SIGNIFICANCE

Cochlear implants provide hearing to people with severe to profound hearing loss. Recipients generally achieve high levels of speech comprehension with their implants, but music perception and speech comprehension in noise is often poor compared to normal hearing. For historical and technological reasons, most cochlear implants in use today discard the temporal fine structure of sound and only transmit slowly varying envelopes. Evidence indicates that temporal fine structure is important for music perception and speech comprehension in noise[1–8]. Historically, some of the earliest cochlear implants used analog stimulation, which conveyed temporal fine structure, but in a manner that caused interference across electrodes that was difficult to control. Consequently, interleaved pulsatile stimulation gained prominence since it mitigated effects of electrical interference[9]. While this solution addressed aspects of electrical interference, it came at the expense of discarding temporal fine structure. Several attempts have since been made to restore temporal fine structure into cochlear implant stimulation while using pulsatile stimulation. The most successful attempt to date is Fine Spectral Processing used with MEDEL devices, which uses dynamic pulse timings, phase-locked to the temporal fine structure of sound, when stimulating the most apical electrode(s). This strategy has shown promise for improving pitch perception for cochlear implant users, particularly when recipients are provided time to learn how to use the new information[10,11].

The extent that restoring temporal fine structure into cochlear implant stimulation will improve outcomes for cochlear implant users is unknown. Psychophysical and physiological studies indicate that temporal fine structure is used in normal hearing for frequencies up to 1500 Hz and perhaps as high as 10 kHz[12,13]. In contrast, studies indicate that cochlear implant users are generally insensitive to stimulation rate, particularly so for rates above 300 Hz[14,15]. In our previous work, we showed that sensitivity to stimulation rate can be improved with training[16]. This is a critical finding. It suggests that the impoverished temporal sensitivity in cochlear implant users might be a result of the simple fact that cochlear implants discard temporal fine structure and only weakly encode temporal periodicity using amplitude modulation for a limited range of frequencies. If so, then it is quite possible that temporal sensitivity can be refined to what is generally observed for normal-hearing listeners, perhaps even improved upon because cochlear implant stimulation can be temporally more precise than normally provided by healthy hearing. The potential impact is profound. At the very least, with better encoding and auditory rehabilitation, voice pitch perception could be enhanced for frequencies above 300 Hz, allowing better perception of children's voices. Beyond, enhancing temporal coding in cochlear implants could broadly improve music perception and speech recognition.

INNOVATION

This proposal brings together psychophysics, electrophysiology, and neural modeling to examine perceptual learning for stimulation cues that are poorly encoded by clinical devices. Studies have shown that sensitivity to pitch can be improved with training even in normal hearing listeners[17–20]. Our work is unique in that we explore the effects of training for a pitch cue, stimulation rate, that is not used or is poorly encoded by existing devices. This key innovation for examining the perceptual plasticity of underlying psychophysical cues is coupled with a comprehensive approach for characterizing mechanisms and models of pitch perception. By considering the effects of learning, our approach challenges existing dogma regarding the limits of temporal sensitivity provided by cochlear implant stimulation. The uniting theme across aims is the power of plasticity.

- **Test the limits of temporal pitch perception when provided as a clear and consistent cue.** This innovation is at the core of our proposal. The extent that fine timing of stimulation can improve music and speech comprehension in noise for cochlear implant users depends on how well they can learn to hear timing differences. We provide extensive laboratory training for pitch cues while working with implant manufacturers to extend fine timing of stimulation into commercial devices and rehabilitation.
- **Develop physiological methods and models to optimize encoding of temporal fine structure.** Encoding temporal fine structure of sound into fine timing of cochlear implant stimulation is challenging because it requires microsecond decisions of pulse timings to be made in a way that transmits the timing information effectively to the auditory nerve. We outline the development of physiological methods and models for refining how cochlear implant stimulation is transmitted to auditory nerve activity. The models established here will guide the development of new stimulation strategies that use fine timing of stimulation to enhance hearing.

AIM 1: TEST THE PERCEPTUAL AND PHYSIOLOGICAL PLASTICITY OF PLACE AND RATE CUES IN COCHLEAR IMPLANT STIMULATION

1.1 Background & Rationale

Cochlear implants provide a sense of pitch using place and rate of stimulation. Place of stimulation is controlled by progressively filtering lower frequencies to more apical electrodes. Presently, most cochlear implants do not use stimulation rate to convey information but use amplitude modulation to transmit slowly varying envelopes[21]. The upper modulation frequency that is encoded depends on the device, but most devices only encode modulation frequencies up to 300 Hz, well below what has been shown to be possible in psychophysical and physiological studies. Further, filtering sound into frequency bands can diminish modulation depth, which tends to weaken pitch salience. Thus, most cochlear implants in use today make poor use of stimulation timing and only provide envelope fluctuations with limited modulation depth and frequency range.

In contrast to the impoverished temporal coding provided by clinical cochlear implants, temporal fine structure is exceptionally well encoded and apparently utilized in normal hearing. Studies of mammalian physiology have shown that the auditory nerve phase locks to acoustic frequencies up to 3 kHz and psychophysical studies of normal hearing typically conclude that temporal fine structure can be used for pitch and spatial hearing tasks at least up to 1500 Hz, perhaps as high as 10 kHz[22]. Given the physiological and psychophysical evidence indicating the importance of temporal fine structure, it has been discouraging to find that cochlear implant users struggle to perceive differences between stimulation rates above 300 Hz. Studies have shown that temporal encoding of electrical stimulation into auditory-nerve activity is not limited by physiology[23–26]. Phase locking of the auditory nerve has been reported to be stronger for electrical than for acoustic stimulation[12,27,28]. Overall, there is strong psychophysical and physiological evidence that temporal fine structure can be well encoded into synchronous auditory-nerve activity, both by acoustic and electric stimulation. We therefore hypothesize that the poor temporal sensitivity of cochlear implant users often reported in the literature is not a fundamental limit but one that could be improved if temporal fine structure was provided in a clear and consistent manner.

In Goldsworthy and Shannon, 2014[16], we showed that pitch discrimination based on stimulation rate can be improved with training. There have been several studies of the plasticity in normal-hearing listeners[20,29], but our approach is unique in that we study plasticity for a cue that is not typically provided during everyday exposure. Because it is not typically provided, we speculate that the time course and potential for improvements with training will differ from studies of normal-hearing listeners. Figure 1 shows cochlear implant rate discrimination thresholds for studies with and without training. The shaded gray region shows the range of thresholds reported by Zeng in 2002. For rates less than 200 Hz, discrimination thresholds without training were between 10 and 25% and deteriorated for rates above 300 Hz. These results are representative of studies in which subjects are not provided training for the rate cue. In contrast, we found in our 2014 study that with 32 hours of training, average discrimination thresholds were about 3% for rates less than 200 Hz and discrimination could be consistently measured as high as 1760 Hz. This is impressive given that aside from our study, the literature contains only a few mentions of star subjects who can pitch rank based on stimulation rates up to 900 Hz. The effect of training is large (Cohen's *d* > 1) and we want to know the extent that further training will produce further improvements. Participants reported that the task was difficult at first, but with practice at higher rates, they could consistently discriminate pitch.

