Published in final edited form as:

Hear Res. 2015 December ; 330(0 0): 221–232. doi:10.1016/j.heares.2015.06.001.

Cortical Development and Neuroplasticity in Auditory Neuropathy Spectrum Disorder

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Abstract

Cortical development is dependent to a large extent on stimulus-driven input. Auditory Neuropathy Spectrum Disorder (ANSD) is a recently described form of hearing impairment where neural dys-synchrony is the predominant characteristic. Children with ANSD provide a unique platform to examine the effects of asynchronous and degraded afferent stimulation on cortical auditory neuroplasticity and behavioral processing of sound. In this review, we describe patterns of auditory cortical maturation in children with ANSD. The disruption of cortical maturation that leads to these various patterns includes high levels of intra-individual cortical variability and deficits in cortical phase synchronization of oscillatory neural responses. These neurodevelopmental changes, which are constrained by sensitive periods for central auditory maturation, are correlated with behavioral outcomes for children with ANSD. Overall, we hypothesize that patterns of cortical development in children with ANSD appear to be markers of the severity of the underlying neural dys-synchrony, providing prognostic indicators of success of clinical intervention with amplification and/or electrical stimulation.

Keywords

Auditory Neuropathy Spectrum Disorder (ANSD); cortical auditory evoked potentials (CAEP); P1 biomarker; cortical phase synchrony; Inter-trial coherence (ITC); current density reconstruction; source analysis; cochlear implants; hearing aids; high-density EEG

1.1 Auditory Neuropathy Spectrum Disorder (ANSD): Description and Background

Among auditory disorders, auditory neuropathy is a relatively recently discovered condition (Starr et al, 1991; 1996). A hallmark of Auditory Neuropathy Spectrum Disorder (ANSD) is the vast inter and intra-subject variability which defines its patient population. This

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variability has lead to historically different classifications or nomenclatures for ANSD (Rapin & Gravel, 2006). The disorder was first described and titled *Auditory Neuropathy* by Starr and colleagues (1996). However, to reflect the common pathophysiology that underlies ANSD—dys-synchronous function of the VIII nerve—others added the word *dys-synchrony* to the title (Berlin et al, 1998; 2001a, 2001b). Currently, the term *Auditory Neuropathy Spectrum Disorder* is used to draw attention to the fact that patients diagnosed with ANSD may each fall somewhere on a continuum that represents the possible combinations of functioning inner and outer hair cells, synaptic issues, and/or post-synaptic neural involvement (Berlin et al, 2010). Thus, while the results of clinical diagnostic assessments may look similar between patients with ANSD, each case of ANSD may be unique in both underlying physiology and behavioral outcome.

It is estimated that 5–15% of all children with sensorineural hearing loss (SNHL) exhibit symptoms of ANSD (Uus & Bamford, 2006; Kirkim et al, 2008; Talaat et al, 2009; Berlin et al, 2010; Maris et al, 2011; Roush et al, 2011; Bielecki et al, 2012; Mittal et al, 2012). The majority of these individuals present with bilateral ANSD. However, there is a subset of patients that have a unilateral form of the disorder—approximately 7% of children with ANSD, according to Berlin et al (2010). In addition to children that present with ANSD, there are also adults in whom ANSD is an issue. Berlin and colleagues (2010) reported approximately 12% of the patients in their database of people with ANSD were over the age of 18 years. Others have reported that about 1 in 4 ANSD patients are diagnosed over the age of 10 years (Sininger et al, 2000; Sininger & Oba, 2001). Adults may be identified with the disorder later in life when symptoms become apparent in relation to other peripheral neuropathies and/or because they are often poor hearing aid users (Berlin et al, 2010).

There is a wide range of etiologies associated with ANSD. Some of the medical findings that most commonly co-occur with ANSD include normal history, prematurity, jaundice, hyperbilirubinemia and kernicterus, exchange transfusion, anoxia, respiratory distress, artificial ventilation, ototoxic drugs, low birth weight, infectious diseases (i.e., mumps), and genetic disorders (e.g., Freidreich's Ataxia, Charcot Marie Tooth syndrome) (see Kraus, 2001; Berlin et al, 2010 for reviews). In addition, there is at least one report in the literature of ANSD occurring transiently when patients experienced elevated fever (Starr et al, 1998). Also, several investigators have produced reports detailing findings regarding the genetic origins of ANSD. For instance, abnormalities found in the OTOF gene, which affects the production of the otoferlin protein found in the cochlea, have been associated with ANSD and DFNB9 (a non-syndromic form of recessive deafness). OTOF-related deafness has been associated with dys-synchrony, causing problems with neurotransmitter release between the inner hair cells (IHC) and auditory nerve (Yasunaga et al, 1999). Furthermore, Delmaghani and colleagues (2006) have singled out another gene (i.e., DFNB59), which is instrumental in coding a protein, *pejvak*, that is important for neural conduction along the auditory pathway, and propose that irregularities in this gene may be related to ANSD.

Cochlear nerve deficiency (CND) is also a comorbid factor in a subset of patients with ANSD. CND is characterized by hypoplasia or aplasia of the VIII nerve (Buchman et al, 2006; McClay et al, 2008; Huang et al, 2010; Roche et al, 2010; Maris et al, 2011). ANSD and CND are particularly related because of the poor neural connectivity and conduction

secondary to reduced functional nerve fibers found in CND (Buchman et al, 2006; Walton et al, 2008). While CND is typically diagnosed using MRI, results from our laboratory have shown that cortical auditory evoked potentials (CAEPs) can also be useful in identifying the disorder and quantifying its effects (Roland et al, 2012).

Like most hearing impairments, ANSD is diagnosed clinically by using a combination of measures. That is, patients with ANSD classically present with present otoacoustic emissions (OAEs), absent or abnormal auditory brainstem response (ABR) that contains a robust cochlear microphonic when the polarity of the stimulus is reversed, absent acoustic reflexes (AR), and speech perception that is often uncharacteristically poor with respect to the patient's auditory threshold levels (i.e., Starr et al, 1996; Berlin et al, 1998, 2003, 2005; Sininger, 2001). Additionally, the auditory thresholds of people with ANSD can be of any configuration and severity—from normal to profound—and in most cases do not accurately predict patients' speech perception abilities (Deltenre et al, 1999; Rance et al, 1999, 2002; Rapin & Gravel, 2003; Zeng et al, 1999). Not unlike those who suffer from neural presbycusis, people with ANSD most often experience great difficulty decoding and understanding complex signals. Speech understanding is almost always severely degraded when these signals are embedded in background noise (Kraus et al, 2000; Sininger, 2001; Rance et al, 2012). Several investigators have provided evidence that the speech perception problems experienced by individuals with ANSD arise especially from temporal processing deficits related to dys-synchronous neural responses to incoming acoustic signals (e.g. Zeng et al, 1999, 2004, 2005; 2006; Rance et al, 2004, 2005; Michalewski et al, 2005; Rance & Barker, 2008; Hassan, 2011).

1.2 Similarities in pathophysiology between SNHL and ANSD

Though SNHL and ANSD may be thought of as entirely distinct disorders of the auditory system, in reality, there may be significant overlap between these clinical diagnoses. That is, SNHL, which may traditionally be categorized as an inner ear disorder whose primary manifestation is related to elevated auditory thresholds, may be also characterized by neurodegenerative, synaptic, and neural firing pattern deficits (Kujawa & Liberman, 2006; 2009; Gourévitch et al, 2014; Nash & Sharma, 2014). Likewise, individuals with diagnosed ANSD, which may typically be considered a neurologic deficiency, often suffer from elevated auditory thresholds as well. Thus, it is plausible to think that any individual with a hearing impairment may be at risk for central auditory developmental deficiencies, due to factors related to both level and pattern of sensory input coding.

Within the diagnoses of SNHL and ANSD, there is wide variability between patients. While the majority of the variance in performance of many individuals with SNHL can be predicted by behavioral auditory thresholds, those with additional neurologic involvement may be more difficult to characterize. In fact, the prediction of behavioral outcomes of this subset of patients with SNHL may be similar to patients with ANSD, who also show significant inconsistency between patients, despite the distinct similarity in clinical diagnostic findings in these individuals. In ANSD, dys-synchrony of the VIII nerve leads to abnormalities in the ABR and AR, for example (Berlin et al, 1998). Although these clinical characteristics are common between patients with ANSD, there are at least three sites of

lesion that have been implicated in the dys-synchrony seen in ANSD. These are: 1) the inner hair cells (IHC) of the cochlea; 2) the synapse between the IHC and VIII nerve; 3) the VIII nerve (i.e., fewer than normal nerve fibers, de-myelination; Starr et al, 1996). Deficiencies at either one, or a combination, of these sites of lesion could lead to synchrony problems at the level of the VIII nerve. For example, loss of VIII nerve fibers and/or demyelination of the same could cause irregular neural timing, constant or variable slowing of neural conduction, or an amalgamation of these two processes (Starr, Picton, & Kim, 2001). Regardless of the underlying cause, such dys-synchronous activity would lead to abnormalities in the ABR, AR, and temporal processing deficits. In light of recent reports of the neurological elements of SNHL related to noise exposure and aging, such as irregularities in the synapses between the IHC and VIII nerve and degeneration of the VIII nerve (Kujawa & Liberman, 2006; 2009), it is reasonable to draw parallels between ANSD and SNHL in terms of neural degradation beyond the cochlea.

Neuronal degradation can have adverse effects on speech perception, especially in the presence of competing signals, such as noise (e.g., Kraus et al, 2000; Sininger & Oba, 2001; Rance et al, 2005; 2007; 2008; 2009; 2012). Zeng and colleagues (1999; 2004; 2006) have presented detailed evidence that much of the difficulty understanding speech experienced by those with ANSD stems from temporal processing deficits. For instance, individuals with ANSD show deficits in pitch discrimination at low frequencies, temporal integration, gap detection, backward and forward masking, signal detection in noise, temporal modulation detection, binaural beats, and sound localization that relies on interaural time differences, all of which are considered critical for speech understanding (Zeng et al, 2004). Though not all people with SNHL demonstrate deficiencies in the above mentioned psychophysical skills, many do, especially elderly patients (i.e., central presbycusis; see Humes et al, 2012 for a review). Given these common deficiencies, it is reasonable to speculate on a possible shared neural pathophysiology between ANSD and SNHL.

