Image-Guided Cochlear Implant Programming: Pediatric Speech, Language, and Literacy

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1.0 Background

This is the history of the problem/disease, and why it is important to study this particular problem/disease. Discuss how this affects the target population, how many are affected.

(Study Purpose and Description – Brief Abstract of the Study)

Although the recent literature has indicated that children receiving cochlear implants (CIs) often have dramatically improved speech and language ability relative to previous generations of children with hearing loss, many pediatric CI recipients display persistent speech and language disorders despite early implantation and associated speech/language intervention. There is a striking paucity and ongoing need for studies that systematically examine the relationship between intracochlear electrode location, audiological profile, and subsequent phonological awareness, speech, language, and literacy in pediatric CI recipients. This project provides a unique opportunity to examine whether individualized, ***image-guided CI programming (IGCIP)*** significantly improves outcomes in pediatric CI patients. The proposed research activities will examine the impact of personalized IGCIP in pediatric CI recipients on measures of basic auditory function (spectral, temporal, and spectrotemporal resolution), word and non-word recognition, speech production, language, phonological awareness, and reading comprehension using a double blind, waitlist control randomized clinical trial (RCT) design. A total sample of 72 children with CIs aged six to twelve years old will be enrolled in the project: half (n = 36) will be randomized to an immediate IGCIP condition and half to a waitlist control condition. The waitlisted participants (n = 36) will undergo IGCIP after 12 months of monitoring and then followed for an additional 12 months after intervention (total time in the study for both groups: 24 months). Those immediately provided with IGCIP will also be followed for a total of 24 months. All participants will undergo extensive audiological assessment as well as tests of phonological awareness, speech, language, and literacy at baseline as well as at regular intervals: 2, 6, 12, 14, 18, and 24 months. We will use predictor analyses to determine the impact of immediate and deferred IGCIP on subsequent auditory, speech, language, and literacy outcomes.

2.0 Rationale and Specific Aims

This is the "why" this study is important to conduct and what you plan to do.

(Study Purpose and Description – How this study adds to the knowledge on this topic)

A. Introduction - Statement of Problem

Although children with cochlear implants (CIs) have significantly improved speech, language, and reading outcomes relative to previous generation CI recipients, too many pediatric CI users still display persistent speech, language, and reading difficulties despite early implantation and early intervention [see (5–7)]. Children with CIs typically lag behind their peers with normal hearing (NH) by 1 or more years on measures of speech, language and/or reading [e.g., (8–15)]. Though these persistent delays can be attributed in part to a period of auditory deprivation prior to inclu (12,16,17), increasing evidence suggests that a degraded CI signal is also implicated in poorer development of auditory, speech, language, and reading skills for pediatric CI recipients (6,18–22). A related developmental path to reading also disrupted from the degraded CI signal is phonological awareness (PA) because PA is predicated, in part, on speech recognition (23).

A procedure developed by Noble and colleagues (4,24–26), ***image-guided CI programming (IGCIP),*** significantly improves auditory function, speech recognition, and distally, receptive language abilities for adult CI users. We have preliminary evidence that pediatric CI recipients also significantly benefit from ***IGCIP*** (4). But there is a need to systematically investigate IGCIP in children to determine whether this individualized intervention yields a) associated benefits in auditory function and b) related improvements in speech, language, PA and/or reading. ***Thus, our primary goal is to evaluate the effects of IGCIP on auditory function, speech recognition, PA and reading, as well as speech and language abilities in pediatric CI recipients within the context of a double blind, waitlist controlled randomized clinical trial (RCT).*** We will obtain psychophysical estimates of auditory function and speech recognition, PA, reading, speech, and language abilities for 60 pediatric CI users in a baseline assessment and repeated time points for 24 months to test the impact of IGCIP. We will examine the immediate (short-term) and longer-term effects over a 2-year period by comparing outcomes between groups for those randomly assigned to immediate (n = 30) or deferred (n = 30) IGCIP using a *waitlist control study design (deferred IGCIP)*. The initial comparison will be for immediate and deferred IGCIP groups at 2, 6, and 12 months. The deferred group will then receive the IGCIP intervention and both groups will be followed for an additional 12 months (total enrollment for 24 months).

B. Specific Aims & Hypotheses

Specific Aims

Aim 1: Auditory function. We will compare auditory function and speech recognition of the immediate and waitlist control participants. <u>Hypothesis 1a</u>: There will be significant positive short-term gains (2-6 months) in spectral and/or temporal resolution as well as speech recognition—particularly in noise—for children immediately receiving IGCIP as compared to waitlist controls. This hypothesis will be tested by comparing the difference in the amount of change in scores within-subjects (pre- to post-IGCIP gain) between the groups (treated vs. untreated) controlling for initial scores. <u>Hypothesis 1b</u>: IGCIP gain in spectral and/or temporal resolution will significantly predict gain in speech recognition. This hypothesis will be tested via regression analyses of change in speech recognition scores on change in resolution, controlling for baseline values and also controlling for baseline levels of speech recognition and working memory.

Aim 2: PA and reading. We will explore the complex relationships amongst auditory function, speech recognition, PA, and reading ability. <u>Hypothesis 2a:</u> **Differential *growth*** in spectral/temporal resolution and/or speech recognition will predict growth in PA, which in turn will predict mediated growth in reading. <u>Hypothesis 2b</u>: Growth in PA will be associated with amount of IGCIP benefit (gain) and will mediate growth in reading, which will be tested via cross-legged panel and path analyses. Note that testing these hypotheses is not dependent on the outcomes of Aim 1 as *only variable gain in the Aim 1 measures (e.g., speech recognition) are required for aim 2 analyses,* not a significant between-group difference for IGCIP in Aim 1.

Aim 3: Speech and language. We will compare pre- and post-IGCIP receptive and expressive language abilities and speech production of pediatric CI recipients to the waitlist control group. We will test these skills at various time points on standardized and clinical measures of 1) receptive language, 2) expressive language, and 3) speech production (articulation and acoustic analyses)*.* Hypothesis 3a: There will be significant differences between groups for positive growth in speech and language and this growth will be *predicted* by the relative improvement in auditory function (aim 1) from IGCIP while controlling for baseline levels of working memory. Hypothesis 3b: Spectral/temporal resolution and speech recognition and/or PA will serve as *mediators* of expressive and receptive language gains and speech production gains both within and between groups. 3a and 3b will also be tested using mixed effects modeling and regression analyses to examine these "downstream" effects. *Even if no between group differences in Aim 1 and/or Aim 2 are seen, we will nonetheless be able to test whether spectral/temporal resolution, speech recognition, and/or PA predict growth in receptive and/or expressive language and/or changes in speech production (including subclinical acoustic analyses).*

C. Background and Significance

Cochlear implant (CI) technology yields significant improvement in auditory function, speech recognition, speech production, language, reading, and overall quality of life for the majority of recipients. Despite such advances, pediatric CI recipients continue to display significant variability in speech and language development with too many recipients continuing to display poor outcomes [e.g., (10,14,15,17,27–31)]. A recent study of pediatric CI users brought these issues into sharp focus: Dettman et al. (2016) investigated speech recognition and language outcomes for a large cohort of pediatric CI recipients (n = 403) who were all educated in an inclusion classroom using listening and spoken language as the primary mode of communication (17). **Figure 1** is a reproduction of data illustrating mean standard scores for language and vocabulary for all children upon entry into 1st grade (14). This figure displays the magnitude and pervasive nature of the deficits across language measures for even the group of children implanted under 24 months (green bars). Indeed, all means were at least 1 standard deviation below the age normative range.

