



2020
AG BELL GLOBAL VIRTUAL
**LISTENING AND
SPOKEN LANGUAGE**
SYMPOSIUM

HEARING AND ITS INTERACTION WITH HEARING TECHNOLOGY

**RESEARCH
PROCEEDINGS**
JULY 9-10, 2020

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The Condition of the Auditory Nerve Matters for Cochlear Implant Users

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Despite the overwhelming success of the cochlear implant (CI), outcomes vary across patients and, even across ears in patients who have bilateral implants. Several studies have identified important factors that contribute to CI outcomes, such as duration of hearing loss, but less is known about how the health of the auditory nerve influences outcomes in CI users. Our research has focused on using a combination of animal and human experiments in order to understand factors that influence performance.

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Early Acoustic Hearing and the Role of Segmental and Suprasegmental Speech Perception for Spoken Language and Literacy

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Our research explores early acoustic hearing (via hearing aid use) on speech perception skills of pediatric cochlear implant (CI) recipients who utilize bilateral CIs or bimodal devices (CI and hearing aid). The contribution of speech perception on receptive language and literacy skills is discussed.

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Binaural Fusion in Children and Adults with Hearing Loss

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Binaural fusion is the perception of sounds entering the two ears as a single sound. In adults with typical hearing, binaural fusion will only occur for similar sounds that are likely to come from a single sound source. In contrast, in adults who use hearing aids (HAs) or cochlear implants (CIs), binaural fusion may also occur for sounds that are very different in pitch, such as different voices. Such abnormal binaural fusion can lead to binaural interference and difficulties with hearing speech in background noise. In children, binaural fusion is still maturing during development, and may depend on the hearing device combination—two hearing aids, a cochlear implant and hearing aid, or two cochlear implants.

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Research in these proceedings was supported by the National Institute on Deafness and Other Communication Disorders, National Institutes of Health, under award number 1R13DC018244-01A1. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The views expressed in written conference materials or publications and by speakers and moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

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Evaluation and Management of Patients with Auditory Neuropathy Spectrum Disorder

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ABSTRACT

This paper focuses on a hearing disorder, known as auditory neuropathy, auditory dys-synchrony, and auditory neuropathy spectrum disorder, that affects neural processing of sound and significantly impacts communication ability. Auditory characteristics of patients with auditory neuropathy are discussed, along with strategies for evaluation, accurate diagnosis, and appropriate management.

Patients ranging in age from infants through adults have been identified with a type of hearing disorder named auditory neuropathy (AN; Starr et al., 1996). Unlike typical sensorineural hearing loss, patients with AN have present cochlear (inner ear) responses and absent or highly abnormal neural responses at the level of the auditory nerve and brainstem. Additional terms used to describe this hearing disorder include auditory neuropathy/dys-synchrony (AN/AD; Berlin et al., 2001), auditory neuropathy spectrum disorder (ANSND; Bill Daniels Center for Children's Hearing, 2008), and auditory synaptopathy (AS; Moser & Starr, 2016). Although these terms have associations with different underlying mechanisms or concepts, at present they often are used interchangeably. In this article, the term AN will be used for convenience; though the interchanged use of the above terms (AN, AS, AN/AD, ANSD) will apply unless specifically noted. More accurate use of these and other descriptors will continue to emerge with advances in understanding of function and underlying processes.

OVERVIEW OF CHARACTERISTICS

Clinical presentation of patients with AN typically indicates difficulty understanding speech, particularly in noisy situations. While many patients with AN demonstrate little or no ability to understand speech in quiet, some patients demonstrate good word recognition ability but only in quiet. All patients with AN demonstrate difficulty listening in noisy situations with poorer word recognition ability than observed in persons with sensorineural hearing loss (Rance et al., 2007). These factors can have significant impact on a child's speech and language ability, and delayed speech and language development in infants and children is a common, though not universal, characteristic.

INCIDENCE

AN occurs in about 10% of individuals who have a dys-synchronous ABR, or an ABR consistent with a severe or profound hearing

loss. This estimate is based on data from several sources that include screening of over 1,000 children with severe to profound hearing loss in North America (Berlin et al., 2000), a similar smaller-scale study in Hong Kong (Lee et al., 2001), a hospital-based study in Australia (Rance et al., 1999), and a multicenter newborn screening study in the United States (Sininger, 2002). A higher incidence of 17.3% and 15.4%, respectively, was reported among children identified with hearing loss following referral from newborn hearing screening (Ngo et al., 2006; Kirkim et al., 2008). Incidence in premature infants and among infants in the Neonatal Intensive Care Unit (NICU) is higher, with rates of AN being 24% and greater in infants who failed ABR in one or both ears (Berg et al., 2005; Rea & Gibson, 2003).

CLINICAL AUDIOLOGIC EVALUATION

Physiologic responses are key components in accurate identification and characterization of AN. Of the physiologic methods in present clinical use, otoacoustic emissions (OAE) and auditory brainstem responses (ABR) together form the most sensitive combination of measures in assessment of AN. Presence of responses related to active cochlear processes is documented by OAEs and cochlear microphonics (CM). In the absence of middle-ear disorders, OAEs are typically present in patients with AN. Since the CM is an electrical response, it is not dependent on reverse transmission back through the middle-ear system. A key factor in distinguishing CM from a neural response is the reversal of the response with change of the stimulus polarity from condensation to rarefaction polarity. The CM will invert while neural responses typically do not completely invert (Berlin et al., 1998).

Neural responses are either directly or indirectly affected. ABRs are most often absent in patients with AN, although some patients demonstrate evidence of limited, reduced neural synchrony for high-intensity signals. Berlin et al. (2010) reported

that approximately 75% of patients in their database had absent ABRs while 25% showed abnormal responses characterized by presence of low amplitude Wave V only at high stimulus levels (75-90 dB nHL). Further evidence of the interruption of neural function is demonstrated by absent and abnormal efferent auditory reflexes: the middle ear muscle reflex (MEMR; Berlin et al., 2005) and the medial olivocochlear reflex (MOCR; Hood et al., 2003).

Behavioral responses, including pure-tone audiometry and speech recognition, are variable among AN patients. Pure-tone thresholds range from normal sensitivity to severe or profound hearing loss (Berlin et al., 2010; Kaga et al., 1996). Configurations vary among sloping, rising, and flat, and thresholds may be asymmetric between ears. In patients where pure-tone thresholds exceed approximately 40 dB Hearing Level (HL) and OAEs are present, the disagreement between these two test results can provide a clue to the presence of AN or another type of neural disorder that warrants further investigation.

Speech recognition in AN patients is typically poorer than expected based on pure tone thresholds, but performance varies across individuals. Some AN patients demonstrate word recognition ability in quiet in ranges similar to persons with sensorineural hearing loss (SNHL) while word recognition ability in noise for AN patients is below what is expected in SNHL (Rance et al., 2007; Starr et al., 1996; Zeng et al., 1999). In a group of 68 patients aged 4 years and older where word recognition was measured using standardized tests, Berlin et al. (2010) reported that 38 of the 68 patients had no measurable word recognition ability, even in quiet. The remaining 30 patients had word recognition scores in quiet that varied from poor to excellent with results in quiet for some patients consistent with SNHL (Berlin et al., 2010; Yellin et al., 1989). Only five of the 68 patients in this cohort had measurable word recognition in noise and scores were poorer than observed in patients with SNHL (Berlin et al., 2010; Rance et al., 2007). This widely varying speech recognition ability presents a particular challenge in planning appropriate management.

UNDERLYING MECHANISMS

The clinical test results observed in patients with AN can occur as a result of absence or disruption of inner hair cell (IHC) activity, interruption in function of the synapse of the IHC and auditory nerve, and/or abnormalities of the auditory nerve. AN is seen in multiple members of some families and can follow recessive, dominant, or mitochondrial inheritance patterns. A number of gene mutations associated with AN have been identified. AN can occur alone, as in non-syndromic recessively inherited AN, as well as part of a syndrome, such as hereditary motor sensory neuropathies (HMSN). AN can be distinguished as

pre- or post-synaptic in origin, based on physiologic response characteristics and underlying genetics (McMahon et al., 2008; Moser & Starr, 2016; Rance & Starr, 2015; Santarelli et al., 2015a,b). An example of pre-synaptic AN involves the *OTOF* gene that encodes otoferlin, a protein that plays a crucial role in the function of the IHC ribbon synapses (Varga et al., 2003; Rodriguez-Ballesteros et al., 2008). Post-synaptic forms of AN include patients with hereditary motor-sensory neuropathies such as Charcot-Marie-Tooth Disease and Friedreich ataxia (Rance & Starr, 2015).

VARIATION AMONG PATIENTS WITH AN

Factors related to variation among patients with AN include time of onset, underlying mechanisms, genetics, presence of risk factors, presence of other conditions, and changes over time. Patients vary along a continuum with some patients displaying no overt delays or auditory complaints and only may be identified as a result of newborn hearing screening or later hearing tests. Other patients display an apparent total lack of sound awareness, reflected in severely affected communication and speech production abilities. Most AN patients fall between these two extremes, showing inconsistent auditory responses with better responses in quiet than in noise. Some patients demonstrate fluctuation in hearing over time. In a limited number of cases, fluctuation in hearing has been linked to changes in body temperature (Starr et al., 1998; Marlin et al., 2010). Most AN patients show bilateral characteristics, though function may be asymmetric between ears, and cases of unilateral AN have been documented. Some AN patients may have risk factors and some forms of AN may be accompanied by neural problems in other systems. It should be noted that many patients with AN have no risk factors and no evidence of abnormal function other than hearing loss.

ANSD IN INFANTS

Infants with characteristics consistent with AN (i.e., present OAEs, absent ABR) are identified at birth in newborn hearing screening programs that utilize ABR as the screening tool. Programs that use OAEs as the screening tool will miss infants with AN and these infants will continue to be identified later, often when parental concern about speech and language development delays arises. The Joint Committee on Infant Hearing (2019) recommends ABR testing for infants in the NICU based on the higher risk for AN in the NICU population. Infants with present OAEs and poor or absent ABR are considered 'at risk' for AN. A diagnostic dilemma exists since the ABR continues to mature through the first 12 to 18 months after birth. Some infants who show AN characteristics at birth develop an ABR over the first year of life; however, the number of these infants is low (Attias & Raveh, 2007; Hayes et al., 2010).

It is important to closely monitor infants suspected of having AN over at least the first year of life, both with ABR and with other indices of auditory development.

