Research Article

Assessing the Electrode-Neuron Interface with the Electrically Evoked Compound Action Potential, Electrode Position, and Behavioral Thresholds

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ABSTRACT

Variability in speech perception scores among cochlear implant listeners may largely reflect the variable efficacy of implant electrodes to convey stimulus information to the auditory nerve. In the present study, three metrics were applied to assess the quality of the electrode-neuron interface of individual cochlear implant channels: the electrically evoked compound action potential (ECAP), the estimation of electrode position using computerized tomography (CT), and behavioral thresholds using focused stimulation. The primary motivation of this approach is to evaluate the ECAP as a site-specific measure of the electrode-neuron interface in the context of two peripheral factors that likely contribute to degraded perception: large electrode-to-modiolus distance and reduced neural density. Ten unilaterally implanted adults with Advanced Bionics HiRes90k devices participated. ECAPs were elicited with monopolar stimulation within a forward-masking paradigm to construct channel interaction functions (CIF), behavioral thresholds were obtained with quadrupolar (sQP) stimulation, and data from imaging provided estimates of electrode-to-modiolus distance and scalar location (scala tympani (ST), intermediate, or scala vestibuli (SV)) for each electrode. The width of the ECAP CIF was positively correlated with electrode-to-modiolus distance; both of these measures were also

influenced by scalar position. The ECAP peak amplitude was negatively correlated with behavioral thresholds. Moreover, subjects with low behavioral thresholds and large ECAP amplitudes, averaged across electrodes, tended to have higher speech perception scores. These results suggest a potential clinical role for the ECAP in the objective assessment of individual cochlear implant channels, with the potential to improve speech perception outcomes.

Keywords: electrically evoked compound action potential, cochlear implants, electrode configuration, imaging, psychophysics

INTRODUCTION

Multichannel cochlear implants (CIs) are successful neural prostheses that provide auditory input, allowing individuals with severe-to-profound hearing loss to perceive complex stimuli such as speech. However, perceptual abilities are highly variable across listeners, in both quiet and noisy listening environments (e.g., Holden et al. 2013; Won et al. 2007). This variability is likely influenced by the degree of auditory nerve degeneration inherent to this population (e.g., Pfingst et al. 2011), but other factors are involved as well. Evaluating the underlying sources of perceptual variability may provide valuable information for clinicians to individualize device programming, help set realistic expectations, and perhaps facilitate auditory training, ultimately leading

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to improved performance outcomes and quality of life for individuals with CIs.

One potential source of variability in CI perception is the electrode-neuron interface, which refers to a number of peripheral factors that can influence activation of the auditory nerve, including electrode placement, bone and tissue growth, and the integrity of the auditory neurons (Bierer 2010; Long et al., 2014). Computational modeling studies have demonstrated that current level requirements are higher and spread of excitation is broader for electrodes distant from the neurons or near a region of neural degeneration (Goldwyn et al. 2010; Kalkman et al., 2015). Broader activation can cause increased channel interaction (i.e., overlapping excitation patterns of two nearby channels), which can distort spectral information and lead to decreased pitch and speech perception (Abbas et al. 2004; Boëx 2003; Crew et al. 2012; Hughes 2008; Jones et al. 2013; Pfingst et al. 2004; Snel-Bongers et al. 2012).

Some insight into the electrode-neuron interface can be obtained via postoperative computerized tomography (CT) imaging, which provides information about electrode placement, such as electrode-modiolus distance, scalar location, insertion depth, and wrapping factor (Holden et al. 2013; Skinner et al. 2007; Teymouri et al. 2011; Verbist et al. 2005). A portion of the variability in speech scores can be explained by electrode insertion depth and scalar location (Finley et al. 2008; Holden et al. 2013; Skinner et al. 2007), with deeper insertion and a greater number of electrodes in the SV correlated with poorer speech perception. Recently, CT data has been used to modify device programming by deactivating electrodes likely to show high levels of channel interaction (Noble et al. 2013). In that study, the programming changes led to improved outcomes on sentence recognition both in quiet and noise, and improved subjective communication. However, CT imaging is costly, exposes patients to radiation, and does not provide information about the integrity of the auditory neurons.

