Binaural cue sensitivity in children and adults with combined electric and acoustic stimulation

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1.0 Background

Combined **E**lectric and binaural **A**coustic **S**timulation (EAS), achieved via hearing preservation cochlear implantation, has become increasingly prevalent. Two cochlear implant (CI) systems have specific FDA labeling for EAS allowing for normal low-frequency (LF) hearing with precipitously sloping high-frequency (HF) hearing loss, and all three FDA-approved systems have integrated hearing aid (HA) circuitry in ear-level sound processors. Despite wide availability of EAS technology and an abundance of studies reporting high rates of long-term hearing preservation[11–13], only 50-69% of adult CI users with acoustic hearing preservation are utilizing EAS technology[14,15]; however, we found that from 2013-2018, adult EAS technology utilization increased from 36% to 69% and our hearing preservation rates improved from 57% to 95% over that same period[15]. Thus, there is evidence that hearing preservation and EAS utilization will continue to increase. In addition to the availability of EAS technology, the combination of bilateral HAs with CI ($CI+HA_{bilat}$) provides significant additional benefit beyond that offered by bimodal hearing ($CI+HA_{contra}$) for speech understanding in noise[3–7,16], reverberation[4], music listening[17], and localization[3,7,8]. However, there is considerable variability in EAS benefit across listeners and different listening environments. This variability in EAS benefit is not reliably related to low-frequency audibility in the CI ear(s)[8,9]—a finding also observed in the bimodal literature. That is, despite a correlation (r=0.25-0.35) between bimodal benefit and audiometric thresholds in the non-CI ear, bimodal benefit for individuals with unaided thresholds from 40-100 dB HL ranges from a negative impact (bimodal *interference*) to over 60-percentage points of benefit for speech in noise[18,19]. Given the increased emphasis on hearing preservation cochlear implantation and accompanying EAS technology available for all CI recipients, *there is a clear impetus for us to understand the underlying auditory mechanisms and to extract the relevant clinical applications to assist clinical management of EAS users today and tomorrow.*

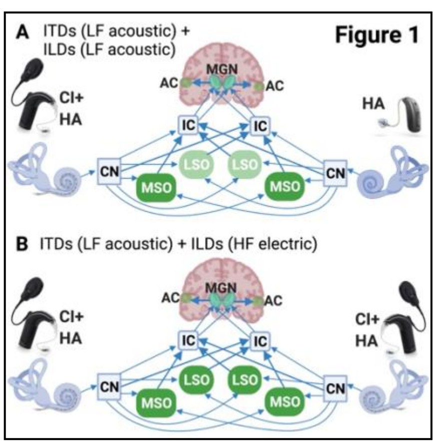
Low-frequency ITDs & ILDs for spatial hearing: EAS users have binaural acoustic hearing in the low-to-mid frequencies offering access to ITDs—which are most prominent for frequencies below 1500 Hz[20–22]. In contrast, ILDs are largest above 1500 Hz[23], but still present for LF stimuli in the range of ~2-6 dB[23]. Adult EAS users demonstrate ITD thresholds for acoustic stimuli in the ecologically relevant range[4,8,9,24], with some EAS users exhibiting near-normal ITD sensitivity. Because most EAS users have a unilateral CI with precipitously sloping HF hearing losses, HF ILDs are generally not available; rather, bilateral acoustic audibility for most adult EAS users is limited above ~750 Hz due to audiometric configuration and severity[2,4,8,25–27].

Adult EAS users also show significantly better localization in listening conditions including bilateral HAs and EAS ($CI+HA_{bilat}$) as compared to the within-subjects bimodal condition ($CI+HA_{contra}$)[3,7,8]. EAS users can also access ITDs[4,8,9,24] and said ITD thresholds are significantly correlated with localization[8] and speech recognition in diffuse noise[4,8,9]. We have also shown that acoustic hearing in the CI ear offers significant benefit for spatial hearing tasks involving static cues such as minimal audible angle (MAA) as well as dynamic cues such as the minimal audible movement angle (MAMA) (see *Preliminary Studies*). In fact, we show that localization (rms error), MAA (degrees), MAMA (degrees), and speech recognition in diffuse noise in the EAS condition are all related to *LF ITD and ILD* sensitivity[9]; however, *only the correlation for ITDs reached statistical significance*[9]. These data provide evidence that at least some individuals with hearing preservation can use LF ITDs and ILDs, despite the fact that ITD and ILD sensitivity is generally poorer than what would be expected for age-matched listeners with NH[9].

Additionally, these data demonstrate that *EAS users can take advantage of underlying binaural cues*—most notably LF ITDs—*using their clinical EAS technology in free-field environments despite the lack of interaural synchronization*[3–5,7,8].

Contributions of ITDs and ILDs to EAS benefit: Though adult EAS listeners appear to use both ITDs and ILDs to obtain significant EAS benefit for tasks of spatial hearing tasks and speech understanding, we do not know how these listeners weight LF ITD and ILD cues, particularly as related to degree of interaural asymmetry and absolute audibility differences across the acoustic-hearing spectrum. It is well known that interaural asymmetry in audibility can disrupt binaural cue sensitivity subsequently resulting in spatial hearing deficits[28]. In fact, interaural asymmetry is known to drive changes in the weighting of ITD/ILD cues[29] resulting in poor binaural cue integration[30]; however, *adult humans*[31–33] *and animals*[34] *have demonstrated adaptation to asymmetry over time with evidence of at least partial restoration of binaural function*. This holds high clinical relevance for the technological design and clinical programming of HAs and CIs. Though loudness balancing across ears via frequency-specific amplification is critical for access to both ITDs and ILDs, there are other clinical considerations for HA and CI parametric manipulation. To make such data-driven decisions regarding development, programming, and management of HA and CI technology, we must have a thorough understanding of the underlying mechanisms driving EAS benefit (or lack thereof) for both adults and children.

Pediatric EAS and binaural development: Binaural hearing is central to several critical auditory phenomena including localization, speech recognition in complex environments, speech/music perception and appreciation, as well as quality of life. The role of binaural stimulation for auditory development is critical as inhibitory synapses in the central auditory system are refined throughout infancy and early childhood. The effectiveness of developmental synaptic pruning is dependent upon *typical activation of excitatory auditory pathways*, or *consistent binaural input*[35]. For children with hearing loss, binaural development can be significantly impacted as auditory deprivation degrades both ITD and ILD coding[36,37]. **Figure 1** displays an anatomical schematic of cochlear, auditory brainstem, midbrain, and brain structures including cochlear nucleus (CN), lateral superior olive (LSO), medial superior olive (MSO), inferior colliculus (IC), medial geniculate nucleus (MGN), and auditory cortex (AC). In **Figure 1A**, unilateral CI with acoustic hearing preservation ($\text{CI+HA}_{\text{bilat}}$) preserves ITDs and LF ILDs via LF acoustic hearing; LSO shading is transparent here (**Fig. 1A**) indicating only partial ILD availability via LF acoustic hearing. In **Figure 1B,** bilateral CIs with bilateral HAs ($\text{CI}_{\text{bilat}}\text{+HA}_{\text{bilat}}$), preserves ITDs and LF ILDs via acoustic hearing, but also transmits more robust HF ILDs via bilateral CIs[38]. In both scenarios, resolution of binaural cues is possible, but the hearing configuration in **Figure 1B**, offers maximum availability of ITDs and ILDs. As displayed here, <u>*chronic EAS use in children could drive developmental changes in binaural excitatory and inhibitory pathways as well as the perceptual weighting of ITD and ILD cues.*</u> Indeed, greater EAS utilization across all populations, could significantly improve spatial hearing abilities for both adults and children.



There is limited research on hearing preservation for pediatric CI users, particularly related to functional outcomes and EAS benefit. All but one recent study[39] has focused on pediatric hearing preservation describing whether it was achieved, rather than describing EAS benefit for speech recognition or spatial hearing[40–48]. For studies reporting speech recognition[45,49–53], none investigated whether acoustic hearing *from the CI ear* provided significant additional advantage over that afforded by acoustic hearing *from the non-CI ear* (CI+HA_{bilat} vs. CI+HA_{contra}). We must understand how children use binaural acoustic hearing with CI, what constitutes realistic and expected EAS outcomes for speech recognition and spatial hearing, and what device configurations yield maximum outcomes; these are critical concerns for children developing binaural hearing, speech and language, as well as social and emotional skills, musical abilities, and academic proficiency.