MANAGEMENT APPROACHES AND OUTCOMES

Variation in underlying mechanisms contributing to AN among patients as well as variable clinical characteristics across individuals dictates the need for individual management approaches. Modifications may be needed as more thorough assessments are possible and in cases where auditory function changes over time. Because discrimination of sound generally is affected to a much greater degree than detection of sound, decision-making and management planning should consider clarity of sound and supra-threshold function.

Amplification

While variation in benefit with amplification across AN patients is reported, trial of amplification is recommended. Challenges exist in determining threshold sensitivity in young infants since reliable behavioral testing is difficult in infants less than 5-6 months of age and clinicians need to rely on physiologic data. With compromised ABRs, this creates a problem in determining sensitivity. Cortical auditory evoked potentials, present in many AN patients, show promise as an objective method to evaluate sound detection and perception [e.g., Gardner-Berry et al., 2015; He et al., 2015]. Studies linking cortical response presence and speech perception ability are promising in the evaluation of AN patients who cannot provide reliable behavioral responses (Narne & Vanaja, 2008; Pearce et al., 2007; Rance et al., 2002). Amplification is fit to provide appropriately audible signals for AN patients who display reduced threshold sensitivity. A key to benefit involves improved sound discrimination, which is necessary to facilitate speech and language development and support auditory communication. Studies report variable benefit, even with appropriately audible signals (e.g., Berlin et al., 2010; Roush et al., 2011). The effectiveness of amplification is monitored and assessed by speech-language pathologists, teachers, early intervention providers, and others who interact with a child. When assessing benefit and making decisions related to proceeding from amplification to cochlear implants, it is important to separate ability to detect sound from ability to discriminate sound. In our practice, we look for at least 3 months progress in language development in 3 calendar months of elapsed time (Hayes et al., 2010). If a child is not meeting this mark, particularly after several months of hearing aid use, then cochlear implants may be recommended for a patient and family to consider.

Assistive Listening Systems

Benefit of assistive listening systems, such as remote microphone technology (FM; alone or with other devices), by patients with

AN is consistent with the particular difficulty that AN patients experience in noisy situations. The improved signal-to-noise ratios provide a clearer signal to an auditory system that cannot cope with interference (Hood et al., 2004). When clear auditory information is not accessible, then inclusion of visual information will facilitate language development in infants and children and assist adults in difficult listening situations (Berlin et al., 2002).

Cochlear Implants

Children and adults demonstrate benefit from cochlear implants in improved speech perception ability and facilitated speech and language development (Berlin et al., 2010; Breneman et al., 2012). Improvement is observed related to detection of sound, but more importantly cochlear implants have been shown to facilitate perception of speech in quiet and in noise. Furthermore, evidence of synchronous neural responses are observed on ABRs and other physiologic measures using electrical stimuli. Outcomes with cochlear implants have been studied in patients with pre- and post-synaptic forms of AN. Santarelli et al. (2015a) demonstrated success with cochlear implants in a cohort of AN patients with a pre-synaptic form of AN, associated with *OTOF* mutations. A post-synaptic form of AN and optic nerve atrophy is associated with certain mutations in the *OPA1* gene where outcomes with cochlear implants are generally good though variable (Santarelli et al., 2015b). As might be expected, more favorable speech perception scores post cochlear implantation are reported for AN patients with an intact cochlear nerve as compared to those with cochlear nerve deficiencies (Buchman et al., 2006).

A TEAM APPROACH

Collaboration with speech-language pathologists, otolaryngologists, educators, early interventionists, neurologists, geneticists, genetics counselors, other physicians, and health care professionals is a key component of successful evaluation and management of patients with AN and their families. While the audiologist is often one of the first professionals to encounter a patient with AN, management should focus on global communication skills, language acquisition, and development of the skills necessary to succeed academically and be self-sufficient.

THE FUTURE

As understanding advances in characterizing underlying mechanisms, genetics, and ability to sensitively measure auditory function, our ability to more accurately evaluate and manage patients with AN/AD/AS/ANSD will also advance. Progress will include the development of methods that can accurately distinguish normal from abnormal function at inner hair cell, synaptic, and neural levels, the identification of specific factors related to various types of AN, and connections between characteristics and outcomes. Advances will have a positive

impact on management and provide knowledge to guide our patients and their families in making informed decisions.

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The Condition of the Auditory Nerve Matters for Cochlear Implant Users

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ABSTRACT

Despite the overwhelming success of the cochlear implant (CI), outcomes vary across patients, and even across ears in patients who have bilateral implants. Several studies have identified important factors that contribute to CI outcomes, such as duration of hearing loss, but less is known about how the health of the auditory nerve (AN) influences outcomes in CI users. Our research has focused on using a combination of animal and human experiments in order to understand factors that influence performance. We use well-controlled experiments in animals to better understand how the condition of the AN can be assessed using non-invasive measures, and then how those same measures relate to performance with a CI. This model has been used to clearly demonstrate that speech outcomes are influenced by the condition of the AN. This research has potential implications for predicting performance in CI users, developing new CI programming techniques, or using biologic approaches to improve performance with CIs.

Cochlear implants (CIs) are remarkable devices that have afforded improved hearing and access to sound for over 300,000 recipients worldwide (National Institutes of Health, 2016). CIs are largely considered to be the most successful prosthetic device. They offer improved speech understanding in adult patients, and promote appropriate spoken language skills in children who receive implants at an ideal age and participate in an auditory-verbal based rehabilitation program (Thomas & Zwolan, 2019; Tobey et al., 2013). A CI consists of a multichannel electrode array, which is inserted into the scala tympani of the cochlea. The array bypasses hair cells, and directly stimulates the auditory nerve (AN) using biphasic, electrical current pulses.

Several factors have been shown to influence performance of adults and children who use cochlear implants (CIs). For example, in adult recipients we know that duration of hearing loss prior to implantation, prior hearing aid use, electrode placement, and cognitive factors all contribute to CI outcomes (Holden et al., 2013). In children, studies have demonstrated that age at implantation, etiology, cognition, consistent participation in auditory-verbal therapy (AVT), maternal factors, and socioeconomic status all play a role in the ultimate success of a pediatric CI recipient (Barnard et al., 2015; Geers et al., 2017; Niparko et al., 2010; Thomas & Zwolan, 2019).

Our work has been primarily focused on how another factor, the health of the AN, might also influence outcomes in CI recipients. Given that the CI directly stimulates the AN, it is logical that the condition of the neurons (spiral ganglion neurons, or SGNs) would play a role in how sound is perceived using CI technology. Not long ago, CI recipients consisted of

a homogenous population who exhibited profound hearing loss and 0% speech understanding with the use of hearing aids (Eshraghi et al., 2012). So, the question of AN function for CI users was likely less important. But there is now sufficient evidence that expanding candidacy criteria to include adult and pediatric patients with more residual hearing and better pre-operative speech understanding is highly beneficial (Carlson et al., 2015; Firszt et al., 2012, 2018; Holder et al., 2018). Thus, contemporary CI candidates are more heterogeneous with respect to pre-operative functional hearing (Holder et al., 2018), and it can be inferred that the condition of the AN likely varies in this group.

The present article will discuss how the condition of the AN might play a role in speech recognition outcomes with a CI. Of course, we acknowledge that the brain plays a huge role in how speech sounds are perceived, but this article will focus on why it is important to understand the specific influence that AN health and function have on CI performance. We will review our work, and the work of others, to discuss current knowledge regarding how the condition of the AN influences CI outcomes. Lastly, we'll discuss how these findings can be used to explain or improve performance in adult or pediatric CI recipients.

ETIOLOGY, HISTOLOGY, AND POST-MORTEM TEMPORAL BONE STUDIES

The CI stimulates the SGNs (Figure 1). Histological studies in animals and humans reveal that deafening or insult to the cochlea results in degeneration of SGN cell bodies (Hinojosa & Marion, 1983; Nadol, 1997; Nadol & Eddington, 2006; Pfingst

et al., 2011, 2017), but it is also assumed that degeneration of SGNs in human ears is quite slow and occurs over many years (Hinojosa & Marion, 1983; Nadol et al., 1989). Furthermore, post-mortem temporal bone studies in humans reveal that causes of hearing loss due to the use of post-lingual aminoglycoside (antibiotic) ototoxicity or unspecified sudden hearing loss result in more favorable and higher residual SGNs in the cochlea when compared to other etiologies, such as labyrinthitis or genetic, congenital conditions (Nadol, 1997; Nadol et al., 1989). Animal studies reveal information about cochlear pathology among inherited etiologies common in the pediatric population. For example, mutations to the GJB2 gene, which encodes the Connexin 26 (Cx26) protein, are one of the most common causes of congenital, non-syndromic hearing loss (Hochman et al., 2010). An animal model of Connexin-related deafness shows that, compared to a 'normal' ear, the number and morphology of SGNs is relatively typical at a young age, while degeneration is noted in older animals (Takada et al., 2014). On the other hand, other congenital hearing loss etiologies, such as CHARGE syndrome, quite often show abnormal cochlear anatomy, such as a small (hypoplastic) or absent (aplastic) auditory nerve otherwise known as cochlear nerve deficiency (CND) (Choo et al., 2017).

Anecdotally, clinicians will often observe patterns in CI outcomes associated with these etiologies. For example, expectations are usually high for a patient who had typical hearing prior to a sudden onset of complete hearing loss and

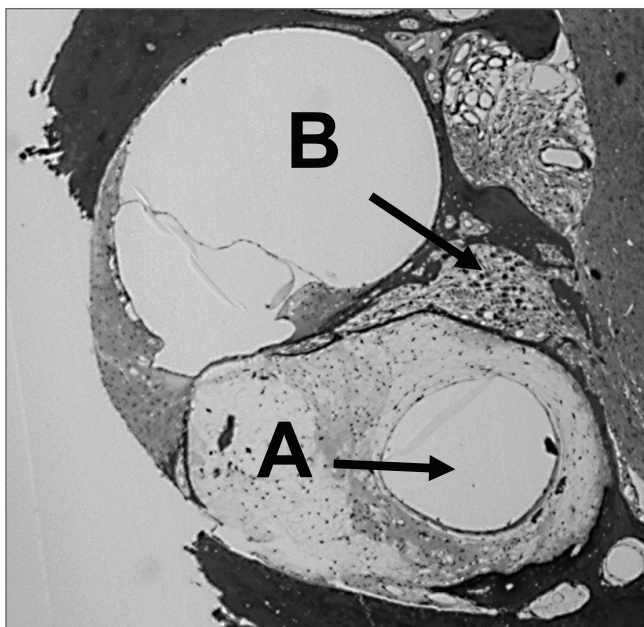


FIGURE 1. A mid-modiolar section of a cochlear-implanted guinea pig cochlea showing the tract of the CI (labeled 'A') within the scala tympani. The spiral ganglion neurons (SGNs) (labeled 'B') are located adjacent to the electrode. The anatomy is similar in guinea pigs and humans with CIs.

receives a CI soon after hearing loss diagnosis; these patients are often observed to achieve the best outcomes with a CI when compared across all adult recipients. Likewise, pediatric patients with a Connexin mutation tend to be those who perform better with their devices, at least when other predictive factors such as early implantation and consistent AVT are also favorable (Fukushima et al., 2002; Popov et al., 2014; Wu et al., 2015). Conversely, families of pediatric patients with CHARGE are often counseled to have guarded expectations, particularly in light of CND (hypoplastic or aplastic AN) as evidenced by Magnetic Resonance Imaging (MRI) (Amin et al., 2019). And likewise, some patients who are diagnosed with auditory neuropathy spectrum disorder (ANS) might express particular variants which directly involve demyelination of the AN (Norrix & Velenovsky, 2014) and CI patients with ANSD demonstrate variable success with CIs (Teagle et al., 2010).