Clearly, there is an ongoing need to improve language outcomes in these children (7). The source of delay is partially attributed to a period of auditory deprivation prior to implantation [e.g., (12,16)]. However, it is also likely that an impoverished CI signal is implicated in ongoing poorer-than-normal development on measures of auditory, speech, language, and reading (8,22,32). Several researchers have documented extremely poor spectral resolution for pediatric CI users—much poorer than that exhibited by adult CI recipients (20,33–37). Such findings suggest that pediatric CI users with prelingual deafness may not depend upon spectral resolution for speech recognition in the same manner as adults, particularly in noisy environments. Indeed Lowenstein & Nittrouer (19) recently demonstrated that children with hearing loss—using hearing aids and CIs—placed ***significantly less weight on spectral cues*** than children with NH. In contrast, the children with CIs placed ***greater weight on amplitude cues***—related to temporal envelope perception—as compared to the children with NH (19). Thus, it is possible that young children with CIs are making use of *different cues*, such as those contained within the temporal envelope, or spectrotemporal contrasts, both of which have been shown to

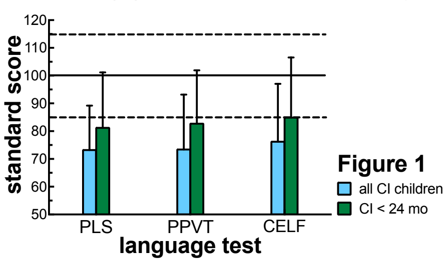

Figure 1

yield high levels of consonant recognition in NH adults (e.g., (38–41)]. Further investigation is warranted to investigate the relationship between spectral resolution, temporal resolution, and speech recognition so that we can identify the underlying mechanisms driving speech recognition in pediatric CI users as well as links to PA, reading, speech, and language abilities. Understanding the underlying mechanisms driving speech recognition in pediatric CI users is not only necessary for theoretical purposes, but this information is critical to maximize a child's auditory abilities in the context of both CI programming and, ultimately, for speech/language/reading intervention. For example, if we learn that children are using different auditory cues to drive speech recognition—such as greater weight on temporal vs. spectral cues—we could select CI stimulation parameters that best transmit a *well-defined temporal envelope* such as high channel stimulation rates [>1500 pulses per second (42–44)] and removal of current steering which can introduce fluctuations in the temporal envelope that are uncorrelated with the incoming signal (45). In contrast, should we find that children rely heavily on spectral resolution and/or spectrotemporal cues as adult CI recipients do, we could choose image-guided programming strategies designed to transmit finer spectral detail—such as patient-specific electrode deactivation to improve spatial selectivity of intracochlear excitation patterns and its psychological correlate, spectral resolution.

Image-guided CI programming (IGCIP)

Our team has pioneered the use of postoperative CT scanning of CI users to delineate the CI electrode-neural interface and use this information to create customized programming maps. We refer to this process as image-guided cochlear implant programming (IGCIP) and here describe how it is performed. We have constructed an atlas based on 10 µCT scans of human cadaveric cochleae in which scala tympani (ST), scala vestibuli (SV), and the modiolus have been manually delineated as these anatomical structures are not visually identifiable on clinical CT scans. Next, on a pre-operative clinical CT scan, this atlas is iteratively fit to the patient's own anatomy to minimize the sum of the squared distance between the bony outline of the cochlea, which is identifiable both on the clinical CT scan as well as via µCT. Next, a post-operative CT scan is obtained, the centerline of the electrode array extracted, and a 3D model of the electrode array fit to the scan. Finally, the pre- and post-op scans are superimposed upon each other as the bony anatomy is consistent. The output (top panel, **Figure 2**) includes 3D surfaces showing the position of individual electrodes relative to the neural endings they are intended to stimulate in the modiolus.

Next, we define the electrode-to-neural interface by calculating the distance-versus-frequency curves from the frequency mapped neural endings within the modiolus to each individual electrode. This is shown in the bottom panel of **Figure 2** where each of the colored curves represents a different electrode and shows the Euclidian distance from the electrode to the modiolus (ordinate) as well as the predicted frequency range of the modiolus (8) at that location (top abscissa). Electrodes are chosen for deactivation to minimize channel interaction—or spread of intracochlear electrical excitation. The premise is that such electrodes would be providing "redundant" electrical stimulation for a given segment of the cochlea. So, by deactivating these electrodes, we theorize that we are able to reduce channel interaction which should increase spatial selectivity of intracochlear electrical excitation. The heuristic we use to achieve this is to deactivate as few electrodes as possible while producing an overall curve with clearly defined local minima and with electrodes centered on the range of frequencies to which they are closest. Following this strategy for the example shown in **Figure 2**, we have deactivated electrodes 2, 3, 4, 6, 8, 10, and 16.

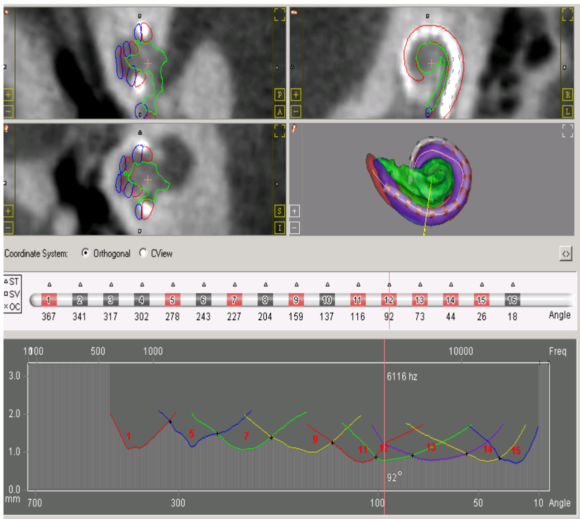

Figure 2: Software module defining electrode-to-neural interface in CT scans and 3D reconstruction (top panel: red=ST, blue=SV, and green=modiolus). Middle panel shows active electrodes in red. Bottom panel shows distance-vs-frequency curves used to deactivate electrodes interfering with neighboring electrodes.

Clinical significance: CI programming

Clinical CI programming includes the mapping of incoming sound using a "one size fits all" approach of current limiting, frequency allocation, and stimulation of all electrodes. For some individuals, it is likely that these default programming methods provide a reasonable approximation to the patient's individualized anatomy and electrode location and that activation of all electrodes yields adequate outcomes. For other patients—particularly those who may exhibit poorer-than-average performance, have atypical cochlear anatomy, electrode dislocation, or extracochlear electrodes—a "one size fits all" approach will not afford the restoration of hearing that could be achieved had the recipient's anatomy and intracochlear electrode positioning been considered. For example, a recent study of 262 CI users showed that 13.4% of patients had at least 1 extracochlear electrode despite surgical reports of complete insertion (46). Active extracochlear electrodes will produce suboptimal high-frequency transmission as the acoustic information being transmitted to the *extracochlear electrodes* will not reach primary auditory neurons. Thus an additional goal of IGCIP is identification of extracochlear electrodes—critical information needed to ensure stimulus delivery of high frequency speech sounds (**Figure 6** preliminary studies). Such considerations are particularly critical for pediatric CI users for whom audibility of high-frequency stimuli is central to the acquisition of auditory-based speech and language.

