highly coherent brain activity in the auditory cortex, localized to the hemisphere contralateral to the perceived tinnitus. The researchers suggest that

tinnitus may be a result of abnormal connectivity (and synchronization) between cortical networks, and that the perception of phantom sounds can be measured and localized through calculations of signal coherence. However, no known studies have used coherence measures in EEG to explore differences in cortical phase synchrony for humans with hearing loss (and no tinnitus) as compared to the human normal hearing population. It is possible that synchrony in patients with hearing loss may actually be reduced, rather than increased, given the reduction in audibility.

In addition to the role of synchrony in perceptual and sensory processing, phase coherence has been associated with cognitive functioning and task preparation. An increase in inter-trial coherence has been associated with an increase in performance for visual tasks, for example. Yamagishi et al. (2008) found that a pre-stimulus increase in ITC corresponded with an increase in performance during a line-orientation judgment task. They suggested that increased inter-trial coherence was a marker of an increase in top-down processing before a task, priming the neural systems for enhanced behavioral performance.

Clinical populations such as those with schizophrenia, Alzheimer's disease, Parkinson's, epilepsy, and autism have been examined for the relationship between neural synchrony and performance. Abnormal synchrony in these groups has been associated with cognitive and motor deficits (for a review, see Uhlhaas and Singer, 2006). While these populations may not have reduced cortical synchrony as a result of peripheral neuropathies, there is ample evidence that synchrony is important at the cortical level for behavioral functioning and learning. An exploration of the evidence in these clinical populations follows below.

Several studies have examined phase synchrony between distributed neuronal populations in schizophrenics during cognitive tasks (Slewa-Younan et al., 2004, Uhlhaas and Singer, 2006, Symond et al., 2005, Spencer et al., 2003), which have found a relationship between impaired neural synchrony and cognitive deficits. Ford and colleagues (2007) found that pre-speech increases in ITC as schizophrenic subjects prepared to vocalize were associated with the suppression of the neural response to the participants' own speech sounds. Inter-trial coherence was lower in schizophrenic participants compared to normal controls, especially in those who presented with auditory hallucinations. The reduction of inter-trial coherence in patients with auditory hallucinations is an interesting contrast to the increase in coherence that was described earlier in this section for patients with tinnitus, and the results from the schizophrenic population suggest that abnormal cognitive functioning may have a greater role in the reduction of cortical phase synchrony than the perception of phantom sounds.

Reductions in cortical phase synchrony have been found in other clinical populations in which neurological functioning is known to be abnormal. In patients with epilepsy, reduced phase coherence in specific frequency bands has been documented as a possible precursor to ictal activity within the brain (Le Van Quyen et al., 2003). Studies of patients with autism have revealed reduced stimulus-locked gamma band activity in the brain (Wilson et al., 2007).

Patients with Alzheimer's Disease (AD) have been shown to have impaired phase coherence in a number of studies (Stam et al., 2007, Stam et al., 2005, Stam et al., 2003), generally indicating impairment in beta and alpha frequency band

synchronization, and a decrease in gamma band synchronization during rest. This reduction in alpha and beta band synchrony in AD patients was connected with performance in a study by Pijnenburg and colleagues (2004). A reduction in synchrony in these frequency bands was observed while AD participants were asked to keep information in working memory, as compared to control subjects. This reduction in synchrony is compatible with the hypothesis that deficits in AD are caused by a decoupling of important cortical areas (Delbeuck et al., 2003).

Not only is cortical synchrony important for cognitive tasks, it is also a prerequisite for normal motor function. There is evidence for increased synchronous activity prior to motor activity and during tasks that require hand-eye coordination (Murthy and Fetz, 1996, Roelfsema et al., 1997). Changes in the cortical synchrony in the Parkinson's population have been associated with difficulties with motor initiation, motor slowness, and tremor in this population (for a review, see Uhlhaas et al., 2006). These studies suggest that ITC is a useful measure of cortical synchrony in neurologically impaired populations, however, its possible clinical utility in the ANSD population remains to be explored.

While many studies have focused on the strength of coherence in specific frequency bands, Thatcher and colleagues suggest that the length of time that coherent activity is present is an indicator of the cognitive load that the neural system is processing at a given time. Extended coherent phase shift durations are suggested to represent the recruitment of larger populations of neurons for processing power. Their model suggests that an increased time range of significant coherence may be a sign of

having fewer cognitive resources available for use in subsequent moments (Thatcher, 2012, Thatcher et al., 2008).

As explained in the review above, ANSD is a disorder that is characterized by a lack of neural synchrony in the brainstem (as evidenced by ABR results). It stands to reason that this dys-synchrony will be measurable at the level of the cortex, which is essential for speech and language acquisition. Given the challenges of obtaining valid behavioral data to guide treatment decisions in this population, and the illustrated importance of phase synchrony for many perceptual and cognitive tasks, it is important to have additional measures available to quantify and characterize the severity of dys-synchrony in patients with ANSD. The current study will examine the utility of phase synchrony measures (specifically ITC) as a tool to describe synchrony at the cortical level in the ANSD population.

CHAPTER 2

PURPOSE AND SPECIFIC AIMS

2.1. Purpose of the Study:

The overall purpose of the study is to examine cortical functioning in children with auditory neuropathy spectrum disorder (ANSD). A two-fold approach will be used: in a first experiment, dense-array EEG will be used to assess cortical maturation and phase synchrony in detail in a school-aged child with unilateral ANSD. This experiment will establish the feasibility of this approach, and refine the analysis parameters for a second, larger study, which will focus on cortical phase synchronization to speech. In the second experiment, inter-trial coherence, a measure of cortical phase synchrony, will be assessed in 91 children with ANSD and compared with 41 children with normal hearing and 50 children with sensorineural hearing loss. The results of the second experiment will provide new evidence regarding the impact on dys-synchrony on cortical functioning in children with ANSD.

2.2. Specific Aims:

Experiment 1:

Specific Aim 1: The aim is to examine cortical maturation and phase synchrony using dense array EEG elicited by a speech sound stimulus in a single pediatric subject with unilateral ANSD.

Hypothesis: Unilateral ANSD will result in abnormal cortical maturation and low phase synchrony in cortical responses.

Experiment 2:

Specific Aim 2: The aim is to describe the normal range of cortical phase synchrony (as measured by inter-trial coherence, or ITC) over the first decade of life and to assess whether phase synchrony is affected by age/development in normal hearing children.
Hypothesis: Cortical phase synchrony is not affected by developmental age changes in childhood.

Given that cortical potentials for normally hearing infants are as robust and well formed relative to normally hearing adults, there is no *a priori* reason to believe that phase synchrony will vary with age or development in single-channel data.

Specific Aim 3: The aim is to measure the degree of cortical phase synchrony in a large group of pediatric patients with ANSD relative to normally hearing peers.
Hypothesis: Children with ANSD will demonstrate less cortical phase synchrony than children with normal hearing.

It is expected that some level of cortical phase synchrony will be present in the EEG recordings from ANSD subjects. However, given that all patients with ANSD demonstrate dys-synchrony at the brainstem level, it is expected that dys-synchrony will also be apparent at the cortical level for these patients.

Specific Aim 4: The aim is to compare cortical phase synchrony in children with ANSD to phase synchrony in other comparable populations, such as children with sensorineural hearing loss (SNHL).

Hypothesis: Children with SNHL will demonstrate higher levels of cortical phase synchrony than children with ANSD.

Since ANSD is described as a disorder of neural timing, it stands to reason that children with ANSD would have decreased phase coherence values in comparison to children with SNHL who do not have underlying synchrony disruptions.

Specific Aim 5: The aim is to describe cortical phase synchrony changes in children with ANSD who receive interventions via hearing aids and/or cochlear implants, and to determine the effect of intervention of phase synchrony.

Hypothesis: Cortical phase synchrony will increase in children with ANSD after intervention with cochlear implants, as compared to those receiving hearing aids.

It is expected that cochlear implants in particular may introduce synchrony into a previously asynchronous neural system, and that the increase in synchrony will be measurable at the cortical level.

2.3. Scope and Limitations of the Study

The scope of this study is to examine cortical development and functioning by measuring cortical phase synchrony to a speech sound in children ranging from 1 month to 16 years of age with normal hearing, sensorineural hearing loss, or ANSD. Time-frequency analyses will be applied retrospectively to existing EEG recordings from a large database of children who have been tested as part of ongoing research on auditory cortical development.

The retrospective nature of this research is one major limitation of the study. The data used were collected over a period of many years, as part of ongoing cortical

development research in the Brain and Behavior Laboratory at the University of Colorado. Therefore, the data are limited to what was already collected and available.

2.4. Human Subjects Assurances and Protection

The research protocols are concordant with procedures to ensure human subjects' protection. All data were collected in accordance with HRC/IRB protocols, including appropriate informed consent procedures and data management. All data analysis proceeded according to these approved HRC/IRB protocols.

CHAPTER 3

EXPERIMENT 1 BACKGROUND

Auditory Neuropathy Spectrum Disorder (ANSD) is a recently documented form of hearing loss. However, it is not a rare form, and is estimated to be present in 10 - 15% of sensorineural hearing loss (SNHL) cases (Talaat et al., 2009). A number of characteristics are associated with a higher risk of pediatric ANSD. These include, but are not limited to: premature birth, low birth weight, hyperbilirubinemia, prenatal infection, exposure to ototoxic medications, and complex syndromic conditions (Beutner et al., 2007, Dowley et al., 2009).

Diagnosis of ANSD is most often accomplished by the acquisition of an absent auditory brainstem response (ABR) which reveals a cochlear microphonic (Berlin et al., 1998, Berlin et al., 2003). In many patients there are evoked otoacoustic emissions (OAEs) present, despite the abnormality or absence of an auditory brainstem response (ABR). Acoustic reflexes are found to be abnormal (Berlin et al., 2005), and efferent suppression of transient evoked otoacoustic emissions appears to be reduced in patients with ANSD (Hood et al., 2003). Thus, cochlear outer hair cell function is assumed to be normal, with a site of lesion occurring at the inner hair cell/VIII cranial nerve level and possibly higher in the auditory pathway (Ptok, 2000, Gibson and Sanli, 2007, Rance and Aud, 2005).

Geneticists have found a disruption of a gene responsible for the expression of otoferlin (OTOF) protein in individuals presenting with ANSD, which affects transmitter release in the inner hair cells of the cochlea (Varga et al., 2006, Varga et al., 2003).

Other mechanisms that may contribute to ANSD include demyelinating disorders or axonal loss, or spiral ganglion cell disorders (Starr et al., 2003, Starr et al., 1996).

Neural dys-synchrony in the central auditory system is a major characteristic of ANSD. Patients show clear abnormalities in subcortical afferent conduction demonstrated by a lack of synchrony in the ABR. In order to produce a normal ABR, VIII nerve and brainstem neural populations have to be synchronously active (Kraus et al., 2000). This does not occur in patients with ANSD; rather, these populations of neurons are activated in a dys-synchronous manner or with atypical patterns of neural synchrony resulting from a possible loss of fibers, constant or variable slowing of fibers, or demyelination. For example, using a computer model of ANSD that summed the action potentials from 1,000 individual fibers, Starr, Picton and Kim (2001) described patterns of dys-synchrony resulting from consistent or variable slowing of fibers, loss of fibers and a combination of slowing and axonal loss. If the auditory nerve is demyelinated in ANSD patients, the slowing of the action potential along axons that have varying degrees of myelination may disrupt synchrony directly. In addition to slowing, axonal loss in these patients may be responsible for a loss of intensity encoding and temporal processing (Starr, 2001). For example, the "volley theory" describes a process in which multiple neurons could encode a rapid temporal envelope through firing at different rates (Edgerton and Doyle, 1982). Axonal loss and demyelination would disrupt the volley process, both through unpredictable slowing of the action potential along nerve fibers and a lack of fibers to carry the signal of interest.

Despite absent or atypical ABR responses, cortical responses can be obtained in patients with ANSD. It appears that less synchrony is required for the acquisition of

these potentials (Kraus et al., 2000). During development, cortical organization and functioning are influenced to a large extent by the pattern of the incoming sensory input (Sur, 1988, Lyckman and Sur, 2002, Pallas, 2001). Therefore, subcortical afferent transmission to the cortex that is disorganized (due to the underlying neural dys-synchrony at the level of the brainstem) has the potential to disrupt normal cortical development. This is confirmed by recent studies (Sharma et al., 2011, Rance et al., 2002), which have shown abnormal cortical responses in a majority of children with ANSD. However, these studies used single (or relatively few) channels for their evoked potential recordings. To date, there are no studies that have employed modern high-density EEG methods or functional brain imaging technology to examine in greater detail the deficits in cortical development in children with congenital ANSD.

It has been proposed that the severity of the underlying neural dys-synchrony, rather than the severity of the hearing loss, is a major factor in the behavioral outcome of individual patients (Sharma et al., 2011, Rance et al., 2002). Unlike individuals with SNHL, whose perceptual abilities and behavioral outcomes are significantly influenced by their degree of hearing loss, patients with ANSD often show little or no correlation between behavioral abilities and hearing thresholds (for a review, see Rance and Aud, 2005). Speech perception results are often poorer than expected for a given amount of hearing loss, and behavioral audiometric results can be highly variable, ranging from mild to profound hearing losses (Cone-Wesson, 2004, Doyle et al., 1998, Rance et al., 2007a, Zeng and Liu, 2006, Starr et al., 1996). Further, there are anecdotal reports of some patients appearing to have “good” and “bad” hearing days. On some days, the patient demonstrates an ability to hear, while on other days the same patient behaves

as if he/she were completely or partially deaf. One study has documented fluctuating hearing losses in patients with ANSD that correspond to rises in body temperature (Starr et al., 1998). Thus, a major clinical characteristic of ANSD is the high degree of inter- and intra-individual variability, which most likely reflects the underlying severity of the neural dys-synchrony.

Neural dys-synchrony at the level of the auditory nerve and brainstem also affects stimulus processing at the level of the auditory cortex (Eggermont, 2007, Japaridze et al., 2002, Robinson and Rudge, 1980, Arrondo et al., 2009). One likely result of dys-synchronous subcortical neural firing will be increased variability in cortical responses (Mazurek and Shadlen, 2002, Lyckman and Sur, 2002, Wang et al., 2010, Stevens and Zador, 1998). EEG measures are often useful in evaluating individual variability in cortical responses. For example, use of time-frequency analyses and inter-trial coherence in EEG allows us to examine phase synchrony and phase locking, which may be a good indicator of neural synchrony in ANSD (Rance et al., 2004, Lachaux et al., 1999). However, to date, there are no reported studies that have examined individual variability in cortical responses in children with ANSD.

Thus, as described above, the disruptions in neural synchrony will affect both cortical organization and functioning. Given that the heterogeneity of the ANSD population often makes it difficult to generalize across patients, case reports are relatively common in the ANSD literature (Stuart and Mills, 2009, Simmons and Beauchaine, 2000, Pearce et al., 2007, Podwall et al., 2002, Cianfrone et al., 2006, Kraus et al., 2000). In this paper, we describe a pediatric case of congenital unilateral ANSD in whom we performed high-density EEG to examine (i) the development and

organization of auditory cortical areas and (ii) the neurophysiological variability underlying cortical responses. The goal was to use high-density EEG to better understand the relationship between cortical functioning and behavioral outcome in pediatric ANSD.

CHAPTER 4

EXPERIMENT 1 METHODS

4.1. Participant History and Audiometric Testing

The subject was a 9-year-old female with a unilateral hearing loss in the left ear that was diagnosed at birth. At the age of two months (and confirmed in later testing), transient evoked otoacoustic emissions were found to be normal in each ear. Auditory brainstem response (ABR) testing revealed normal responses from the right ear, while no responses were obtained for the left ear at the output limits of the equipment. No information on the presence or absence of a cochlear microphonic was reported. The subject had no outer or middle ear abnormality. After consideration of the normal OAE results, and abnormal ABR results, the subject's unilateral hearing loss was clinically diagnosed to be due to ANSD.