Based on these associations linking specific etiologies with CI outcomes, it could be hypothesized that performance with a CI is at least somewhat dependent upon the condition of the cochlea as determined by the morphology and functionality of SGN fibers. However, until recently there has been little data to support this hypothesis. Early and elegant studies using post-mortem temporal bone analyses in humans showed no relationship to SGN density and speech recognition with a CI (Khan et al., 2005; Nadol & Eddington, 2006; Nadol et al., 2001). More recent temporal bone studies, performed in a greater number of subjects or using more controlled methods, do show a positive relationship between SGN density in the cochlea and speech recognition outcomes (Kamakura & Nadol, 2016; Seyyedi & Nadol, 2014). However, this relationship is still neither well understood nor clearly defined. And, post-mortem measures of SGN density do not provide us with a means to estimate SGN density during the life of our CI patients, nor use this information in a clinical manner. The remainder of this paper reviews recent work in our laboratory, and the labs of others, that have worked to develop non-invasive measures to estimate neural function in human CI recipients. We will also discuss how these measures might be used to predict or improve outcomes in our pediatric and adult CI users.

USING AN ANIMAL MODEL TO DEVELOP MEASURES OF NEURAL HEALTH

Auditory brainstem response (ABR) testing is widely used in both animals and humans to objectively measure hearing. Electrical ABRs (EABRs) measure the AN response using an electrical, rather than an acoustic signal and are more appropriate for use in subjects with CIs. Early animal studies documented a relationship between features of the Wave I of EABR and SGN density in laboratory animals (Hall, 1990). These results showed that SGN density was positively and significantly correlated with

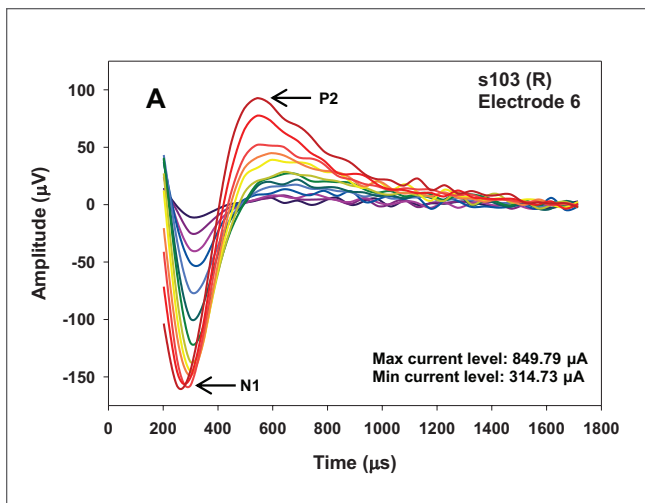


FIGURE 2. Taken from Schwartz-Leyzac et al. (2018). The waveform is an example of an ECAP waveform measured on one electrode in a human subject. The N1 and P2 peaks are labeled, with the respective latencies shown on the x-axis. Various colors corresponding with the color spectrum represent different input current levels; both the minimum (violet) and maximum (red) levels used to achieve these tracings are provided within each panel. As the current level is increased, the voltage response (“amplitude”) also increases. This is referred to as the amplitude-growth function (AGF).

the slope of the EABR amplitude growth function (AGF) as well as the peak-amplitude. This means that the amplitudes increased more quickly with increasing current level (“slope”) and were also overall larger in animals with higher SGN density. The EABR Wave I is analogous with the electrically-evoked compound action potential (ECAP), a measure frequently used in the clinic with CI patients. The ECAP measure in consists of an N1-P2 complex, with latencies ranging from about 150-400 and 600-800 μ s, respectively (Figure 2), and can be recorded easily in animals and humans given that it is objective and requires no response.

Subsequent studies in cochlear implanted animals are consistent with early studies (Hall, 1990; Smith & Simmons, 1983) and have shown that attributes of the ECAP response are correlated with SGN densities (Pfungst et al., 2017; Pfingst, Hughes, et al., 2015; Schwartz-Leyzac et al., Submitted; Schwartz-Leyzac et al., 2019). The results in Figure 3 show the relationship between SGN density and ECAP measures in a group of 35 cochlear implanted guinea pigs. The guinea pigs used in the study were diverse with respect to deafening approaches. One group of animals received an implant in a normal-hearing ear, and therefore had a high number of SGNs. A second group of animals were deafened using Neomycin, an ototoxic drug that typically causes an almost complete loss of SGNs along with other morphological and physiological changes in the cochlea (Zappia & Altschuler, 1989). The third group of animals were deafened

with Neomycin, but they also received neurotrophin drugs which have been shown to protect SGNs from the ototoxic effects of Neomycin (Budenz et al., 2012, 2015; Pfingst et al., 2017). This approach results in a group of animals with a diverse compliment of SGNs, ranging from near-normal to very sparse neural survival. Following implantation and over the course of the lifespan of the animal, ECAPs were measured. We utilize histological procedures to examine how characteristics relate to SGN survival after euthanasia. Results show that, similar to results reported by Smith and Simmons (1987) and Hall (1990), the ECAP AGF slope, peak amplitude, and latency of the N1 response positively and significantly correlated with residual SGN density across the animals (Figure 3).

Recently, we and others have also examined how the ECAP AGF slope and peak amplitude change as the shape of the biphasic pulse used to evoke the response is altered. Specifically, increasing the interphase gap (IPG) between the negative and positive phases of the biphasic pulse also increases excitability of the neural population and subsequently ECAP AGF slope and peak amplitude increase (“IPG Effect”) (Figure 4). In the same group of animals shown in Figure 3, we have shown that SGN density is also related to the IPG Effect for the ECAP AGF slope, peak amplitude, and N1 latency (Figure 4), which is consistent with findings from other labs (Ramekers et al., 2014, 2015). Taken together, these results demonstrate that ECAPs can be used in cochlear implanted animals to estimate SGN density adjacent to the stimulating electrode and have potential application for use in human CI recipients.

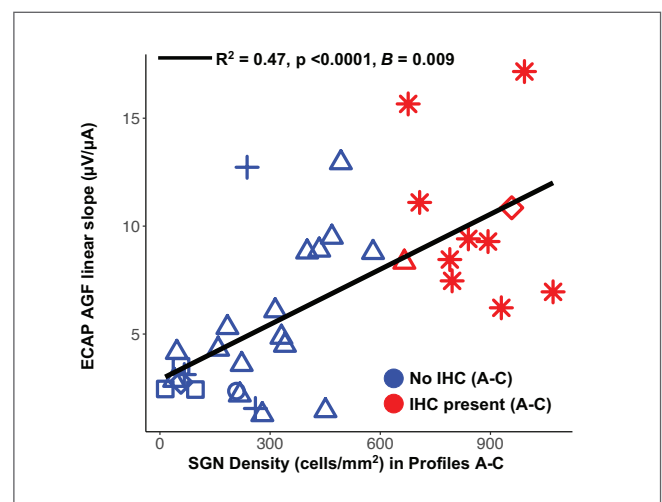


FIGURE 3. Scatterplot showing the relationship between SGN density (cells/mm²) for the area closest to the stimulating electrode and the ECAP AGF linear slope (μ V/ μ A). This figure is a taken from Schwartz-Leyzac et al. (submitted), and shows that about 50% of ECAP AGF slope can be accounted for variance in SGN density across 35 cochlear implanted guinea pigs. The colors indicate if inner hair cells were present (red) or absent (blue) in these animals, and the different symbols represent different deafening treatments.

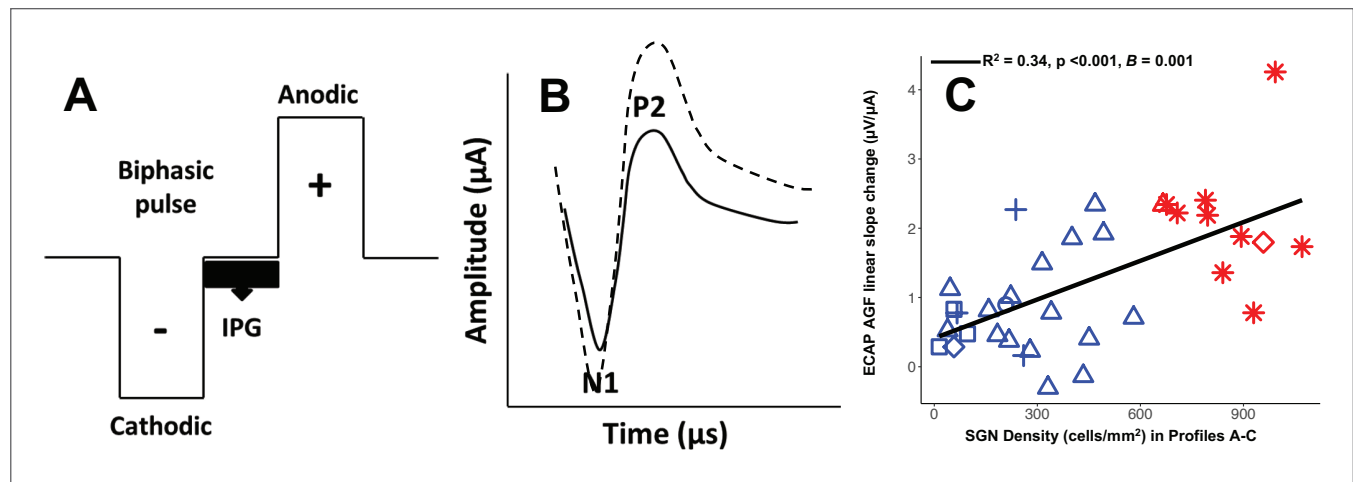


FIGURE 4. Figure 4A shows an example of a single biphasic pulse that is used in cochlear implant stimulation, which involves a leading (cathodic) and following (anodic) phase, with the interphase gap (IPG) being the duration of the interval that occurs between these two phases. When the IPG is increased, this causes an increase in the excitatory response in the neural population, and this can be observed as an increase in the ECAP N1-P2 amplitude (Figure 4B). Here, the solid line represents an ECAP response with a shorter IPG, while the dashed line showed the ECAP amplitude increasing with a longer IPG. Figure 4C is similar to Figure 3, but in this case shows that the change in ECAP AGF slope when increasing the IPG is also related to SGN density in the same cochlear-implanted guinea pigs.