Children are routinely implanted at ~12 months of age—the minimum age referenced by FDA labeled indications. Thus, it is the case that for the first 3 to 5 years of CI use, we are relying on external factors for CI programming and verification of CI map appropriateness. Such factors include "aided" audiometric thresholds, auditory skill development gauged primarily via parental questionnaire, and progress on measures of language and speech production. Even if a child is making progress, it is possible that using an individualized approach to CI parameter manipulation—capitalizing on the underlying hearing mechanisms driving performance as well as individualized anatomy and electrode location—would result in greater performance at a faster rate allowing for higher overall outcomes. Indeed, we have documented that pediatric CI recipients can derive significant benefit from IGCIP on measures of speech recognition in quiet and noise (4).

Underlying mechanisms driving auditory-based speech recognition

For adults with NH, speech recognition is dependent upon a high degree of spectral resolution of the individual components of speech including resolution of individual and relative formant frequencies as well as rapid formant transitions. Speech recognition—as dependent upon spectral resolution—poses a major obstacle for CI recipients and attempts to improve *spatial selectivity* of intracochlear electrical stimulation (i.e. reduction in channel interaction) have resulted in minimal improvements in speech recognition abilities [e.g., (47–50)]. Most attempts at improving intracochlear spatial selectively of electrical excitation patterns and subsequent improvements in spectral resolution, however, have investigated current focusing such as tripolar electrode configuration [e.g., (51–58)] for adult CI users. Attempts at limiting channel interaction via current focusing have resulted in programming parameters and electrode configurations that significantly limit the dynamic range of electrical stimulation as well as significantly increase power demands for the sound processor. Such consequences render the applicability of these strategies clinically prohibitive.

Spectral resolution for CI users is often characterized using tasks of spectral modulation detection (SMD) or spectral ripple discrimination (e.g., (59–62)]. Numerous studies have shown a significant correlation between spectral resolution with a CI and auditory speech recognition *for adult CI users* (e.g., (60,63–69)]. Furthermore, researchers (45,70) have demonstrated that psychophysical measures of spectral resolution are more sensitive to changes in CI processing strategies and central auditory reorganization following implantation than traditional clinical measures of speech recognition (62,70). Thus it is common for researchers to use SMD as a proxy for channel interaction to determine whether CI programming changes may impact this phenomenon. Indeed we have shown that IGCIP yields statistically significant improvements in spectral resolution, via SMD, *in adult CI users* (24,26,49,71). In contrast to these findings, pediatric CI users exhibit extremely poor spectral resolution and estimates of pediatric CI spectral resolution are not significantly correlated with speech recognition [e.g., (20,37,72,73)] or were modestly correlated with vowel recognition in quiet (74). Furthermore there are conflicting reports regarding the relationship between listener age, age at CI, and overall spectral resolution abilities (20,72,74).

Description of underlying auditory mechanisms responsible for pediatric CI speech recognition is not only important for research purposes, but *holds significant clinical relevance*. To maximize outcomes for auditory function and related outcomes for speech, language, and literacy of our pediatric CI recipients, we must identify the auditory mechanisms driving speech recognition, whether those be spectral, temporal, or some combination thereof. The reason is that clinicians have access to a variety of CI signal coding strategies all focusing on different aspects of the incoming stimulus. For example, there are current-steering strategies designed to provide greater spectral representation of incoming stimuli (e.g., Fidelity-120, Optima), strategies designed to provide temporal fine structure in the apical channels via variable rate stimulation [e.g., fine structure processing], and high-rate strategies specifically designed to provide fine detail for temporal envelope representation at each stimulated electrode [e.g., HiRes, high-definition continuous interleaved sampling, and high-rate Advanced Combination Encoder]. Despite the known fact that adult and pediatric CI users demonstrate a significantly different relationship between spectral resolution and speech recognition (20,72,73), clinical audiologists are using the same default programming strategies (i.e. current steering and/or low-to-mid rate stimulation) with both adult and pediatric CI users within a one-size-fits-all philosophy. If we determine that pediatric CI users are more reliant on temporal coding for speech recognition, we can adapt a clinical approach to provide greater representation of temporal envelope with higher channel stimulation rates and removal of current steering. Ideally we would develop a data driven, personalized plan for CI programming capitalizing on the mechanisms driving auditory-based speech recognition combined with selective IGCIP channel activation to improve intracochlear spatial selectivity and resultant spectrotemporal resolution. Based on our published and preliminary data (4,20), our **hypotheses** are that IGCIP will improve 1) auditory function (spectral and/or temporal resolution), 2) speech recognition, and 3) improvements noted for spectral and temporal resolution will mediate improvements on measures of PA, speech production, language, and reading while controlling for confounds [e.g., nonverbal cognition, working memory (75–81)].

Auditory Function, Speech Recognition, PA, and Reading

Researchers and clinicians have been interested in the interrelationship between hearing, speech recognition, speech and language skills, PA, and reading outcomes for more than half a century (82–84). Until recently, speech recognition, speech production, language, PA and reading for children with CIs have been relatively poor and all domains have significantly lagged behind typically developing peers (6,8,21,30,85–88). Advances in CI technology have yielded dramatic improvements in all these domains. Indeed, recent reports have indicated that a number of CI recipients are trending into the typical range and in some cases, even into an advanced range for language and reading outcomes [e.g., (10,14,15,17,21,89)]. Despite these encouraging findings, a significant number of CI users continue to demonstrate relatively poor outcomes for speech, language, PA and/or reading. A likely explanation is that spectral resolution is strongly correlated with PA (90–92). Given the generally poor, but variable, spectral resolution abilities exhibited by pediatric CI recipients (20,72–74), it is not surprising that both PA and reading skills are often poorer than typically developing children. Despite the fact that pediatric CI users have poor spectral resolution and below average PA, some CI recipients are able to approach typical levels of performance on speech, language and reading achievement. ***One must then ask how are some children with CIs capable of achieving such high levels of speech recognition and ultimately high levels of language and reading despite poor spectral and phonological processing?*** In other words, how are children with relatively poor spectral resolution able to bootstrap phonological decoding and subsequent reading? One explanation is grounded in **lexical restructuring theory** (93–96). Lexical restructuring theory posits that a child initially has a global representation of lexical information, and thus does not require fine spectral detail. As a child ages, she begins to learn phonotactic structure within her native language(s) and ultimately builds a more comprehensive lexicon (97). Nittrouer and colleagues reported that "Oral language skills explained more variance in emergent reading for children with CIs than for children with NH" suggesting that children who successfully build lexical and phonotactic representations despite incomplete spectral resolution will bootstrap PA and ultimately achieve higher vocabulary and reading levels (98,99). That is, converging syllable and lexical cues can be utilized to build partial phonotactic representations that are supported by non-spectral cues (i.e., temporal or spectrotemporal) (100). On the other hand, it is also plausible that some children cannot bootstrap the relative weaknesses in spectral resolution to PA (101) and thus continue to display poor vocabulary and reading skills. We hypothesize that improving intracochlear spatial selectivity via IGCIP will lead to improvements in auditory function and speech recognition, which will facilitate bootstrapping of PA. IGCIP could provide a direct unique path to benefit PA—a plausible hypothesis that can be tested in this experimental design.

There is a reliable relationship between speech recognition in noise and spectral resolution [e.g., (20,73,102,103)] and emerging data supporting a relationship between PA and spectral resolution (19). However, in the presence of poor spectral resolution for children with CIs, we must examine the relative contributions of alternative paths taken from speech recognition to PA, speech, language, and reading. **Figure 3** displays theorized models of IGCIP-mediated benefits of speech recognition and the subsequent effects on PA and receptive language. For example, it is plausible that there is an indirect path to PA mediated by a direct path through IGCIP-improved speech recognition. This can also be statistically tested within the context of a longitudinal double-blind, waitlist controlled RCT design, especially with measurements of potential mediators. A similar direct and indirect path can also be tested for IGCIP-gain scores in speech recognition and receptive language. Again, it is possible that IGCIP benefit directly improves receptive language and that this relationship is mediated via improvement in speech recognition resulting from IGCIP gain.