Behavioral audiometric results confirmed that the subject's pure tone thresholds for the right ear are within the normal range, while the left ear presents fluctuating pure-tone thresholds with pure tone averages (at 500Hz, 1KHz and 2KHz) ranging from 45 to 57 dB HL over a 5 year period. Pure tone averages may not be the best measure of change, however, since the greatest threshold shifts have occurred from 2000-8000 Hz. A 35 dB change at 2000 Hz was particularly drastic. Speech perception scores have also ranged from 36% to 80%. The worst pure tone averages have not corresponded to the worst speech perception scores (for example, the highest speech performance score was obtained with the second-worst pure tone audiogram). This variability is consistent with the reports of intra-individual variability in ANSD. The subject has never

worn hearing aids or used assistive listening devices to compensate for her hearing loss in the left ear.

This study was approved by the Institutional Review Board at the University of Colorado at Boulder, and all appropriate informed consent documents were reviewed and signed prior to testing at the Brain and Behavior Laboratory.

4.2. Speech Testing

A clinical test of speech perception in quiet, the Lexical Neighborhood Test (LNT-W, hard list), was performed in quiet to assess the subject's word recognition ability. The word lists were presented with insert earphones, at a level comfortable for the listener (approximately 70 dB HL). The BKB-SIN (Etymotic Research, 2005) was administered to assess her ability to understand speech in noise. The sentence lists were administered directly in front of the patient (0 degrees azimuth), at a presentation level of approximately 70 dB HL, with noise and speech presented from the same speaker.

4.3. EEG Testing

The patient was seated in a comfortable chair. A cap with 64 sintered Ag/AgCl electrodes was used for the collection of EEG waveforms. EEG recordings were made using a Neuroscan SynAmps2 system. Electrode placement on the cap was based on the extended International 10-20 system (Oostenveld and Praamstra, 2001). Ocular movements were monitored with electrodes placed at the lateral canthus and superior orbit positions around the eye. Most of the electrodes had impedance values of less than 5.0 ohms. The filter settings for the recordings were 0.1 – 100 Hz, with an acquisition sampling rate of 1000 Hz. The stimulus used was the speech sound /ba/,

with a length of approximately 97 ms and a 610 ms interstimulus interval. The stimulus was presented with insert earphones at a comfortable listening level for the patient (approximately 70 dB SPL for the right side, and 80 dB SPL for the left side). The methods we describe above, and the /ba/ stimulus, have been used in other studies produced in this lab (Sharma et al., 2005, Sharma et al., 2002c, Sharma et al., 2002b).

4.4. Data Analysis

P1 cortical auditory evoked potential (CAEP)

The continuous EEG data was visually scanned for evidence of muscle artifact and bad electrodes. Sections of recording with large amounts of muscle artifact and recordings from electrodes with high impedance were removed from further analysis. Eyeblink artifacts were removed via a spatial filter, using a linear derivation based upon the average eyeblink. The continuous EEG recording was epoched into windows of -100 to 600 milliseconds around each presentation of the stimulus, and these epochs were baseline corrected. To visualize the overall P1 CAEP response, the epochs were averaged. Methods used were similar to other high-density EEG studies (Gilley et al., 2006, Gilley et al., 2008).

Dipole Source and Current Density Analysis

In order to localize sources of EEG activity in response to auditory stimulation, we performed dipole source analysis and current density analysis. Dipole source analysis was performed using Curry 6.0. A BEM model was used for the analysis, with mirrored placement of the dipoles. The unfiltered, averaged waveforms from each ear

(which included the analysis steps described in section 4.4) were imported into the program. Activations were clipped to 80% power.

Current density analyses were performed using the SWARM (sLORETA weighted accurate minimum norm) algorithm available in the Curry 6.0 software. sLORETA analysis uses the inverse solution to present an image representing normalized probability of cortical activity in specific areas (see Wagner et al., 2007). It is a statistical map of distributed F-values. SWARM differs from sLORETA in that, rather than reporting a statistical map of F-values, it uses the Minimum Norm Least Squares method to convert the sLORETA values back into a current density vector field. SWARM reconstructs current densities, while sLORETA produces unitless statistical values.

Independent Component Analysis

In order to further examine the trials that contributed to these EEG waveform averages, we returned to the unaveraged, unfiltered epochs for in-depth analysis. Independent component analysis (ICA) was performed using the Infomax algorithm (Bell and Sejnowski, 1995) as part of the EEGLAB toolbox for MATLAB (Delorme and Makeig, 2004). ICA is a method that attempts to separate spatially and temporally independent sources of EEG activity within the brain. Epoched files from the Neuroscan recordings were imported into MATLAB, and the right and left ear trials were labeled by type and then concatenated. A total of 3753 epoched trials were used for the analysis: 1823 were recorded from the left (ANSD) ear, and 1930 were recorded from the right (normal hearing) ear. Independent component analysis was performed on the

concatenated trials, so that activity sources could be compared across ears. The sampling rate was maintained at 1000 Hz.

Inter-Trial Coherence

Inter-trial coherence (ITC) is a measure of the temporal and spectral synchronization at a particular time and frequency, relative to the baseline period. Significant inter-trial coherence is an indicator of phase locking in the frequency domain. For our analysis, the EEGLAB time frequency transform function was employed. The EEGLAB function calculates the inter-trial coherence (ITC) of a signal (for a review, see Delorme and Makeig, 2004). Performing ITC calculations on components that have been separated by the ICA process eliminates the confounds of phase cancellation, as each component could be considered to represent a distinct physiological process that contributes to the overall response (Makeig et al., 2004).

Images produced with ITC analysis indicate the level of synchronization and phase locking as a result of these events. Since ITC is performed on the components produced through ICA, the ITC plots could be viewed as a decomposition of the phase components that contribute to the overall ERP response. The colored pixels in this case represent correlation values between trials: a value of 1 would represent perfect synchronization, and 0 would indicate no synchronization at all. For examples of ITC plots, please see Figures 6A and 6B in Experiment 2.

CHAPTER 5

EXPERIMENT 1 RESULTS

5.1. Speech Perception

Speech in quiet

In the normally hearing right ear, the patient obtained a score of 92% correct for the LNT-W test. In the ear with ANSD, the score was 32% correct. When she listened binaurally, she acquired a score of 100%.

Speech in noise

The BKB-SIN is a threshold test where the SNR-50 score corresponds to the signal to noise ratio (in dB) needed for 50% correct responses. For the normally hearing right ear, and in the binaural condition, the average age-corrected SNR-50 was 1.2. A score in the range of 0-3 corresponds to the ability to hear as well or better than normally hearing listeners in the presence of noise. For the left (ANSD) ear, the average age-corrected SNR-50 was 19.2. Any score that is greater than 15 is indicative of a severe level of difficulty listening in noise.

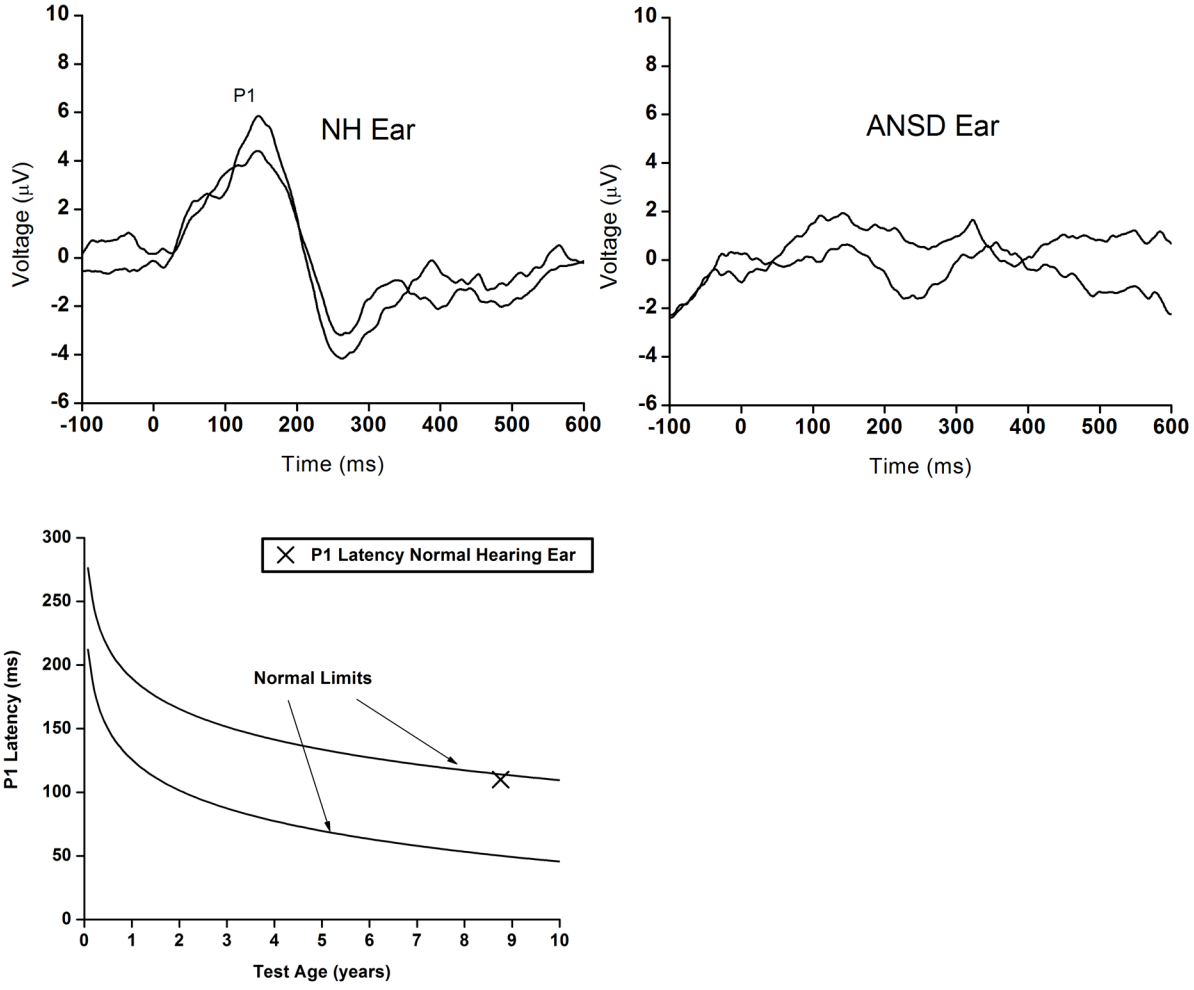
5.2. P1 CAEP Results

A robust, replicable P1 CAEP response of normal morphology was identified for the NH ear. The morphology of the response obtained for the ANSD ear was abnormal; the response was not replicable, and the response amplitude was low in comparison to the normal hearing side. Intra-class correlations between runs were computed to be 0.95 for the normal hearing ear, and only 0.44 for the ANSD ear. Responses for both ears are shown from the FCz electrode (referenced to linked mastoids) in Figure 1. The

amplitudes for the largest positive peaks in two averaged runs for the normal hearing ear were between 4 and 6 microvolts, and in the ANSD ear were less than 2 microvolts. The latency of the P1 response in the NH ear was compared to the 95% confidence interval for normal development P1 responses from Sharma et al. (2002b). As can be seen in Figure 1, the latency of the P1 response from the NH ear was within normal limits.

Figure 1: P1 CAEP Results for the Normal and ANSD Ears

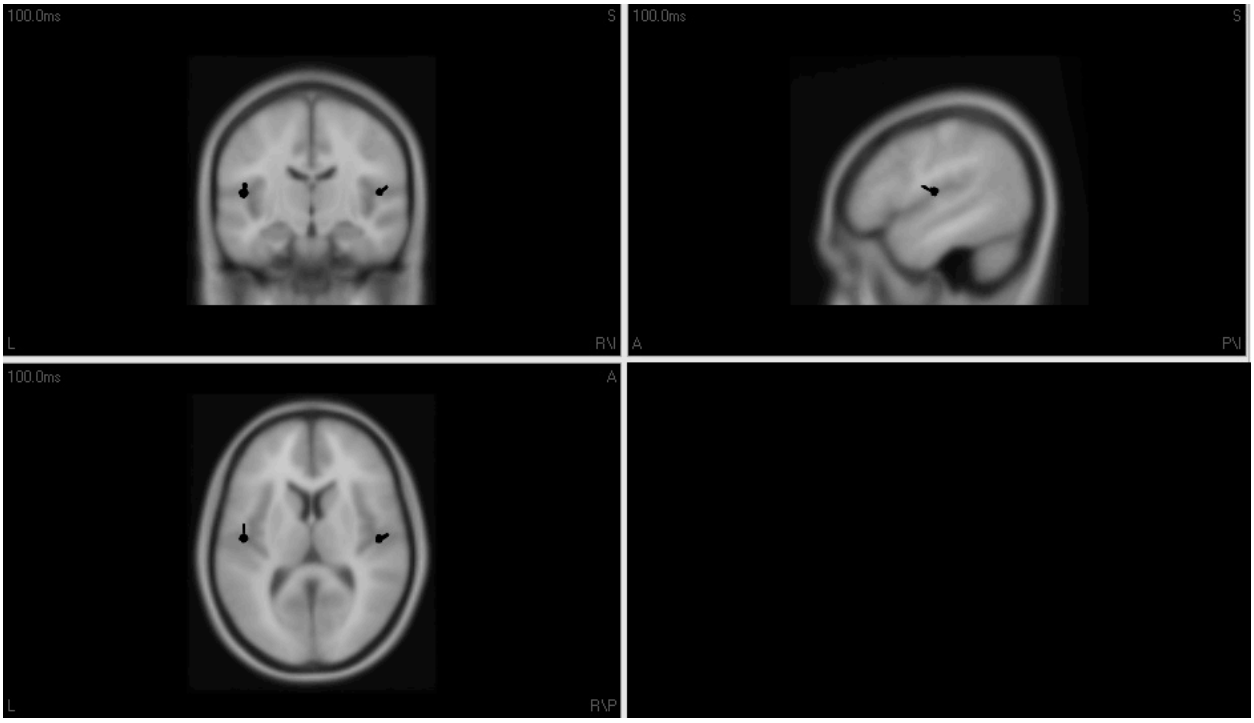
The panel on the upper left includes the P1 CAEP waveform replications for the normally hearing ear, and the panels on the upper right include the P1 CAEP waveform replications for the ANSD ear. The lower left panel is a plot of the P1 latency for the normally hearing ear, as compared to age-related norms. The P1 latency for the normally hearing ear falls within the high end of the normal range. No reliable P1 was observed for the ANSD ear.



5.3. Dipole Source Analysis Results

Dipole source analysis for the NH ear revealed regional dipoles located within the auditory cortex, bilaterally. MNI (X, Y, Z) coordinates were recorded at (-46.7 mm, -13.1 mm, and -0.8 mm) for the left hemisphere, and (47.8 mm, -13.1 mm, and 0.48 mm) for the right hemisphere. Figure 2 depicts the dipole source solutions obtained for the normally hearing ear. Dipole source solutions for the normally hearing ear localized to the auditory cortices (STS and insula), bilaterally.