1.3 How might VIII nerve dys-synchrony alter the central auditory system?

A commonly held tenet of neuroscience is that deprivation of normal stimulation of sensory cortices has the potential to cause maturational abnormalities (see Pallas 2001 for a review). Many may think of deprivation as the overall lack or absence of stimulation. Indeed, this type of deprivation has the ability to alter development (e.g., Wiesel & Hubel, 1963). For example, Sharma and colleagues (2002a, b, c; 2005 a, b) have shown in a number of studies that children diagnosed with SNHL exhibited atypical development of the auditory cortex, unless auditory stimulation is restored (via hearing aids or cochlear implants) during a time of maximal cortical plasticity (i.e., sensitive period) of approximately 3.5 years.

While reduction or lack of sensory stimulation deprives cortices of normal input and has the ability to change development, there may be other types of deprivation that can have similar and equally detrimental effects. We submit that the irregular neural activity that occurs in ANSD leads to an atypical pattern of cortical stimulation. While the beginnings of cortical specification are driven by molecular and genetic factors, later refinement is dependent on sensory input (see Pallas, 2001 for a review). If sensory input, or the mechanism by which this stimulation is delivered to the brain, is abnormal, cortical development can suffer. Sur

and colleagues (1988) illustrated this phenomenon by experimentally altering the course of visual inputs to the thalamus so that they innervated auditory, rather than visual, thalamic areas. By performing these procedures, these investigators effectively provided the auditory cortex with visual stimulation without altering the pathways by which this input was delivered. Upon observation, these researchers found that their methods had induced visual cortex-like changes in structure and functioning of the auditory cortex. Thus, it is evident that cortical maturation is largely dependent on the pattern of the neural activity that it receives from the periphery. Applied to ANSD, this principle implies that the disordered pattern of neural input to the cortex, as a result of VIII nerve dys-synchrony, could have negative effects on the maturation of the auditory cortex in this population. Furthermore, since normal development of the auditory cortices necessarily precedes typical speech and language ability acquisition, disruptions in the maturation of the auditory cortex secondary to auditory dys-synchrony have the potential to place children at risk for delayed oral language development.

In conjunction with deprivation, another important factor in neural development is competition between neurons for resources and synaptic space. That is, as the cortex is developing, regular neural activity leads to axonal growth and the establishment of synapses—continued and consistent activity in these forming neurons and their connections result in increases in synaptic strength (Hebb, 1949). There are many factors that contribute to the strength and durability of certain synapses. For example, release of neurotrophic factors, which changes and improves the structure and function of connected neurons, is activity-dependent. Additionally, the amount of neurotrophic factors contained in the cortex is limited. Thus, developing neurons engage in a competition for these synapse strengthening resources and neurons that don't exhibit consistent activity suffer in this competitive atmosphere. Also, cadherins—a class of proteins that function as a type of synaptic adhesive—greatly strengthen the connections between developing neurons. The proliferation and deployment of cadherins depends, again, on stable neural activity (e.g., Fields & Itoh, 1996). Given the activity-dependent nature of these, and other, factors important to the normal development of the central nervous system, it is reasonable to suppose that irregular or dys-synchronous neural cortical input could lead to developmental abnormalities related to reduced ability to form strong synaptic connections.

A range of levels of neural dys-synchrony within the population of ANSD likely means a coincident gradient of differing patterns of subcortical input to the auditory cortex. These patterns are liable to have bearing on the formation and strengthening of neural connections along the auditory neuraxis, as well as specification of cortical regions during development (Sur et al, 1988; Pallas, 2001). That is, during normal maturation an excess of neurons and neuronal connections is generated by the brain, which is culled to an appropriate amount through a pruning process that is informed by external stimulation. The neurons and connections that are most consistently activated by robust and normal patterns of activity are the ones that persist (see Goodman & Shatz, 1993 for a review). Given this process for synapse formation and cortical specification, dys-synchronous activity would plausibly lead to abnormalities in synaptic pruning, weak synaptic connections, and/or strengthening of abnormal neuronal connections, which would cumulatively result in deficient cortical development and organization.

Homeostatic plasticity—the ability of neural networks to maintain optimal excitatory activity by altering excitatory and inhibitory properties—is also activity-dependent and affected by deprivation (see Turrigiano & Nelson, 2004 for a review). For example, cortical neurons have been shown to be able to alter their level of excitability by manipulating their synapses (e.g., receptor number and sensitivity) based on changes in activity (e.g., Turrigiano et al, 1998; O'Brien et al, 1998). Furthermore, studies examining networks of cortical pyramidal neurons, using *in vitro* preparations, have shown that pharmacologic blockade of excitatory input over long periods of time eventually lead to hyperexcitability. Following the removal of the obstruction, normal levels of excitatory activity were restored (Ramakers, Corner, & Habets, 1990; Corner & Ramakers, 1992; Ramakers et al, 1994; Van Den Pol, Obrietan, & Belousov, 1996). Hyperexcitability (or reduction of inhibitory activity) may have several negative consequences in the auditory modality. For instance, precise neural activity is needed for the highly accurate temporal processing that must take place in the auditory system in order to decode complex acoustic signals (i.e., speech and speech in noise; Frisina & Frisina, 1997). Thus, a downregulation of inhibition, secondary to deprivation-induced homeostatic plasticity, could lead to compromised temporal processing abilities (Gourévitch et al, 2014). In addition, recent reports have linked hyperexcitability and lack of neuronal inhibition to tinnitus, hyperacusis, and aging (e.g., Schaette & Kempter, 2006; Caspary et al, 2008; Gold & Bajo, 2014; Gourévitch et al, 2014). It is plausible that similar changes in central nervous system structure and function could also occur in a system in which deprivation via reduced or abnormally patterned activity was occurring, especially in development.

2.1 Patterns of cortical development in ANSD

Because of the potential for altered neuroplasticity, it is imperative that central auditory development be evaluated and monitored in patients with hearing impairment, including those with ANSD. One non-invasive methodology that can perform this function in humans is cortical auditory evoked potentials (CAEP). These EEG measurements can provide a window into the development of the central auditory system by recording the auditory cortex's responses to sound. In normal hearing individuals, the latency, morphology, and amplitude of the CAEP response are age-dependent (see Steinschneider et al, 2011 for a review). For instance, in infancy and young childhood, a large positive-going peak, known as the P1, that arises from the auditory cortices (Gilley et al, 2008) dominates the CAEP. This waveform component systematically decreases in latency as age increases in typically developing individuals. This latency activity is reflective of the improvements in neural conduction time and synaptic strength improvements that occur in typical development (Eggermont, 1988; Eggermont et al., 1997; Liegeois-Chauvel et al., 1994; Sharma et al., 1997). Sharma and colleagues (1997; 2002 a, b, c) quantified this shift in P1 latency by providing normative data in the form of 95% confidence intervals for normal P1 latency development.

Given this understanding of the normal course of maturation of the P1 CAEP, cortical potentials can be used to evaluate the development of the auditory cortex in individuals with auditory disorders. The ABR is typically grossly abnormal in people with ANSD since the short latency ABR recordings require very high levels of precisely synchronous neural

firing, however, CAEPs which occur over much longer latency are able to absorb greater jitter in the underlying neural synchrony and therefore can be recorded in many patients with this disorder (Michalewski et al., 1986; Kraus et al, 2000). In fact, several reports have argued that CAEPs may be useful biomarkers of cortical maturation in children with ANSD (Rance et al, 2002; Narne & Vanaja, 2008; Sharma et al, 2011; Cardon & Sharma, 2013).

Because of its age-related latency dynamic, the P1 can be used as a biomarker of cortical auditory maturation when compared to the 95% confidence intervals for normal P1 latency development (Sharma et al, 2002 a, b, c; 2005 a, b). We employed this utility to examine the central auditory maturation in children with ANSD (Sharma et al, 2011). Following the recording of P1 CAEP responses in these participants, analysis revealed three distinct cortical response patterns: 1) Children with present and normal P1 CAEP responses; 2) Children with present P1 CAEP responses of delayed latency and reduced amplitudes; 3) Children with abnormal or absent P1 CAEP responses (see Figure 1.i-1.iii). In this manuscript, and elsewhere we refer to these three patterns as *normal*, *delayed* and *abnormal*, respectively (Sharma et al, 2011; Cardon & Sharma, 2013; Nash & Sharma, 2014). These patterns are consistent with those described in studies from other laboratories. For instance, Rance et al (2002) recorded CAEPs in a group of children with ANSD. They reported that approximately 50% of their participants exhibited robust CAEP responses, while the remainder of the group presented with absent CAEP responses. The children who had present CAEP responses also performed significantly better on a measure of speech perception, indicating superior cortical maturation. In another study, (Narne & Vanaja, 2008) children and adults aged 12–39 years fell into two groups based on their speech perception scores—good performers and poor performers. When the CAEPs of these two groups were compared, the group of good performers showed CAEPs of significantly greater amplitude than those of the poor performers, which may be an indication of better auditory neural synchrony. In fact, one of the earliest accounts of ANSD provided evidence that CAEPs could be recorded in some patients with ANSD (Starr et al, 1996). These authors also conjectured that present CAEPs were an indication of lesser dys-synchrony. Thus, it is reasonable to argue that CAEP findings could be used to draw conclusions about the extent of abnormality in subcortical neural firing driving development of the auditory cortex in persons with ANSD. We submit that, absent or abnormal P1 CAEP responses may be indicative of the most severe degree of dys-synchronous neural activity, resulting in abnormal cortical development. In contrast, P1 CAEP responses with normal morphology, latency, and amplitudes reflect more typical development of the auditory cortices and likely indicate a mild level of latent auditory neural dys-synchrony. Delayed P1 responses likely reflect a moderate level of neural dys-synchrony, which allows cortical maturation to progress to some extent, but at a slower (delayed) trajectory.