Deprivation-driven neuroplasticity: Animal and human research demonstrates remarkable neuroplastic changes in response to binaural deprivation, particularly when deprivation coincides with critical periods of auditory development[28,30,31,35,54–56]. Deprivation-driven remapping of the binaural hearing system persists long after asymmetries in binaural hearing have been corrected. The implication of this research is that optimizing EAS as early as possible and within critical periods of development will most potently shape binaural hearing and support basic processes that we know to be important for spatial hearing abilities. However, we know little about the impact of bilateral hearing loss—particularly asymmetric LF hearing loss resulting from threshold elevation following CI surgery—on binaural development in humans. While some tasks of binaural hearing—such as mean MAA and localization in quiet—are adult-like in early childhood[57–60], other aspects of binaural hearing continue to develop through adolescence[10]. Children with NH also exhibit considerable variability in rms error[59] as well as significant uncertainty and immature decision-masking strategies on tasks of binaural cue sensitivity[61]. In addition to these binaural developmental effects for children with NH, little is known about the trajectory of binaural development in children with hearing loss who have access to binaural acoustic hearing. *Specifically, we do not know what additional effects hearing loss, interaural asymmetry in acoustic hearing, and the addition of unilateral electrical stimulation may have on the developing binaural system.* Gorodensky and colleagues[29] showed lateralization was significantly affected by hearing loss severity for 32 children and that interaural asymmetry negatively influenced ITD- and ILD-based lateralization. It may be the case that younger children experience limited utilization of the binaural cues that likely subserve adult EAS benefit in complex listening environments, as described in *Preliminary Studies*. In fact, our pilot data suggest that children who are experienced bimodal listeners (CI+HA_{contra}) do not demonstrate *acute EAS benefits* (CI+HA_{bilat}) when initially fitted with acoustic amplification in the implanted ear(s); however, we show data for three children with chronic EAS use (3+ years) who exhibit significant EAS benefit comparable to adults; 1 of these 3 children was followed longitudinally and demonstrated emergence of EAS benefit and binaural sensitivity following a 4-year period of chronic EAS use. Thus, there is a critical gap in the literature regarding the typical trajectory for binaural development for both children with NH as well as children with bilateral hearing loss, with or without CI.

As mentioned above, binaural development could be influenced by a unilateral CI, which is the typical intervention for individuals with EAS-like audiograms. For NH listeners, across-frequency incongruencies in binaural cues result in elevated ITD and ILD thresholds[62–65]. Similarly, a unilateral CI could cause binaural interference resulting in disruption of LF acoustic cues as shown in our recent study with EAS simulations[66]. However, in contrast to our binaural interference data with EAS simulations, few adult EAS listeners exhibit binaural interference for ITD and/or ILD targets when using a unilateral CI[9]. For the few adult EAS listeners who did exhibit binaural interference, the effect was variable and not related to binaural cue sensitivity in the acoustic-alone condition, absolute target audibility, or degree of interaural asymmetry in audibility[9]. Thus, it is possible that chronic EAS use with unilateral CI (CI+HA_{bilat}) allows for adaptation to the presence of a constant, but binaurally incongruous CI stimulus, as shown in **Figure 1A**. It is also plausible that *bilateral CI* with bilateral hearing preservation (CI_{bilat}+HA_{bilat}) (**Figure 1B)**, results in better preservation of binaural cue sensitivity and spatial hearing abilities given access to LF ITDs as well as both LF and HF ILDs. Investigation of these effects is warranted in both adults and children as these data could significantly impact clinical recommendations and audiological management of EAS patients. As more adults and children with EAS-qualifying audiograms pursue *bilateral CIs* and have bilateral hearing preservation[44,48,67,68], sequential bilateral implantation occurring within our enrolled study participants would allow a naturalistic investigation of these effects in both groups. This investigation can inform clinical practice regarding recommendations for EAS or bilateral CI for children with bilateral sloping sensorineural hearing loss (SNHL); this project will provide the necessary data to help guide these critical clinical decisions.

To understand the contributions of LF binaural cues to EAS, we will assess the relative weighting of ITD and ILD cues as well as compare this weighting to spatial hearing tasks completed in the free field, where cues naturally co-vary. This comparison will be of particular importance to pediatric EAS listeners whose head size and central nervous system maturation both continue to change through adolescence. With the physical growth in head size[69] and the known developmental maturation of neural synchrony or phase locking[70,71]—a critical component for resolution of fine-structure ITDs—we expect children with NH and EAS to exhibit immature spatial hearing abilities in conditions involving roving level[58,59,72], and children using EAS to have poor ITD sensitivity resulting from bilateral SNHL and interaural asymmetry for LF audibility[39] (also see **Figure 4**—*Preliminary Studies*). Though ITD sensitivity for infants with NH rapidly improves from birth to approximately 50 weeks of age[73–75], adult-like ITD thresholds[10] and decision-making strategies[61] may not be achieved until adolescence. Though there is research demonstrating adult-like lateralization and resolution based on both ITD and ILD cues[71,76] and adult-like spatial discrimination for some tasks[57], *we know little about perceptual weighting, and developmental trajectories of binaural hearing even for children with NH.*

Sensory and non-sensory factors: There is likely a difference between sensory-based maturation, as evidenced by infant studies, and some combination of sensory and non-sensory maturation influencing a child's ability to complete behavioral tasks of spatial discrimination and spatial release from masking (SRM). This gap in our knowledge about the developmental trajectory of binaural cue sensitivity, perceptual weighting of said cues, and underlying neural synchrony influencing LF ITD access complicates interpretation of the current literature regarding sensory- and non-sensory factors. As little as we know about development of binaural cue sensitivity in children with NH, *we know even less for children with bilateral SNHL*. Our proposed research will describe the developmental nature of binaural sensitivity and spatial hearing abilities in children with NH and EAS. Further we will characterize the influence of bilateral SNHL as well as interaural hearing asymmetry on binaural cue sensitivity providing theoretical value to the field regarding binaural development. This information will inform hearing technology development and have the potential to improve clinical EAS fittings, thereby holding high public health relevance for CI recipients with bilateral LF acoustic hearing.

Clinically applicable measure identifying EAS benefit: Despite significant EAS benefit for speech recognition in noise, reverberation, and spatial hearing, utilization of EAS technology for CI users with hearing preservation is just 50-69% for adults[14,15] and there are no published reports for children. As previously mentioned, though EAS benefit is significant, it is variable across listeners and not well predicted by the audiogram. This poses a clinical quandary for audiologists who are unsure who to fit with EAS technology, particularly given that many adult CI recipients reject the use of an earmold or non-custom dome in the CI ear. One cited reason is that the CI alone yields significant auditory benefit and CI users already obtain adjunctive benefit from bimodal hearing ($CI+HA_{contra}$). Clinicians need a measure capable of identifying individuals who are most likely to derive significant EAS benefit ($CI+HA_{bilat}$) from availability of LF acoustic ITDs and/or ILDs. Such a measure would inform clinical decisions regarding EAS fitting and would provide a springboard for counseling patients who may be reluctant to add another piece of hearing technology.

We have demonstrated a significant correlation between adult EAS benefit for speech in noise, spatial discrimination, auditory motion perception, and EAS listeners' sensitivity to ITDs[4,8,9] and ILDs in the acoustic-hearing domain[9]. However, psychophysical estimates of ITD and ILD sensitivity can take hours and require a period of listener training for accurate estimation. Although research-proven tasks can inform us regarding potential for EAS benefit, use of said tasks is just not clinically feasible. Rather, *audiologists need a quick and sensitive measure indicative of binaural cue utilization*. Such a measure could be integrated into the pre- and/or post-operative test battery informing us about which listeners are most likely to derive benefit from bilateral acoustic amplification in an EAS configuration ($CI+HA_{bilat}$) and could also help inform implant electrode array selection, surgical approach, and medical management to maximize hearing preservation.

Behavioral measures: The binaural masking level difference (BMLD) and binaural intelligibility level difference (BILD) tasks have the potential to serve as clinically feasible, functional assessments of binaural cue utilization for EAS patients. BMLD is the phenomenon in which a lower threshold is observed in conditions for which the signal and masker differ in interaural phase[77–79] and the BILD is a similar phenomenon using speech stimuli as the target. We currently have pilot data for BMLD with 250- and 500-Hz tones in the presence of a LF noise (100 to 800 Hz) and spondee BILD in the presence of a broad-band noise (BBN). As described in *Preliminary Studies,* we found that both BMLD and BILD magnitude was significantly correlated with EAS benefit obtained for speech recognition in diffuse noise (S_0N_{45-315}) as well as for tasks of spatial hearing—including MAA and MAMA; this relationship is key to understanding binaural mechanisms. There has also been increased attention on the translation of research-proven tasks of psychophysical auditory perception to clinically feasible assessments with a quick behavioral ITD task being particularly relevant here[80–83].

Objective measures: In addition to behavioral measures of binaural sensitivity or binaural cue utilization, there are relevant objective measures which may prove useful for clinical application. These objective measures can be categorized based on the approximate "level" of the binaural auditory system that they test from brainstem to cortex. While binaural hearing undoubtedly begins in the brainstem, brainstem-based metrics may be confounded by methodological issues that make them difficult to interpret [see So and Smith[84] for discussion]. This has led many researchers to favor cortical assays of binaural hearing, which reflect brainstem-initiated processes *inherited* by higher-order auditory structures. Research in listeners with NH has demonstrated that sensitivity to interaural phase differences (IPDs[85,86]), ITDs[87,88], and ILDs[88] are indexed in cortically evoked acoustic change complexes (ACC). ACCs in response to the introduction of a binaural shift in phase (ACC_{IPD}), time (ACC_{ITD}), or level (ACC_{ILD}) indicate that the listener has the *neural capacity* to discriminate the imposed change; however, the binaurally elicited ACC does not necessarily translate to behavioral sensitivity of said cue. **Figure 6** in *Preliminary Studies* displays representative ACC_{IPD} waveforms and correlations with behavioral ITDs. Because research has shown significant relationships between ACC[86] or interaural phase modulation following response (IPM-FR[85]) and spatial listening and/or BMLD tasks in adult listeners with NH, there is evidence that these objective measures are reasonable surrogates for binaural perceptual abilities.

