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Review

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.

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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 variability has lead to historically different classifications or nomenclatures for ANSD (Rapin and Gravel, 2006). The disorder was first described and titled *Auditory Neuropathy* by Starr et al. (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 and 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.

Abbreviations: ANSD, Auditory Neuropathy Spectrum Disorder; SNHL, sensorineural hearing loss; CND, cochlear nerve deficiency; CAEP, cortical auditory evoked potentials; OAE, otoacoustic emissions; ABR, auditory brainstem response; AR, 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

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Berlin et al. (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 and 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 et al. (2006) have singled out another gene (i.e., DFNB59), which is instrumental in coding a protein, *pejvakin*, 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 and 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; Zeng and Liu, 2006; Rance et al., 2004, 2005; Michalewski et al., 2005; Rance and Barker, 2008; Hassan, 2011).

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 and Liberman, 2006, 2009; Gourévitch et al., 2014; Nash-Kille and 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 et al., 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 and 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 and Oba, 2001; Rance, 2005, 2007, 2008; 2009, 2012). Zeng et al. (1999; 2004) and Zeng and Liu, (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

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