Figure 2: Dipole Source Analysis Results

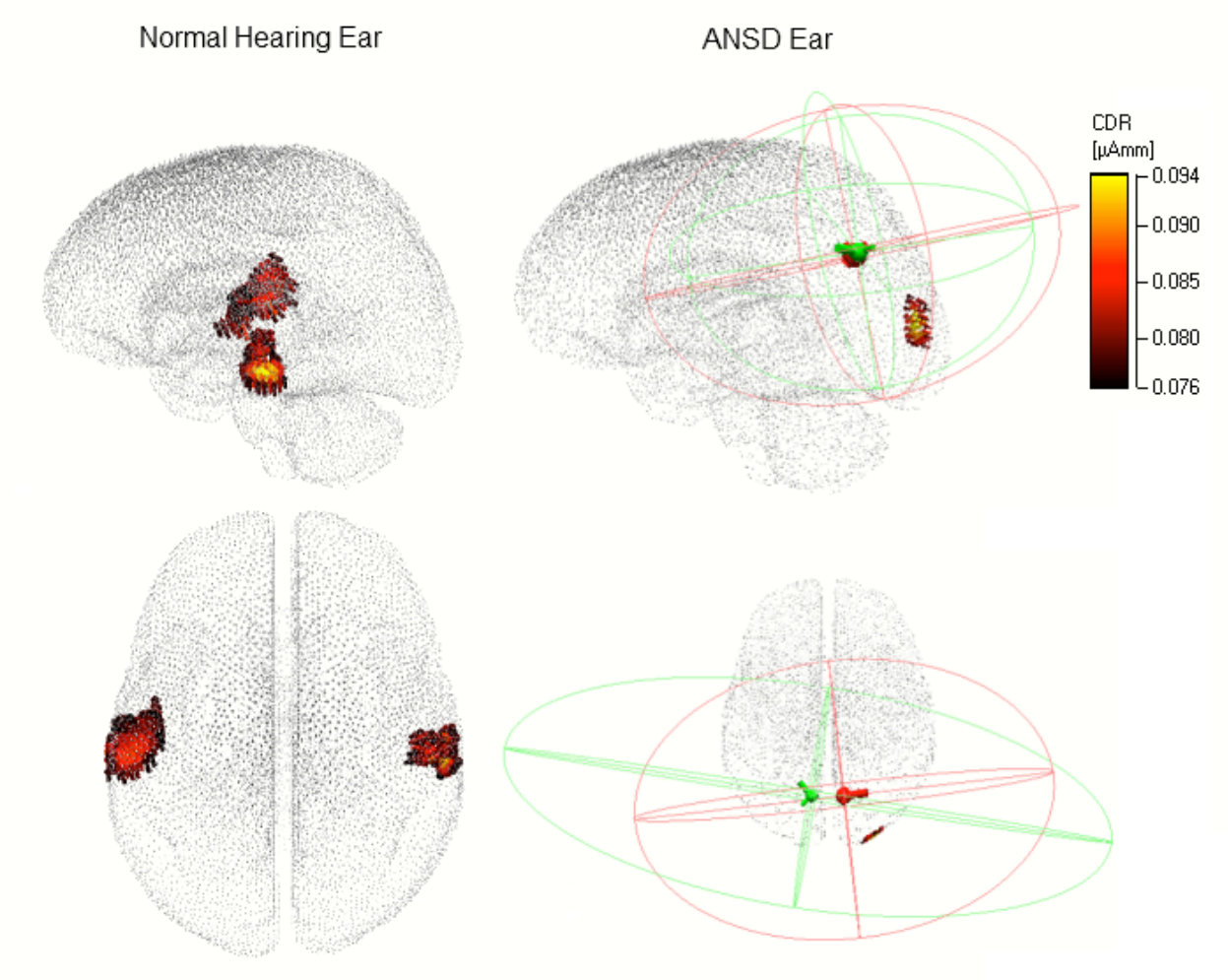


No valid dipole source analysis for the left (ANSD) ear could be completed, due to the lack of synchrony in the data for that side. When attempting to fit a model to the ANSD side, dipoles localized to ventricular areas in the far posterior areas of the brain. Confidence ellipsoids for the ANSD side were very large, indicating a poor level of accuracy in placing dipoles for that side.

5.4. Current Density Results

The left panels of Figure 3 show the results of using the SWARM analysis for current density reconstruction on the NH ear. Leadfield projections were used to create a translucent brain image, with areas of activation and current density values indicated by the colored areas in the auditory cortices (STS and insula), bilaterally. Activity for the normal hearing ear localized to the auditory cortices, bilaterally. Views represented are left and top. Areas of activation for the normal hearing ear corresponded well to the dipole sources noted in Figure 2. The variability of the response from the ANSD ear precluded valid current density analysis in the ANSD ear (see right panels, Figure 3).

Figure 3: SWARM Current Density Results



SWARM current density analysis for the normally hearing ear revealed activation in the superior temporal sulci (STS) and insula, bilaterally. No valid solution could be obtained for the ANSD ear (note the very large confidence ellipsoids).

5.5. Independent Component Analysis and Inter-Trial Coherence Results

ICA produced statistically independent component sources, which could be considered as separate contributors to the overall waveform recordings. These independent components represent distinct sources within the brain, describing the complex processes that underlie an averaged response. Since dipole source and

current density analyses were unsuccessful in the ANSD ear, we wished to determine whether there might be underlying information to indicate that the cortex was responding to acoustic stimuli presented in the ANSD ear.

Components were compared in the ANSD ear and normal hearing ear. Components 1-4 described 66.04, 12.31, 8.21, and 5.33 percent of the variance respectively. Figure 4 shows scalp maps, stacked trials, and averaged responses for Component 1, which describes the largest portion of the variance. Beneath each set of stacked trials are inter-trial coherence values for that point in time. Figure 5 shows the peak ITC values for components 1-4 for each ear.

Figure 4: Scalp Maps, Stacked Trials, and Inter-Trial Coherence for Each Ear

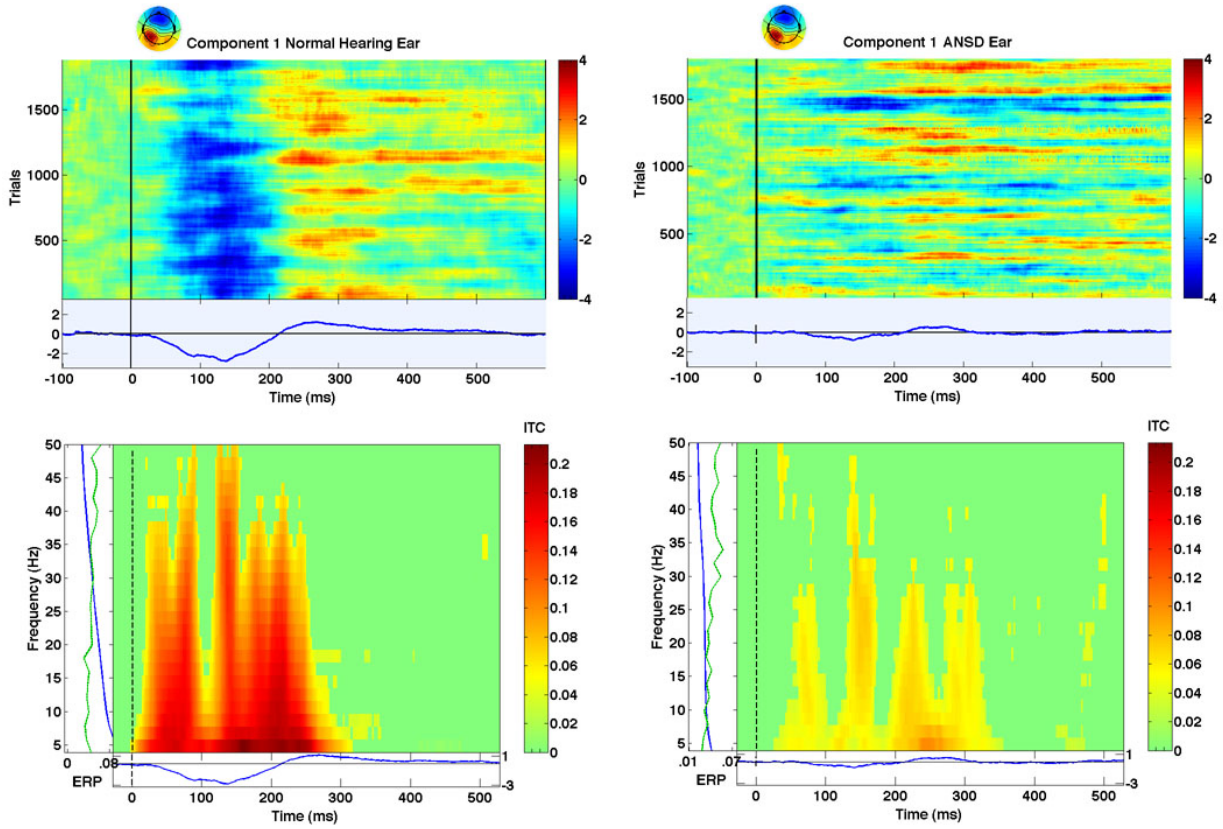


Figure 4 includes scalp maps, stacked trials, and inter-trial coherence measures for the component that describes the largest portion of the variance. The scalp maps (in circles above the panels) are the same for each ear (since they are from the same component for each ear). The upper panels show the stacked trial activations for each ear (the normally hearing ear is on the left, and the ANSD ear is on the right), and the corresponding ITC values are shown in the lower panels. Strong yellow and red colors in the ITC plot indicate a significant level of coherence ($p<0.01$) for the frequencies and time periods indicated on the X axes.

The first column of panels in Figure 4 shows the component activations and inter-trial coherence results for the NH ear. Results can be compared to the second column of Figure 4, which contains component activations and inter-trial coherence results for the ANSD ear. For the stacked trial panels (the upper rectangular panel for each ear), each trial is represented by a line of color to indicate strength of activation as deviations from the baseline period (-100 to 0 milliseconds). These trial lines are stacked along the Y-axis. Polarity differences and strength of activation (in RMS microvolts) are indicated by color: positive activity is in red, while negative activity is in blue. When stacked, the colored lines give an indication of the consistency of the response over time. When examining the stacked trial panels visually, the normally hearing ear has more time-locked, consistent activations for each component (as indicated by the strongly colored blue or red columnar areas in the upper panels of the first row of Figure 4), while the ANSD ear has components with more inconsistent, temporally smeared activation.

Stacked component trials are supported by the inter-trial coherence values calculated for each component and each ear. Time-frequency analyses were performed for the four components, and the analysis for Component 1 is shown in Figure 4. Green areas within the plots are indicative of p values that are >0.01. Areas of the plot that deviate from green are significantly different from baseline ($p<0.01$). Inter-trial coherence was much stronger for the normal hearing side, with higher values indicated by the strong red colors in the ITC panels of Figure 4. These higher values show a greater level of synchronization between trials for the normal hearing side. In every instance, the inter-trial coherence remained low in the ANSD ear when compared

to the normally hearing ear (revealing a lack of synchronization, most likely reflecting induced activity).

Figure 5: ITC Values For Components 1-4

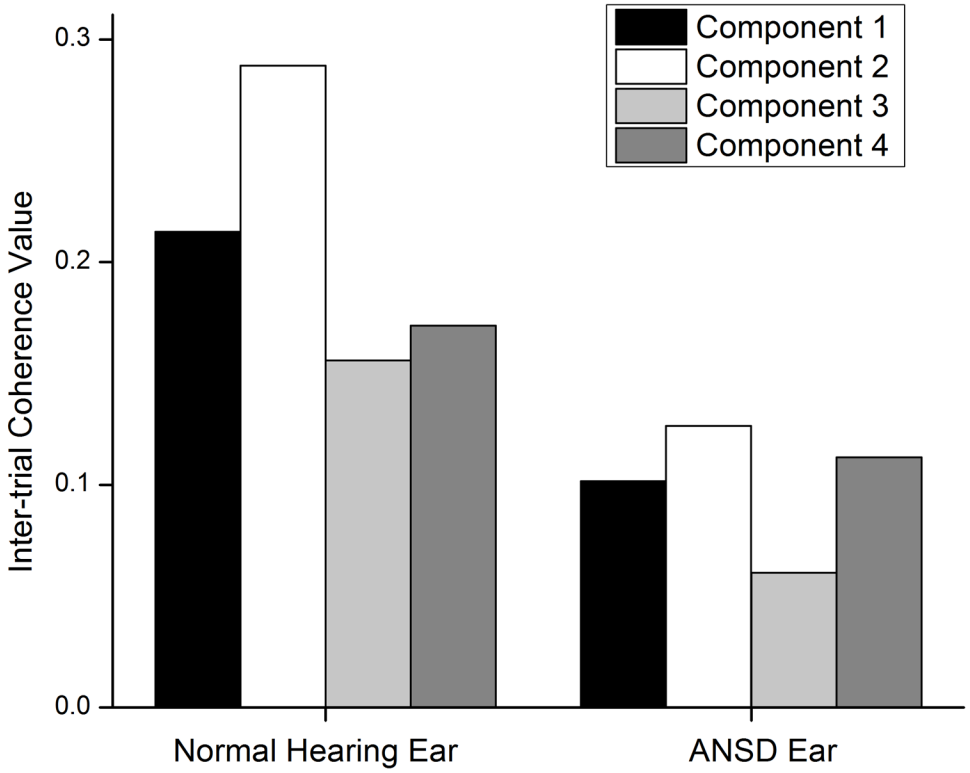


Figure 5 shows peak ITC values for the four components that described the largest portion of the variance. The normal hearing ear had consistently higher peak ITC values than the ANSD ear for each of the four components.

CHAPTER 6

EXPERIMENT 1 DISCUSSION

In this study, we examined auditory cortical organization, underlying neurophysiologic variability, and cortical phase coherence in a pediatric patient with congenital unilateral ANSD. Speech perception testing in quiet and in noise revealed normal, age-appropriate performance in her NH ear. These results are consistent with her functioning in everyday life. She attends a regular elementary school and does well in class according to parent report. These results are also consistent with reports of children with unilateral sensorineural hearing loss or ANSD which suggest that normal hearing in one ear may be sufficient for oral language learning, although subtle deficits may be present (for a review, see Tharpe, 2008). In the ANSD ear, although her hearing loss is generally in the moderate range, we observed a severe to profound deficit in speech perception performance (32% in quiet on the MLNT and a 19.2 dB signal to noise ratio for 50% accurate performance on the BKB-Speech in Noise test). The patient has a fluctuating hearing loss in her left ear; therefore, we had ascertained that the presentation level was comfortable and that the sounds were clearly audible to her in that ear. Our results are consistent with other studies, which have demonstrated a lack of correlation between pure tone audiometric thresholds and speech perception performance in these patients. Our results are also consistent with other reports of near universal difficulties of processing speech in noise for patients with ANSD (Berlin, 2010, Kraus et al., 2000).

6.1. Cortical Auditory Development and Organization

The latency and morphology of the P1 CAEP waveforms corresponded well to behavioral speech testing results for the NH and ANSD ears. Latency of the P1 CAEP in children is considered a biomarker for maturation of the auditory cortical areas (Sharma, 2005, Sharma et al., 2002b, Sharma et al., 2002c), given that neural generators of the P1 include recurrent activity in the auditory cortex which is modulated by feedback and recurrent loops between primary auditory and association areas (Kral and Eggermont, 2007, Eggermont and Ponton, 2003). As expected, P1 latencies recorded from the NH ear of our patient were age-appropriate. On the other hand, we were unable to elicit replicable P1 responses of normal morphology when stimuli were presented to the ANSD ear (Fig 1). The abnormal CAEP response in the ANSD ear is consistent with recent studies, which have shown that as many as 29 to 50% of children with ANSD do not show replicable P1 responses (Sharma et al., 2011, Rance et al., 2002). Consistent with the present results of an abnormal CAEP and poor speech perception performance in the ANSD ear, abnormal P1 responses have generally been correlated with poor speech perception outcomes in children with ANSD (Michalewski et al., 2009, Sharma et al., 2011, Rance et al., 2002).

As can be seen in Figure 2, dipole source and current density reconstruction results revealed bilateral activation of auditory cortical areas (STS and insula) in response to stimulation of the NH ear. These results are consistent with a previous study in NH children of comparable age which used the identical stimulus and recording procedures (Gilley et al., 2008). However, it is interesting to note that the Gilley study analyzed group data, while the present results are in an individual subject, suggesting

that these analysis techniques may be useful for examining cortical activation in individual patients with hearing loss and ANSD (Debener et al., 2008). When the ANSD ear was stimulated using a speech sound /ba/, we were unable to obtain dipole solutions or current density reconstructions (Figure 3). That is, the magnitude of the variance was so large that the activity could not be constrained to a particular source in a reliable manner.