The possibility of using an objective measure of binaural processing holds promise for determining which CI users with hearing preservation are equipped to derive benefit from bilateral LF amplification via EAS ($CI+HA_{bilat}$). This work will allow us to 1) investigate the relationship between IPD- and ILD-evoked ACC in adult and pediatric EAS users, 2) complete a parametric and longitudinal investigation into the emergence of this response in children with NH[89,90] and children with bilateral SNHL, and 3) compare electrophysiologic measures to behavioral estimates of binaural cue sensitivity and ITD/ILD cue weighting. Characterizing neural synchrony via phase coherence (see *Approach*) from these objective measures will provide the field with information regarding the potential differences between underlying physiological sensitivity (sensory factors) and a child's ability to complete tasks of spatial hearing (sensory *and* non-sensory factors). Though rapid technological and surgical advances have made it possible for many patients to utilize EAS, individual and mechanistic factors contributing to EAS benefit are still unclear. Our proposed research activities will help close the gap between what is technologically possible and what is clinically implemented by investigating development of binaural sensitivity and spatial hearing. The resultant data can be used to exploit developmentally driven timing and level cues to maximize EAS technology and related hearing outcomes.

INNOVATION: This innovative proposal will significantly impact the field by providing the first dataset explaining: 1) degree and time course of EAS benefit in pediatric and adult CI users following EAS fitting; 2) developmental trajectory of binaural auditory sensitivity in children with NH and EAS; 3) perceptual weighting of binaural cues in adult and pediatric EAS users including a description of weighting over time for children and adults initially fit with EAS technology; 4) development of clinically relevant behavioral and objective assessments that can inform clinical-decision making for EAS application. We will use data from Aims 1 and 2 to help describe the time course of binaural development using behavioral and objective responses to interaural differences in timing (phase) and level. New insight into the developmental trajectory of the binaural system for children with NH will provide a benchmark for interpreting effects of SNHL, LF asymmetry in audibility, and presence of electrical stimulation on said trajectory. The theoretical framework of our primary outcome measures—EAS benefit for speech recognition and spatial hearing—is outlined in **Figure 2**.

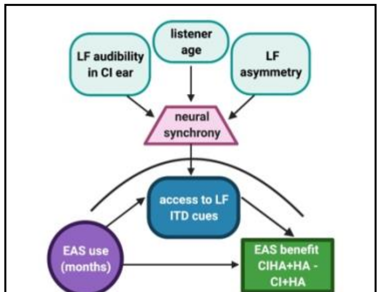


Figure 2. Direct & mediated effects for chronic EAS use and access to ITD cues for EAS benefit.

In Aim 2, we will gain an understanding of the expected magnitude of EAS benefit across a wide range of CI-recipient ages and hearing configurations as well an understanding of which measures may aid clinical decision making regarding successful application of EAS technology. Use of an accelerated longitudinal design will allow us to investigate natural factor variations following a clinical intervention—the EAS fitting—that can be harnessed via mediation analysis (**Figure 2)**. This will allow us to study mechanisms of binaural development in children with SNHL using EAS (CI+HA_{bilat} and CI_{bilat}+HA_{bilat}). Finally, the data obtained from this proposal hold high impact for identification of measures that may be used in a clinical environment to identify patients best suited for EAS benefit. *This latter point is critical given that EAS fittings are underutilized.*

Finally, this proposal has great innovation in the investigative team which brings together a psychoacoustician and clinical audiologist with experience working with EAS patients (Holder), a psychoacoustician and developmental auditory scientist with over 20 years' experience working with adults and children with NH and bilateral CIs (Litovsky), and an electrophysiologist and clinical audiologist who has been focused on objective estimates of binaural function in listeners with NH (Smith). The expertise of this team brings tremendous synergy to the proposed investigation of theoretical and clinical questions for this rapidly growing EAS population. This team will be able to provide the first comprehensive description of behavioral and electrophysiologic measures of binaural hearing in adults and children with NH and EAS and will uncover information about our EAS clinical population holding high potential for clinical application in device fittings as well as audiologic and otologic clinical recommendations regarding cochlear implantation.

PRELIMINARY STUDIES

EAS benefit for adult and pediatric listeners: We recruited 6 CI recipients (5-16 years) with acoustic hearing preservation in the CI ears[39]. Speech recognition was tested in the CI-only, bimodal (CI+HA_{contra}), and EAS (CI+HA_{bilat}) conditions. Only 2 of 6 participants had chronic EAS experience; the others were fitted and tested acutely. CI-only and bimodal conditions used a *full electric bandwidth,* typical for non-EAS fittings. Sentence recognition in noise was assessed with the R-SPACE™ system including 8 loudspeakers in a circular pattern ($S_0N_{45\text{-}315}$). Sentence recognition was assessed via adaptive speech reception threshold (SRT) for Hearing In Noise Test (HINT[91]) sentences as well as for a fixed signal-to-noise ratio (SNR) ranging from +2 to +15 dB for Pediatric AzBio sentences (commonly referred to as BabyBio[92]). The pediatric EAS data reported in Roberts et al.[39] are displayed in the right-hand column of **Figure 3** with BabyBio scores transformed to rationalized arcsine units (RAU)[93]. The left-hand column displays a similar dataset for 31 adult EAS users for AzBio sentences at +5 dB SNR (RAU) and adaptive HINT SRT—portions of this adult dataset appear in our preliminary studies[5,19]. For BabyBio in noise, none of the children exhibited significant EAS benefit considering the 95% confidence interval for sentence test-retest variability[92,94]; however, ceiling effects likely played a role for half the sample. For adult EAS, 12 of 31 (39%) demonstrated significant EAS benefit with mean benefit of 13.0-percentage points (averaged across the 31 subjects). For adaptive HINT, just 1 child in our paper[39] exhibited significant EAS benefit whereas adult EAS users demonstrated a mean 3.2-dB

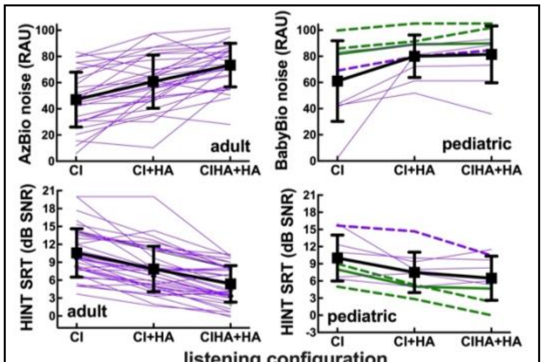


Figure 3. Individual and mean scores for CI, CI+HA, and CIHA+HA for peds and adult EAS listeners. **Pediatric**: **purple lines** represent data from Roberts et al.[39]; **green lines** show new pilot data collected since last submission. Dashed lines represent subjects with chronic EAS experience (3+ years).

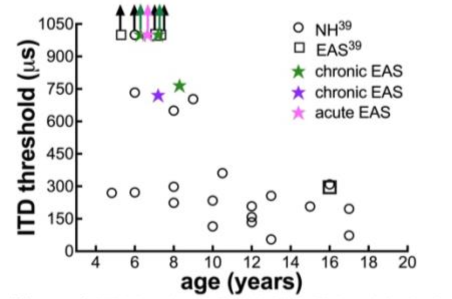


Figure 4. ITD thresholds for 20 NH children (**circles**), 5 EAS from Roberts et al.[39] (**squares**), 2 new EAS children (**purple** & **pink stars**), and a bilateral EAS child followed over time (**green star**). Upper arrows = ITD threshold could not be tracked.

benefit (range 0-6 dB[4,5]). Since the original submission, we have collected additional data from 3 pediatric EAS users as follows: 1) 8.3-year old who was one of the original 6 participants in our pediatric EAS paper[39] but who now has *2 additional years of EAS experience,* 2) 7.2-year old with 6 years' EAS experience, and 3) 6.5-year old fitted with EAS and tested acutely. Newly collected data are displayed in green (**Fig. 3**) with dashed lines representing all children with 3+ years of EAS experience. For adaptive HINT, all children with 3+ years EAS use exhibited EAS benefit ranging from 2.8 to 4.2 dB (mean: 3.3 dB)—which is comparable to our observed adult EAS benefit[5].

Figure 4 highlights the developmental effect on behavioral ITD thresholds for a 250-Hz tone. For 20 children with NH (circles), the mean ITD threshold was 361.3 ms and there was an inverse correlation between ITD threshold and age (r=-0.61, p=0.0026). For EAS users, an ITD threshold could not be tracked for 3 of 5 children as reported in our paper[39]. *For the 3 EAS users with 3+ years EAS use (7.2, 8.3, and 16.2 years—represented by stars and bold square), ITD thresholds were comparable to NH children in the same age range* (**Fig. 4**). The bilateral chronic EAS user (green star) followed over time, showed emergence of ITD sensitivity at 8.3 years (**Fig. 4)**. ITD thresholds for the 2 additional EAS listeners recruited since the last submission (7.2 and 6.5 years) are displayed as purple and pink stars, respectively.