Other measures of cortical maturation in ANSD may be useful in understanding the full extent of the cortical consequences of auditory neural dys-synchrony. In a recent study, we analyzed the sources of cortical activity in a child with unilateral ANSD (Nash & Sharma, 2014). We collected high density EEG to repeated presentations of an auditory stimulus and then performed current density reconstructions to estimate the generators of the recorded cortical activity (Pasqual-Marqui, 2002). The patient in whom we performed these analyses

presented with normal and abnormal P1 CAEP responses in the normal hearing and ANSD ears, respectively. Source localization analysis revealed expected activation of superior temporal sulcus and insula underlying the normal CAEP responses (Figure 1.iv). However, the ANSD ear produced highly variable responses that did not allow accurate estimation of the sources of cortical activity (Figure 1.v). Given these results, we reasoned that dys-synchronous input to the cortex likely leads to disordered and variable cortical activity (Stevens & Zador, 1998; Mazurek & Shadlen, 2002; Wang, Webber, & Stanley, 2010), which is reflected in the inability of the current density reconstruction methods to reliably appraise the sources of this activity in the above study.

While EEG has proven useful in providing a window into the neurophysiological processes at work in ANSD, most, if not all, studies to our knowledge have relied on the averaged evoked potential to supply this view. Methodologically, averaged evoked responses are assumed to reflect a neuronal response that is stable across trials. However, in actuality, the individual trials that ultimately make up the averaged response may differ significantly in latency, amplitude, and/or morphology. Variation between trials, when averaged, can cause waveform misrepresentations, such as amplitude reductions and morphology distortions (Brazier, 1964). Moreover, because of phase cancellation, data representing oscillatory (i.e., induced) brain activity is eliminated during the averaging process (Nash & Sharma, 2014). Thus, much of the information that may be most informative in patients with ANSD, such as variations in neural responses to individual stimuli, is lost when averaging occurs during evoked potential analysis. To investigate this possibility, we studied the single trials underlying the component averages that were identified during independent components analysis (ICA) of the high-density EEG collected in the patient with unilateral ANSD (Nash & Sharma, 2014). The stacked trials are shown in Figure 1.vii. A great deal more variability between trials was observed within the EEG collected for the ANSD ear (Figure 1.vii), versus the normal hearing ear (Figure 1.vi). 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 (as indicated by the strongly colored blue or red columnar areas (Figure 1. vii) while the ANSD ear shows more inconsistent, temporally smeared activation (Figure 1. vi). In other words, sound stimuli did not seem to evoke a reliable response from the auditory cortex when the ANSD ear was stimulated repeatedly with an identical acoustic stimulus, especially when compared to the normal hearing ear. Based on these results, it is reasonable to conjecture that in cases of severe dys-synchrony reflected in ANSD patients who show abnormal CAEP responses, sound-induced cortical activation may have little functional meaning for these patients. That is, when auditory stimulation results in variable responses from the auditory cortex, these weak and variable response patterns may not reach the threshold for forming appropriate synaptic connections allowing auditory learning to occur. In light of this notion, it is easy to see how individuals with abnormal cortical responses most often perform poorly on measures of speech perception and auditory skill development (Rance et al, 2002; Sharma et al, 2011; see also section 3.1). Interestingly, there may be parallels between children with ANSD and many children who have auditory processing disorders (APD) secondary to chronic otitis media with effusion resulting in an intermittent and variable

auditory signal reaching the auditory cortex. Moore et al (2006) has suggested that APD and ANSD may form a continuum, such that ANSD may reflect a severe form of APD.

In an effort to further characterize the relationship between averaged cortical responses and the underlying degree of neural synchrony—or dys-synchrony—we have performed time-frequency analysis on the CAEPs from children exhibiting normal, delayed, and abnormal response patterns. To measure this phenomenon, we used inter-trial coherence (ITC) to reflect cortical phase synchronization. Interruptions in ongoing EEG caused by incoming stimuli result in “phase-locking” of the EEG phase distribution to these events (Makeig et al, 2004). This synchronization of EEG phase can be measured by determining the relationship between the phase of single trials at all time points for recorded frequencies. A higher degree of phase synchrony appears to be associated with functional outcome, and seems to be important for information processing within and across cortical areas (i.e., feature-binding and other cognitive processes; Tass et al, 1998; Palva et al, 2005).

Selected results from this analysis, which are relevant to the current discussion, are presented in Figure 1.viii-xi. For example, Figure 1.viii-x shows ITC time-frequency outputs and grand average CAEP waveforms underlying the normal, delayed, and abnormal CAEP responses from ANSD children. In these graphs, while green area represents essentially non-existent phase synchrony, yellow, orange, and red highlighted areas reflect increasingly higher phase-locking factor. In other words, areas shaded in yellow, orange, and red are those time points and frequencies for which the EEG single trials were highly synchronized. The ANSD group with normal P1 CAEP responses (Figure 1.viii) showed high levels of ITC, while the other two ANSD groups (delayed and abnormal CAEPs) progressively showed less phase synchrony. Figure 1.xi presents a comparison of the peak ITC value recorded for each of the three ANSD groups, as well as for a group of age-matched children with normal hearing. Statistically significant differences were found between the results from the normal hearing group and all of the ANSD groups, as well as the normal ANSD group from all other groups ($p < 0.01$). Interestingly, children with ANSD who presented with “normal” P1 CAEP responses exhibited a significantly lower peak phase locking factor than the children with normal hearing. Thus, it would appear that a completely normal level of cortical synchrony is not needed to drive normal-like development of the CAEP. Overall, the ITC data showed clear deficits in cortical phase synchronization underlying P1 responses in ANSD, suggesting that levels of central auditory maturation are closely related to the levels of cortical synchrony, which is likely tied to subcortical patterns of neural activity.

In addition to signal degradation and auditory cortical maturational deficits, deficits in cortical phase synchrony have been associated with abnormalities with other, higher-order, cognitive processes. These deficiencies include auditory hallucinations in schizophrenic patients (Ford et al, 2007), ictal activity in epilepsy (Le Van Quyen et al, 2003), motor initiation slowness and tremor in Parkinson’s disease (Uhlhaas and Singer, 2006), and working memory difficulties in individuals with Alzheimer’s disease (Pijnenburg et al, 2004). Given these findings, it follows that the compromised phase coherence levels observed in ANSD may be reflective of neurodevelopmental cognitive deficits reported in these individuals (Rance et al, 2007).

Although useful, EEG studies performed in humans may not be able to elucidate the finer details of the pathophysiology underlying ANSD. A deeper understanding of the etiological and neurophysiological aspects of ANSD may necessitate more invasive research methods that can be performed in animals. A number of studies have been published that document the development of animal models for ANSD (Harrison, 1998; Shaia, Shapiro & Spencer, 2005; El-Badry et al, 2007; El-Badry & McFadden, 2007; Gilels et al, 2013). In the first documented animal model for ANSD, Harrison (1998) used carboplatin to induce widespread inner hair cell loss in chinchillas. These animals presented with robust OAEs and CMs, but elevated ABR thresholds. Additionally, this study reported that neurons in the inferior colliculus showed lower than normal response thresholds, which may be an indication of central auditory system abnormality. Similar methods were used to induce ANSD-like symptoms in another group of chinchillas (El-Badry & McFadden, 2007). These authors reported neuronal abnormalities associated with IHC loss that included axonal and myelin loss. Other studies using an animal model with genetically induced ANSD-like clinical characteristics have reported similar neuronal findings (Gilels et al, 2013). While these studies have largely focused on deficiencies in the cochlea, VIII nerve, and brainstem, and not the auditory cortex, they demonstrate the utility of animal models in investigating the pathophysiology of a disorder like ANSD. Future studies have the potential to increase understanding significantly by using animal models to examine the pathophysiology underlying the specific abnormalities in central auditory maturation observed in human patients with ANSD.

3.1 Cortical maturation and behavioral outcome

Recent studies from our laboratory and other laboratories (Rance et al, 2002; Michalewski et al, 2005; Sharma et al, 2011; Alvarenga et al, 2012; Cardon & Sharma, 2013), have found that cortical development and functioning is a strong predictor of behavioral outcome. For example, Sharma et al., 2011 and Cardon and Sharma 2013 reported that behavioral outcome was significantly different between children with ANSD who had normal, delayed, and abnormal P1 CAEP responses such that performance on a measure of auditory skill development (Infant Toddler Meaningful Auditory Integration Scale—IT-MAIS; Zimmerman-Phillips et al, 2000) was appreciably lower for the children with delayed and abnormal P1 CAEP responses, compared to those with normal responses. For this review, we collapsed the data from the Sharma et al., 2011 and Cardon and Sharma, 2013 studies to analyze the relationship between auditory skill development and P1 CAEP latency in a larger group of children with ANSD. As seen in Figure 2, we describe a significant correlation between P1 latency response and auditory skill development as measured by the IT-MAIS. ($r = 0.63$; $p < 0.01$; Figure 2.i). Consistent with our results, Rance et al (2002) also report that children who presented with absent CAEP responses performed significantly worse on tests of speech perception. Moreover, other investigators have presented data showing that CAEPs collected in response to brief gaps in continuous stimuli of different durations were significantly correlated to performance on a behavioral word recognition measure (He et al, 2013). Based on these studies we can conclude that auditory neural dys-synchrony not only has the potential to negatively affect the auditory cortical development

in ANSD patients, but that these effects, in turn, can lead to behavioral deficits in auditory skill development and auditory processing.

While behavioral performance can be predicted to a large degree by auditory thresholds in many patients with SNHL (Yellin et al, 1989), this does not appear to be the case in ANSD (e.g., Deltenre et al, 1999; Zeng et al, 1999; Kraus, 2001; Sininger et al, 2001; Rance et al, 1999; 2002; Rapin & Gravel, 2003; Sharma et al, 2011; Cardon & Sharma, 2013). That is, in a number of studies, including those from our laboratory, behavioral auditory thresholds failed to explain the variance in behavioral outcome in children with ANSD (Rance et al, 2002; Sharma et al, 2011; Cardon & Sharma, 2013). Given the aforementioned relationship between CAEP measures of auditory cortical maturation and behavioral indices of speech perception and auditory skill development, CAEPs may be more useful in monitoring patient development and providing prognoses than results yielded by traditional behavioral audiometry.