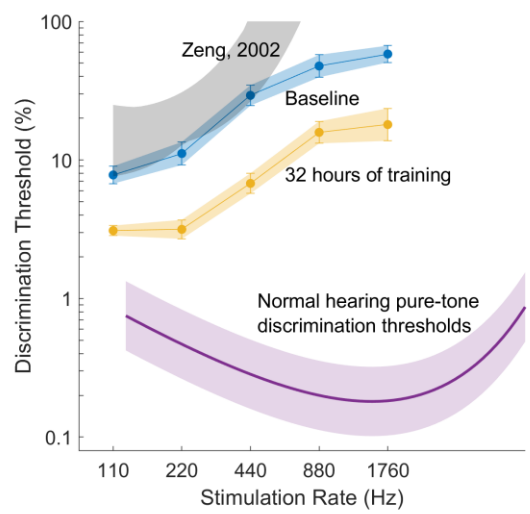

Figure 1: Pitch discrimination based on pulsatile stimulation rate improves with training.

Given the strong evidence that neural encoding of timing is important for music and speech perception and our strong preliminary evidence that temporal sensitivity can be improved if stimulation timing is provided in a clear and consistent manner, we propose to study the fundamental limits of pitch perception based on place and rate within the context of perceptual learning. Our primary hypothesis is that sensitivity to both place and rate as cues for pitch will improve with training, but that the time course and trajectory of improvements will differ for these cues because stimulation rates are not presently used in clinical devices to convey information. Because the rate cue is not presently encoded, we believe the potential for improvements is greater than for place.

1.2 Research Design

The proposed research examines the plasticity of pitch perception in adult cochlear implant users as conveyed by place and rate of stimulation. Adult cochlear implant users will take part in a crossover study to compare changes in pitch sensitivity across two training periods that alternate between training of pitch discrimination based on place and rate of stimulation. Training periods will be 4 weeks in duration with exercises completed 4 times per week during 2-hour training sessions. Psychophysical measures will include pitch discrimination conveyed by place and rate in isolation and as conveyed congruently or incongruently. Psychophysical measures will also include pitch discrimination as conveyed through the clinical processor to gauge the extent that existing devices use the underlying psychophysical potential. Electrophysiological measures will be used to characterize individual differences and changes that occur with training. Electrophysiological measures will include electrically evoked compound action potentials (eCAPs) and electrically evoked auditory change complex (eACC). Participants will be randomly assigned to first train either on place or rate discrimination and will subsequently crossover to train on the other cue. All psychophysical and electrophysiological measures will be conducted at baseline, midpoint, and endpoint. Neural modeling will be used to quantify and predict pitch salience evoked by place and rate of stimulation. Models will be calibrated using the results from psychophysical and electrophysiological measures. The modeling process will inform and facilitate new hypotheses regarding individual differences and pitch processing.

1.2.1 Participants

This study will be completed by 24 adult cochlear implant users. The nature of the study requires substantial psychophysical training and assessment that younger children would struggle with, so while future work should consider perceptual learning in pediatric patients, we focus the initial characterization in adults. Any adult cochlear implant user who can complete the procedures may participate. We have the necessary equipment and expertise to conduct the described procedures with Advanced Bionics, Cochlear Corporation, and MEDEL implants. Equal numbers of men and women will complete the protocol. Both prelingually and postlingually deafened adults will be enrolled and the effects of age and hearing-loss history will be considered. Participants will be scheduled for 2-hour training sessions with 24 to 72 hours between sessions. We will actively recruit participants who use single-electrode cochlear implants as they are of special interest. They are unique in that by having only a single electrode they likely receive and learn to perceive temporal patterns with more resolution. We will also active recruit participants who have residual hearing in the implanted ear. These participants are of special interest because we want to consider how duration of deafness affects temporal sensitivity.

1.2.2 Psychophysics

Psychophysics include computer-controlled electrode psychophysics and through-the-processor psychophysics. Computer-controlled electrode psychophysics will be used to probe pitch salience as conveyed by place and rate of stimulation. Through-the-processor psychophysics will be used to probe how well pitch is conveyed by clinical devices. Assessments are designed to determine how much training on place and rate improves sensitivity, and the extent that benefits transfer to sensitivity measured through clinical devices. Analysis will consider the extent that existing sound processing makes use of available psychophysical sensitivities.

a) _Computer-controlled electrode psychophysics_. Pitch discrimination will be measured as provided independently by place and rate of stimulation, as well as by their congruent and incongruent combinations. For congruent combinations, higher stimulation rates will be presented with more basal stimulation (and with more apical stimulation for incongruent combinations). Stimuli will be dual-electrode pulse trains as described by McDermott and McKay[30], which probe place-pitch perception with greater resolution than possible with single-electrode stimulation. Two-alternative forced-choice procedures will be used in which participants judge which of two stimuli is higher in pitch. Frequency discrimination will be measured near condition frequencies of 110, 220, 440, 880, and 1760 Hz for each of the 4 stimulation conditions (place, rate, congruent, incongruent). Adaptive procedures will be used to measure 75% discrimination accuracy. There are 24 conditions in this assessment with each condition frequency mapped to a corresponding dual-electrode configuration. Thresholds and comfort levels will be measured as a function of stimulation rate and used to balance loudness as described in Goldsworthy and Shannon, 2014[16]. Stimulation levels will be roved between 70 and 80% of the dynamic range and the reference frequencies will be roved ¼-octave around the condition frequency.

Figure 2 shows preliminary results from 7 subjects (10 ears), for independent and incongruent conditions. Participants were naïve in that they did not receive training for either pitch cue. Discrimination threshold based on place of stimulation was roughly flat as a function of frequency, which indicates that electrodes were roughly equally discriminable. The dashed line indicates the discrimination threshold corresponding to a place difference of 1 electrode. Discrimination thresholds based on stimulation rate were better resolved than for place at low frequencies but deteriorated above 220 Hz, as expected for naïve participants. Discrimination thresholds were generally better when place and rate were congruently combined than for either cue alone.

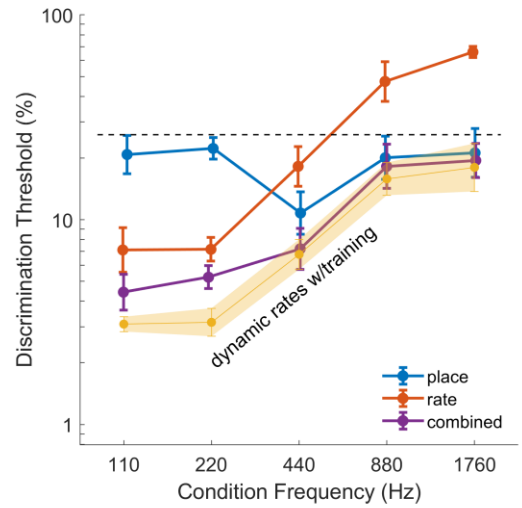

Figure 2: Pitch discrimination is generally better with place and rate of stimulation provided in a congruent manner compared to either cue alone.