Emergence of EAS benefit and binaural cue sensitivity: We now have extensive data for 3 children with chronic EAS experience (3+ years). One is an 8.3-year old bilateral EAS user (CI_{bilat}+HA_{bilat}) followed in the lab annually since CI activation (green star in **Figs. 4 & 5**). At the first 2 study visits, she exhibited no binaural cue sensitivity with ITD thresholds > 1000 ms (**Fig. 4**) and no EAS benefit for speech recognition in diffuse noise. However, after 4 years of chronic EAS use, her ITD threshold at 250 Hz was 765 ms (**Fig. 4**) and she showed EAS benefit of 3.5 dB (HINT) and a 6-dB BILD. While her behavioral ITD threshold does not reflect ecologically relevant sensitivity, *she demonstrated emergence of this skill which translated to functional EAS benefit*. The 2 additional new EAS recruits (6.5- and 7.2-years old) were also tested on tasks of ITD threshold (**Fig. 4**) and BILD. Only the 7.2-year old with 6 years' EAS experience tracked an ITD threshold (720 ms) and also had 3.0-dB EAS benefit for HINT SRT; however, both newly recruited children exhibited a significant BILD (mean: 4.0 dB)—even the 6.5-year old tested immediately following EAS fitting. *This is a critical finding as we show evidence that pediatric EAS benefit resulting from binaural cue sensitivity and binaural cue utilization likely emerges over time following chronic EAS use.*

Figure 5 displays speech recognition for BKB-SIN[95] in co-located (S_0N_0) and spatially separated symmetric noise ($S_0N_{90,180,270}$) for 8 bilateral CI (5-12 years), 10 bimodal (6-15 years), and 2 children with chronic EAS use (7.2- and 8.3-years old, also see **Figs. 3-4**). Though all groups demonstrated similar SRM, the EAS listeners outperformed the other groups and the bilateral EAS listener (green star) approached NH performance, even in symmetrical noise which does not offer head shadow.

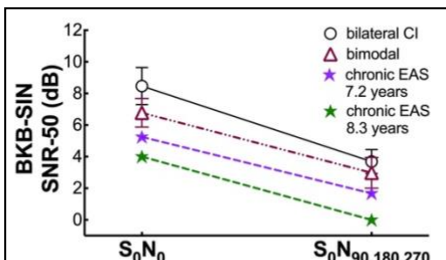


Figure 5. SNR-50 (dB) for BKB-SIN in co-located and spatially separated, symmetrical babble for 8 bilateral CI (**circle**), 10 bimodal (**triangle**), and 2 chronic EAS users (**purple** & **green stars**).

Tasks of spatial hearing and BMLD/BILD: We have data for adult EAS listeners in the bimodal ($CI+HA_{contra}$) and EAS ($CI+HA_{bilat}$) conditions on tasks of horizontal plane localization (n=14)[8], MAA (n = 12), and MAMA (20 deg/sec; n = 20) for a BBN (100-8000 Hz) and LF noise (LFN; 100-800 Hz). We found that *adding acoustic hearing in the CI ear yielded a significant* *improvement in spatial hearing abilities*. We also observed a significant correlation between spatial hearing abilities in the EAS condition for both stimuli (LFN & BBN) and ITD thresholds for localization (r=0.89 & 0.27), MAA (r=0.35 & 0.25), and MAMA (r=0.57 & 0.60). Our MAA and MAMA manuscripts are currently in preparation.

BMLD and BILD tasks are functional measures of binaural cue utilization as a lower (i.e., better) threshold is observed in conditions for which the signal and masker differ in interaural phase[79]. BMLD data were collected for *acoustic-alone hearing* via insert earphones. The signal was either a 250- or 500-Hz tone and adaptive procedure tracked 70.7% correct[96]. BILD was measured with spondees via single interval, also tracking 70.7% correct[96]. The tonal or spondee signal was presented as phase correlated (N_0S_0) and phase inverted (N_0S・), relative to the masker. Our adult pilot data (n=7) showed lower masked thresholds for the phase-inverted signal (N_0S・) for 5 of 7 adult EAS users at 250 Hz and for all 4 adult EAS users tested at 500 Hz. Though preliminary, *those deriving the greatest EAS benefit for speech recognition in noise (S_0N_{45-315}) also exhibited the greatest BMLD (r=0.5-0.6)*. We also obtained BILD thresholds for 8 adult EAS and 3 pediatric EAS users. For adult EAS, there was a strong correlation between BILD and EAS benefit (r=0.91, p=0.0002). For pediatric EAS, all 3 children exhibited significant BILD (mean = 4.0), but only the 2 children with chronic EAS use (7.2 and 8.3 years) exhibited EAS benefit for speech recognition. For the 6.5-year old fitted and tested acutely, she exhibited a 3.5-dB BILD, but no EAS benefit for speech recognition and no viable ITD threshold (> 1000 ms). Given that this acutely fitted child exhibited a significant BILD, it is quite possible we will observe an emergence of EAS benefit and ITD sensitivity following a period of chronic EAS use. *These pilot data suggest that a relatively simple and quick BMLD/BILD task could be used clinically to determine which CI recipients with hearing preservation would most likely obtain significant EAS benefit.*

***CAEPs (ACC_{IPD})*:** To date, we have tested 5 adult EAS listeners on measures of behavioral ITD sensitivity, speech understanding in diffuse noise, spatial hearing (MAA), and ACC_{IPD}. To validate test protocols and verify feasibility, CAEPs were also obtained for a group of 7 younger (23 to 35 years) and 2 older (46 to 62 years) listeners with NH. Pilot data were collected using the IHS DUET with a 2-channel recording with 4 Ag-AgCl scalp electrodes at Cz (+), A1/A2 (-), and Fz (gnd). The stimulus was a 1.6-sec, 250-Hz tone that was sinusoidally amplitude modulated at 40 Hz. The SAM tone was presented either diotically for the entire 1.6-second duration or had a 180-degree IPD applied at the SAM null at 0.8 sec (in one ear) to elicit the ACC_{IPD}. The presentation level was 90 dB SPL for EAS listeners and 70 dB SPL for NH listeners. Two runs of 128 sweeps were averaged for each condition. Preliminary data demonstrate that the ACC_{IPD} was measurable in the 0.8- to 1.2-sec range, for all NH listeners and measurable for our EAS listeners with the best psychophysical ITD thresholds. **Figure 6** displays mean CAEP waveforms for the diotic and dichotic stimuli—with IPD change in right (red) or left (blue) ear—for the 7 younger and 2 older listeners with NH, as well as representative data for an EAS listener with good ITD sensitivity (103 ms for

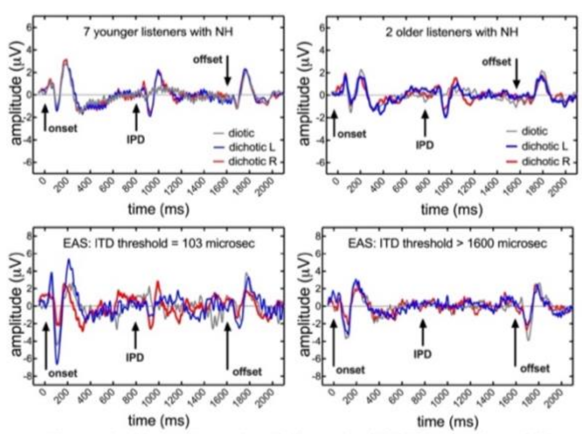


Figure 6. Mean filtered and detrended CAEP data for 7 NH younger listeners, 2 older NH listeners, and 2 representative EAS listeners with differing ITD sensitivity.

250-Hz tone) and an EAS listener with poor ITD sensitivity (>1600 ms at 250 Hz). In addition to obtaining feasibility data, we also observed a trending correlation between ACC_{IPD} magnitude and behavioral ITDs (r=-0.82) as well as with EAS speech recognition in diffuse noise (r=0.71), and EAS MAA (r=0.81). *These pilot data suggest that the use of ACC_{IPD} could help identify CI users with bilateral acoustic hearing who might benefit from EAS and could potentially even be administered in the preoperative period to gauge binaural cue sensitivity.* Such a measure could even be useful for surgeons who might select electrode arrays, steroid dosing, and surgical approaches to maximize hearing preservation for those with greatest potential for EAS benefit.

2.0 Rationale and Specific Aims

Approximately 83-92% of adult cochlear implant (CI) recipients with aidable low-frequency (LF) hearing have acoustic hearing preservation[1,2] affording **E**lectric and binaural **A**coustic **S**timulation (EAS). Numerous studies have shown EAS benefit for adult CI users using *bilateral hearing aids* (HA; $CI+HA_{bilat}$) for speech understanding in complex environments[3–7] as well as spatial hearing in static and dynamic conditions[3,7,8]. We have shown that adult EAS users' sensitivity to interaural time difference (ITD) and interaural level difference (ILD) cues is correlated with EAS benefit for both speech recognition and spatial hearing, and that binaural cue sensitivity may predict EAS benefit even for clinical EAS technology which lacks interaural synchronization[4,8,9]. Despite this active phase of discovery, much about EAS is poorly understood, yet critically important for maximizing outcomes via clinical management of HAs and CIs. We are also seeing growing numbers of pediatric CI users with hearing preservation; however, due to limited research on pediatric EAS outcomes, we do not know the expected trajectory of EAS benefit, underlying mechanisms driving binaural hearing and EAS benefit in this population, as well as the impact of a CI paired with bilateral HAs on binaural development. These knowledge gaps are critical given that adult EAS listeners are known to use both ITDs and ILDs for improved speech recognition in diffuse noise and spatial hearing[9]. *Thus, it is important to know what is driving binaural development in pediatric EAS users—in the presence of bilateral LF hearing loss and central auditory immaturities in binaural processing—particularly given evidence that some aspects of binaural hearing continue to develop through adolescence, even for children with normal hearing (NH)*[10].