CLINICAL APPLICATION IN A HUMAN MODEL

We can easily measure ECAPs in human CI listeners. In a clinical context, the ECAP is typically referred to as Neural Response Integrity (NRI), Neural Response Telemetry (NRT), or Auditory Nerve Response Telemetry (ART), depending on the specific CI manufacturer. In intra- or post-operative clinical settings, use of these measures has been limited to measuring ECAP thresholds. However, research shows that ECAP thresholds provide rather poor correlation with behavioral programming levels (He et al., 2017; Jeon et al., 2010; Thai-Van et al., 2001). Supra-threshold measures, such as the AGF slope, peak amplitude, or N1 latency, are not typically used in the clinical setting.

Based on the animal studies, we propose that we can use suprathreshold ECAP measures in a meaningful way for patients. First, we can use these measures to better understand the relationship between neural health in the cochlea and performance with a CI. Second, we can examine how etiology of hearing loss is linked with estimates of cochlear neural health. Third, we could use ECAP measures to help modify CI programming in order to enhance speech recognition. Finally, we can use ECAPs to help study the efficacy of biological therapy, such as neurotrophin drug delivery to the inner ear, and measure how these approaches affect CI function.

THE RELATIONSHIP BETWEEN SPEECH RECOGNITION AND ECAP MEASURES

Collectively, there is conflicting evidence when examining the relationship between ECAP measures and speech recognition

performance in CI users (van Eijl et al., 2017). Some studies show a relationship between ECAP peak-amplitude using a fixed IPG and phoneme recognition performance (DeVries et al., 2016; Scheperle, 2017), while others have demonstrated a significant relationship between ECAP AGF slope using a fixed IPG and sentence recognition (Kim et al., 2010). Conversely, there are studies that show no relationship between ECAP measures and the speech recognition outcomes for CNC Words and CUNY sentences in quiet (Franck & Norton, 2001). We hypothesize that this discrepancy in findings is due, at least in part, to variables such as central auditory processing and cognition that contribute to speech recognition performance, but vary among CI listeners (Cosetti et al., 2016; Finke et al., 2016; Heydebrand et al., 2007). This problem can be reduced by using within-subject research designs (Zhou & Pfungst, 2014b). Figure 5 shows results published in Schwartz-Leyzac & Pfungst (2018) which used a within-subject design, thereby minimizing the effects of central auditory processing and cognition. In that study, the ECAP IPG Effect for linear slope significantly predicted the ear with better sentence recognition in noise in bilaterally implanted subjects (Schwartz-Leyzac & Pfungst, 2018). Specifically, this figure shows that the ear with better performance on a sentence recognition in noise test (i.e., a lower dB signal-to-noise ratio (SNR) required to achieve 50% accuracy) was also the ear with a higher average ECAP IPG Effect for AGF linear slope across the electrode array. This finding also suggests that, when looking within each CI user, the ear estimated to have a higher density of SGNs is also the ear that can more accurately process complex speech signals, such as sentences in noise.

Based on the animal model, we know that variance in SGN density accounts for about 50% of the variance in suprathreshold ECAP measures (Figure 3 and 4). In a recent study using post-operative computerized tomography (CT) scans, we also showed that suprathreshold ECAP measures in humans are influenced by the medial-lateral location of the electrode (Schvartz-Leyzac, Holden, et al., 2020). In other words, the distance between the electrode and the stimulated neural population also influences the ECAP response when measured with a fixed IPG. Previous studies do show a common pattern for ECAP threshold and suprathreshold measures, with higher amplitudes and AGF slopes but lower thresholds for apical electrodes (Brill et al., 2009; Christov et al., 2019). In the previously mentioned study (Schvartz-Leyzac, Holden, et al., 2020) we showed that the IPG Effect for ECAP thresholds and AGF slopes were not influenced by medial-lateral distance. Therefore, the IPG Effect for suprathreshold ECAP measures might be good measures to use in humans in order to estimate SGN density within and across ears given that they seem to be minimally influenced by non-neural factors such as electrode location.

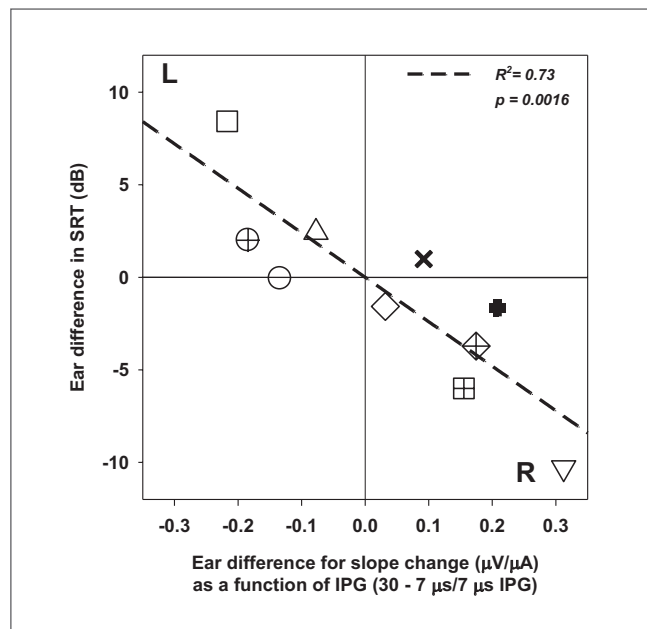


FIGURE 5. Results from Schvartz-Leyzac et al. (2018) that show the relationship between sentence recognition in noise and the ECAP IPG Effect for AGF slope. This study consisted of 10 bilaterally-implanted CI users, and sentence recognition in noise and ECAPs were measured in both ears. In order to better control for patient-level factors (e.g. cognition) that can also contribute to speech understanding, we compared these two variables across ears within the same subject; hence, performance on the sentence in noise task and the ECAP measure were subtracted across the two ears (Right minus Left). These results show that, within each subject, the ear with better speech understanding in noise (R or L) also tended to be the ear with a higher ECAP IPG Effect for ECAP slope. These results suggest that when examined within each subject, the ear that hears best in complex listening environments is also the ear estimated to have a higher SGN density.

USING ECAP MEASURES IN A CLINICALLY-MEANINGFUL WAY

As mentioned previously, current use of ECAP measures in the clinical setting is confined to measurement of thresholds in the intra- or post-operative setting. Several studies have shown that ECAP thresholds do not typically correspond to stimulation levels measured behaviorally during CI mapping. On the other hand, suprathreshold ECAP measures are not typically used in the clinical setting. This could be due in part to the fact that they take longer to collect than ECAP thresholds. However, it is more likely due to the fact that we quite simply haven't fully explored how we can use these measures in the clinical setting. Here, we review some ideas:

Electrode Site-Selection

One such approach has been to select electrode stimulation sites for activation or deactivation based on psychophysical, electrophysiological, or radiology measures (Garadat et al., 2013; Goehring et al., 2019; Noble et al., 2014, 2016; Zhou, 2017; Zhou & Pfingst, 2012, 2014a; Zwolan et al., 1997). Specifically, these studies have modified programming characteristics to remove electrodes based on various criteria in an effort to improve performance. For example, Zwolan et al. (1997) performed a task in which patients were asked to discriminate between two adjacent electrodes. If they could not perceive a difference between electrodes, then one of the electrodes was deactivated. Although removing electrodes might sound counterintuitive, the idea behind using an electrode discrimination test is that, if two electrodes are perceived to be the same by a listener, then removing stimulation on one of the electrodes might reduce redundancy of the signal and reduce "cross-talk" between the electrodes, thereby providing the listener with a cleaner speech signal. Also, due to frequency reallocation when some electrodes are turned off, more information is delivered to the better-functioning stimulation sites.

Recent data from our laboratory (Schvartz-Leyzac, Zwolan, & Pfingst, 2020) show promise for using suprathreshold ECAP measures in a similar manner. We measured the ECAP IPG Effect for peak amplitude on each electrode in 18 cochlear implanted ears of adult patients. We created experimental maps by systematically removing five electrodes with either the highest or lowest ECAP IPG Effect values to maintain tonotopocity. This means that patients listened with a program that was estimated to stimulate a higher density of SGNs, or another program that was estimated to stimulate a lower density of SGNs. CI users were then asked to perform a test measuring sentence recognition in background noise using each program. Our hypothesis was CI users would perform better when using the program that was estimated to stimulate a higher density of neurons. Results are shown in Figure 6.

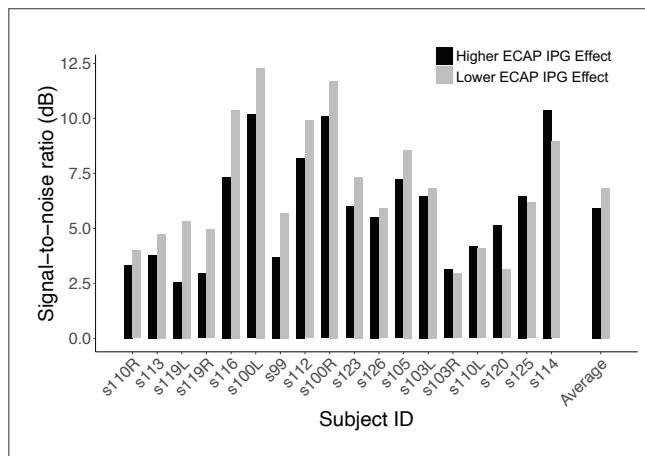


FIGURE 6. Bar graph presented in Schwartz-Leyzac et al. (2020). Bar-graph showing the signal-to-noise ratio (dB) required (y-axis) to achieve 50% accuracy on the CUNY sentence recognition-in-noise test using each of the three programs (Black = Higher Larger ECAP IPG Effect; Light gray = Lower Smaller ECAP IPG Effect). Note that a lower value on the y-axis indicates better performance on the task. Results are shown for each subject ear (x-axis). The last value on the x-axis, beyond the vertical dashed line bars on the far right, represents average performance across all ears. These results show that, on average, performance is better when listening to a program estimated to stimulate a higher population of SGN fibers.