Additional information about the electrode-neuron interface can be obtained via behavioral and electrophysiological measures, which are nonradiologic and more cost-efficient than CT imaging, and sensitive to both electrode position and neural integrity. For example, electrode-to-modiolus distance has been found to explain a portion of the variability in behavioral thresholds obtained with focused stimulation, and the remaining variability is presumed to reflect differences in neural health along the cochlear duct (Long et al. 2014). Other studies have shown that behavioral thresholds, widths of psychophysical tuning curves, and growth of loudness co-vary across the electrode array (Bierer 2007; Bierer 2010; Bierer et al.

2011; Bierer and Faulkner 2010; Cohen 2003; Hughes and Stille 2008; Landsberger et al. 2012; Litvak et al. 2007; Miller et al. 2008; Nelson et al. 2008; Bierer and Nye 2014, Pfingst and Xu 2004), consistent with localized variability in the electrode-neuron interface. Historically, behavioral measures are time-consuming and difficult to obtain, especially in pediatric listeners, although a faster threshold method has recently been validated in adults (Bierer et al. 2015). Alternatively, the electrically evoked auditory brainstem response (EABR) has been used to measure the efficacy of individual CI channels, with EABR wave V thresholds positively correlated with focused behavioral thresholds (Bierer et al. 2011). Although the EABR is an objective measure and an option for difficult-to-test individuals, this measurement requires the placement of scalp electrodes, a sedentary subject, and a lengthy recording period (Miller et al. 2008), conditions that may not be easily met in some clinics or with some patients. Further, EABR measurements are not always possible in humans due to temporal overlap with stimulus artifact (Hall 1990).

An alternative electrophysiological measurement is the electrically evoked compound action potential (ECAP) (Brown et al. 1990). In modern cochlear implant systems, the ECAP is recorded using a two-way telemetry system. Given the existing clinical tools to access the on-board telemetry, the ECAP is relatively easy and fast to measure, making it an appealing alternative to the more time-consuming EABR (Abbas et al. 1999; Briaire and Frijns 2005; Dillier et al. 2002; Mens 2007). As such, the ECAP has been extensively evaluated as a tool to aid clinicians with setting stimulation levels for CI processors in difficult-to-test patients (e.g., see Hughes (2013) for review).

Because the ECAP is generated by excitation of the primary auditory afferents, certain characteristics of the ECAP waveform might be a good indicator of the quality of the electrode-neuron interface across channels. Animal studies, for example, have shown that the peak amplitude of Wave I of the EABR is positively correlated with the number of surviving spiral ganglion neurons following an extended period of deafness (Smith and Simmons 1983; Hall 1990). A similar correlation has been observed with shallow slopes of the EABR wave I amplitude growth function (Miller et al. 1994). In addition, a reduced density of surviving neurons has been shown to decrease the sensitivity of ECAP and EABR amplitudes to changes in pulse duration or interphase gap (Prado-Guitierrez et al. 2006). Ramekers et al. (2014) found that the maximum ECAP amplitude and slope were positively correlated with neural density in deafened guinea pigs; interestingly, the slope and latency of the response were dependent on variations in the interphase gap, though dependency did not extend to

pulse duration. Finally, the slope of ECAP amplitude growth functions has been positively correlated with speech performance in human listeners, though the strength of this correlation is sensitive to device type and relatively weak overall (Kim et al. 2010). It is not clear from these studies, however, if ECAP amplitude is sensitive to localized changes in neural health, and data from human listeners is limited. The available data show that ECAP peak amplitude is variable across electrodes and CI listeners, but the source of that variability is not currently well understood.