Technological advances are outpacing scientific discovery impacting our ability to deliver evidence-based recommendations and audiologic management for a growing EAS population. <u>Our pilot data show EAS benefit immediately following activation for adults, but no acute EAS benefit for children; however, we also provide evidence for emergence of EAS benefit and binaural sensitivity in children following a period of chronic EAS use</u>. Given the protracted maturation of the binaural system, we must understand what additional effects hearing loss, acoustic LF interaural asymmetry, and electrical stimulation may have on the developing binaural system for both scientific and clinical applications. Thus, we propose two independent aims using behavioral and objective measures in adult and pediatric EAS users as well as age- and hearing-matched children and adults with NH. The proposed accelerated longitudinal design allows for a natural factor investigation of a clinical intervention (EAS fitting) via mediation analysis. In this clinical trial, we will define acute and chronic EAS outcomes for speech recognition and spatial hearing as related to binaural cue sensitivity, developmental binaural cue weighting, and underlying neural synchrony necessary for ITD resolution.

AIM 1: Emergence of binaural cue sensitivity in EAS users. We will investigate emergence of binaural sensitivity for ITD and ILD cues as well as ITD/ILD cue weighting, which is critical for children with developing binaural function and underlying neural synchronization. Hypotheses: 1a) Pediatric EAS users will demonstrate an emergence of binaural cue sensitivity following a period of chronic EAS use incorporating bilateral LF acoustic amplification, 1b) there will be a relationship between listener age and ITD/ILD weighting for lateralization with the youngest EAS candidates assigning greater weight to ILDs due to immaturities in neural synchronization, and 1c) the time course of pediatric acoustic ITD/ILD development will be correlated with absolute and interaural auditory sensitivity for LF acoustic hearing.

AIM 2: Degree and time course of EAS benefit for speech and spatial discrimination informed by behavioral and objective estimates of binaural cue utilization. We will describe EAS listener performance ($CI+HA_{bilat}$) and EAS benefit ($CI+HA_{bilat}$ - $CI+HA_{contra}$) for (1) tasks of speech recognition in co-located, diffuse, and spatially separated noise, and (2) tasks of spatial discrimination. We will relate these to ITD/ILD sensitivity measured both behaviorally (Aim 1) and electrophysiologically (Aim 2) via cortical auditory evoked potentials (CAEPs) reflecting brainstem-initiated processes inherited by the central auditory system. Hypotheses: 2a) EAS benefit will be observed for speech recognition and spatial discrimination with chronic EAS use, which will be mediated by access to LF ITD cues estimated via both behavioral and objective measures, and 2b) there will be a relationship between behavioral and objective measures of binaural cue utilization and EAS benefit for speech recognition and spatial hearing.

IMPACT: Integration of HA and CI technology has resulted in a rapidly growing EAS population. While some may question long-term EAS benefit, we are in a unique position to study this intervention which offers what neither bilateral CIs nor bimodal hearing can provide—access to LF ITDs. This project offers an exciting opportunity to study the emergence of binaural cue sensitivity in children with EAS compared with adult EAS users. We will formulate a novel understanding of auditory factors influencing sensitivity to binaural cues and perceptual factors influencing said sensitivity. Our diverse and collaborative team of psychoacousticians (Holder, Litovsky), audiologists (Holder, Smith), a binaural developmental scientist (Litovsky), and an electrophysiologist (Smith) is what makes this innovative and clinically translational proposal possible."

3.0 Animal Studies and Previous Human Studies

N/a

4.0 Inclusion/Exclusion Criteria

We anticipate enrollment of up to 200 study participants (50 recruited for each group) to account for 25% attrition and achieve our target goal of 160 completed participants with 40 in each of the following groups: pediatric EAS, adult EAS, pediatric NH, adult NH. Note that the adult NH listeners will be recruited and tested at a single study visit. The majority of our EAS study participants will be enrolled at Vanderbilt with a smaller number enrolled at UW Madison. Testing of EAS participants will be done at both Vanderbilt and UW-Madison. Pediatric NH participants will be recruited and enrolled at Vanderbilt, UW-Madison, and UT-Austin. Adult NH participants will be recruited and enrolled at Vanderbilt and UT Austin. All research participants will be paid for their participation.

Inclusion criteria for EAS participants:

- Pediatric EAS: aged 5 to 17 years, at enrollment; Adult EAS: aged 18+ years (NOTE: there is no upper age limit provided that the individual demonstrates a passing score on the MoCA or HI-MoCA cognitive screener)
  - Pediatric EAS participants will be recruited evenly across the following enrollment ages expressed in years:months as follows: 5:0 to 6:11, 7:0 to 8:11, 9:0 to 10:11, 11:0 to 12:11, and 13:0 to 17:11.
- Accounting for attrition, we plan to recruit 48 participants across the five age ranges to achieve a complete set of 40 participants.
- At least one CI or a CI candidate in at least 1 ear and *bilateral* mild to profound sensorineural hearing loss with unaided audiometric thresholds ≤ 80 dB HL at 125 and 250 Hz, *in both ears*.
- Willingness to use EAS technology in the implanted ear(s) to be verified via data logging
- Nonverbal cognitive abilities within the typical range
- No co-morbid diagnoses such as autism, auditory neuropathy, neurological disorder, or general cognitive impairment
- Use of spoken English as main mode of communication

Exclusion criteria for EAS participants:

- Single-sided deafness (SSD)
- Nonverbal intelligence standard score < 85 (KBIT-2)
  - Should a participant score < 85 on KBIT-2, we will recommend that the participant be seen by their primary care provider to obtain an appropriate referral.
- HI-MoCA score < 26 (for adult EAS participants)
  - Should a participant score < 26 on HI-MoCA, we will recommend that the participant be seen by their primary care provider to obtain an appropriate referral.

Inclusion criteria for NH participants:

- Pediatric NH: aged 5 to 17 years, at enrollment; Adult NH: aged 18+ years (NOTE: there is no upper age limit provided that the individual demonstrates a passing score of MoCA or HI-MoCA cognitive screener)
- Adult NH listeners will be recruited to match the age range of the adult EAS participants and assessed at a single study visit.
- Pediatric NH listeners will be recruited evenly across the following enrollment ages expressed in years:months as follows: 5:0 to 6:11, 7:0 to 8:11, 9:0 to 10:11, 11:0 to 12:11, and 13:0 to 17:11.
- Accounting for attrition, we plant to recruit 48 participants across the five age ranges to achieve a complete set of 40 participants.
- Pediatric NH participants will have audiometric thresholds ≤ 20 dB HL from 125 through 8000 Hz, in octave steps.

- Adult NH participants will have audiometric thresholds ≤ 25 dB HL from 125 to 4000 Hz, though higher frequency thresholds will also be obtained and recorded.
- nonverbal cognitive abilities within the typical range
- no confounding diagnosis such as autism, auditory neuropathy, neurological disorder, or general cognitive impairment
- Use of spoken English as main mode of communication

Exclusion criteria for NH participants:

- nonverbal intelligence standard score < 85 (KBIT-2)
    - Should a participant score < 85 on KBIT-2, we will recommend that the participant be seen by their primary care provider to obtain an appropriate referral.
- MoCA score < 26 (adult NH participants)
    - Should a participant score < 26 on MoCA, we will recommend that the participant be seen by their primary care provider to obtain an appropriate referral.

5.0 Enrollment/Randomization

Participants will be identified via electronic medical record chart review and discussion amongst our clinical cochlear implant team regarding newly scheduled cochlear implant candidates. All participants will complete the proposed research activities and thus there will be no randomization or blinding/masking. Potential study participants will be approached via telephone or email prior to a scheduled clinic visit or in the audiology clinic at their appointment. Contact will be completed by the clinical coordinator or research personnel. Participants will be made aware that participation is optional and will not impact the clinical care they receive at VUMC.

6.0 Study Procedures

APPROACH

Participants: We are proposing a clinical trial including 4 groups—2 experimental (pediatric & adult EAS) and 2 control (pediatric & adult NH); we will focus on within-subjects analyses given the longitudinal nature of the design and the inherent differences between the pediatric and adult populations. NH participants are included for normative benchmarking. We will recruit 40 pediatric EAS users aged 5-17 years (~70% followed longitudinally at VUMC and 30% at UW-Madison, reflecting differential size of clinical CI programs, budgeted effort across sites, and air travel accessibility). This age range was chosen to be representative of most children receiving CIs with acoustic hearing preservation who are generally older at implantation as they exceed the conventional audiometric profile for cochlear implantation[47]. Also, all children in our preliminary and pilot studies were in this range and were able to complete the proposed test battery. We will also recruit 40 NH children in the same *chronologic- and hearing-age range*, with 1/3 recruited and followed at each of 3 sites (VUMC, UW Madison, UT Austin). None of the children will have confounding diagnoses such as autism, auditory neuropathy, or cognitive impairment. EAS participants must have at least 1 CI and acoustic hearing in the implanted ear(s). We will also recruit 40 adult EAS users (~80% followed at VUMC, 20% at UW-Madison, based on the respective sizes of our clinical CI programs and air travel accessibility) as well as 40 age-matched NH adults. The adult NH group will be seen for a *single experimental time point* to establish normative data with ½ enrolled and followed by VUMC and the other ½ at UT Austin.