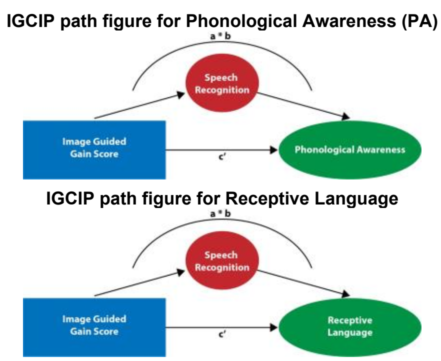

Figure 3. Direct and indirect (mediated) effects for IGCIP & speech recognition on PA and receptive language.

Within the context of the current proposal, we have a unique opportunity to gain a better understanding of factors that predict speech, language, and reading outcomes in pediatric CI recipients. Specifically, the research activities proposed here can compare the growth in spectral and temporal resolution, speech recognition, PA, speech, language, and reading following IGCIP within the context of a double blind, waitlist controlled RCT. That is, hypothesized distal "benefits" resulting from refinement of intracochlear spatial selectivity via IGCIP can be systematically studied with a waitlist control longitudinal RCT. **Figure 3** includes examples of the basic design approach. A putative predictor, namely IGCIP gain scores for auditory function, can be tested as a direct and indirect predictor of speech recognition and PA. The direct path is from IGCIP gain to the outcome which may be PA and/or receptive language. The strength of the longitudinal RCT design is that the indirect path wherein speech recognition as a mediator of the relationship can also be tested. This design approach will also be employed to examine the direct and indirect relationships amongst speech recognition to receptive language, receptive language to expressive language, and receptive language to reading comprehension in addition to speech recognition to PA and PA to reading comprehension.

IMPACT

The impact of a **personalized approach to CI programming** on auditory function, speech recognition, PA, language, speech, and reading will be examined as a step in programmatic research designed to optimize auditory, speech, language, PA and reading outcomes in children with CIs. *Having access to personalized data regarding individualized anatomy, electrode location, and electrode-to-modiolus distances will make this investigation the first of its kind in the space of outcomes-based research for pediatric CI recipients.* The use of a randomized wait-list control design will not only afford a prospective and longitudinal investigation into the effects of IGCIP, but *this design will enable us to describe the expected growth trajectory for validated measures of speech recognition and psychophysical measures auditory perception for children with CIs over the course of a 2-year period*. Such data have never before been described with these measures and thus this project offers high clinical relevance for audiologic management, test interpretation, and subsequent recommendations for pediatric CI recipients and their families

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3.0 Inclusion/Exclusion Criteria

We anticipate enrollment of 72 study participants to achieve our target goal of 60 completed participants (30 in each group).

The following inclusion and exclusion criteria will be used:

Inclusion Criteria:

- children aged 6 to 12 years of age
- prelingual onset of deafness
- at least one CI and *bilateral* moderate to profound sensorineural hearing loss
    - for children with a single CI, audiometric thresholds in the non-CI ear must be consistent with at least a moderate to profound sensorineural hearing loss
- cochlear implantation prior to 4 years of age
- nonverbal cognitive abilities within the typical range
- no confounding diagnosis such as autism spectrum disorder, neurological disorder, or general cognitive impairment
- pre-operative CT scan of head performed as standard of care preoperative CI work-up
- post-operative CT scan—obtained either before enrollment (per VUMC CI program standard of care) or after informed consent, if implanted elsewhere. Note that if an outside implanted participant is recruited for study participation, Co-I Dr. Labadie has an active IRB approved study—which will be linked to this study's IRB application—allowing for Xoran CT scanning of children aged 6 years and older. Six years of age is the youngest age for which this can be reliably completed given the need to sit completely still for ~15 seconds.

Exclusion Criteria:

- severe anatomical abnormality(s) of the temporal bone (e.g., common cavity, cochlear ossification)
- onset of moderate-to-profound sensorineural hearing loss *after* 2 years of age
- nonverbal intelligence standard score < 85

4.0 Enrollment/Randomization

Patients will be recruited from the CI program at Vanderbilt University Medical Center, one of the largest programs in the United States, with an average of 250 CI recipients annually (65% adult) and over 3000 recipients since inception in 1996. Over the duration of the study, We anticipate enrollment of 72 study participants to achieve our target sample size of 60 completed participants (30 in each group). Each year we implant approximately 60 to 80 pediatric CI patients. An analysis of all pediatric CI recipients implanted at Vanderbilt University Medical Center from January 2011 through December 2017 revealed that we have 251 pediatric CI recipients aged 6 to 12 years of age with prelingual onset of bilateral moderate to profound sensorineural hearing loss, who were younger than 3 years of age at implantation. However, there are over 220 additional prospective participants already being followed by our center who will reach the age-inclusion criteria over the course of the project. Informed consent and assent will take place as per our institution's IRB policies and be obtained by the PIs, co-Is, and/or other appropriately trained member of the research team using an IRB-approved consent form.

Study retention will be promoted by providing the parents and children with detailed information regarding their performance on various tasks of auditory processing, speech recognition, speech production, language, and literacy. Following each study visit, we will compile a report of each child's performance to be mailed to the child's home address on file. Study participation will provide value-added information regarding a variety of auditory, speech, language, and literacy tasks that are not typically included in clinical appointments.

A list of pediatric patients who already have a CI will be obtained from our VUMC Cochlear Implant Program database. Only KSP with routine access to these patients' medical records will access their PHI to determine eligibility and contact information. A letter or email describing the study and asking for interest in participation will then be sent and/or a phone call will be made to each individual identified (*the telephone script for the phone call will be the same as the Prospective Study Participant letter which is attached*). Another possibility for enrolling prospective participants is when these patients are seen in clinic for routine follow-up, the surgeon and/or audiologist can pass along the information about this study either verbally or by pointing the patient to a recruitment document. If a VUMC patient expressed interest, the clinician can page one of the KSP and study participation will be discussed with the potential participant. All researchers and/or research assistants who are trained in proper test administration may access EPIC (eStar) for the purposes of verifying participant eligibility prior to initializing contact.

In addition to standard recruitment methods as described here, this study will also be registered with clinicaltrials.gov as it is a randomized controlled trial (RCT). NOTE: As of January 9, 2019, we are in the process of preparing our clinicaltrials.gov submission.

5.0 Study Procedures

First, informed consent will be obtained for all participants. Interested participants will be provided a written form containing the elements of informed consent: description of the experiment, time necessary to complete the experiment, remuneration, a statement that the experiment will not enhance or harm the health of the participant, a statement that the participant may withdraw at any time without prejudice without affecting their medical care at Vanderbilt University Medical Center, a statement that the identity of the subject will be confidential, and an indication of the phone and address of the IRB official to contact if there are questions.

The experimenter will then ask open ended probing questions to ensure that the participant understands the purpose of the study and the study activities such as, "Can you provide a brief explanation of what you will be doing in this experiment?"

We will be looking for dissenting behaviors from the child such as hiding, crying, or not making eye contact.