The ECAP has also been evaluated as a tool to characterize the spatial extent of peripheral excitation, by evaluating channel interaction across electrodes, using a forward-masking paradigm (e.g., Abbas et al. 2004). Like ECAP amplitudes, the shapes of the resulting channel interaction functions (CIFs) are quite variable from channel-to-channel (e.g., Scheperle and Abbas, 2015). CIFs have been shown to strongly correlate with psychophysical tuning curves and forward masking pattern widths (Cohen et al. 2003; Abbas et al. 2004; Hughes and Stille 2008, 2010), suggesting that those two metrics reflect similar underlying processes. Previous studies have not, however, demonstrated a correlation between broad CIFs and poor speech perception scores, but channel interaction has only been characterized for a subset of electrodes (e.g., Cohen et al. 2003; Hughes and Abbas 2006a; Hughes and Stille 2008). By measuring all available electrode CIFs in the present study, the spatial extent of excitation can be more thoroughly evaluated.

The main purpose of this study is to examine whether it is possible to differentiate between electrode position and neural status using an electrophysiological tool. Although a behavioral or electrophysiological measure that is sensitive to both factors might be useful, the clinical strategies to manage a poor electrode-neuron interface may prove to be very different depending on the underlying cause of the deficit. Moreover, site-specific identification of electrode position as the primary contributor to a poor electrode-neuron interface may allow for inference about the role of neural status at a given site. Additional analyses explore the relationships between speech perception and the physical, behavioral, and electrophysiological factors in this study.

In the present study, ECAP measures are compared to focused behavioral thresholds and estimates of electrode position from CT images. The underlying rationale is that radial electrode position, scalar location, and neural status may collectively influence channel-by-channel ECAP measures. The specific hypotheses are the following: (1) Electrodes with higher sQP thresholds will be associated with smaller ECAP amplitudes and broader ECAP CIFs, and (2) electrodes with a more lateral placement and/or

translocated in scalar location will be associated with smaller ECAP amplitudes and broader ECAP CIFs. Comparisons among sQP thresholds, electrode-modiolus distance, monopolar ECAP measurements, the number of electrodes located in the SV, angular insertion depth, and speech perception are also made. Though the use of monopolar ECAPs (a methodological constraint, see “Methods”) and focused stimulation may present limitations in data interpretation, studies have shown variability in CIFs across electrodes and stimulus levels using monopolar ECAPs (e.g., Cohen et al. 2004; Abbas et al. 2004). Similarly, within-subject differences in the sharpness of psychophysical tuning curves have been observed with monopolar stimulation (e.g., Bierer and Faulkner 2010; Nelson et al. 2008). Based on previous work, it is hypothesized that electrode position and sQP thresholds will be correlated with speech perception scores (Finley et al. 2008; Long et al. 2014). Further, by examining ECAP amplitudes and channel-interactions across the entire electrode array, as opposed to previous studies that evaluated a subset of electrodes (e.g., Brown et al. 1990; Hughes and Abbas 2006a), a cross-subject correlation with speech scores is predicted.

Comparing results across different aspects of the electrode-neuron interface within the same individual will be informative with regard to (1) the viability of the ECAP as a site-specific measure of the effectiveness of electrical stimulation, (2) how the diverse measures may be interpreted, and (3) in the future, how they might be used clinically. Although one purpose of exploring ECAPs is to evaluate whether an objective measure can be used as a substitute for a behavioral measure, it may be that each measure provides different information about auditory function and that multiple measures should be combined within a test battery. More broadly, by examining the relationships between ECAP channel interaction and amplitude, focused behavioral thresholds, and CT-estimated electrode positions, this study will provide useful insight into the identification and assessment of poor electrode-neuron interfaces. The findings should help to advance efforts toward tailoring electrical stimulation for individual cochlear implant listeners and ultimately improve perception of complex acoustic stimuli.

METHODS

Subjects

Ten adult subjects were recruited from the University of Washington Communication Studies Participant Pool. Subjects were at least 21 years of age ($M=59.8$, $SD=\pm 13.9$) and unilaterally implanted after 2001 with

Advanced Bionics HiRes90k devices (see Table 1 for demographic information). There were seven males and three females in this study. Eight of the subjects were postlingually deafened and two were perilingually deafened (S40 and S44, profound hearing loss at 4 and 3 years of age, respectively). All subjects were native speakers of American English.