Although individual variability is present, these results show that average performance was better when using the program with the highest ECAP IPG Effect for peak amplitude. These results, as well as some of the electrode site-selection studies cited above, suggest that perception of sentences can be altered, either in a positive or negative direction, by selecting either the “best” or “worst” electrodes for stimulation based on estimates of neural density across the electrode array.

Insights into Etiology and Performance Outcomes

We could also use suprathreshold ECAP measures to better understand how patterns of neural survival differ across various etiologies of hearing loss and how this factor might influence performance outcomes. While not a direct measure of neural survival, we know that suprathreshold ECAP measures do provide some information about the health of the AN, and better understanding the relationship between AN health and etiology could help us to make better predictions about prognosis with a CI, which will help us better counsel our patients.

He and colleagues (He et al., 2018; 2019) have recently examined suprathreshold ECAP measures in patients with CNL, which is often present in pediatric patients with congenital hearing loss and is also common to those with CHARGE syndrome (Amin et al., 2019; Choo et al., 2017). A recent study showed that pediatric patients with CNL had smaller ECAP peak amplitudes and shallower AGF slopes when compared to children without CNL (He et al., 2018). These results suggest

that the responsiveness of the AN in children with CNL is worse than in those without. This might help explain why pediatric CI recipients with CNL tend to have poorer outcomes when compared to those who do not have CNL.

More data are needed to help characterize auditory nerve responses in CI recipients with other etiologies. Propst and colleagues (2006) measured threshold and suprathreshold ECAPs in patients with congenital hearing loss due to Connexin-related deafness and compared results to patients with non-Connexin related deafness, but found no significant differences between the groups. However, a more recent study found that CI patients with Connexin-related deafness had larger ECAP amplitudes and steeper ECAP AGF slopes when compared to non-Connexin patients, suggesting better neural survival in patients with Connexin-related deafness (Xu et al., 2020). These results are important to consider when counseling patients and parents of patients, with respect to anticipated outcomes and could help to explain why patients with Connexin-related deafness tend to perform quite well with CIs, particularly when receiving implants at an early age (Abdurehim et al., 2017; Fukushima et al., 2002; Popov et al., 2014; Yan et al., 2013).

The Argument for Structure Preservation

CI candidacy has expanded significantly in recent years to include patients with significant pre-operative residual hearing (Firszt et al., 2018; Gifford et al., 2010; Holder et al., 2018). As such, when hearing is sufficiently preserved post-operatively, several studies have shown that using a combined acoustic + electric (“Hybrid”) signal presentation is advantageous, particularly for complex speech understanding and music appreciation (Gifford et al., 2013; Welch et al., 2018). The goal of hearing preservation during cochlear implantation has resulted in development of surgical approaches and electrodes designed to help minimize insertion trauma. Even when hearing preservation is not a realistic goal or when it is not achieved, some have argued that using approaches to help minimize insertion trauma are beneficial in order to preserve cochlear structures, such as SGNs, and doing so improves speech understanding (Carlson et al., 2011). ECAPs could be used to better understand how structure preservation influences performance in CI users.

Using Therapeutic Biological Approaches in Cochlear Implant Patients

Recent studies show that gene therapy can be used to help protect or even regenerate cochlear structures, such as SGNs, in animals with cochlear implants (Budenz et al., 2012, 2015; Pfingst et al., 2017; Pfingst, Zhou, et al., 2015). These studies show that gene therapy can be used to insert neurotrophins (proteins that help with the survival and function of neurons in our body) into the ear, and that some animals’ ears treated

with neurotrophin gene therapy are 'protected' from deafening to some extent. While these studies still remain largely experimental and confined to animals, there is much discussion and promise for applying these techniques in humans, and in particular using them in CI patients to enhance speech understanding (Lenarz, 2017; Ma et al., 2019). Because we hypothesize that a healthier, more densely populated group of SGNs will positively influence speech recognition outcomes, it stands to reason that using neurotrophin gene therapy in CI patients might also help improve performance for each listener. More research and evidence will be needed in order to determine the efficacy of this approach.

SUMMARY

CIs provide overwhelming success for the majority of recipients. However, outcomes do vary and it's important to better understand factors that contribute to performance. Additionally, we must learn how to identify factors that can be modified to improve performance within each CI user. We have combined research using animals and humans to show that the condition of the AN influences CI performance. Preliminary work shows that we can change the way a CI is programmed to select the best electrodes for stimulation in order to improve performance. In future work, we will continue to explore the efficacy of various iterations of this approach.

ACKNOWLEDGEMENTS

We would like to thank the subjects for their participation in the research, and are grateful to the University of Michigan Cochlear Implant team for their support and assistance with subject recruitment. We thank other lab members and colleagues at the University of Michigan including Debra Colesa, Donald Swiderski, Christopher Buswinka, and Yehoash Raphael for their contributions to this work. We acknowledge Timothy Holden and Jill Firszt in the Department of Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, for analysis of CT data reported in the study. These studies were funded by NIH NIDCD R01DC015809 and a University of Michigan MCubed grant.

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Early Acoustic Hearing and the Role of Segmental and Suprasegmental Speech Perception for Spoken Language and Literacy

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ABSTRACT

Our research explores early acoustic hearing (via hearing aid use) on speech perception skills of pediatric cochlear implant (CI) recipients who utilize bilateral CIs or bimodal devices (CI and hearing aid). The contribution of speech perception on receptive language and literacy skills is discussed.

The ability to perceive speech provides the foundation for verbal communication. Speech perception abilities may be broadly categorized into two main types of perception: segmental perception and suprasegmental perception. Segmental perception, the ability to perceive individual phonemes in words or sentences, may be thought of as the ability to understand ‘what is said.’ Suprasegmental perception may be thought of as the ability to perceive ‘how it is said’ (Wenrich et al., 2017). This includes changes in pitch and intensity that signal differences in vocal emotion, talker gender, age, and identity as well as linguistic cues to syllable and word stress and intonation cues that differentiate questions from statements. Importantly, both types of speech perception are necessary for effective communication (Abercrombie, 1967; Pisoni, 1997). Moreover, segmental and suprasegmental perception provide the foundation for the development of spoken language skills in children.

Specifically, before typically developing infants with normal hearing encode phonemes unique to their language, they attend to the acoustic cues of intonation, stress, and rhythm (suprasegmental perception) to parse the continuous speech stream into words. For spoken English, infants selectively attend to intonation/pitch changes at the end of clauses and within pairs of syllables that are predominantly trochaic (i.e., stress on the first syllable) to pick out words in connected speech (Jusczyk et al., 1999; Seidl & Cristia, 2008; Seidl & Johnson, 2008; Swingley, 2009). Additionally, newborn infants are able to discriminate amongst at least four different vocal emotions (sad, happy, angry, and neutral; Mastropieri & Turkewicz, 1999), and within months show a preference for positive vocal affect when listening to words (Papousek, et al., 1990; Singh et al., 2002, 2004). These results demonstrate infants’ ability to perceive suprasegmental aspects of speech, and such abilities are thought to be precursors for early language processing and vocabulary acquisition (Werker & Yeung, 2005). Together with

suprasegmental perception, segmental perception involves the ability to encode the acoustic cues of speech related to the individual phonemes of language. These phonemes and phoneme combinations serve as the building blocks for vocabulary and, ultimately, word combinations and sentences.

The presence of a congenital hearing loss disrupts access to these speech perception cues that underlie spoken language development in children. For children with severe to profound hearing loss, cochlear implants (CIs) are considered a viable option for restoring some level of speech audibility. As such, many studies have shown that pediatric CI recipients achieve levels of word and sentence recognition (segmental perception) that surpasses levels that may be achieved with traditional hearing aids (HAs) (Blamey et al., 2001; Boothroyd & Eran, 1994; Osberger et al., 1991). Notably, better speech perception abilities are associated with better outcomes for a variety of spoken language skills (Geers et al., 2003, 2009, 2013).

The acoustic cues that support segmental and suprasegmental perception are not transmitted equally well with acoustic (HAs) and electric (CIs) hearing devices. Segmental features, especially high frequency information for identifying vowels and consonants, are transmitted generally well with CIs and support word and sentence recognition (Ching, 2011). Suprasegmental features, especially low frequency information for supporting fundamental frequency (voice pitch), may not be transmitted as efficiently with CIs, due in part to reduced spectral resolution of current CI systems (Carroll & Zeng, 2007). Acoustic hearing via a HA may benefit CI users for perception of cues related to fundamental frequency and ultimately suprasegmental perception, although the degree of residual hearing necessary for good perception remains unclear (Dorman et al, 2008; Gantz et al., 2005; Gifford et al., 2007; Kong et al., 2005; Zhang et al., 2010). Studies have shown that children with CIs typically

perform better on tests of segmental perception (i.e. word and sentence recognition) than children with severe to profound losses with HAs (Blamey et al., 2001; Boothroyd & Eran, 1994; Osberger et al., 1991). Few studies, other than early studies of CI efficacy, have compared suprasegmental perception of CI users and HA users (Carney et al., 1990). A study of pediatric CI users and HA users with severe and profound hearing loss (HL) revealed that the HA users outperformed CI users on suprasegmental tasks including, word pattern, syllable stress, sentence intonation, and word emphasis (Most & Peled, 2007).

While the studies mentioned above demonstrate that CIs provide perceptual information that enables many children to perceive the individual phonemes necessary for early language learning, the important contribution of suprasegmental listening, which helps bootstrap vocabulary development in children with typical hearing, has received little attention. Examining the unique role of both segmental and suprasegmental perception on spoken language skills of pediatric CI recipients may have implications for decisions related to rehabilitation, especially as it relates to hearing device recommendations. Specifically, examining the benefits of using a HA, combined with a CI, for segmental and suprasegmental speech perception may be beneficial for deciding on candidacy for bilateral CIs (BCI) or bimodal device use (CI and HA with the non-implemented ear).