4.1 Cortical changes after intervention with amplification and/or electrical stimulation

There exists some debate regarding the most effective course of treatment for patients with ANSD. While some people advocate the use of conventional acoustic amplification via hearing aids, citing studies in which hearing aids have appeared to provide benefit to some with ANSD (e.g., Rance et al, 2002; Sharma et al, 2011; Cardon, Campbell, & Sharma, 2012), others disagree (e.g., Berlin et al, 1998; Hood, 1998). In one of our recent studies (Sharma et al, 2011), we concluded that though hearing aids did not seem to promote normal central auditory maturation in many children with ANSD, they did appear to provide benefit for a subset of the study sample—approximately 1/3 of our subjects. We reasoned that acoustic amplification likely assists children with the mildest degree of dys-synchrony (i.e., children with normal P1 responses), but that this treatment method is not enough to overcome more severe cases of ANSD (i.e., delayed and abnormal P1 responses). That is, simply amplifying the incoming auditory signal probably improves synchrony to some degree by: 1) improving phase locking and synchronous discharge of IHCs; 2) increasing the total activity of the IHCs and VIII nerve (Javel, 1986). Since temporal processes, such as phase locking, are most likely to be compromised and overall number of functioning IHCs and/or VIII nerve fibers are reduced in patients with ANSD, improvements such as the above may serve to help certain patients with ANSD with mild levels of dys-synchrony, though they are probably in the minority.

An alternative treatment for individuals with ANSD, which has shown promise, is cochlear implantation (CI). While some have provided compelling evidence of the effectiveness of CIs as a treatment in ANSD (Miyamoto et al, 1999; Trautwein et al, 2000; Shallop et al, 2001; Mason et al, 2003; Peterson et al, 2003; Buss et al, 2002; Rance & Barker, 2008, 2009; Berlin et al, 2010; Teagle et al, 2010; Carvalho et al, 2011; Breneman et al, 2012), others have been more cautious in their advocacy, due to poor outcomes in some CI users with ANSD (e.g., Neary & Lightfoot, 2012).

From the perspective of central auditory maturation, overall, cochlear implants seem to yield more favorable results in a greater number of children than hearing aids (Cardon & Sharma, 2013). For instance, recently published results from our laboratory showed two groups of cochlear-implanted children with ANSD, based on their P1 CAEP responses—normal and delayed. That is, after cochlear implantation, there were no children who exhibited abnormal cortical responses. In other words, though not all pediatric CI users with ANSD presented with *normal* P1 CAEP responses, each of them was found to have present and replicable responses, unlike a subset of patients with ANSD who used hearing aids and showed abnormal cortical responses (Sharma et al., 2011). This finding is consistent with results from other studies that have shown that all participants presented with identifiable CAEP responses (He et al, 2013). In addition to mere presence of P1 CAEP responses, we and others, have shown that CAEPs appear to be significantly correlated with behavioral outcome in CI recipients with ANSD (Alvarenga et al, 2012; Cardon & Sharma, 2013). For instance, Alvarenga and colleagues (2012) presented evidence that the latency of the P1 CAEP response was related to aspects of speech perception in this population. Similarly, we found that P1 CAEP latency was significantly correlated to children's scores on the IT-MAIS (Cardon and Sharma 2013). However, more in-depth analysis of CAEPs using ITC (Nash and Sharma 2014) showed that, on average, children with ANSD presented with lower cortical phase synchrony levels than either children with SNHL or normal hearing, regardless of intervention with hearing aids or cochlear implants (Figure 2.iii). Taken together, these data seem to suggest that even though some individuals with ANSD benefit from amplification via HAs, and more receive significant assistance from CIs, these devices still may not deliver the amount or type of stimulation needed by ANSD patients to reach completely normal levels of neural synchrony. A small number of studies have ventured to propose new kinds of processing strategies for hearing aids and/or cochlear implants which have attempted to overcome the processing deficits associated with neural dys-synchrony in ANSD (e.g., Zeng & Liu, 2006). While these studies have had mixed success, this is an important future direction in ANSD research.

Aside from the *type* of treatment one might recommend for patients with ANSD, one must also consider the *timing* of intervention. That is, when contemplating auditory deprivation (i.e., either by an overall reduction of sound input or an abnormal pattern thereof) and the introduction or restoration of sound via audiologic treatment, one important aspect of cortical plasticity to bear in mind is that of sensitive periods. A sensitive period is a finite period of time during which the brain is highly plastic and adaptable, and after which plasticity is significantly reduced. Sensitive periods occur throughout life, and in the auditory system are particularly important in early childhood for the development of auditory skills and oral speech and language. Deprivation has been shown to have adverse effects on the outcomes of these sensitive periods in the auditory system. In other words, if normal auditory neural activity does not occur during heightened periods of plasticity, developmental abnormalities can arise (Ponton and Eggermont, 2001; Gordon et al, 2003, 2005; Sharma et al, 1997, 2002a, b, c; 2005a, b; 2006; 2007; 2009). For instance, Kral and colleagues (2005) showed that deaf cats that received a cochlear implant following the closing of the sensitive period were unable to form functional synapses, like those observed in normal-hearing, typically developing cats.

The effects of deprivation and treatment on cortical maturation during and after sensitive periods have also been shown in a number of studies in humans with hearing loss. Studies from our group (Sharma et al, 2002 a, b; 2005 a, b; 2007, 2009; Sharma & Dorman, 2006) provided evidence that children fitted with a CI prior to the age of 3.5 years presented with normal P1 CAEP responses within 3–6 months of experience with the device. In contrast, children who received their implants after seven years of age almost never developed a normal P1 CAEP response, even following several years of CI use. Several investigations using other brain imaging techniques have corroborated these findings (Lee et al, 2001, 2007; Oh et al, 2003). These results converge to elucidate a sensitive period for auditory cortical maturation in relation to cochlear implantation in deaf children. It appears that the introduction or restoration of the proper pattern and level of auditory stimulation during this sensitive period tends to lead to appropriate development of neuronal structure and function (i.e., robust synaptic connections) throughout the central auditory system, since the brain is highly plastic during this time (Hammes et al, 2002; Harrison et al, 2005; Kral et al, 2005; Tomblin et al, 2007).

Compatible with the above studies performed in children with SNHL, our studies in children with ANSD also provide evidence that points to sensitive periods for treatment in this population. For instance, it was more likely for children with ANSD who used hearing aids to develop normal cortical responses, if they had been fitted with a hearing aid earlier in life (i.e., < 1 year of age; Sharma et al, 2011). CI users with ANSD who were fitted earlier in life also tended to present with normal P1 CAEP responses (Cardon & Sharma, 2013). Analysis that was aimed at uncovering a sensitive period for auditory cortical development in ANSD revealed that 72% of the children who showed normal P1's were fitted with their CIs before the age of 2 years, while 75% of children who were fitted after age 2 years showed delayed P1 responses (Figure 2.ii) suggesting, in preliminary form, a sensitive period of approximately 2 years for cochlear implantation in ANSD children. Therefore, it would seem that, as in SNHL, sensitive periods may be a factor driving cortical maturation and its outcomes in children with ANSD.

Differences in the timing of the sensitive periods in children ANSD (approx. 2 years) and that reported for children with SNHL (approx. 3.5 years), suggests that individuals who experience different types and/or degrees of deprivation may present with differing sensitive period dynamics. The interplay between extrinsic and intrinsic factors seem to be at work in the alteration of the timing of sensitive periods. For example, a number of investigators have proposed that inhibitory mechanisms may mediate the dynamics of sensitive periods (Fagiolini and Hensch, 2000; Hensch, 2005). Since the development and maintenance of appropriate inhibitory activity is to a large degree activity-dependent, it is possible that varied stimulation patterns may result in deviations in normal neuronal activity that could modify inhibitory function (Turrigiano & Nelson, 2004), possibly leading to an imbalance in excitation and inhibition (Turrigiano et al, 1998; O'Brien et al, 1998; Ramakers, Corner, & Habets, 1990; Corner & Ramakers, 1992; Ramekers et al, 1994; Van Den Pol, Obrietan, & Belousov, 1996). Thus, it is possible that deprivation could lead to deficiencies related to sensitive periods in at least two ways: 1) deprivation that lasts throughout the duration of a sensitive period can lead to irregularities in the development of neuronal connectivity and function. Such abnormalities may not be fully reversible, even if sensory input is restored

following the closing of the sensitive period; 2) If the balance of excitation and inhibition is affected by deprivation, and if sensitive periods are regulated by inhibitory control, lack of sensory input has the potential to alter the management of sensitive periods (Turrigiano & Nelson, 2004). In fact, a number of studies may provide evidence of the latter. For example, studies performed in animals have shown that rearing under abnormal sound conditions has the tendency to alter the maturation of the auditory cortex. In a couple of studies, rodents that were raised in continual noise exhibited delayed central auditory development and modified sensitive periods for auditory cortical maturation (Chang & Merzenich, 2003; Villers-Sidani et al, 2007). Still others have examined the maturation of the extracellular matrix of the cerebral cortex as a marker of changes in plasticity (see Berardi, Pizzorusso & Maffei, 2004, for a review). For instance, chondroitin-sulfate proteo-glycans (CSPGs), which are found in the extracellular matrix, appear to play a role in sensitive period regulation. Functionally, CSPGs serve to hinder axonal regeneration and sprouting (Bradbury et al, 2002; Silver & Miller, 2004). Previous reports have shown increases in CSPGs in the extracellular matrix, starting in developing individuals and culminating in the end of the critical period for ocular dominance development in the visual cortex (Berardi, Pizzorusso & Maffei, 2004). In contrast, studies done in subjects who had been reared in constant darkness provided evidence of delayed sensitive period closure and concomitant decreased levels of CSPGs (Hockfield et al, 1990). Additionally, Pizzorusso and colleagues (2002) performed a procedure in which CSPGs were actively degraded in monocularly deprived adult rats, which lead to a revival of ocular dominance plasticity in these older individuals. Thus, it appears that sensitive periods may be re-opened after their natural closure. These data support the notion that experience dependent changes in the deficient central nervous system can alter the natural schedule of development. These ideas, applied to the current discussion suggest that the disordered stimulation of the auditory cortex due to neural dys-synchrony in individuals with ANSD could result in changes to the initiation and closing of sensitive periods in this population. Furthermore, the fact that a large proportion of children with ANSD are born prematurely may also partially explain potential differences in developmental sensitive periods for example, between SNHL and ANSD. Overall, we propose that, not only must we heed these possible neuronal consequences of VIII nerve dys-synchrony (i.e., sensitive period dynamics), but that future studies should focus on the potential to harness certain aspects of neural plasticity in possibly re-opening sensitive periods for children with ANSD.