Taken together, the P1 CAEP and dipole/current density results suggest that normal sensory input is necessary for the central auditory pathways to develop normally. When the auditory cortex receives an abnormal pattern of input (in this case, resulting from the underlying neural dys-synchrony which characterizes ANSD), then cortical development proceeds in an abnormal fashion, resulting in a fundamental re-organization of cortical areas. Gilley et al. (2008) have described a pattern of cortical re-organization that occurs in long-term deafened children who are given a cochlear implant at a late age. Using identical stimuli and recording procedures to the present study, Gilley and colleagues reported that long-term absence of auditory stimulation to the cortex resulted in activation of multisensory (e.g., parietotemporal) areas. Since we were not able to obtain valid dipole solutions for the ANSD ear in our study, the exact manner in which the cortex gets re-organized in ANSD remains unclear. However, at the very least, our results suggest that auditory stimuli may not activate auditory cortical areas in an appropriate manner in some cases of ANSD. Moreover, unlike in long-term deafened children, we did not see clear activation of non-auditory or multisensory areas.

Our results suggest that the subcortical processing of acoustic stimuli may be so degraded, due to dys-synchronous neural firing, that signals reaching the cortex may be

too weak to engage appropriate cortical processing (Starr, 2001, Eggermont, 2007). In long-term deafness, it has been proposed that lack of sensory stimulation results in a decoupling of primary and higher order cortical areas, leaving higher order areas open to cross-modal reorganization (Sharma et al., 2009). In future studies, we will examine whether cross-modal plasticity is a factor in cortical re-organization in ANSD.

6.2. Phase synchrony in ANSD.

Given that neural dys-synchrony at the level of the auditory nerve and brainstem is a major characteristic of ANSD, it stands to reason that asynchronous neural input to the cortex results in increased variability in encoding and processing of stimuli at the cortex (Mazurek and Shadlen, 2002, Lyckman and Sur, 2002, Wang et al., 2010, Stevens and Zador, 1998). Conversely, it may be assumed that the extent of variability in cortical phase synchrony (as measured by ITC) may be an indicator of the extent of the disruption in underlying neural synchrony. It would be clinically useful if we were able to use cortical responses to get an indirect indication of the severity of neural dys-synchrony in individual patients with ANSD. However, most studies so far have relied on examining aggregate cortical responses. Averaged waveforms are assumed to be representative of a consistent neural response over time. In reality, the individual trials that contribute to an averaged waveform may vary in latency, morphology, and amplitude. Latency jitter, when averaged, may reduce the amplitude of a waveform and distort the overall morphology (Brazier, 1964). Information about induced (oscillatory) activity within the brain is lost in averaging, due to phase cancellation (Gilley and Sharma, 2010). In short, averaged waveforms do not account for variations in neural processes, many of which may be of particular interest in patients with ANSD.

In this case study, we examined the individual trials that contributed to overall independent component averages (ICA), which in turn contributed to the overall cortical response. Results of ICA, shown as stacked trials in Figure 4 (upper panels), revealed that the evoked activity from the normal hearing ear had more time-locked, strongly activated EEG components as compared to the ear with ANSD. The time-frequency analysis results indicated a difference between ears. As seen in Figure 4, the time-frequency analysis of phase synchrony (as measured with inter-trial coherence) confirmed in the frequency domain the greater variability that was noted in the ICA stacked trial results (which are analyzed using the time domain). As shown in Figure 4 (lower panels) inter-trial coherence values were higher in the NH ear relative to the ANSD ear. These data were useful as additional confirmation of the difference in cortical phase synchrony resulting from underlying neural dys-synchrony between the normally hearing and ANSD ears. While we are cautious in our interpretations since our findings are from a single patient, it is plausible that single trial stacked responses and time-frequency inter-trial coherence analyses may be useful indicators of disruption of neural synchrony in patients with ANSD. It would be of interest to perform these analyses longitudinally in ANSD patients who receive intervention with amplification or cochlear implants, to examine whether any increase in neural synchrony results from these interventions and is reflected in their EEG.

6.3. Summary and Conclusions for Experiment 1

In a pediatric patient with unilateral congenital ANSD, we demonstrated that:

1. Speech perception in quiet and in noise were age-appropriate for the NH ear but showed a severe deficit for the ANSD ear, inconsistent with pure tone thresholds in that ear.

2. The P1 CAEP biomarker of cortical maturation was normal in the NH ear and atypical in the ear with ANSD, corresponding well with the behavioral speech perception results.

3. Dipole source and current density analysis revealed activation in the auditory cortices, bilaterally, for the normal hearing ear. No valid source localization analysis could be completed for the ANSD ear.

4. Independent component analysis and results of the stacked trials analyses indicated that the evoked activity from the normal hearing ear had more time-locked, strongly activated EEG components, as compared to the ear with ANSD.

5. Time frequency analysis revealed that inter-trial coherence (ITC) was higher for the normal hearing ear, as compared to the ear with ANSD.

Overall, our results suggest that CAEPs and high density EEG are promising tools for examining cortical development and organization in individual children with congenital ANSD, and these measures may correlate well with behavioral speech recognition. Since this was an exploratory study of only one case, future studies examining group data will be needed before generalizable statements can be made. Single trial and time-frequency analyses such as inter-trial coherence may provide specific information about the cortical phase coherence in individual ANSD subjects, which may prove valuable in making comparisons between patients in a behaviorally variable population.

CHAPTER 7

EXPERIMENT 2 BACKGROUND

Auditory neuropathy spectrum disorder (ANSD) is a recently described disorder, although it is not an uncommon condition. It is estimated that ANSD may be present in 13-15% of infants and children with sensorineural hearing loss (Talaat et al., 2009, Kirkim et al., 2008). While patients with ANSD have essentially normal cochlear function as measured by otoacoustic emissions (OAE) and the acquisition of a cochlear microphonic, neural synchrony is deficient as evident by abnormal or absent auditory brainstem responses (ABR), which is a universally documented result for children with ANSD (Starr et al., 1991, Berlin et al., 1998, Berlin et al., 2003). The degree of hearing loss found in patients with ANSD ranges from mild to profound, and treating ANSD presents a particular challenge to audiologists, as behavioral pure tone thresholds tend to fluctuate, as do speech performance measures (Madden et al., 2002b, Sininger and Oba, 2001, Cone-Wesson, 2004, Doyle et al., 1998, Starr et al., 1996, Zeng and Liu, 2006). In addition, speech performance measures do not necessarily correspond to the levels of hearing loss noted in ANSD patients (Rance and Aud, 2005, Sharma et al., 2011). Therefore, the severity of ANSD may not be related to the severity of the hearing loss and cannot be characterized easily with behavioral measures.

Traditional physiologic measures such as ABR have limited utility in assessing the severity of ANSD since the short latency ABR recordings require very high levels of precisely synchronous neural firing. However, cortical auditory evoked potentials (CAEPs), which occur over much longer latency and are able to absorb greater jitter in the underlying neural synchrony (Kraus et al., 2000, Michalewski et al., 1986), have

been more successfully elicited in ANSD patients (Sharma et al., 2011). Dys-synchronous subcortical firing will result in dys-synchrony at cortical levels (Mazurek and Shadlen, 2002, Lyckman and Sur, 2002, Wang et al., 2010a, Stevens and Zador, 1998), disrupting normal cortical development and functioning that is needed for speech and language acquisition. Studies of cortical development using averaged CAEP responses have shown that CAEPs are a strong predictor of behavioral outcome in children with ANSD (Alvarenga et al., 2012, Campbell et al., 2011, Cardon et al., 2012, Sharma et al., 2011, Rance et al., 2002). However, those studies relied on averaged evoked potential recordings; therefore, they were unable to directly examine underlying cortical synchrony which is assimilated within the aggregate cortical evoked potential response.

Time-frequency analyses adopt a different perspective on the evoked response from the traditional time-only analyses where component peaks are averaged, while the remainder of the evoked potential signal is considered to be noise and disregarded. In time-frequency analyses, the focus is on brain oscillations, which can be detected using a time-frequency decomposition of the EEG. When spontaneous EEG is interrupted by a stimulus event (such as a sound), the distribution of EEG phase becomes “phase-locked” to that event (Makeig et al., 2004) and this phase synchronization of brain oscillations can be determined by computing phase relations across single trials. Phase synchronization of brain oscillations within and between cortical areas is a fundamental mechanism involved in information processing and has been found to be critical for feature-binding and other cognitive processes (Tass et al., 1998, Palva et al., 2005). Inter-trial coherence (ITC) is a measure that is computed from single trial EEG, which

reflects the temporal and spectral synchronization within EEG and thus reflects the extent to which underlying phase-locking occurs, providing valuable information that is not available in the aggregate evoked response waveform (Makeig et al., 2004).

While time-frequency analyses are relatively new, they have been used in recent studies to examine auditory development and processing. Studies of central auditory maturation have shown that there is an increase in stimulus induced phase synchronization in NH children between childhood and adolescence (Bishop et al., 2010, 2011a, Muller et al., 2009). An increase in phase synchrony has been associated with the mismatch negativity event-related potential, which reflects auditory discrimination (Ko et al., 2012). Changes in cortical phase patterns have been described as an important mechanism that allows for accurate speech discrimination - specifically, the intelligibility of syllabic patterns (Howard and Poeppel, 2010 and Luo and Poeppel, 2007). In a recent study from our group (Nash-Kille et al., submitted), we reported decreased cortical phase synchrony to speech presented in the affected ear of a pediatric patient with unilateral ANSD.

It would be useful to have a direct measure of cortical synchrony in children with ANSD, to evaluate the extent of the deficits in cortical phase synchrony associated with auditory processing and the effectiveness of interventions such as hearing aids and cochlear implants in restoring synchrony. In this study, we examined cortical phase synchrony to speech using ITC in children with ANSD who received intervention with hearing aids and cochlear implants. Children with NH and SNHL (who were also fitted with hearing aids and cochlear implants) were evaluated for comparison with ANSD patients.

CHAPTER 8

EXPERIMENT 2 METHODS

8.1. Participants

This was a retrospective study, as the cortical auditory evoked potential data used were collected in the Brain and Behavior Laboratory over a period of 15 years. Data was analyzed from a total of 91 children with ANSD. Since the ANSD population is inherently heterogeneous, a large sample size helped to ensure that individual variations would not be missed. Children with ANSD were further divided into those that received no intervention (NI) or received intervention with hearing aids (HA) and cochlear implants (CI). Forty-one children with normal hearing (NH) were included as controls. Fifty children with SNHL were included, who were further divided into children fitted with HAs or CIs. While efforts were made to include children of similar ages in each group, the data were limited by the retrospective nature of the study. Sample sizes and ages for each group are included in Table 1.

Table 1: Sample Sizes and Ages for Experiment 2

Group	**N**	**Age Range (yrs)**	**Mean Age**	**Median Age**
NH	41	0.1 − 11.1	3.94	2.32
SNHL (HA)	31	0.59 − 14.81	4.23	2.73
SNHL (CI)	19	2.23 − 15.29	6.82	6.05
ANSD (NI)	15	0.21 – 9.95	4.98	5.64
ANSD (HA)	54	0.34 – 11.55	3.42	2.86
ANSD (CI)	22	1.35 – 8.39	4.32	3.75

Each participant with ANSD was confirmed to have been diagnosed clinically through the use of ABR and OAE measures (either through clinician report or access to the tracings). For the children with ANSD with detailed test information (N=65), 100% showed absent or abnormal ABR's with CM reversal (although one CM was unclear, OAE results were available in that case), and 44.3% had present OAE's (either DPOAE or TEOAE). 36.9% were clinically diagnosed as having mild to moderate hearing loss (with unaided pure tone averages of 500, 1000, and 2000 Hz that were less than or equal to 65 dB HL), while 63.1% were diagnosed as having severe to profound hearing loss (with pure tone averages that were greater than 65 dB HL). For ANSD children fitted with hearing aids for whom aided threshold information was available (N=23), average aided thresholds were 43 dB HL. Detailed information about related risk factors and diagnoses were available for 84 of the 91 children included in the ANSD sample. Table 2 includes summaries of the most common risk factors and concomitant diagnoses.

Table 2: Risk Factors and Concomitant Diagnoses for the ANSD Group

Risk Factor or Diagnosis	Percent (N=84)
Prematurity	36.9
Hyperbilirubinemia	26.2
Anoxia at birth or lung disorders	26.2
Neural insult (malformation or injury)	21.4
Exposure to ototoxic medications	16.7
Seizure disorders	10.7
Family history of hearing loss	10.7
Heart disorders	9.5
Syndromic diagnoses	6.0
No reported risk factors/otherwise healthy	11.9

Children with SNHL were confirmed to have been diagnosed clinically through pure tone audiometry and/or ABR measures. Children with sensorineural hearing loss (SNHL-HA and SNHL-CI) had uncomplicated histories in comparison to the children in the ANSD group. Two children in the sensorineural hearing loss groups presented with hearing loss secondary to meningitis, two were affected by congenital CMV, one child had cerebral palsy, and one was diagnosed with perinatal hyperbilirubinemia. One child had a concomitant diagnosis of congenital heart problems.

Each SNHL participant with a hearing aid or cochlear implant had at least 6 months of experience with his or her respective interventions for post-treatment data analysis. Normal hearing participants were confirmed to have normal hearing through

typical audiometric screening methods, with thresholds of less than 15 dB HL in each ear, and no history of previous hearing or speech deficits. All data were collected with appropriate IRB approval and informed consent procedures for human subjects research. Prior to analysis, all data were de-identified and managed with appropriate concern for the confidentiality of information obtained during testing.

8.2. Data Collection

Cortical auditory evoked potentials were recorded on these participants over several years and the procedures are reported in previous studies from our group (e.g., Sharma et al., 2002b,c; 2011). Participants were seated in a comfortable chair or in their parents' laps in a sound-treated booth, and watched a movie of their choice (without sound) during the data collection process, located at 0 degrees azimuth. The synthesized speech stimulus /ba/ was presented in sound field at a level that was comfortably audible for the participant (typically 85 dB SPL/75 dB HL). The stimulus used is identical to that used in other studies from the Sharma lab (Sharma et al., 2002b, Sharma et al., 2002c, Sharma et al., 1997, Sharma et al., 2011). The /ba/ stimulus was 90 milliseconds in length, with voicing for the first 80 milliseconds of the signal. The starting frequencies of F1 and F2 were 234 and 616 Hz, and the center frequencies for the /a/ vowel were 769, 2862, 3600, and 4500 Hz for the formants. The /ba/ was presented with an interstimulus interval of 610 milliseconds at approximately 75dBSPL. Participants who were tested with their HAs and CIs had them set to their usual settings. Audibility was verified by reviewing audiological records and by patient observation during testing. Participants were not given any particular instructions to attend to the stimulus, and in general, attended to the silenced movie instead. At least

two recording sessions of several hundred trials per subject were collected, to determine whether the waveforms were replicable. Enough data were collected to allow for at least 300 trials to remain after artifact rejection techniques.

Evoked potentials were collected using a Compumedics Neuroscan evoked potentials system. Cortical activity was recorded using Ag/AgCl electrodes. For children without CIs, Cz served as the active electrode with the reference on the mastoid or earlobe. In order to minimize the electrical artifact produced by CIs, we recorded responses along the isopotential contour and minimized the artifact using common mode rejection cancellation techniques. An active electrode was placed at Cz and several reference electrodes were placed at locations around the forehead, nasion, orbits, and mastoids. A ground electrode was placed on the forehead. Details of this procedure are discussed in detail in a previous publication by our group (Gilley et al., 2006). Eye blinks were recorded with an electrode at the superior orbit position referenced to an electrode at the lateral canthus.

P1 cortical auditory evoked potential latencies were computed for children with ANSD. These have been reported in previous publications (Sharma et al., 2011 and Cardon and Sharma 2013). As described in those publications, P1s were categorized as having normal latencies, delayed latencies or as being abnormal.