Each participant provided written consent, and the experiments were conducted in accordance with guidelines set by the Human Subjects Division of the University of Washington. Subjects participated in three or four sessions, each lasting for 3–4 h.

Electrical Stimulation

All stimuli were presented using the Bionic Ear Data Collection System version 1.18.315 (Advanced Bionics, Valencia, CA). For behavioral testing, a custom Matlab (Mathworks, Inc. Natick, MA) script controlled the BEDCS software. Two types of electrode configurations were used in this study: monopolar (MP) and steered quadrupolar (sQP). MP stimulation was used for ECAP measurement because the high current requirements to achieve most comfortable level (MCL) for very brief single-pulse stimulation are often unobtainable within the compliance limits of the device with focused stimulation. MP stimulation consists of an active intracochlear electrode and a return extracochlear electrode; the large distance between the source/sink yields a broad electrical field (Litvak et al. 2007). sQP stimulation was used in the present study as sQP thresholds were found to be equivalent to partial tripolar thresholds in another study, in which many of the same subjects participated ($r=.96$; for details, see Bierer et al. 2015). sQP stimulation consists of four intracochlear electrodes: The two middle electrodes serve as active electrodes, and the two outer electrodes serve as return electrodes for a fraction of the active current (an

extracochlear electrode carries the remainder of the return current). Current is steered between the two middle electrodes according to the fraction, α : a value of 1 steers current to the basal electrode and 0 to the apical electrode. By convention, channel number is defined as the basal active electrode when $\alpha=1$. In the present study, this convention was maintained for electrodes 3 to 15. For electrode 2, however, it was necessary to use the same set of electrodes as channel 3 (the most apical channel possible with the 4-electrode sQP configuration) in conjunction with an α value of 0 to center the current on electrode 2. This arrangement is referred to as “channel 2,” even though electrode 3 is the apical active electrode. For current focusing, the outer two electrodes in the sQP configuration receive a fraction of the return current according to σ (Bierer et al. 2015; Landsberger and Srinivasan 2009; Srinivasan et al. 2010). As with the commonly used partial tripolar configuration, higher σ results in a narrower electrical field than MP stimulation (Litvak et al. 2007). The value of σ used in the present study for sQP stimulation was 0.9 in order to retain highly focused stimulation while avoiding unreasonably high current limits and side-lobe activation.

Single-Channel Behavioral Thresholds

Stimuli were biphasic, cathodic-leading pulse trains (102 μ s/ph, 0- μ s interphase gap, 200.4-ms duration, 997.9 pulses per second) presented to electrodes 2 to 15 (apical to basal), using sQP stimulation. Behavioral thresholds were measured for each electrode using a two-interval, two-alternative forced choice procedure (two-down, one-up) that converges on the 70.7 % correct point on the psychometric function (Levitt 1971). Subjects were presented with two visual boxes on the computer screen (one of the boxes appeared at the same time as the sound) and asked “Which

TABLE 1

Demographic information

ID	Implanted ear	Age	Age at profound HL	Age at implantation	Etiology	Electrode array/spacing (mm)
S22	R	74	55	66	Genetic	HiFocus Helix/0.85
S29	L	84	47	77	Noise	HiFocus 1J/1.1
S38	L	50	17-18	46	Otosclerosis	HiFocus 1J/1.1
S40	L	52	3 (perilingual)	50	EVA	HiFocus 1J/1.1
S41	L	49	Birth (R), 42 (L)	43	Rubella	HiFocus 1J/1.1
S42	R	64	50	50	Unknown	HiFocus 1J Positioner/1.1
S43	R	68	50	67	Noise	Mid-Scala/0.85
S44	R	52	4 (perilingual)	51	Antibiotics	Mid-Scala/0.85
S46	R	67	14	66	Unknown	HiFocus 1J/1.1
S47	R	38	28	37	Unknown	Mid-Scala/0.85