5.1 Clinical Implications

Many children with ANSD are diagnosed very early in life, due to physiologic diagnostic testing procedures available to clinicians (i.e., ABR, OAEs). However, beyond diagnosis, very little can be done to evaluate or treat infants and young children with ANSD. This obstacle stems, to a large degree, from the current need for behavioral audiometric thresholds in hearing aid fitting. Thus, clinicians often wait for several months after a child is old enough to participate in behavioral audiometry while they obtain several sets of these test results—to ensure stable results in the face of high inter and intra-individual variability in ANSD. This delay in treatment likely has deleterious effects on central auditory maturation and behavioral auditory skill development in young children with ANSD

(Sharma et al, 2011; Cardon & Sharma, 2013). Furthermore, given the evidence that thresholds obtained via traditional audiometry are not predictive of behavioral ability in individuals with ANSD, some have questioned their value in motivating clinical decisions in this population (Deltenre et al, 1999; Rance et al, 1999, 2002; Rapin & Gravel, 2003; Zeng et al, 1999; Sharma et al, 2011; Cardon & Sharma, 2013). Add to these ideas the fact that auditory thresholds fluctuate in many individuals with ANSD, and one can see that reliance on this measure of auditory abilities may not be optimal in patients with ANSD.

In fact, it appears that the use of CAEPs may be beneficial in the early evaluation of children with ANSD (Cardon, Campbell, and Sharma, 2012). This type of non-invasive physiologic testing of the central auditory system has proven useful in providing prognoses, verifying treatment effectiveness, and making adjustments to treatments in children with ANSD. For instance, in light of the above discussion regarding the use of hearing aids or cochlear implants as interventions for children with ANSD, one could make more informed clinical decisions by using P1 CAEP latency calculations and ITC in combination. That is, if a patient presented with a normal P1 CAEP (i.e., within the 95% confidence intervals for normal P1 latency development) and a high level of ITC, a clinician might conclude that the degree of underlying dys-synchrony was mild and might be treated with a hearing aid—synchrony might be improved enough to allow for normal or near normal behavioral outcome (see Eggermont, 2000 for a discussion on intensity-related improvements in neural synchrony). This decision could be further verified with serial P1 CAEP testing and analysis (Figure 2.iv). On the other hand, if a child's P1 CAEP response was delayed relative to the normal limits, especially after a hearing aid trial, a more severe level of neural dys-synchrony might be assumed. In this case, hearing aids may not be able to promote sufficient synchrony to drive normal development. Thus, a CI might be recommended for this child. In the case presented in Figure 2.v, though hearing aid use did not improve synchrony enough to drive normal auditory cortical development, cochlear implantation appears to have done so.

An additional use for CAEPs in the treatment process for infants and young children with ANSD may be the acquisition of auditory thresholds. Though peripheral auditory thresholds may not be highly related to behavioral auditory capability in individuals with ANSD (Deltenre et al, 1999; Rance et al, 1999, 2002; Rapin & Gravel, 2003; Zeng et al, 1999; Sharma et al, 2011; Cardon & Sharma, 2013), they are necessary for hearing aid programming and determination of cochlear implant candidacy at this time. However, unlike in infants with SNHL, early auditory thresholds cannot be obtained in newborns with ANSD, because their ABR and auditory steady state response (ASSR) results are most often grossly abnormal (Rance et al, 2005). Given this problem, and that auditory thresholds are needed to fit patients' hearing aids, recent work in our lab has been focused on investigating the utility of CAEPs in acquiring auditory thresholds in children with ANSD, since these evoked potentials can be recorded in a large portion of the pediatric ANSD population (Rance et al, 2002; Sharma et al, 2011; Alvarenga et al, 2012; Cardon & Sharma, 2013). Further, the threshold information obtained using CAEPs is likely more reliable than peripheral hearing thresholds since CAEPs thresholds also reflect cortical processing ability. Other investigators have also recently published results showing that CAEPs could not only provide accurate threshold information in a number of cases of children with ANSD, but

also that this method could be clinically feasible (He et al, 2012). In all, we submit that central auditory function and maturation, and the methods that measure it, should be considered and employed regularly in the clinical evaluation and decision-making process when working with individuals with ANSD.

6.1 Summary and Conclusions

Though ANSD is a relatively recently discovered auditory disorder, advances in our understanding of the underlying pathophysiology, evaluation, and management of patients with ANSD have occurred over the past several years. CAEPs have contributed significantly to this understanding by providing a window into central auditory function and maturation in individuals with ANSD. Additionally, recent reports in subjects with SNHL have made it evident that ANSD and SNHL may overlap more than originally considered, with respect to the neural aspects of hearing loss. Data from studies focusing on the neural aspects of hearing loss have provided compelling evidence that auditory deprivation can have adverse effects on central auditory maturation, but that these negative effects can often be avoided, if the appropriate treatment is provided at the right time. Thus, neuromaturational factors in ANSD must be taken into account in order to fully understand and best serve those who suffer from these disorders. CAEPs can aid in assessing the extent of neural insults in hearing loss and in clinical decision-making and verification of these decisions.

Acknowledgements

Research supported by grants from the National Institutes of Health-National Institute of Deafness and Other Communication Disorders (NIH-NIDCD) to A.S. (R01DC0625) and G.C. (F31 DC013218-01A1)

Abbreviations

ANSD	Auditory Neuropathy Spectrum Disorder
SNHL	sensorineural hearing loss
CND	cochlear nerve deficiency
CAEP	cortical auditory evoked potentials
OAE	otoacoustic emissions
AR	auditory brainstem response acoustic reflex
IHC	inner hair cells
ICA	independent components analysis
APD	auditory processing disorder
ITC	inter-trial coherence
IT-MAIS	Infant Toddler Meaningful Auditory Integration Scale
CI	cochlear implant

References

- Alvarenga KF, Amorim RB, Agostinho-Pesse RS, Costa OA, Nascimento LT, Bevilacqua MC. Speech perception and cortical auditory evoked potentials in cochlear implant users with auditory neuropathy spectrum disorders. *Int J Pediatr Otorhinolaryngol.* 2012; 76(9):1332–1338. [PubMed: 22796193]
- Berardi N, Pizzorusso T, Maffei L. Extracellular matrix and visual cortical plasticity: freeing the synapse. *Neuron.* 2004; 44(6):905–908. [PubMed: 15603733]
- Berlin C, Hood L, Morlet T, Wilensky D, St John D, Montgomery P, Thibodaux E. Absent or elevated middle ear reflexes in the presence of normal otoacoustic emissions: a universal finding in 136 cases of auditory neuropathy/dys-synchrony. *J Amer Acad Audiol.* 2005; 16:546–553. [PubMed: 16295241]
- Berlin C, Bordelon I, St John J, Wilensky P, Hurley D, Kuka E, Hood L. Reversing click polarity may uncover auditory neuropathy in infants. *Ear Hear.* 1998; 19(1):37–47. [PubMed: 9504271]
- Berlin CI, Hood LJ, Morlet T, Wilensky D, Li L, Mattingly KR, et al. Multi-site diagnosis and management of 260 patients with auditory neuropathy/dys-synchrony (auditory neuropathy spectrum disorder). *Int J Audiol.* 2010; 49(1):30–43. [PubMed: 20053155]
- Berlin C, Morlet T, Hood L. Auditory neuropathy/dyssynchrony its diagnosis and management. *Pediatr Clin N Am.* 2003; 50:331–340.
- Bielecki I, Horbulewicz A, Wolan T. Prevalence and risk factors for Auditory Neuropathy Spectrum Disorder in a screened newborn population at risk for hearing loss. *Int J Pediatr Otorhinolaryngol.* 2012; 76(11):1668–1670. [PubMed: 22939890]
- Bradbury EJ, Moon L, Popat RJ, King VR. Chondroitinase ABC promotes functional recovery after spinal cord injury. *Nature.* 2002; 416:636–640. [PubMed: 11948352]
- Brazier MAB. Evoked responses recorded from the depths of the human brain. *Ann N Y Acad Sci.* 1964; 112:33–59. [PubMed: 14188106]
- Breneman AI, Gifford RH, Dejong MD. Cochlear implantation in children with auditory neuropathy spectrum disorder: long-term outcomes. *J Amer Acad Audiol.* 2012; 23(1):5–17. [PubMed: 22284837]
- Buchman CA, Roush PA, Teagle HFB, Brown CJ, Zdanski CJ, Grose JH. Auditory neuropathy characteristics in children with cochlear nerve deficiency. *Ear Hear.* 2006; 27(4):399–408. [PubMed: 16825889]
- Buss E, Labadie RF, Brown CJ, Gross AJ, Grose JH, Pillsbury HC. Outcome of Cochlear Implantation in Pediatric Auditory Neuropathy. *Otol Neurotol.* 2002; 23(3):328. [PubMed: 11981390]
- Cardon G, Sharma A. Central auditory maturation and behavioral outcome in children with auditory neuropathy spectrum disorder who use cochlear implants. *Int J Audiol.* 2013; 52(9):577–586. [PubMed: 23819618]
- Cardon G, Campbell J, Sharma A. Plasticity in the developing auditory cortex: evidence from children with sensorineural hearing loss and auditory neuropathy spectrum disorder. *J Amer Acad Audiol.* 2012; 23(6):396–411. quiz 495. [PubMed: 22668761]
- Carvalho ACM, de Bevilacqua MC, Sameshima K, Costa Filho OA. Auditory neuropathy/Auditory dyssynchrony in children with Cochlear Implants. *Braz J Otolaryngol.* 2011; 77(4):481–487.
- Caspary DM, Ling L, Turner JG, Hughes LF. Inhibitory neurotransmission, plasticity and aging in the mammalian central auditory system. *J Exper Biol.* 2008; 211(11):1781–1791. [PubMed: 18490394]
- Chang EF, Merzenich M. Environmental noise retards auditory cortical development. *Science.* 2003; 300(5618):498–502. [PubMed: 12702879]
- Corner MA, Ramakers GJA. Spontaneous firing as an epigenetic factor in brain development — physiological consequences of chronic tetrodotoxin and picrotoxin exposure on cultured rat neocortex neurons. *Devel Brain Res.* 1992; 65(1):57–64. [PubMed: 1551233]
- Delmaghani S, del Castillo FJ, Michel V, Leibovici M, Aghaie A, Ron U, et al. Mutations in the gene encoding pejvakina, a newly identified protein of the afferent auditory pathway, cause DFNB59 auditory neuropathy. *Nat Genet.* 2006; 38(7):770–778. [PubMed: 16804542]