8.3. Data Analysis

Continuous data files were epoched into segments of 700 milliseconds, including a 100-millisecond pre-stimulus interval (-100 to 600 milliseconds). Eye blinks were identified and rejected using a combination of microvolt threshold rejection (+/- 100 microvolts) and spatial filtering (in the case of 64-channel cap data). Epoched files were

averaged and examined for appropriate morphology before using the single trials in additional analysis.

For the purposes of this study and for continuity, Cz referenced to mastoid was chosen as the electrode of interest. The exception to this was the subjects with cochlear implants - for these participants, the electrode with the least visible electrical artifact was used. Determination of the electrode with the least visible artifact was accomplished through the agreement of at least two trained observers. Unaveraged epoched files from each participant were imported into MATLAB using the EEGLAB toolbox, and a time-frequency analysis was performed on the concatenated trials for each individual. Since the EEGLAB program cannot analyze data that include a measurement of zero microvolts at any time within the recording, a small amount (0.00001 microvolts) was added to all microvolt levels to attempt to avoid the potential mathematical error of division by zero. Wavelet length was limited to 0.5 Hz (so, 0.5 Hz at the lowest, and 3.2 Hz at the highest), and the frequency analysis was oversampled with a padding ratio of 4, to give a smoother looking plot. It should be noted that time-frequency analysis of this type has trade-offs for time and frequency resolution: increased resolution in one domain leads to smearing of information in the other. The program divides the recording into sampling bins of 200 time points (from -28.4 ms to 528.4 ms) and 24 linearly spaced frequencies (from 3.9 to 50 Hz). The bootstrap significance level for identifying significant levels of ITC for a given sampling bin was set to 0.01. Inter-trial coherence plots were created, and the peak inter-trial coherence value was identified for the post-stimulus interval.

While some studies identify a particular time or frequency range of interest in ITC results, such as gamma band information to glean information about cognitive function, for the purposes of this study, there was no *a priori* reason to confine the area of interest to a particular window. To date, inter-trial coherence has not been examined in patients with ANSD, so consistent methods have not been established. While it could be argued that phase coherence around specific peaks are of the most interest, since some patients with hearing disorders have abnormal EEG morphology and/or no identifiable peaks whatsoever, the peak ITC value and the overall ITC time and frequency ranges from the larger window provide the most consistent basis for comparison across subjects (Thatcher, 2012, Thatcher et al., 2008).

For this study, peak ITC values were identified from the time-frequency plot as the area of strongest phase coherence. In addition, the time range (in ms) and frequency range (in Hz) for significant ITC were determined for each participant. The criteria used for the selection of this time range were as follows:

1. The largest area of significant ITC was identified (as measured by the number of bins with significant ITC values). If another area of significant ITC with more than 3 bins was within 20 ms of the first, it was included in the measured area.
2. The time range was determined by identifying the earliest and latest points (in ms) at any center frequency that had significant ITC within this area. Subtracting the earliest time point from the latest time point provided the ITC time range (in ms).
3. The frequency range was determined by identifying the lowest and highest center frequencies (in Hz) at any time point within the largest area of significant ITC.

Subtracting the lowest center frequency from the highest center frequency provided the frequency range (in Hz).

8.4. Statistical Analysis

A 95% confidence interval was calculated for the normal hearing group, to establish a normal range for peak ITC, time range of ITC, and frequency range of ITC. Correlations between age and ITC measures were examined for significance in the NH group.

Children with ANSD were divided into subgroups based upon technology intervention type (hearing aid or cochlear implant) and cortical maturation as measured by the P1 cortical auditory evoked potential (Sharma et al., 2011; Cardon and Sharma, 2013): those with normal P1s, those with delayed P1s, and those with abnormal P1s. These groups were compared to each other and to the control groups (NH, SNHL-HA, and SNHL-CI) in a multivariate regression analysis to compare ITC peak values, time ranges, and frequency ranges. Three-frequency (500 Hz, 1 kHz and 2 kHz) pure tone averages (PTA) and speech results (where data were available) were examined for significant bivariate correlations with the ITC measures. As a result of the correlations found between PTA and ITC measures, children with sensorineural hearing loss and hearing aids (SNHL-HA) were also divided into subgroups based upon their audiometric PTA results: a Mild to Moderate group (with PTAs of 65 dB HL or better), and a Severe to Profound group (with PTAs worse than 65 dB HL).

For the multivariate regression analysis, group (or subgroup, as appropriate) were treated as fixed factors, while peak ITC, the range of ITC in ms, and the range of ITC in Hz were treated as dependent variables. Type III Sums of Squares was used to

account for unequal group comparisons. Levene's test for the equality of variances was utilized to determine whether there were significant differences in the homogeneity of variances for each group. Tukey-Kramer HSD pairwise comparisons were used within the analysis to examine differences between groups, including a report of the 95% C.I. for each group. Significant pairwise group comparisons were noted ($p <= 0.05$).

CHAPTER 9

EXPERIMENT 2 RESULTS

9.1. Sample Plots of Inter-trial Coherence

In Figure 6A, we show sample plots for the ITC for individual children with normal hearing (NH group, first column, first row), sensorineural mild to moderate hearing loss with hearing aids (SNHL-HA-MM group, first column, second row), sensorineural severe to profound hearing loss with hearing aids (SNHL-HA-SP group, first column, third row), sensorineural hearing loss with cochlear implants (SNHL-CI group, second column, first row), auditory neuropathy spectrum disorder with hearing aids (ANSD-HA group, second column, second row), and auditory neuropathy spectrum disorder with cochlear implants (ANSD-CI group, second column, third row). In Figure 6B, we show auditory neuropathy spectrum disorder with a normal P1 CAEP (ANSD-N group, top panel), auditory neuropathy spectrum disorder with a delayed P1 CAEP (ANSD-D group, center panel), and auditory neuropathy spectrum disorder with an abnormal P1 CAEP (ANSD-A group, bottom panel).

In each plot, the Y-axis shows the frequency range and the X-axis shows the time range over which the ITC was computed. The ITC is represented by the color scale to the right where green indicates non-significant ITC, and red represents strong, significant ITC at $p<0.01$. Beneath each ITC plot is the averaged ERP response for that individual (in blue), with the amplitude scale to the right of the averaged waveform (in microvolts). It should be noted that the amplitude scale for the ERP response is not the same from individual to individual (for instance 10 to -5 for the NH group, as compared

to 4 to -8 for the SNHL-CI group, and 2 to -4 for the ANSD-HA group), since plotting to the same scale would make visualization difficult for the lower-amplitude waveforms.

To the left of each ITC plot is a panel with a blue line that shows the average power of ITC for that individual at each center frequency, and a green and black dotted line that shows the significance threshold for ITC at each center frequency relative to the baseline period ($p<0.01$).

Figure 6A: Sample Individual ITC Plots for NH, SNHL-HA-MM, SNHL-HA-SP, SNHL-CI, ANSD-HA, and ANSD-CI Groups

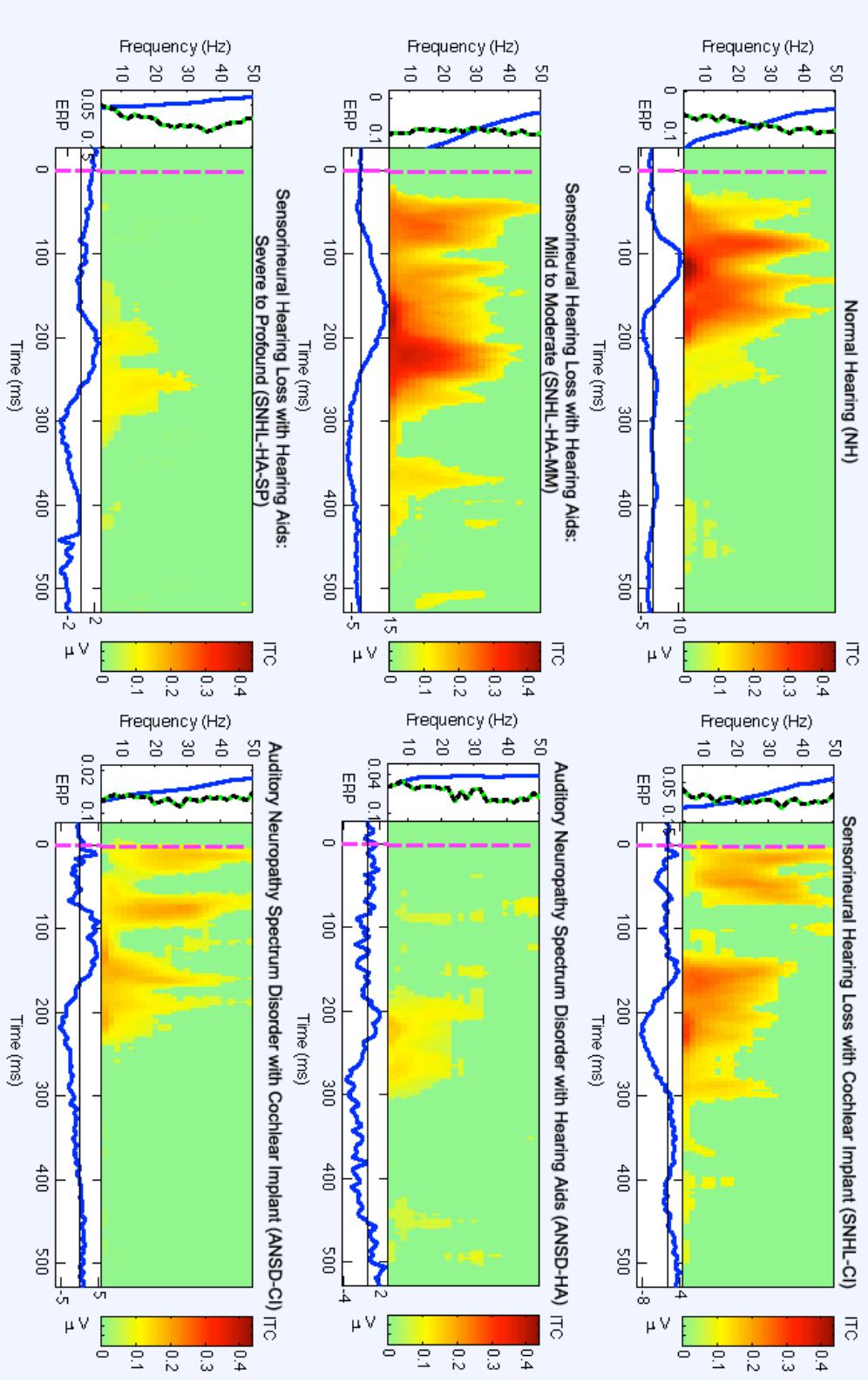
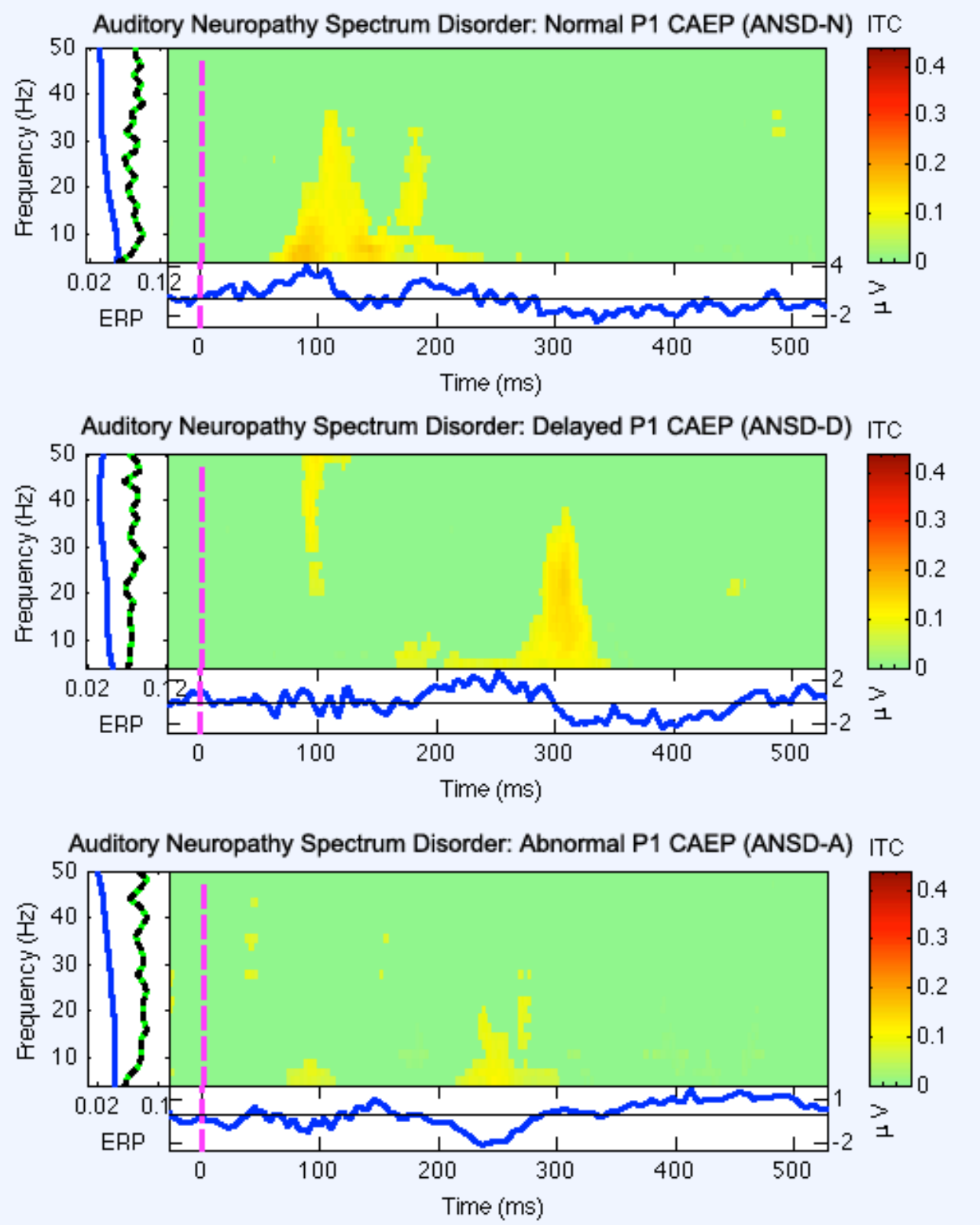


Figure 6B: Sample Individual ITC Plots for ANSD-N, ANSD-D, and ANSD-A Groups



9.2. Normal Hearing Results

Forty-one children, ranging from 0.1 to 11.1 years of age, were included in the normal hearing (NH) group. The average age at testing was 3.94 years of age, and the median was 2.32 years of age. Peak ITC values ranged from 0.1424 to 0.4779, with an average peak ITC value of 0.2508 (95% CI = .2234 - .2783). The range of significant ITC in milliseconds ranged from 58.7 to 396.63 ms, with an average range of 235.56 (95% CI = 209.47 – 261.66). The range of significant ITC in Hz ranged from 12.02 to 46.09 Hz, with an average frequency range of 37.34 Hz (95% CI = 34.2 – 40.48 Hz). See Table 3 for detailed statistics that describe the normal hearing group results.