The proposed research tests the independence and plasticity of place and rate cues. Independence will be examined using congruent and incongruent combinations of the two cues. Independence of these cues has been sparsely explored, with most studies underpowered and with no studies considering plasticity of the underlying cues. Importantly, the shaded yellow region of Figure 2 shows the rate discrimination thresholds after 32 hours of training. Rate discrimination with training is better than even the combined cue condition in naïve subjects. This comparison demonstrates the remarkable plasticity and resolution of rate discrimination and its potential for enhancing the overall pitch percept.

b) <u>Through-the-processor psychophysics</u>. Pitch sensitivity and speech comprehension as conveyed by clinical processors will be measured to test how well existing devices take advantage of underlying psychophysical cues and to consider transfer of learning. Pure tone frequency discrimination will be measured for frequencies from 125 Hz to 8 kHz in octave steps. Harmonic complex fundamental frequency (f_0) discrimination will be measured for f_0s of 110, 220, and 440 Hz for high-pass filtered complexes and low levels of background noise to mask low frequency components. This is done to avoid access to a place-of-excitation cue associated with the fundamental. In previous work[6,31], we showed that correlations between these measures of pitch perception were correlated with consonant and vowel identification in fluctuating noise, which suggests that improving pitch discrimination might partially transfer to phoneme identification. Consonant and vowel identification will be measured in quiet and in multi-talker background noise as an adaptive speech reception threshold procedure. These measures are as described in Goldsworthy, 2015[31], with the following specifications. Frequency discrimination will be measured with ¼-octave roving about the condition frequency and 6 dB level roving about 65 dB SPL with sound presented through an audio speaker in the free field. Consonant and vowel identification will be measured in quiet and in two-talker maskers as described in Goldsworthy, 2015[31], but using the web-enabled technology described for pediatric assessment in Goldsworthy and Markle, 2019[32].

1.2.3 Electrophysiology

We will measure eCAPs and eACCs to characterize individual differences and the effects of training at different levels of the auditory pathway. eCAPs will be measured to characterize spatial tuning and temporal synchronicity at the auditory nerve. eACCs will be measured to characterize changes in cortical response evoked by place and rate of stimulation. These measures will be used to consider individual differences, to examine plasticity of the neural response, to refine models of cochlear implant pitch perception, and to encourage the development of new hypotheses.

a) <u>eCAPs</u>. Spread of excitation will be measured using a two-pulse forward-masking paradigm in which the probe electrode is fixed, and the masker is varied across the electrode array[33–35]. Stimuli will be as described by Hughes and Abbas, 2006[35], presented at 80% of the behavioral dynamic range. Measures will be collected and used to calculate the channel separation index as described by Hughes. Temporal responsiveness and synchronicity will be measured based on the composite response to individual pulses of a pulse train as described in He et al., 2016, for a 400 ms pulse train. Temporal responsiveness will be characterized by refractoriness and recovery, neural adaptation and adaptation recovery[23,26,33]. Temporal synchrony will be characterized by the autocorrelation and power spectral density of composite eCAP responses across pulse presentations. This measure of temporal synchrony will connect the electrophysiology to the physiology studies of Cariani and Delgutte[36,37], which explore models of pitch perception based on interspike interval information.

b) <u>*eACCs*</u>. eACCs will be measured for changes in place and rate of stimulation. Spatial resolution will be probed in response to dual-electrode stimulation as specified for the computer-controlled electrode psychophysics. Scheperle and Abbas[38] found that subjects had large eACCs associated with place of stimulation changes of a single electrode. Dual-electrode stimulation allows intermediate steps to probe spatial resolution with better resolution[30]. In control conditions, the ratio of charge delivered to the dual-electrode configuration remains constant throughout an 800 ms recording interval. In experimental conditions, the eACC will be elicited by introducing a change in the dual-electrode charge configuration 400 ms after the onset of the pulse train. Scheperle and Abbas[38] found that eACCs typically saturate with a separation of 2 electrodes; consequently, we will measure eACCs for electrode spacings from ±2 electrodes in ¼-electrode steps. eACCs will also be measured for changes in stimulation rate. For control conditions, stimulation rate remains constant throughout the 800 ms recording interval. For experimental conditions, the eACC will be elicited by introducing a change in rate 400 ms after the onset of the pulse train. Probed contrasts will be based on measured psychophysical rate discrimination thresholds (*i.e.*, higher stimulation rates require larger rate changes to elicit a response). Probed conditions will typically span an octave but with narrower ranges used as needed.

1.2.4 Neural Modeling

Models of the auditory periphery and midbrain will be used to first characterize neural response to pure and complex tones in healthy physiology. Models of electrical current spread and action potential generation will be used to produce a comparison set of auditory-nerve responses predicted for cochlear implant stimulation. Using these models of normal auditory-nerve response and of response to electrical stimulation, we will characterize relationships between neural responses and psychophysics. Our initial approach will follow the work of Co-Inv. Dr. Carney, as described in Bianchi *et al.*, 2019[39], where they examined the effects of hearing loss on f_0 discrimination and temporal fine structure processing. In that study, auditory nerve responses were simulated for normal and impaired hearing for complex tones and used to estimate frequency and modulation encoding at the level of the inferior colliculus. Distance metrics will be used to characterize differences in place and rate coding of frequency at both the level of the auditory nerve and inferior colliculus. Neural modeling will be adjusted based on measured electrophysiology. For example, measured eCAPs characterizing channel interaction will be used to adjust the estimated electrode-to-neural distance in a current spread model. Likewise, measured eCAPs characterizing neural synchrony will be used to adjust membrane time constants in a charge integration model. The adjusted model will be used to calculate corresponding distance metrics derived from changes in place and rate of implant stimulation and relationships will be examined with measured discrimination thresholds. Modeled thresholds will be estimated using the same stimuli used for psychophysical and physiological measures, allowing direct comparison of modeled and measured thresholds. This approach will allow systematic tests of specific functional relationships between neural and perceptual responses, as follows.