Adults and children with greater levels of residual hearing are being considered for CIs in at least one ear (Cadieux et al., 2013; Gifford et al., 2010; Mowry et al., 2012; Sampaio et al., 2011). Thus, bimodal device use has become more prevalent as individuals with greater levels of hearing and some with asymmetric hearing loss (e.g., profound HL at one ear and moderate-to-severe HL at the opposite ear) receive a CI at their poorer ear. Thus, clinicians now focus on the most appropriate device for each ear. Most clinicians agree that children with profound levels of hearing should be considered for early BCIs; however, for children with varying degrees of hearing loss from severe to profound or with asymmetric HL, the decision is less clear (Peters et al., 2010). As illustrated in Figure 1, device candidacy decisions are generally guided by the degree of residual hearing, with those ears with more residual hearing considered for HAs and those ears with less residual hearing considered for CIs. As discussed previously, candidates with bimodal devices may have different degrees of residual hearing across ears. These various device configurations vary from a full complement of acoustic hearing (HAs) to a full complement of electric hearing (BCIs). Figure 1 illustrates the continuum of acoustic to electric hearing as degree of hearing loss increases.

Bilateral input to the auditory system, as opposed to unilateral, may prevent bilateral auditory deprivation and ultimately facilitate good binaural listening skills that are critical for

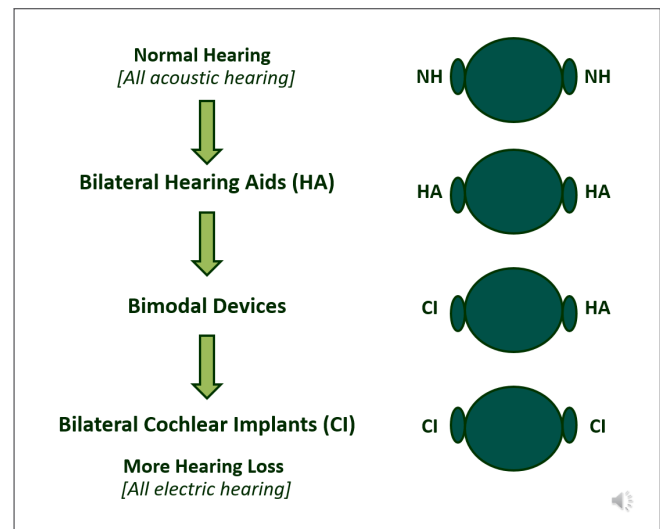


FIGURE 1. Device recommendations are based on degree of residual hearing and should be considered for each ear. Individuals with greater degrees of residual hearing at each ear (or less hearing loss) are generally considered as candidates for traditional hearing aids (HAs) at each ear. These devices deliver, similar to typical hearing (NH), deliver acoustic information to each ear. Individuals with less residual hearing at each (more hearing loss) may be considered as candidates for cochlear implants (CIs) at each ear and receive electric hearing at each ear. Those with different degrees of hearing at each ear (greater hearing loss at one ear and less hearing loss at the opposite ear) may receive a CI at one ear and a HA at the non-implemented ear (bimodal devices) and receive acoustic and electric hearing combined.

localizing sound and listening in noisy environments (Bauer et al., 2006; Gordon et al., 2013; Litovsky & Gordon, 2016). These listening abilities are thought to provide a foundation for developing spoken language skills necessary for effective communication in daily listening and learning environments, and ultimately for academic success (Boons et al., 2012; Litovsky & Gordon, 2016; Sarant et al., 2014, 2015).

Recent research in our lab addressed two questions: 1) What are the unique contributions of segmental and suprasegmental speech perception to spoken language skills for pediatric CI recipients? and 2) Is there an optimal level of hearing and duration of HA use that facilitates segmental and suprasegmental speech perception skills for pediatric CI recipients (Davidson et al., 2019a)?

One hundred seventeen children ranging from 5-9 years of age with cochlear implants, either BCIs or bimodal devices, were administered a spoken language test battery that included both segmental (phoneme and word recognition) speech perception, suprasegmental speech perception (talker discrimination, stress discrimination, emotion identification), receptive vocabulary, and receptive language. A continuum of residual hearing levels and length of HA use were represented by calculating the unaided pure-tone average (PTA) of the ear with the longest duration of HA use for each child. Our results revealed that

good suprasegmental perception skills contribute to better receptive language skills, and that both segmental and suprasegmental skills contribute to better receptive vocabulary scores. Furthermore, for children with severe levels of HL (~73 dB HL), a period of ~3.6 years of HA use was associated with better suprasegmental and segmental perception that continued even after some children had received BCIs. For children with profound levels of HL (~92 dB HL), the benefits of HA use for suprasegmental perception were less and there were no benefits for segmental perception. Lastly, for those with the most profound losses (~110 dB HL), there were no benefits of HA use for segmental or suprasegmental perception (Davidson et al., 2019a).

In addition to receptive language and vocabulary, we are examining the unique contributions of suprasegmental speech perception to literacy skills in pediatric CI recipients. The majority of research in literacy for this population has concentrated on examining the role of segmental speech perception on phonemic awareness skills that facilitate reading. However, evidence from typically developing children suggests that suprasegmental speech perception has a unique and equally important role in reading outcomes (Zhang & McBride-Chang, 2010). Early suprasegmental perceptual skills (i.e. syllable stress and intonation) that allow infants to segment words may support later phonological processing ability that underpins good reading. Follow up testing was conducted on the CI recipients in the Davidson et al. study when children were between the ages 7-10 years of age. One hundred four children

returned and completed early literacy assessments that included decoding and reading comprehension subtests. The mean standard scores for these CI recipients were within the average range for typically hearing age-mates (range = 85–115) for both decoding and comprehension (102.2 & 98.5, respectively). Analyses of literacy data revealed that suprasegmental perception operates independently from segmental perception to promote both decoding and reading comprehension.

In summary, for children with losses in the severe range, a period of bimodal device use provides complementary acoustic information, primarily through suprasegmental perception, that supports better receptive vocabulary and language (ages 5-8 years) and better early reading (ages 7-9 years). The transmission of segmental and suprasegmental perception via each path is illustrated in Figure 2. For children with the most profound losses, early BCIs provide the greatest opportunity for developing good spoken language skills. Clinicians should consider that early device decisions may have long term benefits for spoken language and literacy. Future studies should address how acoustic hearing experience affects binaural listening skills (like localization and listening in noise), auditory plus visual perception, complex linguistic and communication skills, and social functioning.

ACKNOWLEDGEMENTS

This research was supported National Institute on Deafness and other Communication Disorders NIDCD grant RO1 DC012778.

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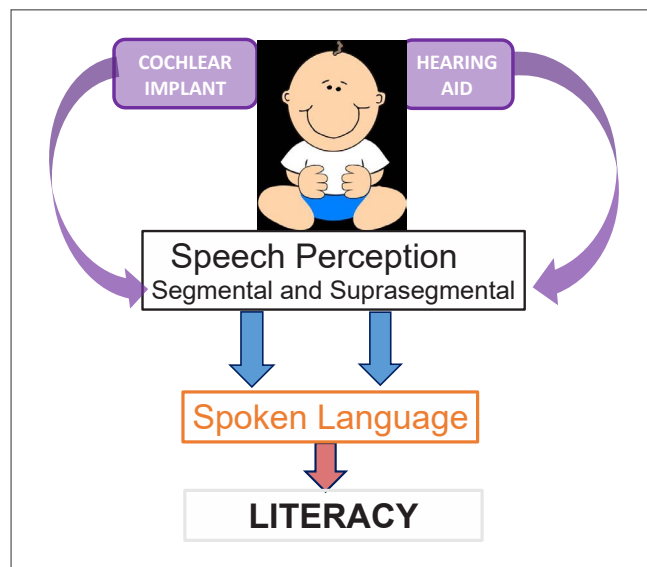


FIGURE 2. Infants who listen with a cochlear implant at one ear and a hearing aid at the non-implanted ear (bimodal devices) may receive complementary information from each device related to segmental and suprasegmental speech perception respectively. Both types of speech perception may operate independently to facilitate spoken language and ultimately literacy.

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Binaural Fusion in Children and Adults with Hearing Loss

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ABSTRACT

Binaural fusion is the perception of sounds entering the two ears as a single sound. In adults with typical hearing, binaural fusion will only occur for similar sounds that are likely to come from a single sound source. In contrast, in adults who use hearing aids (HAs) or cochlear implants (CIs), binaural fusion may also occur for sounds that are very different in pitch, such as different voices. Such abnormal binaural fusion can lead to binaural interference and difficulties with hearing speech in background noise. In children, binaural fusion is still maturing during development, and may depend on the hearing device combination—two hearing aids, a cochlear implant and hearing aid, or two cochlear implants.

INTRODUCTION

Fusion is the perceptual integration of different inputs into a single, cohesive object. In vision, binocular fusion is the integration of visual features received by the two eyes into a single visual object or image. In hearing, binaural fusion is the integration of acoustic stimuli received by the two ears into a single auditory object. Such stimuli can include simple stimuli such as pure tones, or more complex stimuli such as speech sounds.

For a single source, fusion is necessary for the perception of a single object from multiple receivers (eyes or ears). However, there are cases where fusion is inappropriate, such as when multiple objects need to be perceived as separate objects instead of as a single object. Listeners with typical hearing (TH) and normal central auditory processing are able to fuse when appropriate to do so, and segregate otherwise. However, as we will show below, this is not always the case for listeners with a hearing loss.

BINAURAL FUSION IN ADULTS WITH TYPICAL HEARING AND WITH HEARING LOSS

In adult listeners with TH, two different sounds presented simultaneously and dichotically to the two ears over headphones will only fuse perceptually if they are similar in frequency or pitch (Figure 1A-B). For pure tones, the limits of interaural frequency differences tolerated by adult TH listeners are typically less than ~10% of the tone frequency, or 0.1–0.2 octaves (Odenthal, 1963; Perrott et al., 1970; Reiss et al., 2017; Thurlow & Bernstein, 1957; van den Brink et al., 1976). This difference is less than a musical semitone—the difference in pitch between two adjacent piano keys.