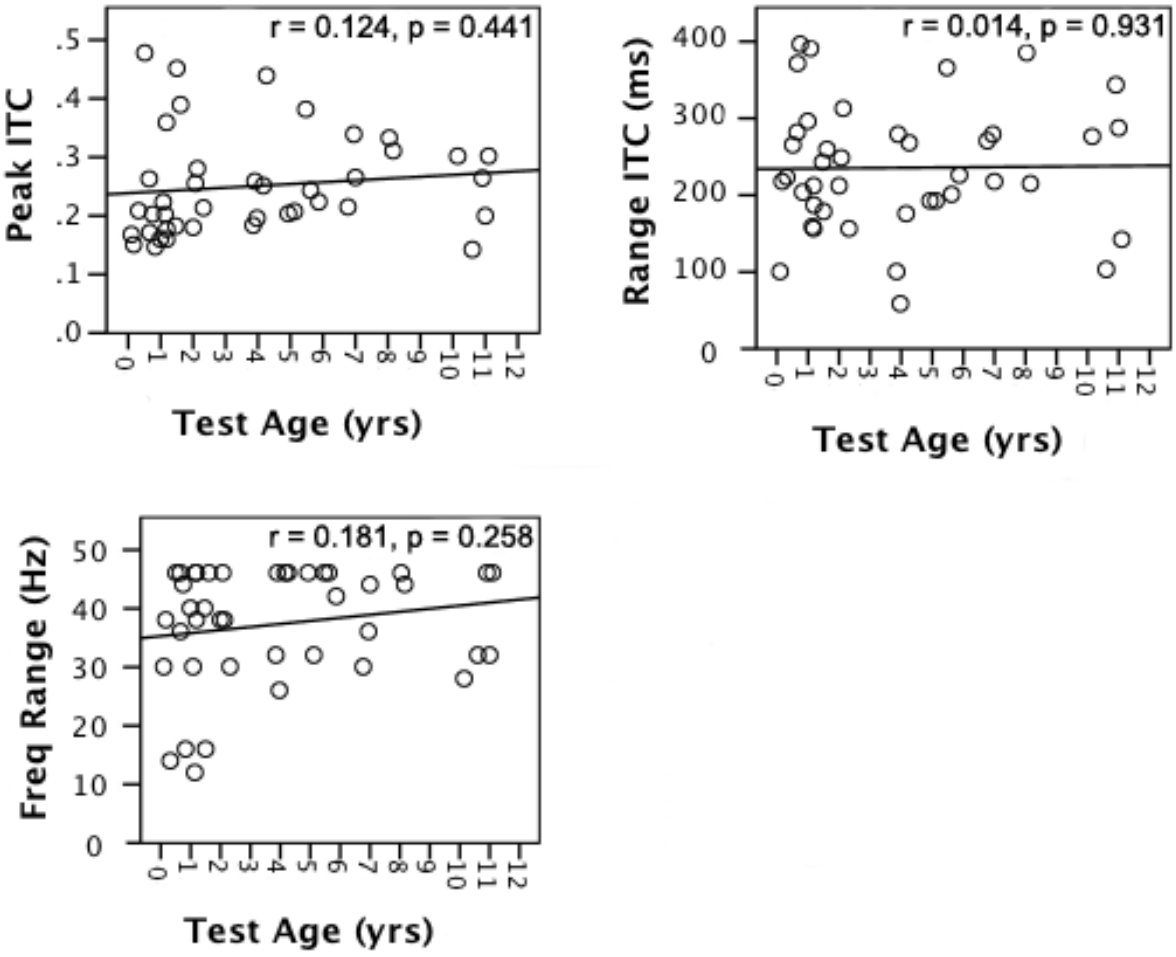
Table 3: Normal Hearing Group Statistics

Statistic	Test Age	Peak ITC	Time Range of ITC (ms)	Freq Range of ITC (Hz)
Mean	3.94	0.2508	235.56	37.34
Std. Deviation	3.46	0.0869	82.67	9.94
Lower Bound of 95% CI	2.85	0.2234	209.5	34.2
Upper Bound of 95% CI	5.04	0.2783	261.7	40.5

Test age was not significantly correlated with any ITC measure: peak ITC ($r=0.124$; $p=0.441$), time range for ITC ($r=0.014$; $p=0.931$), or frequency range of ITC ($r=0.181$; $p=0.258$). Therefore, it was concluded that the peak strength of ITC and the time and frequency ranges of ITC do not vary as a function of age over the age range that we selected. Figure 7 shows scatterplots for the correlations of ITC measures with test age for the NH group. The upper left panel shows the correlation between test age and peak ITC, the upper right panel shows the correlation between test age and the

time range of significant ITC, and the lower left panel shows the correlation between test age and the frequency range of significant ITC.

Figure 7: Normal Hearing Group Age and ITC Measures Correlation



9.3. ITC in Children with Sensorineural Hearing Loss

9.3.1 Children with SNHL Fitted with Hearing Aids

Results from 31 children with sensorineural hearing loss who used hearing aids were analyzed. The children ranged in age from 0.59 to 14.81 years of age (mean = 4.23, median = 2.73). For 26 of the 31 subjects, unaided thresholds were available.

Subjects with SNHL were further divided into two subgroups: those with mild to moderate hearing loss (N=14) and those with severe to profound hearing loss (N=17). Those in the mild to moderate group included those with unaided pure tone averages (PTA) of up to and including 65 dB HL, and the severe to profound group included those with unaided PTAs of higher than 65 dB HL. One subject had only aided thresholds available, with an aided PTA of 25 dB HL (this subject was placed in the mild to moderate group). For the 4 subjects without threshold data, a severe to profound hearing loss could be inferred, since these subjects later went on to receive cochlear implants.

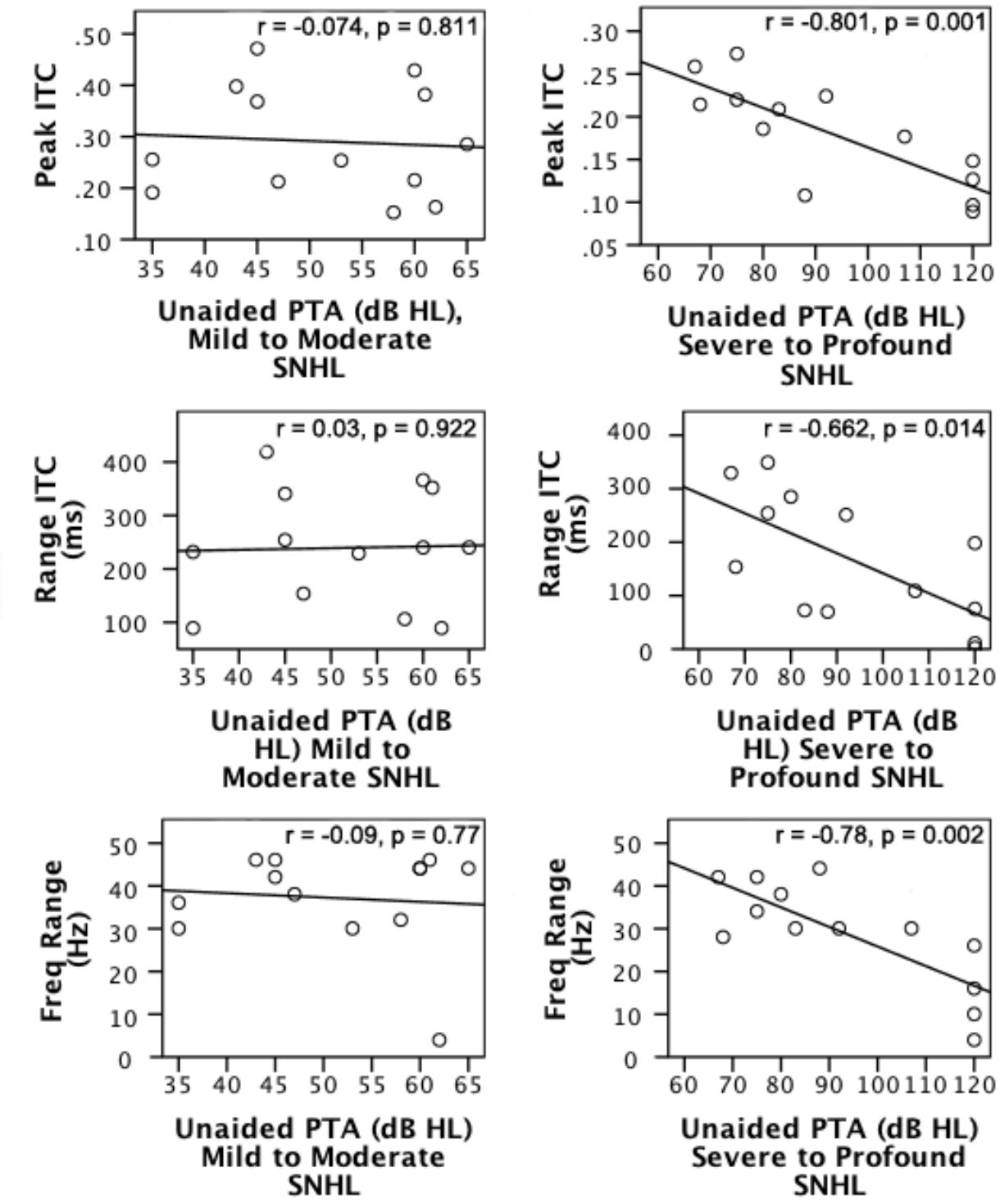
Unaided pure tone averages (PTA) for 26 children were significantly correlated with each ITC measure: the peak ITC ($r = -0.635$, $p<0.01$), the time range of ITC in ms ($r = -0.499$, $p=0.01$), and the frequency range of ITC in Hz ($r = -0.575$, $p<0.01$). The correlation was negative, meaning that as hearing loss levels worsened, ITC measures tended to decrease.

In exploring further detail within these correlations, an interesting result was obtained: when the SNHL-HA Group was divided by hearing loss severity levels, it became apparent that the correlation between unaided PTA and ITC measures is driven almost entirely by the portion of the SNHL-HA group that has a severe to profound hearing loss (see Figure 8). For subjects with severe to profound hearing loss, the following significant correlations with unaided PTA were found: peak ITC ($r=-0.801$; $p=0.001$), time range of ITC ($r=-0.662$; $p=0.014$) and frequency range of ITC ($r=-0.78$; $p=0.002$). Correlations between unaided PTA and ITC measures were not significant for the subjects with mild to moderate hearing loss: peak ITC ($r=-0.074$, $p=0.811$), time

range of ITC (r=0.03; p=0.922), and frequency range of ITC (r=-0.09, p=0.77). Overall, participants with severe to profound hearing loss show a deficit in ITC measures as compared to peers with milder hearing loss.

In Figure 8, the left column includes scatterplots for the participants with SNHL and a mild to moderate hearing loss. The right column includes scatterplots for the participants with SNHL and a severe to profound hearing loss. The top row shows correlations between peak ITC and unaided pure tone averages (PTAs) at 500, 1000, and 2000 Hz, the middle row shows correlations between the time range of significant ITC and unaided PTAs, and the bottom row shows correlations between the frequency range of significant ITC and unaided PTAs.

Figure 8: Unaided PTA and ITC Measures in SNHL-HA Group



9.3.2 SNHL-HA Correlation of ITC with Word Recognition Scores

Word recognition scores (WRS) obtained as part of the typical audiological test battery were only available for 9 of the 31 total participants in the SNHL-HA group. The lack of complete speech score data was likely due, in part, to young ages at the time of testing (19 of those with no data were under the age of 4 years; 15 of whom were also under the age of 2.5 years), and due partially to the level of hearing loss involved (only two participants with speech scores had severe to profound hearing losses (unaided PTAs were 75 and 83 dB HL for these two subjects). The subject with the worst hearing loss had the lowest speech score with a WRS of 64%. The rest of the participants had WRS scores of 88% or greater, which limited the range of scores available to examine. There was no significant correlation found between WRS and ITC measures: peak ITC ($r=0.267$; $p=0.487$), time range of ITC ($r=0.449$; $p=0.225$) and frequency range of ITC ($r=0.525$, $p=0.147$), which, given the limitations of the speech data available, is unsurprising and probably not representative of the true relationship between these measures.

9.3.3 Comparison of Children with SNHL Fitted with Hearing Aids and Cochlear Implants

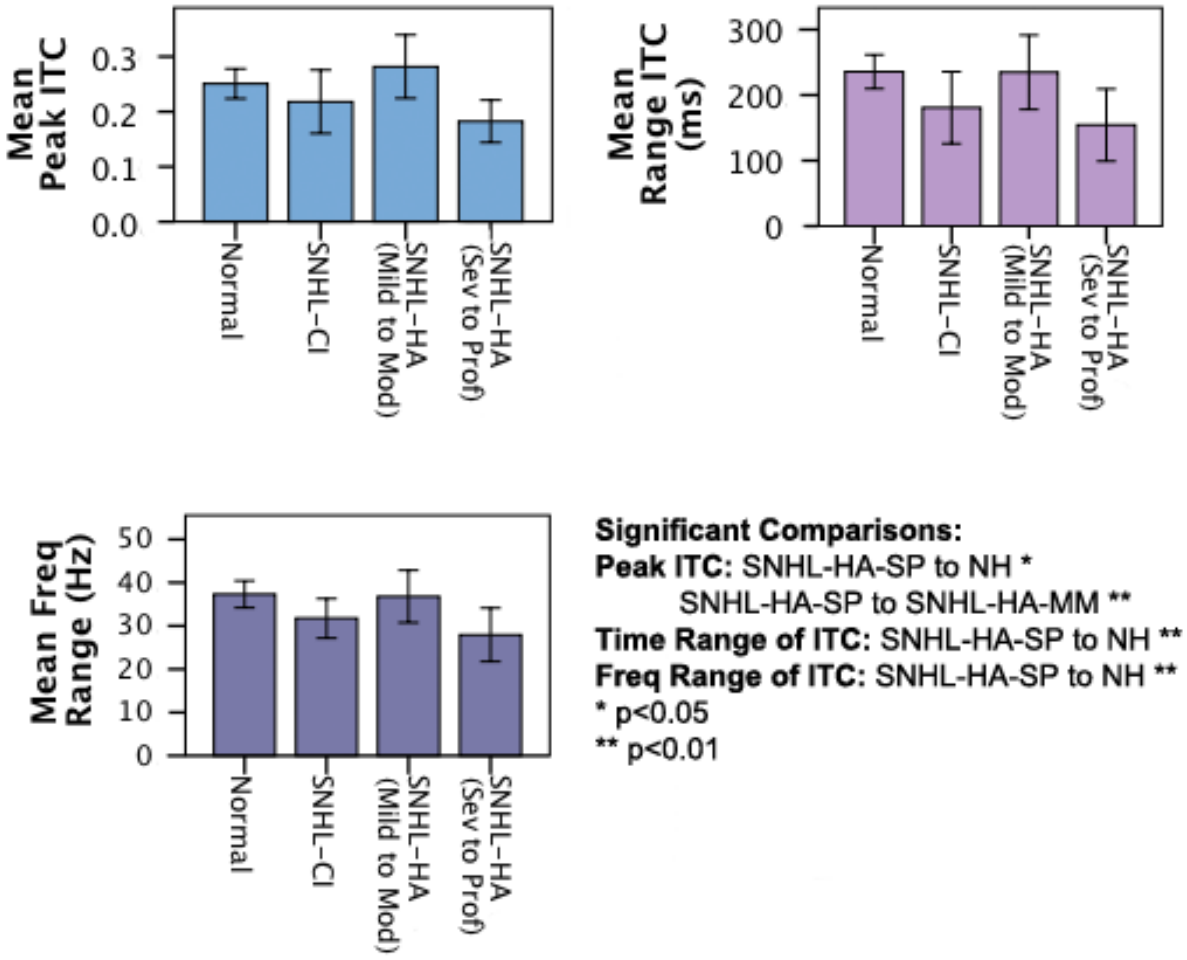
Given our results of decreased ITC in children with severe to profound hearing (detailed above) we decided to examine the effect of intervention with cochlear implants on ITC for severe to profoundly hearing impaired children. Participants with cochlear implants (N=19) were compared to the SNHL-HA Mild to Moderate (N=14), SNHL-HA Severe to Profound (N=17) and Normal Hearing (N=41) groups. Children with cochlear implants ranged from 2.23 to 15.29 years of age, with an average age of 6.82, a median

age of 6.05, and had a minimum of 6 months of implant experience at the time of testing. Since the SNHL-HA group showed differences between the mild to moderate and the severe-to-profound subgroups, these subgroups were left in place for comparing each of the ITC measures (peak ITC, time range of ITC in ms, and frequency range of ITC in Hz).