One functional relationship that will be examined is the pooled interspike interval distributions of the estimated auditory-nerve response. Cariani and Delgutte demonstrated that periodic stimuli that evoke a strong sense of pitch produce pooled interval distributions with relatively high peak-to-mean ratios. It is expected that pulsatile stimulation and modeling of such will produce higher peak-to-mean ratios compared to normal physiological encoding and we will consider individual differences based on electrophysiological measures. Further, we will use the predicted neural response to acoustic and electric stimulation as inputs to the temporal pitch processing model described by Bahmer and colleagues[40,41]. As described by Cariani and Delgutte[36,37], evidence for a physiological mechanism for decoding temporal oscillations into place-of-excitation would provide a unified explanation of different aspects of pitch perception. The modeling work of Bahmer and colleagues[40,41] clarifies how networks of cells in the cochlear nucleus could perform such temporal processing. Our work will combine the modeling efforts of Dr. Carney and collaborator Dr. Bahmer and will characterize the response of the cochlear nucleus oscillatory network models to auditory-nerve response estimated for both acoustic and electric stimulation.

1.2.5 Data Analysis Plan

The psychophysical measures are continuous variables and will be described as means and standard deviations. Of primary interest is whether measures change with training. The difference in means will be analyzed using a repeated-measures analysis of variance. The study is overpowered on the main hypothesis that pitch ranking will improve with experience. For comparison, the data published in Goldsworthy and Shannon 2014[42] is of similar design and can be used to guide expectations. That data set consisted of 6 subjects who trained on pitch ranking for a total of 32 hours across 4 weeks. In the proposed design, training periods are 16 hours in duration. Analysis of variance based on the earlier data set over the initial 16 hours indicates a large training effect

($F_{4,74}$ = 17.3, p < 0.001). The corresponding thresholds improved by more than a factor of two (from 4.2 to 1.8 semitones, d_{Cohens} > 1). The experimental design is overpowered on the main effect of training to provide power to detect transfer of learning to untrained measures, which are expected to be smaller. Power analysis of this design with 24 subjects and a 0.05 significance criterion indicates a 95% likelihood of detecting effects as small as 0.19, corresponding to a 10% improvement in thresholds. This level of resolution will be useful when testing secondary hypotheses associated with the salience and time course of learning when comparing pitch evoked by place and rate of stimulation.

Electrophysiological measures will be collapsed into summary statistics and analyzed for relationships with psychophysical measures. Planned summary statistics were briefly described in the electrophysiology section and include measures of spectral tuning and temporal responsiveness. Correlation between electrophysiological and psychophysical measures will be tested. Power analysis of this design with 24 subjects and a 0.05 significance criterion indicates an 80% likelihood of detecting correlations of 0.48 or greater (explaining 23% of the variance). As multiple stimulation sites will be examined (e.g., apical/basal), correlations will also be examined within participants across stimulation sites. For example, correlation between the change in psychophysical and electrophysiological measures across stimulation sites. Such correlations predicting within-subject changes in measures has been used in cochlear implant psychophysics to characterize individual differences with much smaller participant population than generally required for across subject analyses.

Planned modeling analyses include variations of the approach described by Co-Inv. Dr. Carney and colleagues in Bianchi *et al.*, 2019[39]. For example, spectral tuning will be modeled for normal physiological response using the model of normal physiology developed by Dr. Carney. Spectral tuning of cochlear implant stimulation will be modeled using the computational model of auditory-nerve response to electrical stimulation developed by Dr. Frijns, which has been validated with animal data for modulated and unmodulated pulse trains. Modeled response to electrical stimulation will be simulated for the conditions probed for measured eCAPs and will be analyzed in terms of spread of excitation. Simulated neural responses will be described by summary statistics; for example, the psychophysical channel separation index described by Hughes[34] but based on simulated response properties. Direct comparisons of thresholds, as well as trends with place and rate of stimulation, will be examined to characterize relationships between modeled and measured sensitivity.

1.3 Expectations, Contingencies, and Explorations

We expect to learn the extent that pitch ranking based on place and rate of cochlear implant stimulation can be improved through psychophysical training. We will clarify the extent that place and rate of stimulation are independent. We will characterize relationships between such measures of pitch perception and electrophysiological measures of neural response at the level of the auditory nerve and cortex. We will refine models of pitch perception by comparing modeled and neural responses to acoustic and electric stimulation. We expect these efforts to inform the unexplored limits of stimulation rate to convey information in the next generation of sound processing strategies for cochlear implants.

Aim 1 is supported by strong preliminary data and there is a high likelihood that we will successfully characterize the plasticity of pitch perception provided by place and rate of stimulation, and that we will characterize the dependence/independence of these cues. Primary concerns/obstacles are associated with the efficacy of the planned psychophysical training. The psychophysical training presently must be performed in the laboratory since we use computers and special hardware to provide specific stimulation patterns. Psychophysical training at home, rather than in the laboratory, would avoid practical issues associated with optimal training. Training at home would facilitate training durations that have generally been shown to be more effective, such as using shorter training blocks around 30 to 40 minutes a day. Short sessions are impractical for laboratory training since participants often have long commutes. We have developed web-based training software that participants can access at home, but we need to develop customized maps for participants that would allow for carefully controlled electrode psychophysics to be completed at home. For example, for Advanced Bionics devices, participants would need to be able to enter a research program on their clinical devices that would be configured to having a single electrode configured for a processing strategy such as HiRes that provides temporal envelopes with high precision. Likewise, single-electrode configurations for Cochlear devices would be developed using FAST and PDT algorithms to allow single-electrode and dual-electrode psychophysics to be trained and evaluated remotely. Long-term plans for developing electrode psychophysics to be conducted at home will allow our research to flexibly respond to contingencies associated with optimal paradigms for perceptual learning including: optimized stimulus presentation, multisensory facilitation, and consistent reinforcement of training stimuli[43], which have individually contributed to increasing the speed[44], magnitude[44,45], and generality of learning[46,47].

AIM 2: DETERMINE IF DYNAMIC-RATE STIMULATION IMPROVES PITCH PERCEPTION AND PHYSIOLOGICAL ENCODING OF PERIODICITY

2.1 Background & Rationale

Most cochlear implants use amplitude modulation of constant stimulation rates, an exception being Fine Spectral Processing for MED-EL devices, which uses a restricted form of dynamic rates on the most apical electrode(s). In terms of stimulation control, dynamic-rate stimulation is temporally more precise than amplitude modulation, yet few studies have examined differences produced by these two stimulation paradigms. Baumann and Nobbe[48] found that dynamic rates provide better pitch resolution than provided by amplitude modulation, with larger effects observed above 200 Hz. Vandali and van Hoesel[49] found an advantage of dynamic rates for pitch ranking at 275 Hz. In contrast, Kong and colleagues[50] did not find differences between the two for pitch ranking. Our preliminary results, summarized within the research design, indicate that dynamic rates provide better pitch discrimination and that the resulting sense of pitch is more robust to interference.