- Deltenre D, Mansback P, Bozet A, Christaens C, Barthelamy F, Paulissen P. Auditory neuropathy with preserved cochlear microphonics and secondary loss of otoacoustic emissions. *Int J Audiol*. 1999; 38(4):187–195.
- Eggermont JJ. On the rate of maturation of sensory evoked potentials. *Electroen Clin Neurophysiol*. 1988; 70(4):293–305.
- Eggermont JJ. Sound-induced synchronization of neural activity between and within three auditory cortical areas. *J Neurophysiol*. 2000; 83(5):2708–2722. [PubMed: 10805671]
- Eggermont JJ, Ponton CW, Don M, Waring MD, Kwong B. Maturation delays in cortical evoked potentials in cochlear implant users. *Acta Oto-Laryngol*. 1997; 117(2):161–163.
- El-Badry MM, Ding D-L, McFadden SL, Eddins AC. Physiological effects of auditory nerve myelinopathy in chinchillas. *Eur J Neurosci*. 2007; 25(5):1437–1446. [PubMed: 17425569]
- El-Badry MM, McFadden SL. Electrophysiological correlates of progressive sensorineural pathology in carboplatin-treated chinchillas. *Brain Res*. 2007; 1134:122–130. [PubMed: 17198689]
- Fagioli MHT. Inhibitory threshold for critical-period activation in primary visual cortex. *Nature*. 2000; 404:183–186. [PubMed: 10724170]
- Fields RD, Itoh K. Neural cell adhesion molecules in activity-dependent development and synaptic plasticity. *Trends Neurosci*. 1996; 19(11):473–480. [PubMed: 8931273]
- Foeller EFD. Synaptic basis for developmental plasticity in somatosensory cortex. *Curr Opin Neurobiol*. 2004; 14:89–95. [PubMed: 15018943]
- Ford JM, Krystal JH, Mathalon DH. Neural Synchrony in Schizophrenia: From Networks to New Treatments. *Schizophr Bull*. 2007; 33(4):848–852. [PubMed: 17567628]
- Frisina DR, Frisina RD. Speech recognition in noise and presbycusis: relations to possible neural mechanisms. *Hear Res*. 1997; 106:95–104. [PubMed: 9112109]
- Gilels F, Paquette ST, Zhang J, Rahman I, White PM. Mutation of Foxo3 causes adult onset auditory neuropathy and alters cochlear synapse architecture in mice. *J Neurosci*. 2013; 33(47):18409–18424. [PubMed: 24259566]
- Gilley PSADM. Cortical reorganization in children with cochlear implants. *Brain Res*. 2008; 1239:56–65. [PubMed: 18775684]
- Gold JR, Bajo VM. Insult-induced adaptive plasticity of the auditory system. *Front Neurosci*. 2014; 8:110. [PubMed: 24904256]
- Goodman CSC. Developmental mechanisms that generate precise patterns of neuronal connectivity. *Cell*, Vol. 72/Neuron. 10(Suppl.):77–98.
- Gordon KA, Papsin BC, Harrison RV. Activity-Dependent Developmental Plasticity of the Auditory Brain Stem in Children Who Use Cochlear Implants. *Ear Hear*. 2003; 24(6):485. [PubMed: 14663348]
- Gourévitch B, Edeline J-M, Occelli F, Eggermont JJ. Is the din really harmless? Long-term effects of non-traumatic noise on the adult auditory system. *Nat Rev Neurosci*. 2014; 15(7):483–491. [PubMed: 24946762]
- Hammes DM, Novak MA, Rotz LA, Willis M, Edmondson DM, Thomas JF. Early identification and cochlear implantation: critical factors for spoken language development. *Ann Otol Rhinol Laryngol Suppl*. 2002; 189:74–78. [PubMed: 12018355]
- Harrison RV, Gordon KA, Mount RJ. Is there a critical period for cochlear implantation in congenitally deaf children? Analyses of hearing and speech perception performance after implantation. *Devel Psychobiol*. 2005; 46(3):252–261. [PubMed: 15772969]
- Harrison RV. An Animal Model of Auditory Neuropathy. *Ear Hear*. 1998; 19(5):355. [PubMed: 9796644]
- Hassan DM. Perception of temporally modified speech in auditory neuropathy. *Int J Audiol*. 2011; 50(1):41–49. [PubMed: 21047293]
- He S, Grose JH, Teagle HFB, Woodard J, Park LR, Hatch DR, Buchman CA. Gap detection measured with electrically evoked auditory event-related potentials and speech-perception abilities in children with auditory neuropathy spectrum disorder. *Ear Hear*. 2013a; 34(6):733–744. [PubMed: 23722354]

- He S, Teagle HFB, Roush P, Grose JH, Buchman CA. Objective hearing threshold estimation in children with auditory neuropathy spectrum disorder. *Laryngoscope*. 2013b; 123(11):2859–2861. [PubMed: 23620187]
- Hebb, DO. The organization of behavior: a neurophysiological theory. New Ed edition: Psychology Press; 1949. 2002.
- Hensch T. Critical period plasticity in local cortical circuits. *Nat Rev Neurosci*. 2005; 6:877–888. [PubMed: 16261181]
- Hockfield S, Kalb RG, Zaremba S, Fryer H. Expression of Neural Proteoglycans Correlates with the Acquisition of Mature Neuronal Properties in the Mammalian Brain. *Cold Spring Harbor Symposia on Quantitative Biology*. 1990; 55(0):505–514. [PubMed: 2132834]
- Hood L. Auditory Neuropathy: What is it and what can we do about it? *Hear Journal*. 1998; 51(8) 10, 12–13, 16–18.
- Huang BY, Roche JP, Buchman CA, Castillo M. Brain stem and inner ear abnormalities in children with auditory neuropathy spectrum disorder and cochlear nerve deficiency. *Amer J Neuroradiol*. 2010; 31(10):1972–1979. [PubMed: 20595372]
- Hubel D, Wiesel T. The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J Physiol*. 1970; 206(2):419. [PubMed: 5498493]
- Humes LE, Dubno JR, Gordon-Salant S, Lister JJ, Cacace AT, Cruickshanks KJ, et al. Central presbycusis: a review and evaluation of the evidence. *J Amer Audiol*. 2012; 23(8):635–666.
- Javel, E. Basic response properties of auditory nerve fibers. In: Altschuler, RA.; Hoffman, DW.; Bobbin, RP., editors. *Neurobiology of Hearing: The Cochlea*. New York: Raven Press; 1986. p. 213–245.
- Kirkim G, Serbetcioglu B, Erdag TK, Ceryan K. The frequency of auditory neuropathy detected by universal newborn hearing screening program. *Int J Pediatr Otorhinolaryngol*. 2008; 72(10):1461–1469. [PubMed: 18674822]
- Kral A, Tillein J, Heid S, Hartmann R, Klinke R. Postnatal cortical development in congenital auditory deprivation. *Cereb Cortex*. 2005; 15(5):552–562. [PubMed: 15319310]
- Kraus, N. Auditory neuropathy: An historical and current perspective. In: Sininger, Y.; Starr, A., editors. *Auditory neuropathy: A new perspective on hearing disorders*. San Diego, CA: Singular; 2001. p. 1–14.
- Kraus N, Bradlow A, Chetham M, Cunningham J, King C, Koch D, Nicol T, et al. Consequences of a neural asynchrony: a case of auditory neuropathy. *J Assoc Res Otolaryngol*. 2000; 1:33–45. [PubMed: 11548236]
- Kujawa SG, Liberman MC. Acceleration of age-related hearing loss by early noise exposure: evidence of a missed youth. *J Neurosci*. 2006; 26(7):2115–2123. [PubMed: 16481444]
- Kujawa SG, Liberman MC. Adding Insult to Injury: Cochlear Nerve Degeneration after “Temporary” Noise-Induced Hearing Loss. *J Neurosci*. 2009; 29(45):14077–14085. [PubMed: 19906956]
- Le Van Quyen M, Navarro V, Martinerie J, Baulac M, Varela FJ. Toward a neurodynamical understanding of ictogenesis. *Epilepsia*. 2003; 44(Suppl 12):30–43. [PubMed: 14641559]
- Lee DS, Lee JS, Oh SH, Kim SK, Kim JW, Chung JK, et al. Cross-modal plasticity and cochlear implants. *Nature*. 2001; 409(6817):149–150. [PubMed: 11196628]
- Lee H-J, Giraud A-L, Kang E, Oh S-H, Kang H, Kim C-S, Lee DS. Cortical Activity at Rest Predicts Cochlear Implantation Outcome. *Cerebral Cortex*. 2007; 17:909–917. [PubMed: 16731883]
- Liégeois-Chauvel C, Musolino A, Badier JM, Marquis P, Chauvel P. Evoked potentials recorded from the auditory cortex in man: evaluation and topography of the middle latency components. *Electroen Clin Neuro*. 1994; 92(3):204–214.
- Makeig S, Delorme A, Westerfield M, Jung T-P, Townsend J, Courchesne E, Sejnowski TJ. Electroencephalographic brain dynamics following manually responded visual targets. *PLoS Biol*. 2004; 2(6):e176. [PubMed: 15208723]
- Maris M, Venstermans C, Boudewyns AN. Auditory neuropathy/dyssynchrony as a cause of failed neonatal hearing screening. *Int J Pediatr Otorhinolaryngol*. 2011; 75(7):973–975. [PubMed: 21596446]