A multivariate linear regression was performed with hearing loss group as a fixed factor, and peak ITC, time range of ITC in ms, and frequency range of ITC in Hz as dependent variables. Hearing loss group was found to be a significant predictor of differences for peak ITC ($F=3.228$, $p=0.026$), the time range of ITC in ms ($F=3.43$, $p=.021$), and the frequency range of ITC in Hz ($F=3.711$, $p=0.015$). Tukey post-hoc pairwise comparisons were performed to obtain more specific information about which group differences were significant. For peak ITC, the SNHL-HA subgroup with severe to profound hearing loss (SNHL-HA-SP) was significantly different from both the normal hearing (NH) group ($p<0.05$) and the SNHL-HA subgroup with mild to moderate hearing loss (SNHL-HA-MM)($p<0.01$). For both the time range and the frequency range of significant ITC, the SNHL-HA-SP subgroup was different from the NH group ($p<0.01$). These differences are illustrated in Figure 9.

In Figure 9, the differences in peak ITC are shown in the upper left panel, the differences in the time range of significant ITC is shown in the upper right panel, and the differences in the frequency range of significant ITC is shown in the lower left panel. Overall, as can be seen from Figure 9, although not significant, the SNHL-CI group did show a slight trend of increased ITC values relative to the SNHL-severe to profound group with hearing aids.

Figure 9: ITC Measure Comparison in SNHL-HA, SNHL-CI, and NH Groups



9.4. ITC in Children with Auditory Neuropathy Spectrum Disorder

Ninety-one children with ANSD were examined retrospectively for this study, and their data yielded ITC results, which were compared to the results of children with sensorineural hearing loss. The ages at the time of testing for children with ANSD ranged from 0.21 to 11.55 years of age (mean = 3.89 years, median = 3.1 years).

Of the 91 children in the ANSD group, 50 had unaided pure tone audiometric thresholds available. A mild but significant correlation was found between unaided pure

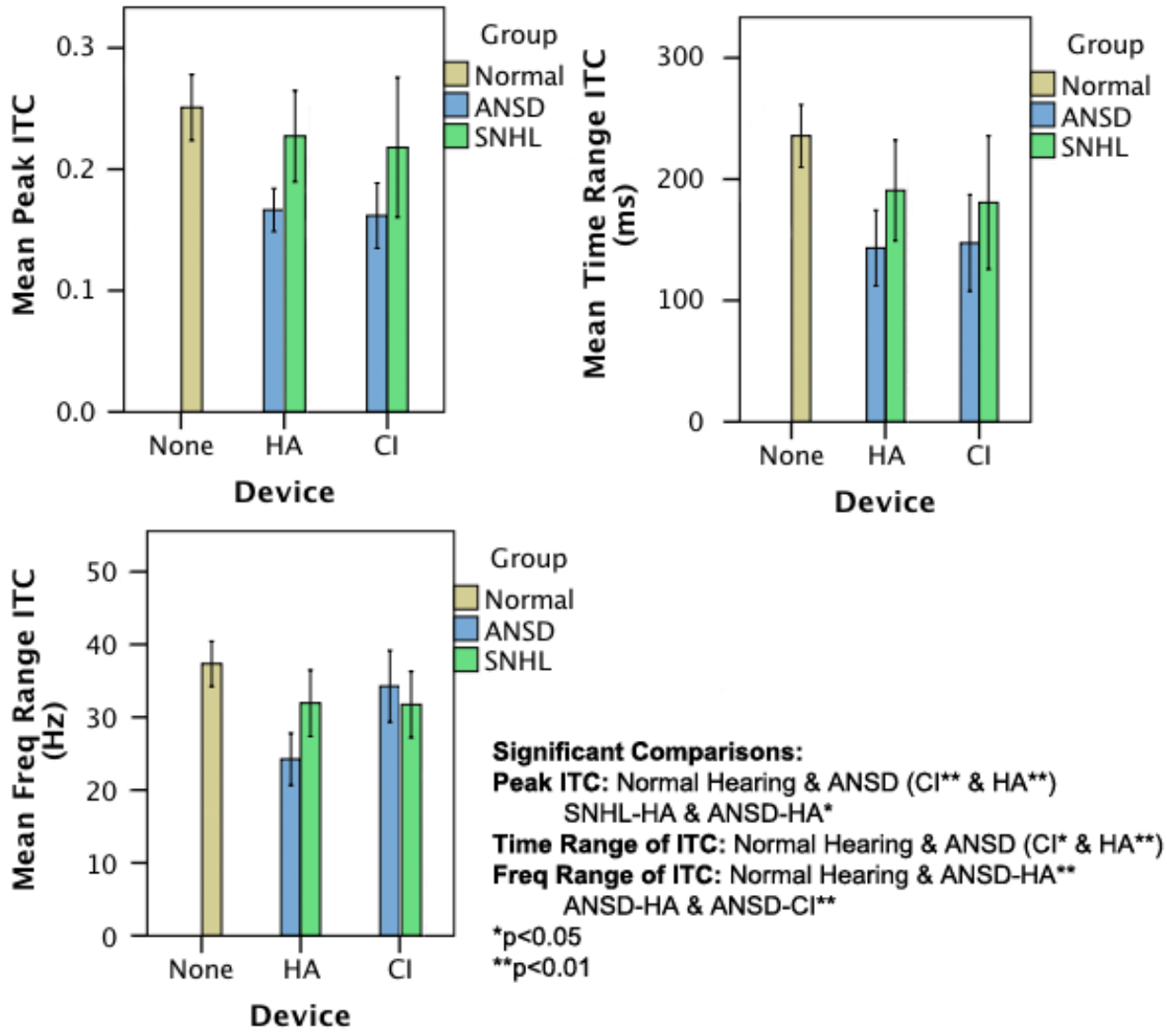
tone averages and the peak ITC measure (r=-0.342, p=0.015). Like their peers with SNHL, as hearing loss worsens, ITC appears to decrease for children with ANSD. However, the correlation between PTA and ITC measures was weaker for children with ANSD compared to the overall SNHL-HA group.

9.4.1 Technology Intervention Comparison for the ANSD and SNHL Groups

Twenty-two children in the ANSD group were wearing cochlear implants at the time of testing (ANSD-CI), and 54 of them were wearing hearing aids (ANSD-HA). These subgroups were compared with the NH (N=41), SNHL-HA (N=31) and the SNHL-CI (N=19) groups. When comparing ITC measures for intervention in a multivariate regression analysis with subgroup as a fixed factor and ITC measures as dependent variables, it was found that subgroup was a significant predictor of each ITC measure: peak ITC ($F=7.478$, $p<0.001$), time range of significant ITC ($F=5.070$, $p=0.001$) and the frequency range of significant ITC ($F=7.908$, $p<0.001$). Significant pairwise comparisons in a Tukey post-hoc analysis were as follows: for peak ITC, the NH group was significantly different from both the ANSD-HA and ANSD-CI subgroups ($p<0.01$), and the SNHL-HA subgroup was significantly different from the ANSD-HA subgroup ($p<0.05$). For the time range of significant ITC, the NH group was different from both the ANSD-HA ($p<0.01$) and ANSD-CI ($p<0.05$) subgroups. For the frequency range of significant ITC, the NH group was different from the ANSD-HA group ($p<0.01$), and the ANSD-HA subgroup was different from the ANSD-CI subgroup ($p<0.01$). Children with ANSD generally have lower coherence in ITC measures than children with SNHL (with the exception of frequency range of ITC in children who wear cochlear implants). See Figure 10 for a comparison of technology intervention by group.

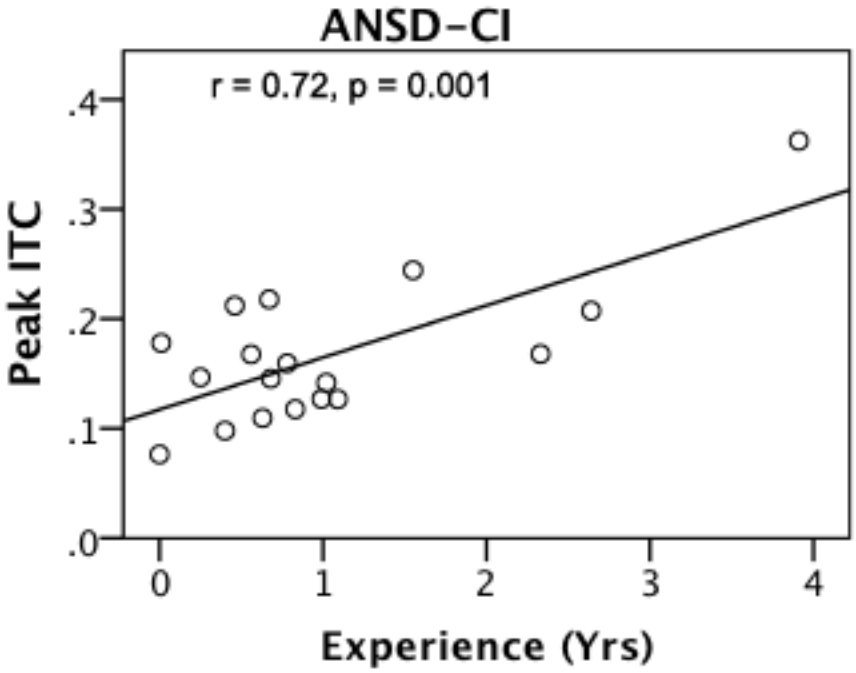
In Figure 10, the differences between groups (ANSD, SNHL, and NH) and intervention (no intervention for the NH group, and hearing aids and cochlear implants for the ANSD and SNHL groups) are shown in three panels. The upper left panel shows differences for peak ITC, the upper right panel shows differences for the time range of significant ITC, and the lower left panel shows differences for the frequency range of significant ITC.

Figure 10: Technology Intervention Comparison for SNHL and ANSD, with NH Group



For children with SNHL and ANSD, the age of device fitting for HA and for CI did not correlate significantly with ITC measures, with the exception of a mild correlation of frequency range of ITC with age of fit in ANSD-HA users (r=0.282, p=0.047). However, experience with the device correlated strongly with peak ITC for the children with ANSD who were cochlear implant wearers (r = 0.702, p= 0.001). As experience with the implant increased, peak ITC also increased. No similar effects were found when examining experience with hearing aids for children with ANSD. Figure 11 is a scatterplot that illustrates the significant correlation between experience time with a cochlear implant and peak ITC in the ANSD-CI group. On the x axis is experience time in years, and on the y axis is peak ITC strength.

Figure 11: Correlation Between Device Experience and Peak ITC in ANSD-CI Group



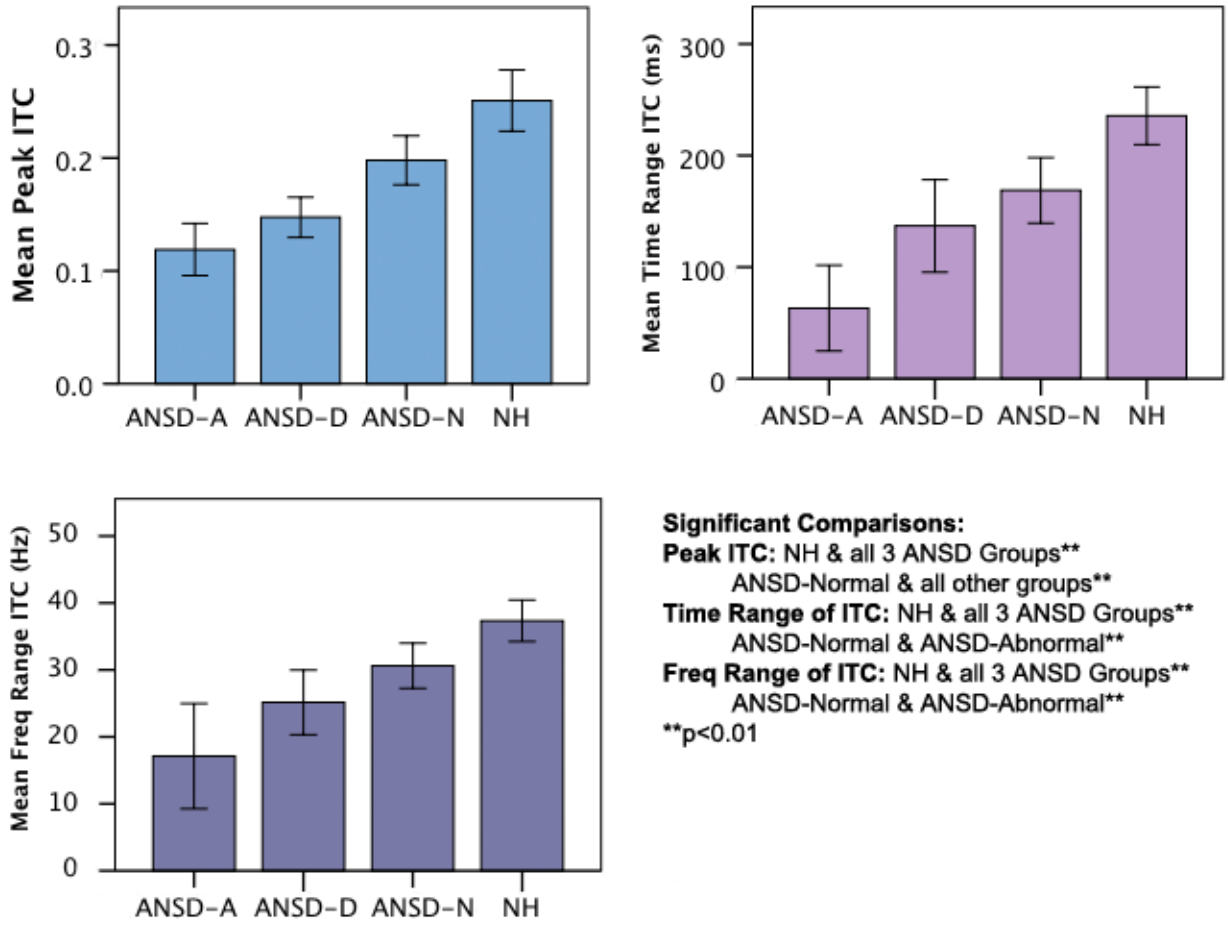
9.4.2 Comparison of ITC in Children with ANSD with Normal, Delayed, and Abnormal P1 Results

Since previous studies have described the P1 CAEP as a good predictor of outcomes for children with ANSD, we decided to examine the relationship between the averaged P1 CAEP and the ITC underlying the aggregate response. To examine the relationship between the P1 CAEP and coherence, the larger ANSD group (N=91) was broken into categories based upon P1 latencies. Those with normal P1 latencies (latencies within normal values from Sharma et al., 2002b) were placed within the ANSD-Normal group (N=47). Those with delayed latencies were placed in the ANSD-Delayed group (N=31), and those with abnormal morphology (and absent P1s) were placed within the ANSD-Abnormal group (N=13). See Sharma et al., (2011) and Cardon and Sharma (2013) for a detailed description on how the P1 latencies were computed. These three ANSD subgroups were compared with the NH group of control subjects.

When comparing the ITC values for these three subgroups with a multivariate linear regression with Tukey post-hoc pairwise comparisons, subgroup was found to be a significant predictor of all three ITC measures: peak ITC ($F=17.919$, $p<0.001$), range of ITC in ms ($F=12.76$, $p<0.001$), and range of ITC in Hz ($F=12.188$, $p<0.001$). Means and significant pairwise differences are described in Figure 12. The upper left panel shows group comparisons for peak ITC, the upper right panel shows group comparisons for the time range of ITC, and the lower left panel shows group comparisons for the frequency range of ITC. ANSD-Normal is abbreviated to ANSD-N, ANSD-Delayed is abbreviated to ANSD-D, and ANSD-Abnormal is abbreviated to ANSD-A.

For peak ITC, the normal hearing (NH) group was significantly different from all three ANSD subgroups (ANSD-N, ANSD-D, and ANSD-A) ($p<0.01$), and the ANSD-N group was also significantly different from the other two ANSD subgroups ($p<0.01$). For the significant time and frequency ranges of ITC, the NH group was significantly different from all three ANSD subgroups ($p<0.01$), and the ANSD-N subgroup was significantly different from the ANSD-A subgroup ($p<0.01$).