While only a few studies have compared amplitude-modulated and dynamic-rate stimulation, other studies have examined general effects of modulation depth and waveshape in both acoustic and electric hearing. Bernstein and Trahiotis showed that temporally compact waveshapes provide better interaural timing sensitivity[51–59]. In 2002[57], they showed benefits of transposed envelopes compared to sinusoidally amplitude-modulated (SAM) envelopes; in 2009[60], they showed increased spatial hearing resolution driven by sharper temporal envelopes along a continuum of waveshapes. Several studies have extended this work to bilateral cochlear implants and have shown that interaural timing sensitivity generally improves with sharper temporal envelopes. Comparable studies have considered the effect of waveshape on pitch by considering the extent that pitch can be evoked by unresolved harmonics. Kaernbach and Bering, 2001[61], showed that discrimination thresholds for unresolved harmonics can be as low as 1.2% when represented using multiple harmonics, which would provide better temporal precision in the decoded neural envelope. A few studies have considered the effect of modulation waveshape on cochlear implant pitch perception. Kreft and colleagues, 2015[62], found that SAM and transposed envelopes provide similar pitch discriminability, but several other studies have shown that more aggressive envelope sharpening improves pitch sensitivity[49,63–65]. In summary, there is strong evidence that temporal envelope sharpening improves pitch and spatial hearing for normal-hearing listeners when provided unresolved harmonics and for cochlear implant users when listening to amplitude modulation. Dynamic-rate stimulation is in many ways an extreme form of envelope sharpening in which envelope periodicity is replaced by singular pulses representing the pitch period. Consequently, if any advantage can be derived from sharper temporal representation, we expect it to be most pronounced when using dynamic rates.

Physiologically, there is clear evidence that sharper temporal envelopes evoke a more compact response from the auditory nerve. Dreyer and Delgutte[66] showed that phase locking of the auditory nerve is better for transposed compared to SAM tones, and that phase locking is better for pure tones than either form of amplitude modulation. Further, Jeng *et al.*, 2009[67], characterized auditory-nerve response to amplitude-modulated electrical pulse trains in guinea pigs and found that modulations can be distorted when presented at low presentation levels. These results indicate that temporal coding in the auditory nerve is generally more precise with increasing sharpness of the acoustic/electric envelope. Phase locking is more precise for pure tones in acoustic stimulation than for modulated tones, even when using transposed stimuli[66], which is consistent with psychophysical results indicating that resolution of pitch and spatial hearing is best for low frequency tones but can be transmitted by modulation of high frequency tones. In summary, psychophysical and physiological studies have shown that temporal pitch perception tends to be better when conveyed by temporally compact or sharpened waveforms. Acoustically, performance is better for low frequency tones compared to modulated high frequency tones; electrically, we hypothesize better performance for dynamic rates compared to modulation of constant rates.

There is strong evidence that cochlear implant stimulation excites a highly synchronous response in the auditory nerve. Studies of normal and impaired hearing suggest that temporal periodicity is a fundamental pitch cue. Normal-hearing listeners can discriminate tones based on period differences as small as 1.2% when provided temporal cues associated with unresolved harmonics. The primary goal of Aim 2 is to determine the extent that dynamic-rate stimulation can be used to engage this temporal periodicity mechanism to provide implant users with better pitch perception on par with normal-hearing performance when restricted to unresolved harmonics. We hypothesize that dynamic-rate stimulation provides better resolution and more tolerance to interference than provided by modulation of constant-rate stimulation. Aim 2 is designed to test this hypothesis and to characterize the limits of temporal processing in the auditory system.

2.2 Research Design

Aim 2 is designed to examine differences between amplitude-modulated and dynamic-rate stimulation. The study protocol compares pitch salience and tolerance provided by sinusoidal amplitude-modulated (SAM) stimulation with that provided by dynamic-rate stimulation. The study protocol examines salience and tolerance of pitch in the context of perceptual learning. Since conventional devices do not typically use dynamic rates, participants may require experience to learn to use the more precise representation of periodicity provided by dynamic-rate stimulation. The salience and tolerance of pitch provided by SAM and dynamic-rate stimulation will be examined across training periods that provide participants with experience with temporal periodicity. A crossover design will be used for Aim 2 with psychophysical and physiological measures designed to probe modulation and rate-based encoding of periodicity. Participants will be randomly assigned to train first either on SAM or on dynamic-rate stimulation and will subsequently crossover to train on the other method of stimulation. Training periods, as for Aim 1, will be 4 weeks in duration with on average 4, 2-hour, training sessions provided each week. Assessment measures will be conducted at baseline, midpoint, and endpoint. This research is designed to determine if dynamic-rate stimulation provides better pitch perception for cochlear implant users and to test the extent that pitch sensitivity can be progressively refined through experience.

2.2.1 Participants

This study will be completed by 24 adult cochlear implant users. Subjects will be recruited from the Aim 1 cohort as well as outside of that cohort. Prior experience with psychophysical measures conducted both in our lab and outside studies will be considered in data analysis. Subjects will include AB, Cochlear, MEDEL, and single-electrode device users. The single-electrode device users are a special population in that they receive information purely through temporal cues, though some might argue a small spatial effect can be controlled using single-electrode stimulation, but that effect if any would be small. Cochlear implant users who have substantial residual hearing in the non-implanted ear are also a special population as they allow for pitch-matching comparisons to be made with the residual acoustic hearing.

2.2.2 Psychophysics

Our primary hypotheses are that dynamic-rate stimulation provides a sense of pitch that is better resolved and more tolerant to interference than SAM stimulation. These hypotheses are connected to the Aim 1 hypothesis concerning the plasticity of pitch provided by dynamic-rate stimulation. If dynamic-rate stimulation provides a better sense of pitch, then it is likely that the degraded representation provided by amplitude modulated stimulation will result in physiological deterioration. Consequently, we are not only interested in differences between amplitude modulated and dynamic-rate stimulation in naïve subjects, but also in the differences that emerge with dedicated psychophysical training.

a) _Computer-controlled electrode psychophysics_. As for Aim 1, computer-controlled psychophysics will be used to characterize basic sensitivities to electrical stimulation. These measures by-pass clinical sound processing and the associated limitations related to discarding temporal fine structure and reduced modulation encoding. A battery of measures has been collected to probe pitch sensitivity and tolerance to interference for amplitude modulated and dynamic-rate stimulation:

1) Beat-frequency distortion. This measure tests sensitivity to beat-frequency distortions that occur with amplitude modulation of pulsatile stimulation. The standard stimulus is a SAM pulse train with the carrier rate an integer multiple of the f_0 (no beating). The target stimulus is identically defined except having a small (~10 Hz) shift in the carrier rate. For low harmonic multiples (equivalently, pulses per period), the shift in carrier rate produces audible beating. For rates approaching 8 to 10 pulses per pitch period, this beating becomes weak and eventually inaudible. Figure 3 shows preliminary results from 8 subjects (10 ears). The carrier rate needed to avoid artifactual beating between carrier and envelope is plotted as a function of modulation frequency. Results indicate that higher carrier rates are needed to encode higher modulation frequencies to avoid