Study procedures:

The proposed study is a relatively straight-forward, double blind, waitlist controlled RCT. The *total initial sample* (n=72) will be randomly assigned to either immediate IGCIP intervention (n=36) or a deferred waitlist condition (n=36). Both groups will be monitored for 24 months (**Table 3**), with testing at time 1 (baseline), time 2 (2 months), time 3 (6 months), and time 4 (12 months). After 12 months, the deferred treatment group will receive the IGCIP intervention and testing will then continue *for both groups* at time 5 (14 months), time 6 (18 months), and time 7 (24 months). At completion, we will have 12 months of data on untreated growth, 12 months of treated growth in the deferred group, and 24 months of growth in the immediate IGCIP group. Note that "growth" can be positive, negative or neutral within in this design. Importantly, a between-group comparison of treated and untreated growth will be completed for data collected at 12 months. The study also permits comparison of growth at 24 months between groups (immediate vs. deferred treatment), which provides strong testing of IGCIP intervention effects.

TABLE 3	Baseline	1 mo**	2 mo	6 mo	12 mo	13 mo**	14 mo	18 mo	24 mo
Spectral, temporal, & spectrotemporal res	x		x	x	x		x	x	x
Speech rec	x	x	x	x	x	x	x	x	x
Subjective questionnaires	x		x	x	x		x	x	x
Speech production	x		x	x	x		x	x	x
Working memory, language, non-verbal cognition, PA, & literacy	x				x				x

**SmartPhone app at home

We will ensure optimization of CI mapping including <u>CI-aided thresholds in the range of 20 to 25 dB HL from 250 through 6000 Hz</u> (119,120) as well as <u>verification of upper stimulation levels via electrically evoked stapedial reflex thresholds (ESRTs)</u> (121–123). For unilateral CI users with a hearing aid in the non-CI ear, <u>we will verify hearing aid settings via real-ear measures using the desired sensation level v5 prescriptive fitting formula</u> (124). If clinical CI mapping was not completed per this protocol, we will program the child's CI and wait at least 2 months prior to completing a baseline assessment. If middle ear status does not allow ESRT measurements (e.g., effusion and/or PE tubes), upper stimulation levels will be obtained behaviorally, per clinical protocol. We will also complete thorough listening checks and test external equipment for signs of malfunction at every study visit.

Procedures

IGCIP. IGCIP provides an automated electrode position analysis accounting for non-rigid variations in individualized cochlear anatomy requiring pre- and post-implant CT for all study participants. Pre- and post-operative CT scans are considered standard of care treatment for all CI recipients at Vanderbilt given the electrode information provided by the image-guided analysis. We will define the electrode-to-modiolus interface by calculating distance-versus-frequency curves and then implementing a minimum error neural network to determine which electrodes for which their local minima (shortest electrode to modiolar distance) would be completely encompassed by adjacent electrodes. The goal is to maximize the number of active electrodes [>8 electrodes (125,126)] but also eliminate electrodes providing "redundant" electrical stimulation (i.e. channel interaction) or extracochlear electrodes. With IGCIP deactivation, we hypothesize a reduction in channel interaction which should increase spatial selectivity, and hence spectrotemporal resolution and speech recognition in noise. For bilateral CI users, IGCIP will be implemented for just 1 CI, targeting the poorer performing ear or the 2nd CI ear in the absence of interaural performance differences. This has been the IGCIP approach for all previous studies (4,71,127) and offers built-in control of the non-IGCIP ear as well as the bilateral CI condition (also see data presented in *Preliminary Studies*).

Spectrotemporal Resolution. All tasks of spectral, temporal and spectrotemporal resolution will utilize a 3-interval, 2-alternative forced-choice procedure with broadband noise (125 to 8000 Hz) presented at 65 dB SPL in the sound field. For **spectral resolution**, the participant will be asked to discriminate between noises with a flat spectrum and those with spectral modulation at rates of 0.5 and 1.0 cyc/oct—these rates have been shown to be significantly correlated with various measures of speech recognition (60,61,128). **Temporal resolution** will be assessed using amplitude modulation detection tasks in which the listener is asked to discriminate between noises with a flat temporal envelope and those with sinusoidal amplitude modulation at rates of 4, 32, and 128 Hz. These rates were chosen to define the plateau of the temporal modulation transfer function (4-32 Hz) as well as the sloping portion of the function (128 Hz) [e.g., (129)]. 4 Hz is also highly relevant for speech as it represents the peak modulation rate of the speech envelope modulation transfer function (130). Temporal modulation threshold will be expressed in 20 log m (dB), where m is the modulation index (0 to 1). We have experience administering and interpreting these tasks in this age range as discussed in *Preliminary Studies*. *No prior study has described longitudinal auditory function for spectral, temporal, or spectrotemporal resolution in pediatric CI users in this age range within the context of an intervention-based RCT.*

We will also investigate spectral and temporal cue weighting using synthesized speech with word-initial voicing F0 and voice onset time (VOT). Both F0 and VOT can be used as reliable cues for voicing for word-initial stop consonants with VOT generally considered a more robust cue [e.g., (131)]. However, research has shown that in the presence of signal degradation—such as with the introduction of masking noise and/or low-pass filtering—greater weight may be placed on F0 [e.g., (132)]. For CI recipients, F0 information is poorly transmitted with envelope-based signal coding; hence in the presence of background noise or very poor spectral resolution, it is unclear how effective CI recipients will be able to shift cue weighting from VOT to F0 and no such data exist for pediatric CI recipients, a group with poor spectral resolution. Thus we will investigate speech perception outcomes by synthesizing a two-dimensional continuum varying both initial F0 and VOT. Synthesis will be accomplished using Praat by interpolating between a /pa/ and a /ba/ exemplar along each dimension. Exemplars in this continuum will be presented to CI recipients and NH controls to quantify /pa/-/ba/ classification. Responses from a control group of children with normal hearing will provide best-case speech perception in this continuum as well as estimates of the weighting of cues on classification. This pediatric normative classification mapping will be used for comparison to pediatric CI recipients. These data will provide estimates of perceptual success as well as whether pediatric CI recipients are using different cues and/or are able to re-weight cues.

Speech Recognition. We will assess speech recognition in each CI ear alone as well as the bilateral aided condition (bilateral CI or CI plus contralateral hearing aid) including monosyllabic words, non-words, as well as sentences in quiet and co-located noise (+5 dB SNR) with speech presented at 60 dB SPL in quiet and 65 dB SPL in noise. We will use CNC (106) monosyllables, non-word repetition tasks (114,133), BabyBio sentences (107) presented in quiet and at +5 dB SNR, as well as the BKB-SIN test (108). We will also obtain an adaptive speech receptive threshold for HINT sentences (134) presented at 0 degrees with semi-diffuse noise originating from 45 to 315 degrees as described in our previous publications (1,2). The semi-diffuse noise will be fixed at 72 dB SPL [typical restaurant noise level (135,136)] and the HINT sentences will be varied adaptively to yield 50% correct. *CNC, BabyBio, and BKB-SIN are all recommended by the Pediatric Minimum Speech Test Battery* (3) *and thus hold high clinical relevance.* Further, all measures have a sufficient number of lists allowing for longitudinal administration without repetition. We chose an SNR of +5 dB for fixed SNR assessment given that children aged 6-12 years spend ~80% of their day in noise including classrooms, school cafeterias, and playgrounds (137) and +5 dB is representative of the mean SNR encountered in everyday environments for elementary school-aged children (114-117). The additional measure of non-word repetition should be more sensitive to manipulations of IGCIP spatial selectivity and subsequent spectral resolution as non-words do not hold lexical meaning (114,139). Despite the ubiquity of the speech recognition measures, *there are no published data documenting the longitudinal performance trajectory for these measures of speech recognition and thus these data offer high clinical value.*