In contrast, the situation is different for many adult listeners with hearing loss, where many listeners fuse sounds differing

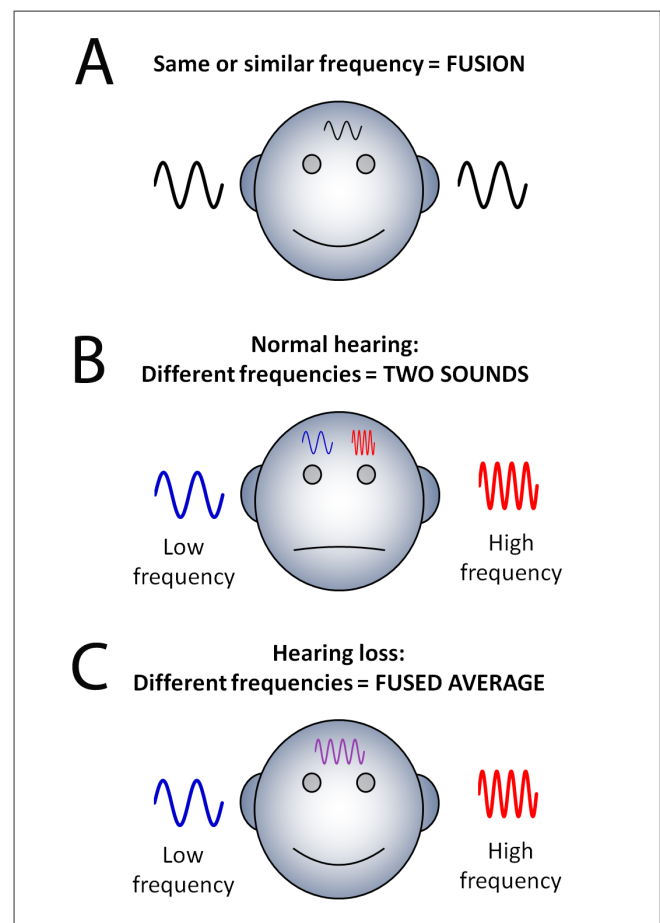


FIGURE 1. Illustration of how binaural fusion of tones presented over headphones differs in listeners with typical hearing and with hearing loss. A. Diotic presentation of the same tone to both ears will usually lead to perception of a single sound, or fusion, in most listeners. B. In listeners with typical hearing, dichotic presentation of tones of different frequencies to the two ears will usually lead to perception of two sounds of different pitches. C. In listeners with hearing loss, dichotic presentation of tones of different frequencies will usually lead to perception of a single sound, or fusion, with the fused pitch heard as an average of what would have been heard for each tone monaurally.

greatly in frequency (Figure 1C). Our first study of binaural fusion was conducted in adult bimodal cochlear implant (CI) listeners, who wear a CI in one ear together with a hearing aid (HA) in the other ear (Reiss et al., 2014). We stimulated a single electrode in one ear, while simultaneously playing an acoustic tone via headphone to the other ear, and asked listeners to indicate if they heard one sound or two. By varying the acoustic frequency presented, we found the range of acoustic frequencies that were perceptually fused with each CI electrode. The binaural fusion range varied across electrodes for each participant, as well as across participants, but generally the fusion range was much wider than observed in TH listeners (compare adult group data in dark bars in Figure 2). In other words, the CI listeners would fuse a CI electrode with a low pitch with low, medium, and high pitch tones in the other ear. The fusion range was found to be as broad as 3–4 octaves for some participants, even over the whole acoustic frequency range that could be tested. This is analogous to fusion of musical notes separated by 3–4 octaves on the piano, even when these notes are not harmonically related.

Abnormally broad fusion has also been demonstrated recently in bilateral HA users, of a single tone in one ear with a tone frequency in the other ear differing by as much as 1–4 octaves (Figure 2; Reiss et al., 2017). Similarly, in many bilateral CI users, a single electrode in one CI ear was found to be fused with all of the electrodes in the contralateral CI ear (Figure 2; Kan et al., 2013; Long et al., 2003; Reiss et al., 2018; van Hoesel et al., 1993; van Hoesel & Clark, 1997). Essentially, regardless of

hearing device combination, a consistent finding has been that many listeners who are deaf and hard of hearing fuse sounds of very different pitches, even very low and very high pitches, across the ears together into a single sound.

Note that there was variation across listeners in each of these groups; some participants had broad fusion, while others had narrow fusion more similar to TH listeners. In the bilateral HA group, demographic analysis of this variation revealed that broad fusion range was correlated with younger age, longer duration of deafness, and earlier age of deafness and onset of HA use (Reiss et al., 2017). As these variables were also correlated with each other, it remains unclear which of the variables is important in determining the breadth of binaural fusion; further research is ongoing to analyze this in a larger subject population. However, it seems unlikely that binaural fusion would improve in these subjects with aging, so early age and long duration of deafness are more likely factors in the development of abnormal fusion. Our preliminary findings in children, which we will show below, are consistent with this interpretation.

Other factors may also contribute to abnormally broad fusion, such as poor peripheral frequency resolution or top-down processing and attention factors.

CONSEQUENCES OF ABNORMAL BINAURAL FUSION

What is the impact of this abnormal fusion on pitch and speech perception? In other words, what is heard when two different sounds are fused into a single percept?

For pitch perception, it turns out that if two sounds of different pitches are fused, a new pitch intermediate between the two is often perceived. In the visual system, this is analogous to the averaging of color between the two eyes, as illustrated visually in Figure 1C. Averaging of pitch for different tone frequencies across ears has been documented for TH listeners (Thurlow & Bernstein, 1956; van den Brink, 1976), as well as listeners who are deaf and hard of hearing with bilateral HAs and bimodal and bilateral CIs over a larger fusion range (Oh & Reiss, 2017; 2020). Interestingly, when the original pitches are an octave or more apart yet fused in listeners with hearing loss, the pitch may also be dominated by the lower pitch.

In the case of listeners with acoustic hearing—those with TH and those who wear bilateral HAs—the dichotic listening situation does not necessarily happen in the real world. However, in the case of individuals who use bimodal or bilateral CIs, something similar to this dichotic listening may occur. The CI often introduces pitch mismatches between the two hearing devices, such that a single sound played individually to each ear will evoke different pitches. This occurs because CIs are inserted to

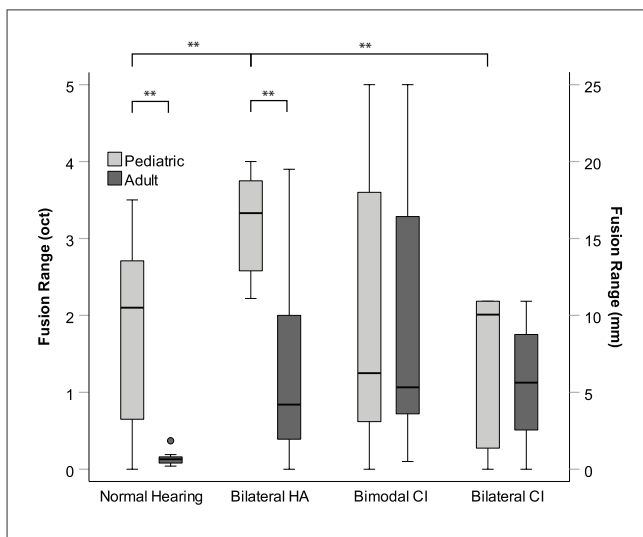


FIGURE 2. Summary of fusion range findings in children and adults with normal hearing, bilateral HAs, bimodal CI and HA, and bilateral CIs. Fusion ranges are shown in octaves for the normal-hearing, bilateral HA, and bimodal CI groups, and in mm at the right axis for the bilateral CI group.

Replotted from Hartling et al., 2020.

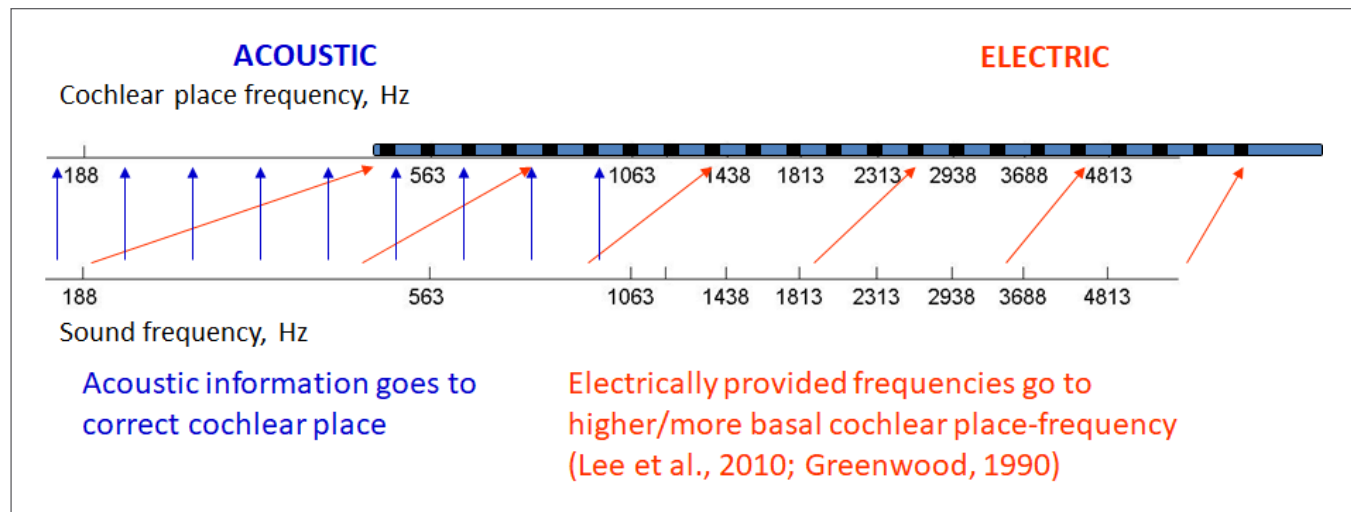


FIGURE 3. Schematic of the mismatch between the CI speech processor mappings and the actual cochlear place of stimulation for each frequency. The lower axis is the acoustic frequencies from the environment that are processed by the CI, and the upper axis is the cochlear place of stimulation that the CI assigns each sound frequency to.

different insertion depths in the cochlea for each individual so that the deepest electrode might be stimulating 0.5 kHz in one CI recipient, and 1.1 kHz or 1.8 kHz in other CI recipients (e.g., Lee et al., 2010).

More importantly, CI mapping does not account for this individual variation in insertion depth, and assigns the same input frequency range (e.g. 100–300 Hz) uniformly to the deepest electrode for all patients regardless of how deep the electrode array is inserted. Hence, as shown in Figure 3, in response to a 188 Hz tone in the environment, a bimodal CI listener may hear a 563 Hz in the CI ear simultaneously with 188 Hz in the HA ear. If these are fused, then the fused pitch will be some pitch intermediate between 188 and 563 Hz, leading to distortion of the original pitch. Similarly, bilateral CI listeners also have differences in insertion depth across ears, with similar pitch averaging and distortion effects. In fact, one bilateral CI user commented that voices heard through one CI will be heard as higher in pitch than in the other CI, but when both CIs are worn together, the fused pitch is somewhere in between (Personal Communication, 2020).