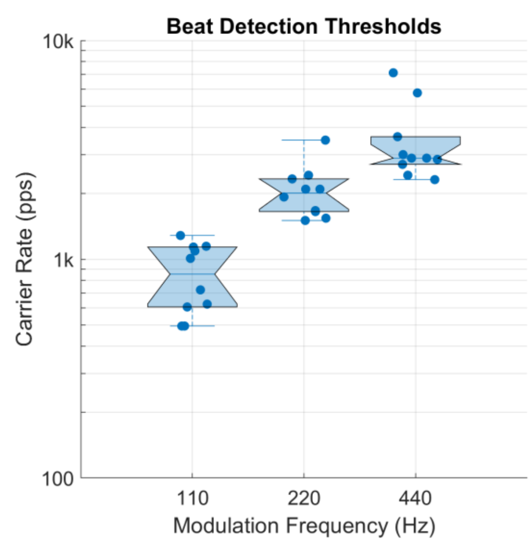

Figure 3: Cochlear implant users require higher rate pulsatile carriers to convey higher modulation frequencies to avoid beat-frequency distortions.

distortion. Two subjects were particularly sensitive to beat-frequency distortions for f_0s near 440 Hz and required carrier rates above 5 kHz to avoid distortions. Consequently, subsequent psychophysical measures of modulation sensitivity will use carrier rates of 6400 Hz when possible (N22 users use 4 kHz carrier rates).

2) Pitch discrimination. This measure is designed to test differences in pitch discrimination provided by SAM and dynamic-rate stimulation. The standard stimulus is either a SAM or dynamic-rate pulse train and the target stimulus is identically defined as the corresponding standard but having an adaptively higher modulation frequency or carrier rate. Protocol conditions include f_0s of 110, 220, 440, and 880 Hz with dual-electrode stimulation of apical and basal locations for a total of 8 conditions that will be repeated 3 times within an hour. Stimuli will be 400 ms in duration and presented at comfortable listening levels controlled as a function of stimulation rate[16]. Figure 4 shows preliminary results from 7 subjects (11 ears). Pitch discrimination was better for dynamic-rate compared to SAM stimulation ($F_{1,138}$ = 13.15, p < 0.01). The difference between discrimination thresholds provided by dynamic-rate and SAM stimulation was large (d_{Cohens} = 2.2) when measured for f_0s near 220 Hz and medium (d_{Cohens} = 0.7) when measured near 440 Hz. It is exciting to compare these results with the results reported in Goldsworthy and Shannon, 2014[16]. The shaded yellow region of Figure 4 indicates average rate discrimination thresholds achieved after 32 hours of training. Even though dynamic rates provide better discrimination than SAM stimulation, these benefits could be further improved with training. By considering perceptual learning of temporal pitch provided by these two stimulation methods, we will determine the extent that pitch sensitivity is limited by the stimulating waveform as opposed to an underlying physiological limitation.

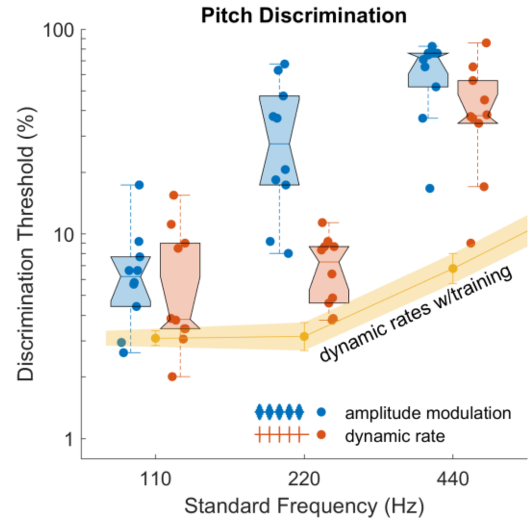

Figure 4: Pitch discrimination thresholds are better for dynamic-rate compared to SAM stimulation; the difference is significant and most pronounced for rates near 220 Hz where modulation encoding diminishes.

3) Tolerance to interference. Tolerance to interference will be measured for SAM and dynamic-rate stimulation. Conditions will include f_0s of 220 Hz with single-electrode stimulation of apical and basal electrodes with interfering electrodes 0, 2, or 4 electrodes away, as well as a condition without interference. Tolerance will be measured as the lowest target-to-interference level at which subjects can discriminate stimuli that differ by an octave in f_0. The 8 conditions (f_0 = 220 Hz, apex and base, and 4 interference conditions) will be repeated 3 times within an hour. Figure 5 shows preliminary results from 5 subjects (8 ears). As for pitch discrimination in quiet, the target sound was defined identically as the standard, but having a higher modulation frequency/stimulation rate. For this tolerance measure, the rate difference is held constant at 1 octave, but the relative target level is adaptively controlled. Notably, for dynamic rates, subjects achieved average discrimination thresholds for which the interference was louder than the target. Analysis of variance and post-hoc multiple comparisons indicated that the relative target level was significantly lower for dynamic-rate stimulation compared to SAM stimulation both as a main effect and for each masker separation (p < 0.01 for all comparisons).

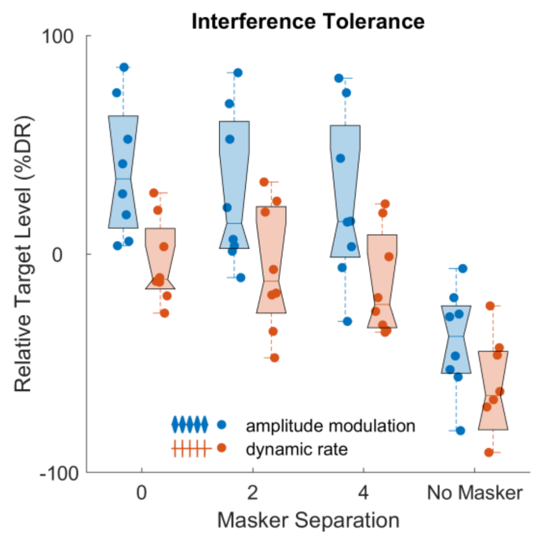

Figure 5: Pitch ranking using dynamic-rate stimulation is more tolerant to interference.

4) Pitch discrimination with interference. Pitch discrimination will be measured for the same conditions as the tolerance measure but f_0 discrimination thresholds will be measured at a set relative target level. Similar measures have been reported in the literature for SAM pulse trains tested at a relative target levels of 0 (i.e., target and interference at the same level). Kreft *et al.*, 2013[68], found that subject's struggled to perform the task at relative target level with SAM stimulation. Our method for first measuring tolerance across conditions allows us to adjust relative target levels to avoid floor effects encountered by Kreft *et al.*, 2013[68]. Figure 6 shows preliminary results from 5 subjects (8 ears) for discrimination thresholds measured with interference.