Both adult and pediatric EAS users will be recruited beginning at or very close to implantation allowing for an assessment of the impact of the electric stimulation on ITD and ILD sensitivity longitudinally following surgery and activation. This will allow us to investigate whether EAS users adapt to a unilateral "distracter" stimulus over time, or in other words, overcome the effects of binaural interference demonstrated by listeners with NH[66]. Enrolling at or close to CI activation within this longitudinal design will allow us to complete a natural factor investigation of a clinical intervention, the EAS fitting, via mediation analysis as displayed in **Figure 2**. Relatedly, we will also collect and store child/family variables known to influence hearing, speech, and language outcomes for children with SNHL including age at assessment, age at CI, age at identification, etiology, CI wear time (via datalogging), nonverbal IQ, maternal level of education, socioeconomic status, family size, and preschool educational environment (i.e., mainstream preschool, parent-infant program, etc.) These variables may be used in data analysis as covariates or to subdivide groups for descriptive analyses.

Experimental design: Children will be recruited based on age at enrollment via *accelerated longitudinal design,* allowing us to study binaural development longitudinally over a 5-year period for children aged 5-17 years. To ensure an even distribution of chronological age, we will recruit evenly across the following 5 age ranges expressed in years:months as follows: 5:0 to 6:11, 7:0 to 8:11, 9:0 to 10:11, 11:0 to 12:11, and 13:0 to 17:11. We plan to complete 4-postoperative visits for each child over 2 years, spaced in 6-month intervals in the 1st year and a 1-year interval thereafter. Adult EAS users will be seen over 3 time points following activation beginning at or within 1 month of CI activation with 2 additional visits spaced in 6-month intervals. See **Table 1** in *Human Subjects* for a visual timeline of research activities. *All EAS users will ideally be recruited prior to implantation allowing for the investigation of pre- and post-operative binaural sensitivity*—though the pre-operative session is not reflected in **Table 1** as it is not a requirement for study inclusion.

Clinical battery: Clinical testing will be completed for all CI users including unaided pure-tone audiometry and aided speech recognition via CNC[97] words, AzBio[94] or BabyBio[92] sentences at +5 dB SNR, and BKB-SIN[95]. Listening conditions include bilateral HAs, CI-alone, bimodal (CI+HA_{contra}), and EAS (CI+HA_{bilat}). To assess functional communication and spatial hearing, we will administer the Speech, Spatial, and Qualities (SSQ[98]) questionnaire to adults and the parent or child SSQ[99] for pediatric participants aged 5-10 and 11+ years, respectively. Adults will be required to pass a cognitive screener via the Montreal Cognitive Assessment (MoCA[100]) or the MoCA hearing-impaired version (HI-MoCA[101]) for EAS users. For all participants, we will also assess non-verbal intelligence using the KBIT-2[102] as well as auditory working memory over time via the Numbers Reversed from the Woodcock-Johnson IV (WJ-IV[103]). We will also assess receptive language for all children (NH and EAS) annually using the Receptive One-Word Picture Vocabulary Test-4 (ROWPVT-4[104]) and the Clinical Evaluation of Language Fundamentals (CELF-5[105]). A certified SLP at VUMC will train investigators and administer audio- and video-recorded assessments.

Programming & verification of HA & CI: Acoustic amplification will be applied for LF stimuli with audiometric thresholds up to 90 dB HL—as specified by the software for all EAS systems. Regardless of one's unaided thresholds above 1000 Hz, we will limit the HA response to 1000 Hz thereby restricting acoustic amplification to the frequency region over which ITDs are most robust[106]. HA settings will be verified via real-ear measures verifying target audibility for DSL v5.0 Child[107] for children and NAL-NL2[108] for adults. We will also obtain CI-aided thresholds requiring aided thresholds to be in the range of 20-30 dB HL from 250 through 6000 Hz. *CI and HA equipment will be verified at all visits prior to experimentation*. For participants with LF thresholds > 45 dB HL in CI ear(s), custom earmolds will be fitted for LF acoustic amplification. EAS crossover frequency will be manipulated *for all EAS users* using 3 LF CI cutoffs corresponding to 1) full electrical bandwidth (full EAS overlap), 2) audiometric frequency corresponding to a 70-dB-HL threshold (minimal EAS overlap—largely consistent with clinical EAS programming software), and 3) the audiometric frequency corresponding to 90 dB HL (no EAS overlap). These 3 conditions will afford comparison to existing adult EAS data[5,109] for speech recognition in **Aim 2** and will build our sample for experimental populations and will inform clinical practice guidelines.

AIM 1: <u>ITD/ILD sensitivity and cue weighting</u>*:* ITD and ILD thresholds will be measured using tonal and noise-band carriers. Pure tones will be 250 and 500 Hz and noise stimuli will include BBN (100-8000 Hz) and LF noise (100-800 Hz). BBN will be a Gaussian noise burst, band-pass filtered from 100 to 8000 Hz to encompass the frequency range transmitted by CI processors. LF noise will be filtered from 100-800 Hz including attenuation of 48 dB/oct. Stimulus duration will be 300 ms with 10-ms cos^2 ramping. Stimuli will be delivered acoustically via ER-3A earphones at a fixed level (EAS: 90 dB SPL; NH: 70 dB SPL) and fixed sensation level (SL; 20 dB SL) across ears. We will complete this task using both acoustic only and EAS stimulation with the latter via direct connection to the CI sound processor allowing for investigation of binaural interference and comparison to adult data from our previous studies[9]. Fixed-SL testing will be determined from the audiogram using frequency specific HL-to-SPL corrections at octave and inter-octave frequencies within the noise band. Equal SL will be applied to the acoustic stimuli via inserts; the stimulus delivered to the CI processor will be presented unprocessed at a level of 65 dB SPL. A cued 3-interval, 2-alternative forced-choice procedure will be used as described by Peng and colleagues[61]. **Figure 7** displays the video game interface we will use for this task for pediatric participants; note that we will not utilize eye tracking as 20 children have successfully completed this task behaviorally[61]. **Figures 7 A & B** prompt "get ready to listen" as the penguin dives in the water (**Figure 7C**). The child is asked to indicate which iceberg the penguin is hiding behind and correct answer feedback is shown in **Figure 7D**. Level will be roved to help avoid monaural level cues. A method of constant stimuli will be used to estimate ITD and ILD sensitivity over a range of ITDs and ILDs: ITDs: 0, ±50, ±100, ±200, ±400, and ±800 msec; and ILDs: 0, ±1.5, ±3, ±6, ±9, ±15, and ±20 dB. For adult participants, we will also use a method of constant stimuli with the same ranges of ITDs and ILDs; however, we will use a standard visual interface displaying illuminated squares on a screen representing the cued 3-interval, 2-alternative forced-choice paradigm. For all listeners, thresholds will be estimated at 70% correct on a standard logit function using the MATLAB function glmfit.

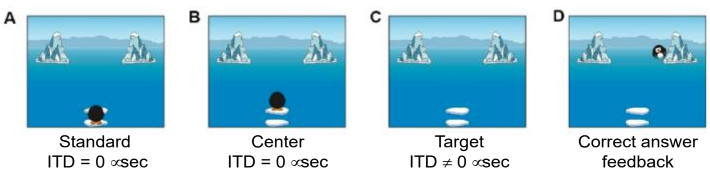


Figure 7: Panels A & B are displayed as the penguin's hops are synchronized with binaurally presented stimuli at ITD = 0 ∝s (penguin in center). When penguin disappears (panel C), the third "target" tone is presented with a left or right-leading ITD. After the listener selects the moving direction of the target tone (i.e., left or right iceberg), correct answer feedback is provided (panel D).

ITD/ILD cue weighting—lateralization paradigm: We will investigate ITD and ILD cue weighting within a lateralization task in which we will independently vary ITD and ILD for the same stimuli described above (BBN & LF noise). ITDs and ILDs will vary over the same ranges described above. These ITD and ILD ranges were chosen to incorporate the physiologically relevant range for adult listeners and has also been used in past pediatric studies, including our pilot data. Stimuli will be delivered acoustically via ER-3A insert earphones at both a fixed level and fixed sensation level across ears, as described above. We will also complete this task using both acoustic and electric stimulation with the latter achieved via direct connection to the CI sound processor. The lateralization task will gauge intracranial perception of sound location allowing us to quantify the full extent of lateralization. This task will utilize a touchscreen tablet on which a cartoon image of a head and face is displayed. The participant will touch along a visual scale corresponding to the perceptual location of each sound. This procedure has been extensively used in both adult and pediatric listeners[71,110,111] documenting feasibility of this task for our target populations. Each participant will be provided with a period of training to ensure familiarization and understanding of the task. We will use the approach of Stecker[112] to fit psychometric functions relating intracranial position to ITD and ILD via non-linear least squares fitting. The relative ITD and ILD slopes will be used to determine the perceptual weighting of ITD and ILD cues for each participant. In addition, response-ITD and response-ILD functions will be generated to estimate the extent of laterality with one cue fixed (e.g., zero) and with coherent ITD and ILD cues.