We will use a SmartPhone app to assess word recognition at the baseline and 12-month visits via Bluetooth or direct audio input. One month following baseline and 12-month visits, a caregiver will re-administer this test at home. In the event that word recognition has significantly declined relative to the immediately preceding visit—using 95% confidence intervals for test-retest variability of word tasks (140)—we will offer the option of returning the child to her previous CI map or giving an additional month with follow-up at the next scheduled appointment (at either 2 months or 14 months, per **Table 3**). Neither participant nor experimenter will not know whether the child is in the immediate IGCIP or waitlist deferred group. Should the child be withdrawn from the study due to negative outcomes, this will require that we break the blind for a given participant (see *Data Safety and Monitoring Plan*); however, we would continue to study auditory, speech, PA, language, and reading outcomes over a 2-year period for this child. *This will allow us to investigate underlying mechanisms responsible for those that are IGCIP responsive (estimated at over 75% of enrolled participants) as compared to non-responders—an important research question for clinical translation of this technology.*

Subjective questionnaires (Auditory Skills & Quality of Life). We will obtain subjective reports of auditory skills as well as overall quality of life for our pediatric participants using validated questionnaires: Auditory Skills Checklist [ASC (141)], Parents' Evaluation of Aural/oral performance of Children [PEACH (142)], Vanderbilt Fatigue Scale.

Language Ability. Language ability will be measured at two levels: expressive and receptive. Additionally, estimates of each domain will have multiple measures including vocabulary, morphology, and syntax. Receptive language abilities will be measured using the Receptive One-Word Picture Vocabulary Test-4 [ROWPVT-4 (144)], Peabody Picture Vocabulary Test-4 [PPVT-4 (145)], and the TACL-4 (146) which includes separate subscale scores for vocabulary, morphology, and elaborated sentences. The receptive composite of the Clinical Evaluation of Language Fundamentals-4 [CELF-4 (147)] will also be administered to all participants. Expressive language will be measured using the Expressive One-Word Picture Vocabulary Test-4 [EOWPVT (148)], the Structured Photographic Expressive Language Test-3 [SPELT (149)], and the expressive composite on the CELF-4 (147).

Speech production (standardized assessment and acoustic analyses). Because children with hearing loss potentially display clinical speech disorders as well as subclinical speech alterations that can be detected only within the context of acoustic analysis, we will complete both standardized clinical measures and acoustic analyses. Traditionally speaking, due to the large amount of time spent on hand-analyses of speech production, a single dependent acoustic measure is chosen 'a priori'. This is often performed on a norm-referenced test of articulation such as the GFTA-3 (150), which we plan to administer; however, we will also supplement the GFTA-3 with acoustic analyses of speech samples obtained at each visit. The value of an objective speech acoustic analysis is that a very large number of measures can be computed with no subjective input thereby allowing us to investigate acoustic measures, or clusters of acoustic measures, that are related to the independent variable, i.e. implementation of IGCIP. We audio record the administration of the Renfrew bus story (151) as well as asking the child to repeat the Ling 6 sounds and "Twinkle Twinkle Little Star". We will obtain these speech samples at baseline and all subsequent study visits (**Table 3**). We will use Aural Analytics software (152) to obtain automated measures of 1) vocal quality (i.e. harmonic-to-noise ratio), 2) pitch (F_0: mean, stdev, range), 3) articulatory control [articulatory entropy (153)]; the envelope modulation spectrum; formant frequencies for consonants and vowels, vowel space; long-term average spectrum; speaking rate), and, 4) nasality (energy < 500 Hz). The algorithm for measuring articulation precision was calibrated using over 1000 hours of native English speech for adults and children and used to generate a normative distribution. In addition, we will manually investigate: a) differentiation between voiceless postalveolar affricates /ch/ and voiceless alveolar stop /t/—looking at peak amplitude and spectral mean of the fricative portions, b) differentiation of alveolar and postalveolar voiceless fricatives (/s/ vs /sh/), c) whole-word variability, and d) presence of atypical error patterns.

Nonverbal assessment of cognition. Nonverbal cognition will be assessed using the 3rd edition of the Leiter International Performance Scale [Leiter-3 (154)]. This is a standardized nonverbal estimate of cognitive abilities and was successfully administered with the participants in our pilot studies. All participants must exhibit nonverbal cognitive abilities within the typical range for inclusion. Should we identify a child exhibiting nonverbal cognitive abilities below the age-normative cutoff, we will refer to the developmental psychologist on the Vanderbilt CI Team.

Working Memory. Three tasks will be used: 1) Numbers Reversed from the Woodcock-Johnson IV (155) is a traditional test of memory span in which the child hears progressively longer strings of numbers and recalls in backwards order. Numbers will be audiorecorded with calibration and normalization of level (in dB SPL) for standardized auditory presentation across all participants and visits. Children will be asked to repeat each number prior to testing to ensure accurate recognition. 2) A serial recall task will be used to assess one's ability to use phonological structure to store words in a working memory buffer. This task has been used frequently, including pediatric CI users (75,76). The child sits in front of a touchscreen monitor and hears a string of 6 non-rhyming consonant-vowel-consonant, high-frequency nouns. After presentation, pictures of the 6 items appear on the display and the child is asked to touch the pictures in the order heard. The same 6 words are used across all trials and word recognition is confirmed both before and after testing. The serial recall task is used as it is more sensitive to phonological coding than free recall (156). 3) A visual-spatial task will be used, to assess working memory in the absence of verbal material. In this task, the touchscreen monitor is divided into 6 squares, and squares illuminate one at a time. The child is asked to tap on the squares in the order recalled. Reasons for using all three tasks of working memory are as follows: 1) The 1st task is a standardized task and will provide standardized scores that can be interpreted according to age norms and provide W scores, which are weighted raw scores that yield an estimate of ability level independent of age. 2) The 2nd task will assess children's abilities to use phonological structure in service to verbal working memory. Research has shown this task to be especially sensitive to differences in verbal working memory between children with NH who have typical language abilities and either children with CIs (referenced above) or children with NH, but phonological deficits (157). 3) The 3rd task will assess whether the participants have working memory deficits extending beyond simple verbal material.

PA. As with speech and working memory, we include standardized measures of PA as well as additional in-depth measures (developed in consultation with Dr. Nittrouer). PA is defined as the ability to segment, discriminate, and operate on phonological units [speech sounds; see (158)]. The Comprehensive Test Of Phonological Processing [CToPP-2 (159)] is a norm-referenced and widely used standardized assessment of this ability and in our preliminary study of PA in children with hearing loss (94). To obtain multiple standardized estimates of PA, we will also administer the Test of Auditory Processing Skills [TAPS-3 (160)]. Both of these tests have been used extensively in previous studies of PA including several with children with CIs (161). In addition, Nittrouer and colleagues have developed an individualized set of tasks designed to provide an in-depth assessment of PA (8). They have argued that in parallel to subclinical alterations in speech production, specific aspects of PA may also illuminate the relationship between impoverished and/or altered access to the auditory CI signal and key aspects of PA. Because of this, in addition to the CToPP and the TAPS, we will also be administering the PA battery designed and studied in detail by Nittrouer including: Non-word Repetition, Initial Consonant Discrimination (Same-Different), Initial Consonant Choice, Final Consonant Choice, Phoneme Deletion, and Backwards Words (21). Although many of these tasks are sub-items on the CToPP and/or the TAPS, the in-depth PA battery includes multiple items that are developmentally ordered in each of these domains so that we can 1) accurately identify functional level for each skill at intake and 2) have sufficient sensitivity to capture short-term growth on one or more of these skills. Because there has been considerable variability in the relationships between speech recognition and PA in this population, we hypothesize that the IGCIP data will yield insight into the relationship between speech recognition, PA, and reading ability as well as receptive language with a specific focus on bootstrapping of PA.