- Mason JC, De Michele A, Stevens C, Ruth RA, Hashisaki GT. Cochlear Implantation in Patients With Auditory Neuropathy of Varied Etiologies. *Laryngoscope*. 2003; 113(1):45–49. [PubMed: 12514381]
- Mazurek ME, Shadlen MN. Limits to the temporal fidelity of cortical spike rate signals. *Nat Neurosci*. 5:463–71. [PubMed: 11976706]
- McClay JE, Booth TN, Parry DA, Johnson R, Roland P. Evaluation of pediatric sensorineural hearing loss with magnetic resonance imaging. *Arch Otolaryngol*. 2008; 134(9):945–952.
- Michalewski H, Starr A, Nguyen T, Kong Y, Zeng F. Auditory temporal processes in normal-hearing individuals and in patients with auditory neuropathy. *Clin Neurophysiol*. 2005; 116(3):669–680. [PubMed: 15721081]
- Mittal R, Ramesh AV, Panwar SS, Nilkanthan A, Nair S, Mehra PR. Auditory neuropathy spectrum disorder: Its prevalence and audiological characteristics in an Indian tertiary care hospital. *Int J Pediatr Otorhinolaryngol*. 2012; 76(9):1351–1354. [PubMed: 22795739]
- Miyamoto RT, Kirk KH, Renshaw J, Hussain D. Cochlear implantation in auditory neuropathy. *Laryngoscope*. 1999; 109(2):181–185. [PubMed: 10890762]
- Moore DR. Auditory processing disorder (APD): Definition, diagnosis, neural basis, and intervention. *Audiological Medicine*. 2006; 4:4–11.
- Narne V, Vanaja C. Speech identification and cortical potentials in individuals with auditory neuropathy. *Behav Brain Func*. 2008; 4(15)
- Nash-Kille A, Sharma A. Inter-trial coherence as a marker of cortical phase synchrony in children with sensorineural hearing loss and auditory neuropathy spectrum disorder fitted with hearing aids and cochlear implants. *Clin Neurophysiol*. 2014; 125:1459–1470. [PubMed: 24360131]
- Neary W, Lightfoot G. Auditory neuropathy spectrum disorder: Examples of poor progress following cochlear implantation. *Audiol Med*. 2012; 10(3):143–150.
- O'Brien RJ, Kamboj S, Ehlers MD, Rosen KR, Fischbach GD, Haganir RL. Activity-dependent modulation of synaptic AMPA receptor accumulation. *Neuron*. 1998; 21(5):1067–1078. [PubMed: 9856462]
- Oh S-H, Kim C-S, Kang EJ, Lee DS, Lee H-J, Chang SO, et al. Speech perception after cochlear implantation over a 4-year time period. *Acta Oto-Laryngol*. 2003; 123(2):148–153.
- Pallas S. Intrinsic and extrinsic factors that shape neocortical specification. *Trends Neurosci*. 2001; 24(7):417–423. [PubMed: 11410273]
- Palva JM, Palva S, Kaila K. Phase synchrony among neuronal oscillations in the human cortex. *J Neurosci*. 2005; 25(15):3962–3972. [PubMed: 15829648]
- Pascual-Marqui RD. Standardized Low-Resolution Brain Electromagnetic Tomography (sLORETA): Technical Details. *Methods Find Exp Clin Pharmacol*. 2002; 24D:5–12. [PubMed: 12575463]
- Pearce W, Golding M, Dillon H. Cortical auditory evoked potentials in the assessment of auditory neuropathy: two case studies. *J Amer Acad Audiol*. 2007; 18(5):380–390. [PubMed: 17715648]
- Peterson A, Shalloo J, Driscoll C, Breneman A, Babb J, Stoeckel R, Fabry L. Outcomes of cochlear implantation in children with auditory neuropathy. *J Amer Acad Audiol*. 2003; 14(4):188–201. [PubMed: 12940703]
- Pijnenburg YAL, vander Made Y, van Cappellen van Walsum AM, Knol DL, Scheltens P, Stam CJ. EEG synchronization likelihood in mild cognitive impairment and Alzheimer's disease during a working memory task. *Clin Neurophysiol*. 2004; 115(6):1332–1339. [PubMed: 15134700]
- Pizzorusso T, Medini P, Berardi N, Chierzi S, Fawcett JW, Maffei L. Reactivation of ocular dominance plasticity in the adult visual cortex. *Science*. 2002; 298(5596):1248–1251. [PubMed: 12424383]
- Ponton CW, Eggermont JJ. Of Kittens and Kids: Altered Cortical Maturation following Profound Deafness and Cochlear Implant Use. *Audiol Neuro-Otol*. 2001; 6(6):363–380.
- Ramakers GJA, Corner MA, Habets AMMC. Development in the absence of spontaneous bioelectric activity results in increased stereotyped burst firing in cultures of dissociated cerebral cortex. *Exper Brain Res*. 1990; 79(1):157–166. [PubMed: 2311692]
- Ramakers G, Van Galen H, Feenstra M. Activity-dependent plasticity of inhibitory and excitatory amino acid transmitter systems in cultured rat cerebral cortex. *Int J Dev Neurosci*. 1994; 12(7):611–621. [PubMed: 7900543]

- Rance G. Auditory neuropathy/dys-synchrony and its perceptual consequences. *Trends Amplif.* 2005; 9(1):1–43. [PubMed: 15920648]
- Rance G, Beer D, Cone-Wesson B, Shepherd R, Dowell R, King A, et al. Clinical findings for a group of infants and young children with auditory neuropathy. *Ear Hear.* 1999; 20(3):238. [PubMed: 10386850]
- Rance G, Barker E. Speech perception in children with auditory neuropathy/dyssynchrony managed with either hearing aids or cochlear implants. *Otol Neurotol.* 2008; 29:179–182. [PubMed: 18165792]
- Rance G, Barker E, Mok M, Dowell R, Rincon A, Garratt R. Speech perception in noise for children with auditory neuropathy/dys-synchrony type hearing loss. *Ear Hear.* 2007; 28(3):351–360. [PubMed: 17485984]
- Rance G, Barker EJ. Speech and language outcomes in children with auditory neuropathy/dys-synchrony managed with either cochlear implants or hearing aids. *Int J Audiol.* 2009; 48(6):313–320. [PubMed: 19925339]
- Rance G, Cone-Wesson B, Wunderlich J, Dowell R. Speech perception and cortical event related potentials in children with auditory neuropathy. *Ear Hear.* 2002; 23(3):239–253. [PubMed: 12072616]
- Rance G, McKay C, Grayden D. Perceptual characterization of children with auditory neuropathy. *Ear Hear.* 2004; 25:34–46. [PubMed: 14770016]
- Rance G, Ryan MM, Carew P, Corben LA, Yiu E, Tan J, Delatycki MB. Binaural speech processing in individuals with auditory neuropathy. *Neuroscience.* 2012
- Rapin I, Gravel J. “Auditory neuropathy”: physiologic and pathologic evidence calls for more diagnostic specificity. *Int J Pediatr Otolaryngol.* 2003; 67:707–728.
- Rapin I, Gravel JS. Auditory neuropathy: a biologically inappropriate label unless acoustic nerve involvement is documented. *J Amer Acad Audiol.* 2006; 17(2):147–150. [PubMed: 16640067]
- Roche JP, Huang BY, Castillo M, Bassim MK, Adunka OF, Buchman CA. Imaging characteristics of children with auditory neuropathy spectrum disorder. *Otol Neurotol.* 2010; 31(5):780–788. [PubMed: 20593543]
- Roland P, Henion K, Booth T, Campbell JD, Sharma A. Assessment of cochlear implant candidacy in patients with cochlear nerve deficiency using the P1 CAEP biomarker. *Cochlear Implants International.* 2012; 13(1):16–25. [PubMed: 22340748]
- Roush P, Frymark T, Venediktov R, Wang B. Audiologic management of auditory neuropathy spectrum disorder in children: a systematic review of the literature. *Amer J Audiol.* 2011; 20(2): 159–170. [PubMed: 21940978]
- Schaette R, Kempter R. Development of tinnitus-related neuronal hyperactivity through homeostatic plasticity after hearing loss: a computational model. *Eur J Neurosci.* 2006; 23:3124–3138. [PubMed: 16820003]
- Shaia WT, Shapiro SM, Spencer RF. The Jaundiced Gunn Rat Model of Auditory Neuropathy/Dyssynchrony. *Laryngoscope.* 2005; 115(12):2167–2173. [PubMed: 16369161]
- Shalloo JK, Peterson A, Facer GW, Fabry LB, Driscoll CL. Cochlear implants in five cases of auditory neuropathy: postoperative findings and progress. *Laryngoscope.* 2001; 111(4 Pt 1):555–562. [PubMed: 11359119]
- Sharma A, Dorman M, Spahr A. Rapid development of cortical auditory evoked potentials after early cochlear implantation. *Neuro Report.* 2002a; 13(10):1–4.
- Sharma A, Martin K, Roland P, Bauer P, Sweeney M, Gilley P, et al. P1 latency is a biomarker for central auditory development in children with hearing impairment. *J Amer Acad Audiol.* 2005a; 16:564–573. [PubMed: 16295243]
- Sharma, A.; Dorman, MF. Central Auditory Development in Children with Cochlear Implants: Clinical Implications, in *Cochlear and Brainstem Implants*. In: Moeller, A., editor. *Adv Otorhinolaryngol.* Vol. 64. Basel, Karger; 2006. p. 66-88.
- Sharma A, Cardon G, Henion K, Roland P. Cortical maturation and behavioral outcomes in children with auditory neuropathy spectrum disorder. *Int J Audiol.* 2011; 50(2):98–106. [PubMed: 21265637]