Shows demographic information for all 10 subjects including implanted ear, age, age diagnosed with a profound hearing loss, age at implantation, etiology (if known), electrode array type, and electrode spacing

interval contained the sound?” Subjects indicated the interval in which they thought the sound occurred using the computer mouse and were provided with feedback. Each run continued for six reversals in current level, and the average of the last four levels was taken as threshold. For the first two reversals, the signal was adjusted by 2 dB; step size decreased to 0.5 dB for the remaining four reversals. For each electrode, four runs were collected and averaged. If the four thresholds had a standard deviation greater than 2 dB, a fifth run was collected; all five runs were then averaged. For S44, thresholds were only collected for electrodes 4–10 due to reports of non-auditory percepts on the other electrodes. These auditory percepts included a “tingling” sensation for basal electrodes and an “uncomfortable sound quality” for apical electrodes. This subject also had non-auditory percepts clinically, and electrode 11 was deactivated from her clinical map.

Electrically Evoked Compound Action Potential Measurements

ECAPs were obtained using a forward-masking, channel-interaction paradigm (Cohen et al. 2003; Abbas et al. 2004; Scheperle and Abbas 2015). Stimuli were biphasic, cathodic-leading pulses (32 μ s/phase, 0 μ s interphase gap) presented at a probe rate of 20 per second in the MP configuration. Stimulus level was determined behaviorally using the Advanced Bionics clinical loudness scale (Advanced Bionics, Valencia, CA) and was increased as subjects verbally identified each rating until they reached “8” (“Maximal Comfort”). The MCL was considered a rating of “7.” Loudness balancing was performed at MCL by presenting the stimulus across four electrodes sequentially to assess subjective equal loudness. Electrodes differing in loudness were adjusted accordingly, and the signal was presented again on the same four electrodes. This continued until all four were perceived as equally loud, then the next four (one overlapping with the previous set) were stimulated, and the procedure repeated for all available electrodes. Both masker and probe stimuli were fixed at the loudness-balanced MCL for ECAP testing. Over a sequence of ECAP recordings, all available electrodes served as a probe channel in combination with all available electrodes as masker channels.

For each measurement series, the probe stimulus was fixed and the location of the masker stimulus varied across the electrode array. The masker pulse preceded the probe pulse by 500 μ s. The recording electrode was positioned two electrodes apically relative to the probe, except when the masker and recording channel targeted the same electrode, in which case the recording electrode was moved basally

by two electrodes for those conditions. For recording, gain was set to 300 and the sampling rate at 56 kHz. “After stim” was selected as the start recording option in the BEDCS software. One hundred repetitions were obtained for each masker-probe pair and averaged. The neural response was derived by subtracting averaged recordings of the masker+probe, masker alone, and system signature (i.e., no stimulation) from a probe alone stimulus condition (Lai and Dillier 2000; Cohen et al. 2003; Abbas et al. 2004). For the duration of the measurements, subjects were required to sit near the computer but were otherwise allowed to read, talk, eat, or sleep.

After data collection using custom Matlab software, the experimenter visually examined each derived waveform and manually set markers at the location of the first negative peak (N1; occurring at approximately 240 μ s) and a later positive peak (P2; occurring at approximately 440 μ s), after onset of the probe. Peak-to-peak amplitudes smaller than 0.03 mV were considered too small to discern from the noise floor and were considered as “no response” (i.e., 0 mV). Peak-to-peak amplitudes were stored in Matlab for further analysis. For reasons mentioned above, ECAP measures were only collected for electrodes 4–10 for S44.

For each subject, CIFs were created for each probe electrode by plotting ECAP amplitude as a function of masker electrode distance from the most apical electrode, in millimeters, such that all data were plotted on the same x -axis (subjects were implanted with arrays with different electrode spacing; see Table 1). From these functions, peak amplitude and equivalent rectangular bandwidth (ERB) were calculated. Peak amplitude was quantified by selecting the maximum amplitude regardless of the masker electrode; therefore, in some cases, peak amplitude occurred when the masker and the probe were on different channels. However, this occurred for only 20 CIFs (out of 129 possible) and was typically masker-probe displacement of only one electrode. Additionally, these amplitudes differed by less than .001 mV compared to amplitudes when the masker and probe were on the same electrode. The ERB quantifies the spatial extent of masker-probe interaction by equating the CIF to a rectangular function of equivalent amplitude. It is calculated by dividing the area under the CIF (i.e., the sum of amplitudes across all masking electrodes) by the peak ECAP amplitude (i.e., a normalized area). Note that CIFs for probes near the end of the electrode array were not fully characterized on one side due to the lack of electrodes to use as maskers. Partial functions were defined as those for which the peak amplitude decreased to 0 mV on only one side of the function. Under the assumption that excitation patterns would