Reading Ability. Reading ability includes two key factors, decoding and reading comprehension (162); we will obtain multiple measures of each of these factors. Standardized tests include the Woodcock Reading Mastery Tests [WRMT™-III (163)] and the Gray Oral Reading Test-5 [GORT-5 (164)]. Both instruments have been widely used with typically developing children and children with disabilities and, as with PA, have been applied to children with hearing loss in several studies. The WRMT™-III includes decoding assessments (e.g., letter word identification) and assessment of reading comprehension (e.g., Passage comprehension). Similarly, the GORT-5 includes estimates of decoding and reading comprehension including reading vocabulary comprehension and passage comprehension.

Auditory Evoked Potentials (AEPs). Auditory brainstem response (ABR) and Frequency Following Response (FFR) We will be presenting acoustic stimuli to the ears via insert earphones using a foam eartip. The stimuli will either be click, tone, speech sound (such as /da/ sound), or a complex stimulus (such as a harmonic complex of pure tones that is amplitude modulated). The stimuli will be presented at a level of 70 dBnHL that is consistent with raised speech levels encountered in everyday life. We will place surface electrodes on the participant's scalp (Cz), forehead (Fz), and earlobes (A1 & A2). The participant will be asked to sit quietly, relax, but to avoid excessive blinking. The participant will be seated in a comfortable chair in a sound treated room. Breaks will be given as necessary. The AEP experiments will take approximately 30 to 40 minutes. AEP data will be analyzed following acquisition using MATLAB to extract timing and frequency information specify to the response

Time-based description of assessments administered:

BASELINE visit (after consent and assent):

- Randomization to either immediate or waitlist deferred IGCIP
- CI programming according to randomization
- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)

- Surveys administered to child and parent (ASC, PEACH, andVanderbilt Fatigue Scale)

All baseline testing described below will be administered with the child's original clinical program:

  - Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
  - Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
  - Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks
  - Language assessment: ROWPVT-4, PPVT-4, TACL-4, CELF-4, EOWPVT-4, SPELT-3 (will be audio & videorecorded)
  - Speech production assessment: GFTA-3, Renfrew bus story, and Twinkle Twinkle little star (will be audiorecorded)
  - Nonverbal cognitive assessment: Leiter-3
  - Working memory: Numbers Reversed from the Woodcock-Johnson IV, serial recall task, and visual-spatial task (will be audio and videorecorded)
  - Phonological awareness (PA): CToPP-2, TAPS-3, Non-word Repetition, Initial Consonant Discrimination (Same-Different), Initial Consonant Choice, Final Consonant Choice, Phoneme Deletion, and Backwards Words
  - Reading ability: WRMT™-III and GORT-5
  - Auditory Evoked Potentials (AEPs): ABR and FFR

Phone call (1 month after baseline): Experimenter will call parent or primary caregiver to get information about the bluetooth administered word recognition task

Visit 2 (2 months after baseline):

- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- CI programming as needed (using the same assigned programming method)
- Surveys administered to child and parent (ASC and PEACH)
- Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
- Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
- Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks

Visit 3 (6 months after baseline):

- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- CI programming as needed (using the same assigned programming method)
- Surveys administered to child and parent (ASC and PEACH)
- Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB

SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
- Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
- Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks

Visit 4 (12 months after baseline):
- Participants randomized to waitlist deferred IGCIP group will be programmed with IGCIP method (following assessments listed below)
- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- Surveys administered to child and parent (ASC, PEACH, and Vanderbilt Fatigue Scale)

All visit 4 testing described below will be administered with the child's program that has been used up to this visit (i.e. not with any new programming changes made today)
  - Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
  - Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
  - Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks
  - Language assessment: ROWPVT-4, PPVT-4, TACL-4, CELF-4, EOWPVT-4, SPELT-3 (will be audio & videorecorded)
  - Speech production assessment: GFTA-3, Renfrew bus story, and Twinkle Twinkle little star (will be audiorecorded)
  - Nonverbal cognitive assessment: Leiter-3
  - Working memory: Numbers Reversed from the Woodcock-Johnson IV, serial recall task, and visual-spatial task (will be audio and videorecorded)
  - Phonological awareness (PA): CToPP-2, TAPS-3, Non-word Repetition, Initial Consonant Discrimination (Same-Different), Initial Consonant Choice, Final Consonant Choice, Phoneme Deletion, and Backwards Words
  - Reading ability: WRMT™-III and GORT-5

Phone call (13 months after baseline): Experimenter will call parent or primary caregiver to get information about the bluetooth administered word recognition task

Visit 5 (14 months after baseline):
- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- CI programming as needed (using the same assigned programming method)
- Surveys administered to child and parent (ASC and PEACH)
- Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN

(S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
- Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
- Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks

Visit 6 (18 months after baseline):
- CI aided detection thresholds in the sound field (250-6000 Hz)
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- CI programming as needed (using the same assigned programming method)
- Surveys administered to child and parent (ASC and PEACH)
- Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
- Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
- Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks

Visit 7 (24 months after baseline):
- CI aided detection thresholds in the sound field (250-6000 Hz)
- CI programming, as needed
- HA settings verification (for children with unilateral CI and HA in the non-CI ear)
- Surveys administered to child and parent (ASC, PEACH, and Vanderbilt Fatigue Scale)

All visit 7 testing described below will be administered with the child's program that has been used up to this visit (i.e. not with any new programming changes made today)
- Speech recognition testing: CNC monosyllables, non-word repetition, BabyBio sentences in quiet, BabyBio sentences in multi-talker babble at +5 dB SNR (S0N0), BKB-SIN (S0N0), adaptive HINT in R-SPACE™ system NOTE: speech in quiet calibrated to 60 dB SPL, speech in noise (S0N0) calibrated to 65 dB SPL, adaptive HINT in R-SPACE™ noise calibrated to 72 dB SPL
- Spectral resolution: spectral modulation detection for 0.5 and 1.0 cyc/oct in sound field at 65 dB SPL, adaptive tracks
- Temporal resolution: temporal modulation detection for rates of 4, 32, and 128 Hz in sound field at 65 dB SPL, adaptive tracks
- Language assessment: ROWPVT-4, PPVT-4, TACL-4, CELF-4, EOWPVT-4, SPELT-3 (will be audio & videorecorded)
- Speech production assessment: GFTA-3, Renfrew bus story, and Twinkle Twinkle little star (will be audiorecorded)
- Nonverbal cognitive assessment: Leiter-3
- Working memory: Numbers Reversed from the Woodcock-Johnson IV, serial recall task, and visual-spatial task (will be audio and videorecorded)
- Phonological awareness (PA): CToPP-2, TAPS-3, Non-word Repetition, Initial Consonant Discrimination (Same-Different), Initial Consonant Choice, Final Consonant Choice, Phoneme Deletion, and Backwards Words

- Reading ability: WRMT™-III and GORT-5

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

The PIs and all study personnel will comply with requirements regarding the reporting of adverse events (AEs), including plans for reporting of AEs to the IRB and appropriate regulatory agencies. AEs must be reported to the IRB within 10 working days after learning of the event or problem.