On average, discrimination thresholds were better with dynamic-rate compared to SAM stimulation ($p < 0.001$). Multiple comparisons for each masker separation condition indicates that thresholds were significantly lower for dynamic-rate stimulation for every condition tested ($p < 0.05$). For comparison, results are plotted with the average thresholds measured after training for the 220 Hz condition from Goldsworthy and Shannon, 2014[16]. Comparison with the previous data indicates that the trained thresholds are better, a pertinent remaining question is to what extent training can not only enhance discrimination thresholds, but also tolerance to interference.

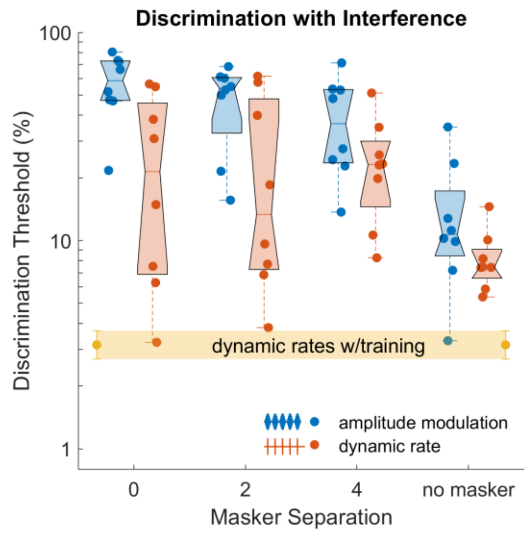

Figure 6: Pitch discrimination is better for dynamic-rate stimulation compared to amplitude modulated stimulation when tested in the presence of electrical interference.

5) Synthetic vowel pitch discrimination in quiet. Pitch discrimination of synthetic vowels will be measured using carefully controlled multi-electrode complexes. A synthetic vowel will be characterized by a f_0 and 3 formant frequencies. The formant frequencies will be mapped to electrode position using each subject's clinical frequency allocation. For both SAM and dynamic-rate stimulation, the formant frequency would be used to control an electrode dyad comprised of stimulation of adjacent electrodes. For example, if a specific formant frequency corresponded to a virtual electrode location of 4.2, then electrodes 4 and 5 would comprise the dyad with the ratio of stimulation levels controlled by the relative location of the virtual electrode. Note, that only for AB devices is such stimulation simultaneous, with other devices the stimulation across electrodes will be done with as small as delay as possible, typically less than 100 µs. For stimulation of 3 formants, stimuli would typically be represented with activity presented across 6 electrodes. Standard stimulation is presented with a nominal f_0 and target stimulation is identically defined in terms of place-of-excitation but having an adaptively higher f_0. Figure 7 shows preliminary results from 4 subjects (5 ears). Average discrimination thresholds were lower for dynamic-rate compared to SAM stimulation ($p < 0.001$). With 4 subjects tested, multiple comparisons of dynamic-rate versus SAM stimulation for each condition do not significantly differ. These preliminary results indicate that the better pitch salience provided by dynamic-rate stimulation seems to be maintained for multi-electrode stimulation in a manner that mimics vowel excitation.

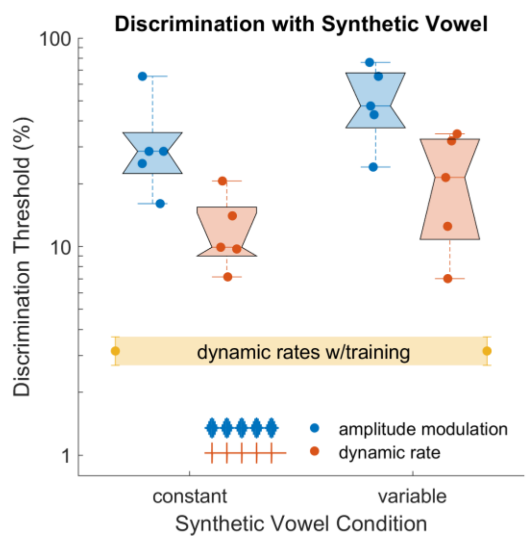

Figure 7: Pitch discrimination is better for dynamic-rate stimulation compared to amplitude modulated stimulation when tested using multi-electrode synthetic vowels.

b) <u>Through-the-processor psychophysics</u>. Through-the-processor psychophysics will be used to test the extent that clinical devices make use of underlying psychophysical cues. These methods generally use SAM tones or high-pass filtered pulse trains as way of producing acoustic analogs of electrode psychophysics.

1) Modulation detection thresholds. This measure probes sensitivity to amplitude modulations. The standard stimulus is a 400-ms pure tone and the target is identically defined but is a SAM tone. Adaptive procedures are used to measure modulation detection threshold corresponding to the minimum modulation depth that can be detected with 75% accuracy. Modulation frequencies of 10, 110, 220, and 440 Hz will be tested for carrier frequencies of 500 and 2000 Hz.

2) Pitch discrimination. This measure is an acoustic analog of the pitch discrimination task outlined for electrode psychophysics and probes sensitivity to temporal pitch. The standard stimulus is a 400-ms bandpass-filtered harmonic complex and the target is identically defined except having an adaptively higher f_0. Conditions will include modulation frequencies of 110, 220, and 440 Hz for bandpass center frequencies of 500 and 2000 Hz. Stimuli will be presented in pink background noise to reduce the likelihood that participants attend to place-of-excitation cues for performing the task.

3) Pitch discrimination with interference. This measure is an acoustic analog of the electrode psychophysical task and probes tolerance to interference. The standard and target stimuli are as defined for pitch discrimination but having an additional harmonic complex with independently controlled f_0 and filter center frequency. Conditions will include the same conditions as for the pitch discrimination task but for combinations of interfering tones.

4) *Melodic contour identification*. This measure does not have an electrode psychophysical analog, but more generally probes how well pitch cues are available for performing a melodic contour identification task. This measure will allow us to test whether focused psychophysical training on periodicity cues transfers to this more complex representation of melody.

5) Phoneme identification in quiet and competing speech. Consonant and vowel identification will be measured in quiet and in competing speech as background noise. The consonant database consists of 20 vowels spoken by five male and five female talkers in /a/–C–/a/ context[6,69]. The vowel database consists of 12 vowels spoken by five male and five female talkers in a /h/-V-/d/ context[6,70]. Listeners will respond using a computer interface with alternatives for the appropriately labeled phonemes. For the measures in noise, the signal-to-noise ratio will be adaptively controlled to converge to 50% recognition accuracy.