For speech perception, if similar spectral averaging occurs as for pitch, distortion of the original sound will occur. In fact, binaural interference was demonstrated in both HA and CI users with abnormally broad fusion, especially if one ear is worse than the other (Reiss et al., 2014). This is illustrated for perception of various continua between pairs of synthetic vowels in Figure 4. Vowels are identified mainly based on the frequency location of the first two peaks in their spectra, called formants. In this experiment, synthetic vowels were generated to vary in the first formant between a pair of vowels with the same second

formant, such that stimuli at one end of the continuum sounded more like the first vowel, stimuli at the other end sounded more like the second vowel, and stimuli in between sounded intermediate between the two original vowels. Each of the stimuli was presented individually in the free field to the left, right, or both ears (hearing devices turned off and ears plugged/muffed as needed). Listeners were instructed to pick just one of the two vowels as the one they heard. As shown in Figure 4A, for a TH listener listening to a continuum from “AH” to “UH”, the likelihood of hearing “UH” increased as the stimulus became more “UH”-like, and the slope and midpoint of the function was similar for the left, right, and both ears. However, for a bilateral HA listener with broad binaural fusion, the left ear function was similar to the TH listener, but the right ear function indicated that the listener heard nearly all of the stimuli as “AH” (Figure 4B). When both HAs were used, the function was an average of the left and right function, indicating spectral averaging with a lower slope, and thus worse performance than with the better (left) ear alone. The case was different for a bimodal CI listener with similar asymmetry in that the CI ear performed well, but the HA ear did not; this listener had narrow binaural fusion, which may explain the lack of spectral averaging and dominance of the binaural response by the better CI ear (Figure 4C). Finally, another bimodal CI listener with broad binaural fusion experienced non-linear interference, in that the performance with both the CI and HA was worse with a shallower slope than either the CI or the HA alone (Figure 4D). This non-linear effect is likely due to the spectral mismatch between the CI and the HA combined with broad binaural fusion and spectral averaging.

Recent data also show that even in the absence of pitch mismatches, abnormal binaural fusion is associated with

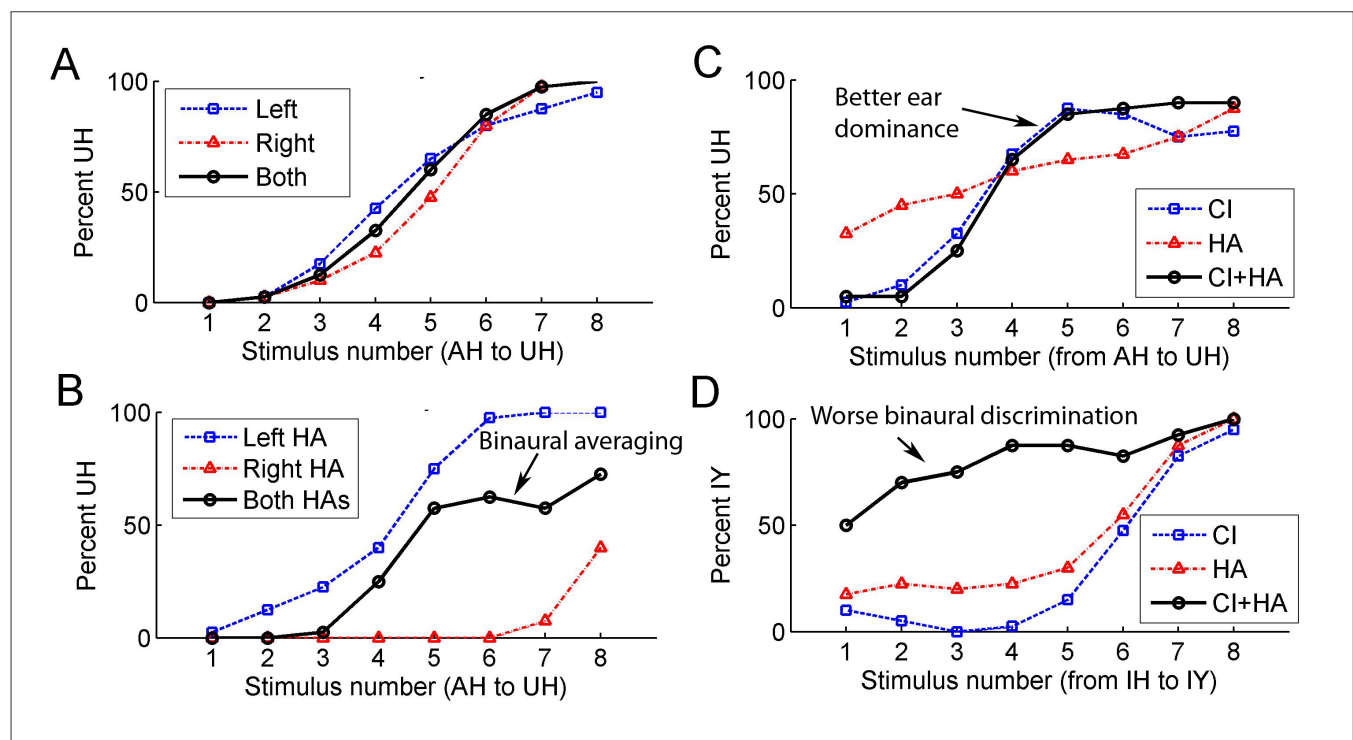


FIGURE 4. Examples of four types of binaural spectral integration. A TH subject with normal classification of the /α/-/Λ/ pair, with no significant differences between monaural and binaural conditions. B Better ear dominance (with the CI ear) in a bimodal CI + HA subject with the /ε/-/Ι/ pair. C Binaural averaging in bilateral HA subject with the /Λ/-/υ/ pair. D Binaural interference in a CI + HA subject with the /Ι/-/ι/ pair. Dash-dot and dashed lines indicate the monaural right and left ear conditions, respectively, and solid lines indicate the binaural conditions.

Modified from Reiss et al., 2016.

difficulties with hearing speech in background talkers (Oh & Reiss, 2020). In listeners with individual variation in binaural fusion, the fusion range was negatively correlated with the benefit from voice pitch differences in a closed-set speech recognition test with competing talkers in the background. Similar correlations of fusion range with the ability to benefit from voice pitch differences were observed in TH, bilateral HA, and bimodal CI listeners regardless of hearing device type.

This correlation of fusion range with ability to benefit from voice pitch differences for speech understanding in noise is likely to arise because abnormal fusion leads to fusion of different voices, regardless of voice pitch difference, such that words spoken by different talkers are blended. Participants with abnormally broad fusion often reported hearing new words caused by fusion and blending of different color words together, such as “green” and “red” blending into “grain”. This is in contrast to participants with normal, sharp fusion who simply reported energetic masking such that the background voices were too loud for the target to be audible.

It should be noted that bilateral CI listeners were also tested, but were uniformly unable to derive any benefit from voice pitch differences for separating voices to understand speech in

noise. So no variations in benefit were observed that could be correlated with binaural fusion range.

BINAURAL FUSION IN CHILDREN

Over the past five years, we started a longitudinal study to measure binaural fusion in children with TH, bilateral HAs, bimodal CI, and bilateral CIs, and how this changes during development. The goal of the study was to compare binaural fusion across hearing device combinations in children, and track how this changes during development. The experiments were conducted similarly as in adults, with games and small prizes as additional incentives for children to complete the behavioral tasks. The children ranged in age from 6–11 years old in the first year of testing.

Preliminary binaural fusion range results for the first year of testing are shown in the gray bars in Figure 2 (Hartling et al., 2020). Two trends are apparent from the figure. First, children with bilateral HAs had uniformly broader fusion of 3–4 octaves, compared to children with TH, bimodal CI, and bilateral CIs who showed more variation in fusion range. This differs from adults (dark bars), who had similar binaural fusion ranges across the three hearing loss groups. Second, children with TH and children

with bilateral HAs had broader fusion than their adult counterparts with TH and bilateral HAs, respectively. Bimodal and bilateral CI children were similar in fusion range to their adult counterparts.

Together, the findings suggest that hearing loss in early childhood has a detrimental effect in that it may contribute to the development of abnormally broad binaural fusion. This interpretation would be consistent with the correlation of abnormally broad fusion in adult HA users with early childhood onset of hearing loss. In addition, the finding that children with TH have broader fusion than adults with TH suggests that binaural fusion is still developing in childhood up to the age of 12, consistent with similar studies of binocular integration and multi-sensory integration over this age range (Vedamurthy et al., 2007; Gori et al., 2008; Nardini et al., 2010).

Another interesting finding was that in children with bilateral CIs, binaural fusion range was correlated with duration of acoustic experience and bimodal CI use before the second CI. In other words, children who were bimodal for a longer time had narrower binaural fusion more like that of TH children. Narrow binaural fusion ranges were also observed in children with bimodal CIs, some as narrow as those of TH children. This suggests that the use of the bimodal CI combination, a CI with a HA in the other ear, may help counteract the effects of hearing loss and promote the development of normal, narrow binaural fusion similar to that observed with TH. Further research is ongoing to see if these preliminary results hold with a larger number of pediatric subjects with each hearing device combination.

SUMMARY AND CONCLUSION

The findings to date indicate that adult listeners with hearing loss are likely to have abnormally broad binaural fusion compared to TH listeners. This abnormal binaural fusion and associated binaural spectral averaging may have negative consequences, including binaural interference in CI users and difficulties in separating voices in background noise in both HA and CI users. Preliminary findings in children indicate that children with hearing loss can also have abnormally broad binaural fusion, though this may differ depending on hearing device combination.

Further research is ongoing to better understand the causes of abnormal binaural fusion, and the clinical implications, especially for speech perception in background talkers. Understanding the causes of abnormal binaural fusion will help indicate ways to sharpen binaural fusion to be more like the fusion experienced by TH listeners so that fusion only occurs at appropriate times for sounds from a single source, and not for sounds from multiple sources that should not be fused together.

ACKNOWLEDGMENTS

We thank Cochlear, MED-EL, and Advanced Bionics for providing equipment and software support for interfacing with the cochlear implant, and Ruth Litovsky for providing templates for child-friendly experimental software. This research was supported by grants R01 DC013307 from the National Institutes of Deafness and Communication Disorders, National Institutes of Health.

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