Figure 12: ITC in NH, ANSD-Abnormal, ANSD- Delayed, and ANSD-Normal Groups



CHAPTER 10

EXPERIMENT 2 DISCUSSION

We examined cortical phase synchrony (or phase-locking) of cortical oscillations elicited to a speech stimulus in children with ANSD. Our measure of cortical phase synchronization was inter-trial coherence (ITC), which computes phase relations across single EEG trials. We examined the peak strength of ITC and its time and frequency ranges in children with ANSD, SNHL and NH. Our aim was to better understand the extent to which the disruption in neural synchrony, which characterizes children with ANSD, affects phase cortical synchronization, which is an important mechanism associated with auditory and speech discrimination, feature binding, and other cognitive processes.

Our main findings can be summarized as follows: (i) for NH children, ITC measures did not correlate with age; (ii) for children with SNHL, ITC decreased significantly as hearing impairment increased, especially within the severe to profound hearing loss range; (iii) children with ANSD showed lower ITC values as compared to their peers with SNHL and similar technology interventions (i.e., hearing aids or cochlear implants); (iv) NH children with normal P1 CAEP responses had higher ITC values than children with ANSD who had either normal, delayed or abnormal P1 CAEP responses; and (v) children with ANSD who showed normal P1 CAEP responses had higher ITC values than those with delayed or abnormal CAEP responses.

ITC changes at the Cz electrode were examined in NH children who ranged in age from infancy to pre-adolescence (0.1-11 years). There were no significant ITC correlations with age across this range. Our results contrast with recent findings of

Bishop et al. (2011a), who examined ITC as part of a study of CAEP responses elicited by tones in children aged 7-11 years, and reported age-related changes in ITC at the Cz electrode and a few other fronto-central sites. The difference in results may be explained by a methodological difference in ITC strength quantification (power at specific frequency bands versus peak strength and time and frequency ranges), or the smaller age range studied in the Bishop et al. study. It is possible that the changes Bishop and colleagues found in phase synchrony for specific areas relate to myelination of the axonal sheath, since myelination (or rather, a lack thereof) has been shown in previous work to have a greater effect on the timing of the cortical response than a small neuronal population (Rance et al., 2012).

Overall, our results showed that children with SNHL showed a significant decline in ITC values as a function of the degree of hearing loss (Figures 8 and 9). Children with mild-to-moderate hearing loss showed normal ITC values; however, cortical phase coherence appeared to decline significantly as sensorineural hearing loss worsened in the severe-to-profound hearing range. Previous studies of cortical auditory evoked potentials have shown that lack of audibility experienced by children with SNHL results in significant deficits and delays in auditory cortical maturation (Sharma et a., 2005), likely including deficits in cortical phase synchronization. In our study, children with mild to moderate hearing loss who were fitted with hearing aids showed normal ITC, suggesting that appropriate amplification restores normal phase-locking of cortical oscillations to speech sounds. This is an encouraging result since recent studies have described the importance of cortical oscillations for auditory processing (Giraud and Poeppel, 2012).

Contrary to children with mild to moderate SNHL, children with severe to profound SNHL showed lower than normal values of ITC and decreasing ITC values as a function of the severity of their hearing loss (Figure 9). Children with even a severe degree of SNHL typically show reasonably good brainstem synchrony (as evidenced by repeatable ABR and Auditory Steady State Recordings (ASSR) recordings at suprathreshold levels), which is likely to carry over to cortical levels. Therefore, the deficit in cortical phase coherence may be explained in large part due to the relatively decreased audibility that accompanies severe to profound hearing loss even after intervention with amplification.

However, it is curious that children with severe to profound SNHL who were fitted with cochlear implants did not show a significant improvement in ITC (Figure 9) and their ITC levels did not reach those of children with mild-moderate SNHL or NH (although there was a trend for improvement in ITC levels for SNHL-CI children compared with SNHL-HA children). Cochlear implants in general allow for sufficient audibility of the speech signal. Thus, it may be the case that cortical deficits in phase synchrony associated with severe to profound SNHL may never quite be ameliorated to the levels of a mild hearing loss, even after intervention with a cochlear implant. This might be particularly relevant if implantation occurs after a sensitive period of 3.5 years in childhood (Kral and Sharma, 2012). In this study, the mean age of implant fitting for children with cochlear implants in our sample was 5.19 years, and the median age of implant fitting was 4.6 years –both ages are well after the sensitive period---which suggests that late implantation does not restore cortical phase coherence consistent with the abnormal cortical maturation and re-organization reported in late-implanted

children (Sharma et al., 2009). Future studies should examine ITC before and after cochlear implantation, as a function of age of implantation, to directly examine the possible effects of electrical stimulation on cortical synchronization.

Overall, children with ANSD showed a trend for lower levels of ITC compared with children with SNHL (Figure 10), and children with SNHL showed a different relationship between ITC and hearing thresholds, as compared with children with ANSD. Relative to children with SNHL ($r = -0.635$, $p<0.01$), children with ANSD showed a much weaker correlation between peak ITC and hearing thresholds ($r=-0.342$). In addition, separating the children with SNHL into subgroups based upon hearing loss strengthened the correlation between PTA and ITC measures for those with severe to profound hearing loss in particular, with correlation values as strong as $r=-0.8$, however, the correlation of PTA with ITC measures disappeared when trying a similar method with the ANSD group. These results suggest that although the lack of audibility impacts ITC in ANSD, the decreased phase coherence in ANSD cannot simply be explained as a function of degree of hearing loss. These results are consistent with reports that audiometric thresholds are not as predictive of performance in ANSD as they are in SNHL (Deltenre et al., 1999, Rance et al., 1999, Rance et al., 2002, Rance et al., 2007b, Rapin and Gravel, 2003, Rance and Aud, 2005, Sharma et al., 2011)

Cortical development is driven by both intrinsic factors, such as genetic expression, and extrinsic factors, such as sensory input (Pallas, 2001). Reductions in spontaneous neural activity result at least in part from neural inhibition, and sensory experience is strongly connected to inhibition in the cortex (Foeller and Feldman, 2004). An abnormal reduction of neural fibers has been suggested as a possible mechanism of

the loss of synchrony in ANSD (Amatuzzi et al., 2001, Butinar et al., 1999, Starr, 2001). In children with ANSD, the degradation of the signal through demyelination or a loss of axonal fibers creates lower levels of EEG coherence regardless of the level of hearing loss (essentially, an intrinsic deficit). On the other hand, for children with SNHL, coherence remains intact except when audibility is significantly decreased in severe to profound hearing loss (essentially, an extrinsic deficit). Our results provide a window into cortical deficits for children with ANSD that go well beyond the effects of the loss of audibility on cortical development and functioning.

Cortical auditory evoked potentials like the P1 CAEP response have been used widely to examine cortical development in children with NH, SNHL and ANSD. Synchronization of neural oscillations is important for the maturation of cortical networks (Uhlhaas et al., 2010). ITC measures provide information beyond the averaged P1 CAEP by giving information regarding the phase synchrony and frequency content of the EEG. Our results showed that, in general, ITC measures corresponded well with P1 CAEP results (Figure 12). Children with ANSD with abnormal P1 results also had the lowest levels of ITC, and children with normal P1 results had the highest levels of ITC. However, the ITC measure provided information about cortical functioning that went beyond the information that P1 latency provides alone, since children with ANSD and normal CAEPs had significantly lower ITC levels than children with normal hearing. Although potential contributors to the dys-synchrony in ANSD include neural pathologies such as axonal loss and demyelination (Butinar et al., 1999, Starr, 2001), it is possible that less populous or less efficient neuronal clusters are still capable of producing a normal P1 latency. However, a more detailed look at the phase synchrony

behind the averaged response tells us that cortical functioning in children with ANSD is not identical to normal hearing children, even if cortical maturation measures like the P1 CAEP latency are normal. This might be especially true if the underlying pathology is related to axonal loss, rather than demyelination, the latter of which might be expected to produce delayed or temporally smeared responses (which would be consistent with Rance, 2012). An important direction for future research is to answer the question as to whether normal cortical maturation is sufficient for good performance outcomes in this population, or whether a particular level of phase synchrony is also required.

In investigating the effects of technology intervention on ITC measures in children with ANSD, it was found that ITC was positively correlated with duration of cochlear implant use, but not hearing aid use (Figure 11). Although ITC remained lower post-implantation for children with ANSD compared to children with SNHL, the increase in coherence with increasing implant use supports the idea that cochlear implants hold promise for children with ANSD as a method of reintroducing synchrony to a dys-synchronous system. Middlebrooks (2008) has described how cortical neurons in implanted guinea pigs are capable of phase-locking to amplitude-modulated electrical pulse trains that are produced by a cochlear implant, a process considered important for speech recognition in humans. Reports vary as to the specific envelope frequencies that are useful for speech processing in the cortex for people with normal hearing and those with cochlear implants (Drullman et al., 1994, Fu and Shannon, 2000, Rosen, 1992, Shannon et al., 1995, Van Tasell et al., 1987, Xu and Zheng, 2007, Xu et al., 2005), and the upper value of that frequency range has been stated to be as high as 50 Hz (Rosen, 1992). In the current study, additional phase-locking in the gamma range

was observed for children with ANSD who received cochlear implants (Figure 10, lower left panel). These changes are encouraging from this standpoint, as restoration of high frequency phase locking may be of assistance in processing speech information. In the present study, it was possible to follow children only for a short time post-implantation (mean experience with the implant was 1.34 years, median 1.02 years). It would be useful for future studies to track changes in ITC as a function of implant use over a much longer time scale.

Cortical phase synchrony is modulated by cognitive demands. Using a visual line-orientation judgment task, Yamagishi et al. (2008) showed that increased ITC was associated with improved behavioral performance. In clinical populations, abnormal phase synchrony has been associated with various higher-order cognitive neurological deficits including auditory hallucinations in schizophrenic patients (Ford et al., 2007), ictal activity in epileptic patients (Le Van Quyen et al., 2003), motor initiation, slowness and tremor in Parkinson's disease (Uhlhaas et al., 2006) and working memory deficits in patients with Alzheimer's disease (Pijnenburg et al., 2004). While our paradigm did not specifically examine cognitive processing, the generally low levels of ITC seen in children with ANSD in our passive task may be a precursor to cognitive deficits seen in language development for these children (Rance et al., 2007b). Future studies should examine ITC changes in ANSD in a cognitive behavioral task.

This study was limited by the retrospective nature of the data analysis. Speech recognition data were limited for this study, and it would be useful to obtain additional information in this area to compare behavioral speech performance with ITC measures. Finally, while ITC was examined across time and frequency ranges, the mean change

of spectral power within specific frequency bands (e.g., event related spectral perturbations) was not examined. It would be useful for future studies to describe possible differences in spectral perturbations in this population.

10.1. Summary and Conclusions for Experiment 2

We examined cortical phase synchrony to speech, using inter-trial coherence in children with NH, SNHL and ANSD. The results provide normative values for ITC in the first decade of life, which might assist the use of this measure in other clinical populations. Children with ANSD had decreased phase synchrony in comparison to the normal hearing population, and ITC was sufficient to distinguish normal hearing children from those with ANSD, even if cortical maturation was normal in both groups. This provides evidence that ITC provides information that is not readily available from analysis of the P1 CAEP latency alone. The current study also shows that lack of audibility in severe to profound SNHL results in decreased cortical coherence relative to children with milder degrees of SNHL, consistent with generally better behavioral outcomes reported for the latter group. Children with ANSD showed generally lower phase coherence compared with children with SNHL, regardless of intervention. However, there was evidence that cochlear implantation resulted in an increase in phase synchrony with increasing experience for children with ANSD. Overall, this study shows that inter-trial coherence provides a window into examining cortical phase synchrony deficits for children with ANSD. Differences in cortical phase coherence between children with SNHL and their peers with ANSD highlighted the role of cortical synchrony needed for the appropriate processing of speech for children with ANSD.

CHAPTER 11

SUMMARY AND CONCLUSION

In Experiment 1, dense array EEG in response to speech was used to examine cortical development in a pediatric patient with unilateral ANSD. As expected, EEG recordings revealed normal morphology P1 CAEP responses, which were localized to the temporal cortex and showed a high degree of underlying phase-locking and coherence in the patient's non-ANSD ear. Results from the ANSD ear revealed abnormal morphology CAEPs that could not be localized to a distinct neural generator and showed reduced phase-locking and phase synchrony, as measured by inter-trial coherence. These results supported the hypothesis (Specific Aim 1) that ANSD results in abnormal cortical development, and corresponded well with the patient's excellent speech perception in the non-ANSD ear and poor speech perception in the ANSD ear.

In Experiment 2, cortical phase synchrony elicited by speech, using inter-trial coherence, was examined in large groups of children with ANSD, NH and SNHL. For NH (n=41) children, phase synchrony measures did not correlate with age. The results of Experiment 2 support the hypothesis (Specific Aim 2) that cortical phase synchrony is not affected by age or development. Given a previous result (Bishop et al., 2011a) which found age-related ITC increases in NH children at fronto-central electrode sites, but no change or decreases in ITC at other sites, it is possible that high-density techniques, such as those used in Experiment 1, are more appropriate methods for examining developmental changes in the normal hearing population. It is interesting to note that in Experiment 1, the peak phase synchrony for the normal hearing ear in the patient with unilateral ANSD case was comparable to the levels of peak ITC observed in

normal hearing children in Experiment 2 (peak value of 0.2137), while the ITC in the ANSD ear was consistent with those seen for ANSD children in Experiment 2 (peak value of 0.0749).

Overall, results of Experiment 2 support the hypothesis (Specific Aim 3) that children with ANSD exhibit less cortical phase synchrony than children with normal hearing. Children with ANSD presented less phase synchrony on each ITC measure: peak ITC, the time range of ITC in ms, and the frequency range of ITC in Hz. In addition, children with ANSD exhibited lower levels of phase synchrony if their P1 latency was abnormal or delayed, which provides evidence that ITC could be used as one measure of the severity of ANSD. Children with normal cortical development (as measured by the P1 CAEP) were found to have greater peak ITC values and larger time and frequency ranges of significant ITC than those with delayed or abnormal cortical development. However, children with normal hearing also had higher levels of ITC than children with ANSD and normal cortical development, which indicates that ITC provides additional information about cortical functioning beyond P1 latency results alone.

For children with SNHL, phase coherence decreased significantly as hearing impairment increased, especially within the severe-to-profound hearing loss range, suggesting an important role for audibility in cortical functioning. However, in children with ANSD, the correlation between audiometric pure tone averages and ITC measures was not significant, which is consistent with reports that pure tone thresholds are not always predictive of performance in this population. Furthermore, children with ANSD who wore cochlear implants had a trend towards lower ITC values compared with children with SNHL fitted with cochlear implants, while comparable groups of children

who wore hearing aids showed some significant differences in ITC. These results generally supported the hypothesis (Specific Aim 4) that children with ANSD would show lower phase coherence compared with children with SNHL in comparable conditions.

Children with ANSD who were fit with cochlear implants showed a significant positive correlation between ITC and experience with the implant. While additional data should be analyzed before making generalizable conclusions, this trend supported the hypothesis (Specific Aim 5) that cochlear implants may introduce synchrony into an asynchronous system, driving normal cortical development.

Overall, time-frequency analysis appears to be a promising tool for examining cortical phase synchrony, which is important for normal cortical functioning. Given the importance of normal cortical functioning for speech and language acquisition in children, the results suggest new evidence for poor behavioral outcomes associated with children with ANSD. It is expected that future research will further clarify the relationship between technology interventions and subsequent increases in cortical phase synchrony in ANSD using a longitudinal design. Future directions for research should also include exploration of the relationship between cortical phase synchrony and cognitive speech and language tasks in SNHL and ANSD, and detailed examination of event-related spectral perturbations (ERSP) in these populations.

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