2.2.3 Electrophysiology

As for Aim 1, we will measure eCAPs and eACCs to characterize individual differences and the effects of training but with emphasis on modulation encoding. eCAPs will be measured to characterize modulation encoding in the auditory nerve as functions of modulation depth and stimulation level. eACCs will be measured to characterize changes in cortical response evoked by changes in modulation frequency and by rate of stimulation. As for Aim 1, These measures will be used to consider individual differences, to examine neural plasticity, to refine models of cochlear implant perception, and encourage the development of new hypotheses.

a) *eCAPs*. Aim 2 centers on understanding psychophysical and physiological differences between amplitude modulated and dynamic-rate stimulation. eCAPs will be measured using modulated and unmodulated stimuli and will be analyzed in terms of periodicity encoding. Stimuli will be as described by Tejani *et al.*[71] for SAM stimuli and first-order analysis based on the modulation response amplitude. Temporal responsiveness and synchronicity will be further characterized based on the composite response to individual pulses of a pulse train as described in He *et al.*, 2016[23], for a 400 ms pulse train. Temporal responsiveness will be characterized by refractoriness and recovery, neural adaptation and adaptation recovery. Temporal synchrony will be characterized by the autocorrelation and power spectral density of composite eCAP responses across pulse presentations. These measures will be used to determine if any of the perceived differences in pitch salience and tolerance can be predicted by observed differences in periodicity encoding of the eCAPs.

b) *eACCs*. eACCs will be measured for changes in modulation frequency for amplitude modulated stimulation and for changes in stimulation rate for dynamic-rate stimulation. In control conditions, the modulation/dynamic rate remains constant throughout an 800 ms recording interval. In experimental conditions, the eACC will be elicited by introducing a change in the modulation/dynamic rate 400 ms after the onset of the pulse train. Probed conditions will be based on measured psychophysical thresholds but will typically span an octave with narrower spacings as needed. eACCs will be measured for psychophysically derived spacings for sinusoidally amplitude modulated stimulation will be examined as a function of modulation depth and presentation level. eACCs will be measured for dynamic-rate stimulation as a function of level. For both stimulation methods, eACCs will be measured near modulation frequency or stimulation rates of 110, 220, 440, and 880 Hz.

2.2.4 Data Analysis Plan

Of primary interest is characterizing differences between pitch salience and tolerance provided by amplitude modulation of constant-rate stimulation and by dynamic-rate stimulation. Analysis of the preliminary data guides expectations. Considering preliminary data shown in Figure 4, the associated effect sizes comparing the better pitch discrimination thresholds provided by dynamic-rate stimulation to that provided by amplitude modulation are: d_{Cohens} = 0.20, 1.8, and 0.71, for the 110, 220, and 440 Hz conditions, respectively. With 11 ears tested, these effects were significant at the 0.05 level for the comparisons at 220 and 440 Hz. Power analysis of this design with 24 subjects and a 0.05 significance criterion indicates a 95% likelihood of detection effects as small as 0.19, which would provide needed power to detect effects at 110 Hz and for training improvements of 10% or greater. This level of resolution will be useful when testing secondary hypotheses associated with the interference tolerance and plasticity when comparing amplitude modulation and dynamic-rate stimulation.

3 Study Team and Timeline

The proposed work brings together researchers with multiple lines of independent research into a cohesive team to examine the plasticity of pitch in cochlear implant users. As the PI, my own research has focused on cochlear implant pitch perception, the effects of experience through psychophysical training, and relationships between pitch perception and speech recognition[6,31,42,72,73]. Co-investigator Dr. Eisenberg leads research on childhood development after cochlear implantation and her team at USC has developed a hierarchy of speech recognition measures and they have published on the responsiveness of this hierarchy for tracking emergent skills after cochlear implantation[72,74–82]. Co-investigator Dr. He leads multiple projects to characterize neural encoding of auditory perception in pediatric and adult cochlear implant users. Dr. He has expertise in how the temporal response properties of the auditory-nerve response and ascending pathway affect cochlear implant outcomes[23,24,83–86]. Co-investigator Dr. Carney leads research that bridges physiology and psychophysics through computational modeling of the auditory system. Dr. Carney's expertise in neural modeling of the auditory nerve and ascending brainstem will guide analyses of the proposed research and will inform the development of new hypotheses based on predicted neural response. Together, the project team includes a broad range of expertise overlapping the disciplines of psychophysics, physiology, and neural modeling.

The proposed aims will run concurrently. The psychophysical procedures described for both aims have been piloted and the preliminary results indicate large effect sizes for psychophysical training and for the comparison of amplitude modulated and dynamic-rate stimulation. During the first six months of the project period, we will focus on setting up the proposed electrophysiological measures at USC. Drs. Goldsworthy, Eisenberg, and Loeb will meet twice a month with Drs. He and Carney joining remotely to discuss amendments to procedures such as details of stimulus design and recording analysis. During this period, Drs. He and Carney will visit USC to help establish the electrophysiological procedures and neural modeling. The goal of neural modeling during the first 6 months will be to provide a common framework for comparing the auditory nerve and ascending circuitry model developed by Dr. Carney with the auditory-nerve response model developed by Dr. Frijns. At the end of the initial six-month period, the psychophysical and electrophysiological procedures will be finalized, and subjects will be recruited through emails, newsletters, and direct patient contact (as IRB approved). Results will be analyzed as acquired and active enrollment is expected through the second year of the project period, at which time emphasis will be given to retainment and consolidation as opposed to new enrollment.

The proposed research for Aim 2 will also be further piloted during the first six months of the project. All psychophysical training and assessment measures (or close analogs) have been used in our previous work[6,72]. During piloting, we will enroll participants and evaluate initial results to consider modifications to the protocol. A focal point that we intent to examine more thoroughly before commencing the crossover design is the effect of stimulation level and modulation depth on the salience of amplitude modulated stimulation. Once piloting is complete, participants will be enrolled on a rolling basis throughout the project period. Once the core protocols described in this proposal are underway, key variations will be considered as new experiments. For example, new experiments investigating the salience of pitch as conveyed by different modulation waveshapes, and new experiments on the salience of auditory-tactile and auditory-visual integration. These experimental variations will be started once the primary experimental line has consolidated.

Across each aim, electrophysiology will be used to examine cortical activation in response to key auditory contrasts relevant to the respective aims. The combined use of EEG and eCAP methodologies is a new direction for my lab and we have assembled a strong team to facilitate integration of these methods into our research program. During this first six months, we will arrange for multiple site visits with Dr. He to work closely with the USC team to set up a new EEG system. By the middle to end of the first year, we expect to transition into formal testing of activation contrasts associated with the aural contrasts outlined in this proposal. Electrophysiology would then run concurrently with the psychometrics and would be used as part of the longitudinal characterization of the plasticity of pitch perception.

A potential obstacle that could arise in this research is that it may difficult to obtain high completion rates because of the substantial amount of laboratory training and assessment that is required. The proposed research has built-in contingencies at a core level. We will work closely with implant manufacturers to develop methods for providing psychophysical training for electrode contrasts at home. The project team is balanced and flexible enough to modify our approach as needed to achieve the goal of characterizing the psychophysical potential of periodicity encoding in a rigorous and informative manner. The proposed research will thus contribute to scientific understanding of how perceptual learning affects brain and cognitive development, and will clarify the potential of temporal fine structure for improving music and speech perception for cochlear implant users.

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