AIM 1 expected outcomes and alternative hypotheses: Aim 1 hypotheses are: 1) Pediatric CI users will demonstrate an emergence of binaural cue sensitivity following chronic EAS use, 2) There will be a relationship between age and cue weighting for lateralization with the youngest EAS users assigning greater weight to ILDs—due to immaturities in neural synchronization—resulting in a restricted range of laterality, and; 3) The time course of pediatric acoustic ITD and ILD development will be correlated with LF acoustic audibility and interaural asymmetry. Our hypotheses were built upon the binaural development literature showing altered maturation due to both poor audibility and significant interaural asymmetry[29,113]. ***Alternative hypotheses*** were based on the notion that EAS creates a "problem" introducing interaural differences in neural synchrony due to highly synchronized firing in electrically stimulated neurons[114] and/or binaurally incongruent cues resulting in overrepresentation of laterality to the implanted side. This alternative hypothesis has been referred to as "aural preference syndrome" which is well-documented in children with unilateral CI[115], though never investigated in EAS users. *A second* ***alternative hypothesis*** is that over the course of study, both adult and pediatric EAS users will exhibit adaptation to the presence of the binaurally incongruous stimulation demonstrating an initial over-representation of the CI side, that is ultimately corrected following a period of chronic EAS use—the latter interpretation is supported by our preliminary work in adult EAS users[9].

AIM 2: Developmental EAS benefit; objective & behavioral measures of binaural sensitivity

Speech recognition in diffuse noise: Speech recognition in diffuse noise will be obtained using developmentally appropriate sentence stimuli (AzBio adults, BabyBio children) presented at 67 dBA with uncorrelated restaurant noise at 62 dB SPL (S_0N_{45-315}). Listening conditions tested for all participants will include bilateral HA (HA+HA), CI alone (acoustic ears occluded), bimodal ($CI+HA_{contra}$), as well as EAS ($CI+HA_{bilat}$). We will assess speech recognition for Aim 2 using the 3 LF CI cutoffs described in *Programming & verification of HA & CI.*

Spatial release from masking (SRM): SRM will be assessed using laboratory- and clinical-based measures. Laboratory measures include the Basic English Lexicon (BEL[116]) sentences using one female talker. Maskers will be two different male or female talkers taken from the IEEE corpus whose speech samples will either be presented from separate speakers ($S_0N_{90\&270}$) or concatenated to provide a continuous stream that will be rms-normalized prior to combining in a single channel (S_0N_0, S_0N_{90}, S_0N_{270}). BEL sentence recognition will be assessed at 0 dB SNR for 4 target-masker configurations: S_0N_0, S_0N_{90}, S_0N_{270} and $S_0N_{90\&270}$ Clinical measures will use the BKB-SIN[95] test in a co-located (S_0N_0) and 3 spatially separated conditions (S_0N_{90}, S_0N_{270} and $S_0N_{90\&270}$)—**Figure 5** shows representative data for S_0N_0 and $S_0N_{90,180,270}$. These configurations will reveal SRM due to head shadow (asymmetric masker) or binaural integration (symmetric maskers). Speakers are distanced 1 meter from the listener's head and target speech will be fixed at 70 dB SPL. BEL sentences were chosen as this corpus has been used in previous CI studies for children of the same age range and 0 dB SNR was based on a previous study showing ceiling effects for some children at +5 dB SNR[117]. BKB-SIN was chosen for its normative data to 5 years of age and its pseudoadaptive design which avoids ceiling effects. Further, BKB-SIN is commonly used in clinic as it takes just 3 minutes per paired list. We will assess performance for $CI+HA_{contra}$ and $CI+HA_{bilat}$. Should time allow, we will also obtain a CI-alone score.

Spatial discrimination: MAA thresholds will be obtained in an anechoic chamber by presenting 2 successive stimuli from different positions in the horizontal plane. The listener will indicate whether the 2nd stimulus was to the left or right of the standard. Spatial separation between the 70-dB-SPL stimuli will be varied from trial to trial to track 70.7% performance[96]. Noise stimuli will include a BBN and LF noise as described for Aim 1. For the MAA task, 3 listening conditions will be tested: 1) bilateral HA (HA+HA), 2) bimodal ($CI+HA_{contra}$), and EAS ($CI+HA_{bilat}$). Level roving will be applied.

BMLD & BILD: BMLD and BILD data will be collected via ER-3A earphones for delivery of acoustic stimuli. Noise levels will be fixed at equal SPL (EAS: 90 dB SPL; NH: 70 dB SPL). BBN and LF noise maskers will be used as described for Aim 1. For BMLD and BILD, the signal will be phase correlated (N_0S_0) or phase inverted ($N_0S_{\cdot}$) relative to the masker. The BMLD task will use a 3-interval, forced-choice paradigm with a 2-down, 1-up adaptive procedure to estimate 70.7% correct performance[96]. BMLD signal frequencies will be 250 and 500 Hz. As described in *Preliminary Studies*, our BILD task uses pediatric-friendly spondees within a single interval, 2-down, 1-up adaptive procedure to determine the SNR yielding 70.7% correct[96].

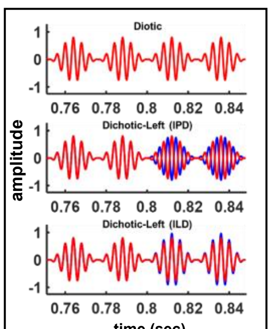


Figure 8. Example waveforms for the 3 ACC conditions.

ACC_{IPD}, ACC_{ILD}, and interaural modulation following response (IM-FR): CAEPs will be obtained for a 250-Hz carrier that is sinusoidally amplitude modulated (SAM), with 100% modulation, at an 83-Hz rate; carrier tones are amplitude modulated only so that the change can be applied at stimulus nulls, thus avoiding spectral splatter from an immediate change to acoustic parameters of an ongoing sound. The 83-Hz rate allows for subcortical envelope following responses (EFRs) to be obtained without significantly impacting ACC characteristics[118]. While the EFR is a secondary interest, the stimuli allow for cortical (ACC) and brainstem (EFR) responses to dichotic stimuli to be simultaneously acquired. The SAM tone will be 1.6 sec followed by 1.4 sec silence. Stimuli will be presented using electrically shielded ER-3A earphones at a level of 90 dB SPL for the EAS listeners and 70 dB SPL for the NH

listeners. Three conditions (**Fig. 8**) will be tested: 1) Diotic SAM tones, 2) Dichotic-Right SAM tones for which the carrier IPD (45°, 90°, and 180°) or ILD (±5 dB and ±10 dB) will be adjusted at 0.8 sec for the stimulus presented to the right ear, 3) Dichotic-Left SAM tones for which the carrier phase (IPD) or level (ILD) will be adjusted at 0.8 sec for the stimulus presented to the left ear. *We recognize that the 90- and 180-degree IPD exceeds the "ecologic range"; however, "super ITDs" are important for evaluating coarse ITD sensitivity if fine-grained thresholds are not observed.* This information will be useful for estimating listener ability to potentially acquire and subsequently exploit more fine-grained, ecologically relevant IPD cues. Each condition will be presented in a random and counterbalanced order. All AEP testing will be completed within approximately 90 minutes in a single-walled, shielded sound booth with a minimum of two recording channels: Cz-right ear lobe and Cz-left ear lobe.

As shown in **Figure 6** *(Preliminary Studies),* robust ACC_{IPD} responses were evoked when an IPD change was applied at the midpoint of an ongoing stimulus for NH and EAS listeners with physiologically relevant ITD thresholds. As with other objective tests of auditory function, time domain analysis may become challenging when responses are absent or have poor morphology. This has motivated others[85] to adapt the ACC paradigm to make CAEP analysis possible in the frequency domain, allowing for more objective and noise-resilient measurements (e.g., auditory steady state response). In the interaural modulation following response (IM-FR) paradigm, multiple ACCs are evoked in succession by a stimulus that dichotically alternates in either IPD (from left-leading or right-leading) or ILD (from left-higher or right-higher) at a fixed rate (e.g., 7 Hz). The IM-FR waveform is converted to the frequency domain, and response magnitude is assessed at the interaural modulation rate (e.g., 7 Hz). *Thus, a sub-aim of this work is to parametrically compare time domain ACCs and frequency domain IM-FRs across development in NH and EAS groups to assess which tool holds more promise for the primary research aims and potentially for clinical application*. We plan to use the same IPD and ILD manipulations as the ACC method for the IM-FR method. Stimulus length differs between each measurement type, but overall testing time will be the same.

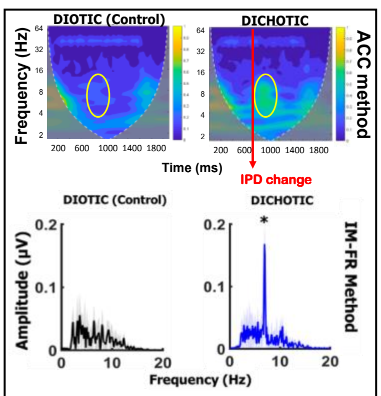


Figure 9: EEG data displayed in the freq-time domain via wavelet transform (top); component spectral magnitude displayed via FFT (bottom).