7.0 Study Withdrawal/Discontinuation

The investigation involves a new method of programming cochlear implants based on a comparison of pre- and post-operative CT scans. The risk to the patient is radiation exposure due to the postoperative CT scan; however, *we complete postoperative scanning routinely for all CI recipients at VUMC (unless declined by the patient) given that the information gained by the scan and image processing has been determined by the Vanderbilt CI team to offer significant clinical value to the patient for CI programming optimization (e.g., identification of extracochlear electrodes, tip foldover).* Thus, this is NOT a risk to patients currently implanted at VUMC. Should a potential study participant not have a postoperative CT scan, s/he must be first consented and enrolled in Dr. Labadie's CT imaging study (IRB #090155 "Assessment of Electrode Placement and Audiologic Outcomes in Cochlear Implantation") prior to consent and enrollment in the current study. For this reason, the current study has been linked to Dr. Labadie's study.

The other portions of the research–namely deactivating CI electrodes–are within the scope of practice of audiologists for CI programming and thus utilize CI clinical software that is FDA approved and regulated. Oversight for all study procedures will be provided by the Vanderbilt's Institutional Review Board and managed by the study PIs.

If participants do not sign the consent form, no research data will be collected. Participants will leave with no negative consequences. If at any point, a participant indicates verbally that he/she no longer wants to continue with the study, he/she will NOT be forced to cooperate and he/she will be given the options of taking a break, discontinuing and rescheduling the session, or stopping participation in the study.

No subject will be excluded from participation due to gender, race, or ethnicity. Cochlear implant and hearing aid users will be drawn from the current patient population at Vanderbilt Bill Wilkerson Center aged 6 to 12 years. The investigator(s) will be blind to race and ethnicity of participants prior to their actual date of participation. Thus, the same group of participants will benefit from the results of the research as those who will be participating.

8.0 Privacy/Confidentiality Issues

Discuss the methods for ensuring participant privacy, and the methods for protecting privacy and confidentiality.

(Research, Activities, Procedures, and Schedule of Events for Study Participants - Describe the procedures that will be utilized to protect the privacy of the research participant.)

Data will be entered and stored in REDCap.

REDCap is a secure, web-based application that is flexible enough to be used for a variety of types of research. REDCap provides an intuitive user interface that streamlines project development and improves data entry through real-time validation rules (with automated data type and range checks). REDCap also provides easy data manipulation (with audit trails for reporting, monitoring and querying patient records) and an automated export mechanism to common statistical packages (SPSS, SAS, STATA, R/S-Plus).

Audio and video recordings will be obtained of participants' spoken word responses to speech production and language assessment tests for offline analysis of speech rate, formant frequency representation, and energy distribution of speech production. Audio recordings will be stored on a password protected, encrypted server hosted by the Vanderbilt Bill Wilkerson Center. The audio and video recordings will be labeled with a subject ID code and will not include name or any other identifying data.

We will use paper case report forms (CRFs) to record data during experimentation. No identifying information will be placed on the CRFs. The CRFs along with signed informed consent forms will be stored in a locked file cabinet in the Cochlear Implant Research Laboratory (MCE South 10326). Only the investigators and research assistants assigned to the project will have access to the REDCap databases as well as the locked file cabinet (all personnel will have completed human subjects training as well as good clinical practice training).

(Research, Activities, Procedures, and Schedule of Events for Study - Describe how the confidentiality of participants' data will be assured. Include a description of any issues specific to the study that might increase the risk of breach of confidentiality.)

All appropriate measures will be taken to ensure the confidentiality of study participants. All data will be labeled and coded. These unique identification numbers will be used on all source materials, including self-reported questionnaires, paper assessments, and computerized data. Data will be stored on secure, password-protected networked computers, in locked offices, and on dedicated REDCap databases. Only research staff will have access to participant data.

A list linking names to identification numbers will be available only to authorized personnel for recruitment purposes. This will be kept on a password-protected roster stored on a secure server accessible only by the PI and her designees. Data will be destroyed 10 years following final study closure.

The maintenance of all subject-relevant data will comply with the Health Insurance Portability and Accessibility Act (HIPAA), on which all lab personnel will be fully certified. Clinical information will be collected from patients' medical records by researchers with approved epic/estar access.

Prospective assignment of one or more human subjects. All participants will receive intervention; however, half of the participants will be randomly assigned to immediate intervention and the other half will be assigned to the deferred intervention group using a waitlist control study design. Randomization to IGCIP or waitlist IGCIP will occur after written informed consent and will proceed in the same way for both testing periods. As described in the Approach, we will be using identical procedures for all participants regardless of arm to which they randomize including generation of an IGCIP plan, and longitudinal assessments performed by an audiologist and speech-language pathologist.

A randomization schedule will be generated by Co-I and study statistician, Mary Dietrich, PhD, and provided to the PIs (Gifford and Camarata) prior to study commencement. To ensure equal numbers of participants in each arm, a computer-generated, permuted blocking algorithm (blocks of 4 participants) will be used to develop the schedule. The schedule will be password protected and saved on an encrypted server housed at the Vanderbilt Bill Wilkerson Center. As described in the Approach, we will be using identical procedures for all participants regardless of arm to which they randomize including (a) post-operative CT scanning (if needed and completed per IRB #090155), (b) generation of an IGCIP plan, and (c) longitudinal assessments performed by an audiologist and speech-language pathologist.

Blinding. Both the experimenters and the participants will be blinded. The experimenters will be notified of the randomization for a given participant on the day of the baseline visit. Only the PIs and Co-I Dr. Dietrich, who will generate the randomization scheme, will know whether the participant is in the intervention or deferred waitlist group until the end of the study. Neither PI nor Dr. Dietrich will be personally administering assessments nor scoring tests for the participants.

Provisions for breaking the blind. To ensure that IGCIP does not impair auditory-only word recognition—an important ethical control in this clinical trial—we will use a SmartPhone app, (e.g., Hear Coach) to assess word recognition during the respective baseline as well as at 1 month and 13 months following enrollment—as neither the participants nor the tester will know whether the subject is in the immediate or deferred intervention group. Words will be transmitted from the SmartPhone app via Bluetooth or direct audio input at a comfortable level. Study staff will administer the assessment at baseline; a caregiver will be asked to re-administer smartphone word task at home during the subsequent periods. In the event that word recognition has decreased relative to scores obtained during the previous study visit—using 95% confidence interval data for test-retest variability of word recognition tasks containing 25 items—we will offer the option of returning the child to a previous program or giving the child one additional month of study participation to be followed up at the regularly scheduled appointment for each group (Table 3). Note that it is possible that there will be some cases where no changes were made to the child's previous program for those in the deferred intervention. If no changes have been made to the child's CI program—as in the case of the waitlist deferred group at the 1-month post enrollment appointment—we would not expect changes in word recognition. However, should there be an aberrant/unexplained change in the child's hearing status and a change in word recognition *without a change to the CI*

9.0 Follow-up and Record Retention

List the duration of the study. List the duration of record retention and the method for destruction or the possibility of indefinite archiving of information.

(Data and Safety - Provide a general description of the data and safety monitoring plan)

In accordance with Vanderbilt guidelines and as outlined to the subjects in the consent form, the subjects' confidentiality will be ensured throughout the study. All data will be identified by code numbers only and no description of individual patients will be included in any publication. Data obtained as part of this research will be maintained in PC computers accessible only to the investigators and research staff that they designate. The data may be maintained for an indefinite period of time since scientific progress may indicate that new analyses be carried out on previously obtained data. Future studies/analyses will be carried out with approval of the IRB. If paper records are to be destroyed, those containing subject identifiers will be shredded directly or transferred to the hospital's shredding service. If electronic data containing subject identifiers is to be destroyed, it will be disposed of using a medium-appropriate destruction method to prevent recovery. Data not containing subject identifiers will be disposed of by any convenient method.