extend to neurons beyond the array, partial functions were completed by extrapolating the missing data points by mirroring the ECAP amplitudes from the measured data on the side with a full complement of masking electrodes. Although CIFs are often asymmetrical, we assumed that including the extrapolated data points would provide a better estimate of the spread of excitation than using partial functions.

CT Images

CT scans were performed at the University of Washington Medical Center. Briefly, ANALYZE software was used to create three-dimensional image volumes by combining information from each subject's postoperative scan and a single body donor cochlea (for details, see Skinner et al. 2007; for verification of the method, see Teymouri et al. 2011). Preoperative CT scans were not available for the subjects participating in the present study; therefore, a scan of the nonimplanted ear was used to identify structural anatomy, and this image was co-registered with the image of the implanted ear. Micro CT and orthogonal-plane fluorescence optical sectioning (OPFOS) images from a donor cochlea were used to locate and visualize the non-bony structures. The two primary metrics from the CT imaging data that were analyzed in this study were electrode-to-modiolus distance and scalar location (similar to metrics used in Long et al. 2014). Electrode-to-modiolus distance refers to the radial distance (mm) of an electrode from the medial wall of the cochlea. Scalar location denotes the positioning of an electrode in the fluid-filled cochlear compartments: ST, intermediate, and SV. Intermediate was used to denote those electrodes that could not be clearly determined to be in ST or SV. A third metric, angular insertion depth was also calculated from the CT imaging data for the purpose of comparing to previous studies (i.e., Finley et al. 2008; Holden et al. 2013). Angular insertion depth is derived using the sum of the length along the electrode trajectory and the distance along the electrode array from the cochleostomy (Holden et al. 2013).

Speech Testing

Speech perception testing was performed in a double-walled sound-treated booth (IAC RE-243 with an internal size of 7' by 7'). Stimuli were played through an external A/D device (SIIF USB SoundWave 7.1), amplified by a Crown D75 audio amplifier, and presented through a Bose 161 speaker, placed at 0° azimuth and 1 m from the subject's head. Custom software was used to present the stimuli (ListPlayer version 2.2.11.49; Advanced Bionics, Valencia, CA).

Speech stimuli consisted of recordings of one male and one female Pacific Northwest talker uttering 10 naturally spoken vowels in the /hVd/ context (heed, hid, hayed, head, had, hod, who'd, hood, hoed, and hud). Sixteen consonants in the /aCa/ context (aba, ada, afa, aga, aja, aka, ala, ama, ana, apa, asa, asha, ata, atha, ava, and aza) were also used. The speech tokens were calibrated using a B&K Type 2250 sound level meter and presented at 60 dB-A in the sound field. During each trial, subjects were presented visually with either the vowel or consonant closed sets on a computer screen and were instructed to choose which word they heard. Within a run, each token was presented three times, and the test was scored as percent correct. Subjects were given a practice run (not included in the final averaged score) and then two test runs. If the difference between the first and second test run was greater than 10 %, a third run was collected and all three runs were averaged. Results from vowel and consonant data were evaluated separately and found to be relatively similar across the variables of interest. Vowel identification was found to be significantly correlated with ECAP amplitude ($T_8=2.84$, $p=.02$) and sQP threshold ($T_8=-2.31$, $p=.05$), but not for electrode-to-modiolus distance ($T_8=-1.69$, $p=.13$) and ECAP ERB ($T_8=.42$, $p=.69$). Consonant identification was found to be significantly correlated with ECAP amplitude ($T_8=2.31$, $p=.05$), sQP threshold ($T_8=-3.20$, $p=.01$), and electrode-to-modiolus distance ($T_8=-2.48$, $p=.04$), but not for ECAP ERB ($T_8=.23$, $p=.83$). Scores from both vowel and consonant data were averaged to provide an overall estimate of performance across all speech sounds.