CAEPs will be post-processed and filtered in MATLAB to remove eyeblinks and other artifacts. Cleaned responses will be analyzed to extract 3 key pieces of information: 1) Normalized *ACC_{IPD} and ACC_{ILD} power*: EEG power will be calculated in the 4-16 Hz frequency band of the 0.8- to 1.2-sec epoch of diotic and dichotic conditions (**Fig. 9**, top). Normalized ACC power will be quantified as the ACC power for dichotic conditions divided by the power within the same epoch for the diotic (control) condition. 2) *IM-FR magnitude*: IM-FR waveforms will be transformed into the frequency domain using fast Fourier transform over the steady-state portion of the response (0.5-4.5 sec). Spectral magnitude at the interaural modulation rate (7 Hz, denoted by asterisk in **Fig. 9**) will be used to quantify IPD and ILD sensitivity, respectively. 3) *Neural synchrony*: Phase locking values (PLVs[119,120]) will be extracted from ACC and IM-FR waveforms at 83 Hz and 7 Hz, respectively. PLV is a number between 0 and 1 reflecting trial-by-trial phase coherence of neural activity within specified time-frequency bins. A PLV of 0 indicates no phase coherence within a bin, whereas a value of 1 indicates complete phase coherence. PLV is calculated by epoching continuous EEG trials corresponding to each stimulus presentation, creating spectrograms of each trial, and extracting the normalized phase vector at each time-frequency point of the spectrogram. Averaging normalized phase vectors at each time-frequency point across all stimulus presentation trials results in the PLV, a proxy for neural synchrony. Specifically, 83-Hz PLV provide an index of subcortical neural synchrony, whereas 7-Hz PLV from IM-FRs provide an index of cortical neural synchrony during IPD or ILD manipulations.

Aim 2 expected outcomes and alternative hypotheses: Aim 2 hypotheses are: 1) Children will derive EAS benefit from binaural acoustic hearing for speech in noise, SRM, and spatial discrimination, 2) EAS benefit will *develop over time for children* following a period of chronic EAS use (EAS benefit will be mediated by binaural LF information), and 3) there will be a relationship between objective estimates of binaural sensitivity and EAS benefit for speech recognition and spatial hearing. These hypotheses are built upon a wealth of literature demonstrating the importance of access to LF ITD cues for spatial hearing[121,122] and the role of neural synchrony—estimated electrophysiologically—for ITD coding and perception[20,36]. An **alternative hypothesis** is that having access to LF ITD cues may not accurately predict EAS benefit for spatial hearing tasks, particularly for pediatric EAS users, given the peripheral acoustic delays inherent in electric and acoustic hearing[123,124]; however, we have considerable evidence from both the adult EAS literature[3–9,16] *and from 3 pediatric chronic EAS users discussed in Preliminary Studies demonstrating EAS benefit—indicative of binaural cue sensitivity—in the free field using clinical HAs and CIs. Thus, it is reasonable to anticipate interaural delays imposed for LF binaural acoustic amplification can be overcome with EAS experience despite lack of CI/HA synchronization, as evidenced in our preliminary work*[9].

7.0 Risks

There are no more than minimal risks for the audiometric testing completed for this study in relation to the standard audiometric test battery. There is a risk of loss of confidentiality while participating in the research study. All tests will use acoustic stimuli presented in the sound field or direct connection to the subject's cochlear implant sound processor at comfortable levels experienced in everyday life. Auditory evoked potentials are also minimal risk and routinely completed in both clinical and research environments. There may be unknown or unanticipated adverse effects which would be reported to the VUMC IRB within 7 calendar days as described below.

8.0 Reporting of Adverse Events or Unanticipated Problems involving Risk to Participants or Others

Review of any unanticipated problems will occur throughout the study. Adverse events will be reported to the VUMC Institutional Review Board within 7 calendar days.

9.0 Study Withdrawal/Discontinuation

Participants can withdraw from the study at any time by contacting study personnel.

10.0 Statistical Considerations

Statistical analysis will be completed using collected auditory perception data using mixed model design (within- and between-subjects analyses). Biostatistician, Dr. Mary Dietrich, is a co-investigator and will guide preparation and execution of statistical analyses.

11.0 Privacy/Confidentiality Issues

All reasonable efforts will be made to keep information collected private and confidential. Each individual will be assigned a unique study identifier and the collected information will be de-identified. Information may be shared with institutional and/or governmental authorities, such as the Vanderbilt University Medical Center Institutional Review Board as indicated.

12.0 Follow-up and Record Retention

The duration of the study will be 6 years.

13.0 Summarized study protocol

Summary of assessment battery defined by current clinical practice:

Tasks to be administered at baseline visit only

- KBIT-2
- MoCA

Tasks to be administered at each study visit

CNC monosyllabic word recognition

- CI ear (in EAS condition—CI + ipsilateral acoustic component)
- Bilateral best-aided (CI + bilateral HAs)

AzBio or BabyBio sentence recognition at +5 dB SNR S_0N_0

- CI ear (in EAS condition—CI + ipsilateral acoustic component)
- Bilateral best-aided (CI + bilateral HAs)

BKB-SIN S_0N_0

- CI ear (in EAS condition—CI + ipsilateral acoustic component)
- Bilateral best-aided (CI + bilateral HAs)

SSQ or SSQ-parent

Unaided, pure-tone audiometry in implanted ear via insert earphone

- 125-8000 Hz
- AC & BC

CI-aided, pure-tone audiometry in sound field with FM tones and acoustic ears occluded via EAR foam plug

- If CI-aided thresholds are in the range of 20-30 dB HL, no further programming is needed.

- If CI-aided thresholds are lower or higher than this range, CI programming is required.

HA/acoustic component verification using audioscan verifit to DSL-Child or NAL-NL1 for pediatric and adult EAS participants, respectively.

- SII at 50, 60, and 70 dB SPL
- If targets are poorly met, re-program HA(s) and re-verify.

Tasks to be administered at baseline and in 1-year increments

- Numbers reversed subtest on Woodcock-Johnson IV (WJ-IV)
- Receptive One-Word Picture Vocabulary Test-4 (ROWPVT-4[104])
- Clinical Evaluation of Language Fundamentals (CELF-5)
- Unaided audiometry for non-implanted ear (EAS group only)

AIM 1: Summary of assessment battery

ITD & ILD thresholds and cue weighting tasks—completed at baseline and all subsequent study visits

- Acoustic only hearing using insert earphones
- Acoustic plus electric using insert earphones and direct audio input to CI
    - For participants without a CI, acoustic-only ITD & ILD thresholds will be assessed

AIM 2: Summary of assessment battery

Spatial release from masking (SRM)—baseline and all subsequent visits

BEL sentence recognition

Test conditions include: 1) CI ear (CI+acoustic component—optional), 2) bimodal (CI+contralateral HA), and 3) best-aided EAS (CI + bilateral HAs)

- BEL sentences presented at 70 dB SPL (A weighting) at 0 dB SNR for the following 4 target-masker configurations:
    - S_0N_0
    - S_0N_{90}
    - S_0N_{270}
    - $S_0N_{90\&270}$

BKB-SIN

Test conditions include: 1) CI ear (CI+acoustic component—optional), 2) bimodal (CI+contralateral HA), and 3) best-aided EAS (CI + bilateral HAs)

- BEL sentences presented at 70 dB SPL (A weighting) at 0 dB SNR for the following 4 target-masker configurations:

- S_0N_0
- S_0N_{90}
- S_0N_{270}
- $S_0N_{90\&270}$

Minimum audible angle (MAA) in the anechoic chamber—baseline and all subsequent visits

BBN and LF noise bursts will be presented at 70 dB SPL (A weighted) with level roving (+/-7 dB) using the anechoic chamber. The following listening conditions will be tested:

- bilateral HA (HA+HA)
- bimodal (CI+HA_{contra})
- EAS (CI+HA_{bilat})

Binaural masking level difference (BMLD) and binaural intelligibility level difference (BILD) (baseline and all subsequent visits)

BMLD and BILD data will be measured via ER-3A earphones for delivery of acoustic stimuli. BBN and LF noise will be presented as follows:

EAS participants:

- 90 dB SPL
- phase correlated (N_0S_0) or phase inverted (N_0S_π)

NH participants:

- 70 dB SPL
- phase correlated (N_0S_0) or phase inverted (N_0S_π)

Auditory evoked potentials (AEPs) including ACC_{IPD}, ACC_{ILD}, and interaural modulation following response (IM-FR) (baseline and all subsequent visits)

A 250-Hz tone (1.6 sec) will be sinusoidally amplitude modulated at 83 Hz and presented using electrically shielded ER-3A earphones at the following levels:

EAS participants

- 90 dB SPL in both ears

NH participants

- 70 dB SPL in both ears

The following AEP conditions will be completed at each study visits:

- Diotic SAM tone
- Dichotic-Right SAM tones for which the carrier IPD (45°, 90°, and 180°) or ILD (±5 dB and ±10 dB) will be adjusted at 0.8 sec for the stimulus presented to the **right ear**
- Dichotic-Left SAM tones for which the carrier phase (IPD) or level (ILD) will be adjusted at 0.8 sec for the stimulus presented to the **left ear**.