- Sharma A, Dorman MF, Kral A. The influence of a sensitive period on central auditory development in children with unilateral and bilateral cochlear implants. *Hear Res.* 2005b; 203(1–2):134–143. [PubMed: 15855038]
- Sharma A, Dorman MF, Spahr AJ. A sensitive period for the development of the central auditory system in children with cochlear implants: implications for age of implantation. *Ear Hear.* 2002b; 23(6):532–539. [PubMed: 12476090]
- Sharma A, Dorman M, Spahr A, Todd NW. Early cochlear implantation in children allows normal development of central auditory pathways. *Ann Otol, Rhinol Laryngol Suppl.* 2002c; 189:38–41. [PubMed: 12018346]
- Sharma A, Gilley PM, Dorman MF, Baldwin R. Deprivation-induced cortical reorganization in children with cochlear implants. *Int J Audiol.* 2007; 46:494–499. [PubMed: 17828665]
- Sharma A, Kraus N, McGee TJ, Nicol TG. Developmental changes in P1 and N1 central auditory responses elicited by consonant-vowel syllables. *Electroencephalog Clin Neurophysiol.* 1997; 104:540–545.
- Sharma A, Nash AA, Dorman M. Cortical development, plasticity and reorganization in children with cochlear implants. *J Commun Disord.* 2009; 42(4):272–279. [PubMed: 19380150]
- Silver J, Miller JH. Regeneration beyond the glial scar. *Nat Rev Neurosci.* 2004; 5(2):146–156. [PubMed: 14735117]
- Sininger, Y.; Starr, A. Auditory Neuropathy: A new perspective on Hearing Disorders. San Diego, CA: Singular; 2001.
- Sininger, Y.; Oba, S. Sininger: Patients with auditory neuropathy: who are they and what can they hear?. In: Starr, A.; Sininger, Y., editors. Auditory Neuropathy: a New Perspective on Hearing. Sand Diego: Singular; 2001. p. 67-82.
- Starr A, McPherson D, Patterson J, Don M, Luxford W, Shannon R, et al. Absence of both auditory evoked potentials and auditory percepts dependent on time cues. *Brain.* 1991; 114(3):1157–1180. [PubMed: 2065245]
- Starr, A.; Picton, TW.; Kim, R. Pathophysiology of auditory neuropathy. In: Sininger, Y.; Starr, A., editors. Auditory neuropathy: A new perspective on hearing disorders. San Diego, CA: Singular; 2001. p. 67-82.
- Starr A, Sininger Y, Winter M, Derebery MJ, Oba S, Michalewski HJ. Transient deafness due to temperature-sensitive auditory neuropathy. *Ear Hear.* 1998; 19:169–179. [PubMed: 9657592]
- Starr A, Picton TW, Sininger Y, Hood LJ, Berlin CI. Auditory neuropathy. *Brain.* 1996; 119(Pt 3): 741–753. [PubMed: 8673487]
- Steinschneider, M.; Liégeois-Chauvel, C.; Brugge, JF. Auditory Evoked Potentials and Their Utility in the Assessment of Complex Sound Processing. In: Winer, J.; Schreiner, C., editors. The auditory cortex. Boston, MA: Springer US; 2011. p. 535-559.
- Stevens CF, Zador AM. Input synchrony and the irregular firing of cortical neurons. *Nat Neurosci.* 1(3):210–217. [PubMed: 10195145]
- Sur M, Garraghty PE, Roe AW. Experimentally induced visual projections into auditory thalamus and cortex. *Science.* 1988; 242(4884):1437–1441. [PubMed: 2462279]
- Talaat HS, Kabel A, Sammy H, Elbadry M. Prevalence of auditory neuropathy (AN) among infants and young children with severe or profound hearing loss. *Int J Pediatr Otorhinolaryngol.* 2009; 73(7):937–939. [PubMed: 19409623]
- Tass P, Rosenblum MG, Weule J, Kurths J, Pikovsky A, Volkmann J, et al. Detection of n:m Phase Locking from Noisy Data: Application to Magnetoencephalography. *Phys Rev Lett.* 1998; 81(15):3291–3294.
- Teagle HFB, Roush PA, Woodard JS, Hatch DR, Zdanski CJ, Buss E, Buchman CA. Cochlear implantation in children with auditory neuropathy spectrum disorder. *Ear Hear.* 2010; 31(3):325–335. [PubMed: 20090530]
- Tomblin JB, Barker BA, Hubbs S. Developmental constraints on language development in children with cochlear implants. *Int J Audiol.* 2007; 46(9):512–523. [PubMed: 17828667]
- Trautwein PG, Sininger YS, Nelson R. Cochlear implantation of auditory neuropathy. *J Am Acad Audiol.* 2000; 11(6):309–315. [PubMed: 10858002]

- Turrigiano GG, Leslie KR, Desai NS, Rutherford LC. Activity-dependent scaling of quantal amplitude in neocortical neurons. *Nature*. 1998; 391:892–896. [PubMed: 9495341]
- Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. *Nat Rev Neurosci*. 2004; 5(2):97–107. [PubMed: 14735113]
- Uhlhaas PJ, Singer W. Neural synchrony in brain disorders: relevance for cognitive dysfunctions and pathophysiology. *Neuron*. 2006; 52(1):155–168. [PubMed: 17015233]
- Uus KBJ. Effectiveness of population-based newborn hearing screening in England: ages of interventions and profile of cases. *Pediatrics*. 2006; 117(5):e887–e893. [PubMed: 16651292]
- Van Den Pol AN, Obrietan K, Belousov A. Glutamate hyperexcitability and seizure-like activity throughout the brain and spinal cord upon relief from chronic glutamate receptor blockade in culture. *Neuroscience*. 1996; 74(3):653–674. [PubMed: 8884763]
- Villiers-Sidani E, Chang EFm, Bao S, Merzenich M. Critical period window for spectral tuning defined in the primary auditory cortex (A1) in the rat. *J Neurosci*. 2007; 27(1):180–189. [PubMed: 17202485]
- Walton J, Gibson WPR, Sanli H, Prelog K. Predicting cochlear implant outcomes in children with auditory neuropathy. *Otol Neurotol*. 2008; 29(3):302–309. [PubMed: 18317399]
- Wang Q, Webber RM, Stanley GB. Thalamic synchrony and the adaptive gating of information flow to cortex. *Nat Neurosci*. 13(12):1534–1541. [PubMed: 21102447]
- Wolfe J, Clark JL. Intervention for a child with auditory neuropathy/dys-synchrony. *The ASHA Leader*. 2008 Jul 15.
- Wiesel TN, Hubel DH. Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol*. 1963; 26(6):1003–1017. [PubMed: 14084161]
- Yasunaga S, Grati M, Cohen-Salmon M, El-Amraoui A, Mustapha M, Salem N, et al. A mutation in OTOF, encoding otoferlin, a FER-1-like protein, causes DFNB9, a nonsyndromic form of deafness. *Nat Genet*. 1999; 21(4):347–349. [PubMed: 10192378]
- Yellin MW, Jerger J, Fifer RC. Norms for disproportionate loss in speech intelligibility. *Ear Hear*. 1989; 10(4):215–269. [PubMed: 2776981]
- Zeng F, Kong Y, Michalewski H, Starr A. Perceptual consequences of disrupted auditory nerve activity. *J Neurophysiol*. 2004; 93:3050–3063. [PubMed: 15615831]
- Zeng FLS. Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear Res*. 2006; 49:367–380. [PubMed: 16671850]
- Zeng F, Liu S. Speech perception in individuals with auditory neuropathy. *J Speech Lang Hear R*. 2006; 49:367–380.
- Zeng F-G, Kong Y-Y, Michalewski HJ, Starr A. Perceptual consequences of disrupted auditory nerve activity. *J Neurophysiol*. 2005; 93(6):3050–3063. [PubMed: 15615831]
- Zeng F-G, Oba S, Garde S, Sininger Y, Starr A. Temporal and speech processing deficits in auditory neuropathy. *Neuro Report*. 1999; 10(16):3429–3435.
- Zeng F-G, Liu S. Speech perception in individuals with Auditory Neuropathy. *J Speech Lang Hear Res*. 2006; 49:367–380.
- Zimmerman-Phillips S, Robbins AM, Osberger MJ. Assessing cochlear implant benefit in very young children. *Ann Otol Rhinol Laryngol Suppl*. 2000; 185:42–43. [PubMed: 11140998]

Highlights

1. Cortical developmental patterns in ANSD reflect severity of neural dys-synchrony.
2. Sensitive periods for central auditory development affect outcomes in ANSD.
3. Cortical neuroplasticity predicts success with clinical intervention in ANSD.

Figure 1. Cortical development and functioning in ANSD

The P1 CAEP is considered a biomarker of auditory cortical development. When compared to normative data, P1 responses show three developmental patterns in ANSD children; normal, delayed, and abnormal (i-iii) reflecting an increased severity (respectively) in the degree of neural dys-synchrony in the ascending input affecting cortical maturation. Current source density reconstructions reveal bilateral activation of auditory cortical areas (e.g., superior temporal sulcus) underlying normal P1 responses (iv). However, the high degree of variability contributing to abnormal responses may not allow for accurate localization of

cortical sources (v). Independent Component Analyses (ICA) of stacked individual trials reveal more time-locked, consistent activations subserving the components (as indicated by the strongly colored blue or red columnar areas) underlying the aggregate normal P1 response (vi). On the other hand, single trials underlying an aggregate abnormal P1 response in ANSD shows more inconsistent, temporally smeared activations to sound (vii). Time-frequency analysis of cortical phase coherence using inter-trial coherence (ITC) (reflecting phase-locking of brain oscillations to sound) show higher ITC values underlying a normal P1 response and relatively lower ITC underlying delayed and abnormal P1 responses in ANSD respectively (viii-x). Peak cortical coherence analyzed for 91 children with ANSD show significantly decreasing ITC values for normal, delayed and abnormal P1's respectively (xi). ITC values underlying normal P1 response for children with ANSD are significantly lower than for P1 responses recorded from age-matched typically developing children (xii), suggesting that ITC is a sensitive measure of cortical synchrony in ANSD. Overall, the single trial EEG analyses (iv-xi) describe the differences in intra-individual variability, cortical coherence and phase synchrony leading to the patterns of cortical development seen in ANSD. Panels (i-iii) and (iv-vii) reproduced with permission from Sharma et al., (2011) and Nash, Gilley and Sharma, (2014), respectively. Data in panels (viii-xi) modified from Nash and Sharma, (2014).

Figure 2. Cortical correlates of behavioral outcome in ANSD

Latency of the P1 CAEP biomarker is significantly correlated with auditory skill development on the IT-MAIS test in 27 children with ANSD who are fitted with hearing aids and cochlear implants (i). P1 latencies are plotted against 95% confidence intervals for normal P1 development (from Sharma et al., 2005) and show that the proportion of children who received cochlear implants and showed normal P1 responses was significantly different for children implanted under and over 2 years of age ($p=0.05$), suggesting a sensitive period of approximately 2 years for auditory cortical development in children with ANSD (ii).

Cortical phase synchrony as reflected by inter-trial coherence (ITC) is lower for children with ANSD compared to children with NH or SNHL regardless of intervention with hearing aids or cochlear implants, suggesting that neither intervention completely overcomes the deficits in cortical synchrony in ANSD (iii). Morphology and latency of serial P1 CAEP responses when compared to normative data can guide clinical decision making in children with ANSD who show progress in cortical development with hearing aid use (iv) or who do not benefit from hearing aids and therefore are good candidates for cochlear implant use (iv). Panel (i) data collapsed from Sharma et al., (2011) and Cardon and Sharma (2013). Panels (ii) and (iv-v) reproduced with permission from Cardon and Sharma (2103) and Cardon, Campbell and Sharma (2012), respectively. Data in panel (iii) modified from Nash and Sharma (2014).