Statistical Analysis

SPSS statistical software was used to perform two multiple linear regression analyses for between-subject comparisons (IBM Corp. Released 2013. IBM SPSS Statistics for Windows). The first analysis included sQP threshold as the dependent variable, electrode-to-modiolus distance, ECAP peak amplitude and ERB as independent variables of interest, and MCL, and subject as adjustment variables. The second analysis included everything in the first except behavioral threshold with electrode-to-modiolus distance as the dependent variable. Two regression models were needed because fewer data points were available for threshold measures (only up to 14 electrode sites were evaluated) compared to all other outcome measures (up to 16 electrode sites).

Additional analyses were conducted to evaluate the effects of scalar location on all variables of interest. A priori, electrodes located in the intermediate position or in SV are expected to have larger electrode-to-

modiolus distances than electrodes in the ST. By design, certain array types may better facilitate insertion into the target scala (ST) (e.g., Aschendorff et al., 2007), though effect of array type is not explored here due to a small sample size. One-way ANOVAs were conducted for scalar location relative to electrode-to-modiolus distance, behavioral threshold, and ECAP measures. Adjustments using Welch's Test for unequal variances were made as appropriate and noted. Lastly, a simple linear regression analysis was conducted to evaluate mean speech performance with the variables of interest. A Bonferroni correction was applied to all multiple comparisons.

RESULTS

Electrode-to-Modiolus Distance Using CT Imaging

Figure 1 shows the variability in electrode array positioning observed in 3D cochlear reconstructions for all subjects, arranged by electrode array type. The green area represents the reconstructed cochlea, and the red circles located within represent the individual electrodes. The red/yellow horizontal and vertical axes represent the mid modiolar axis, which is used to assign scalar location and determine insertion depth. Across subjects, electrode-to-modiolus distances ranged from 0.18 to 2.3 mm ($M = .1.23$ mm, $SD = .53$; for individual data, see Table 2). In general, the electrode trajectories in Fig. 1 are consistent with the designs of the four types of arrays, which partially determine how far the electrodes are from the modiolus and thus how close they are to the closest auditory neurons. The IJ electrode array (S29, S38, S40, S41, and S46) has a lateral design, whereas the IJ Helix (S22) is precurved to achieve a more medial position. The IJ with positioner (S42) pushes the array even more medially. The Mid-Scala array (S43, S44, S47) is precurved and designed for mid-scalar placement in an effort to protect cochlear structures. However, due to a small sample size, differences between electrode array types cannot be examined further.

Focused Behavioral Thresholds and Electrode-to-Modiolus Distance

Figure 2A shows electrode-to-modiolus distance (left ordinate) and sQP threshold (right ordinate) profiles for each subject. Scalar information is indicated by symbol (see legend). sQP thresholds range from 28.8 to 55.7 dB rel. to 1 μ A ($M = 45.45$ dB rel. to 1 μ A, $SD = 6.54$) across subjects and electrodes (Table 2). Figure 2B illustrates the relationship between sQP threshold and electrode-to-modiolus distance, with

individual subject data distinguished by color. Consistent with previous studies (Long et al., 2014; Cohen et al., 2003), a strong association between sQP thresholds and electrode-to-modiolus distance was observed; results from the multiple linear regression analysis showed a significant, positive correlation between electrode-to-modiolus distance and sQP threshold ($T_{83} = 4.42$; $p < .001$). Increases in electrode-to-modiolus distance trended with increases in sQP thresholds, both across subjects and to a lesser extent, across electrodes within individual subjects, although a within-subject correlation was only observed for some subjects (S42, S43, S47; $p < .01$). For the majority of participants, a correlation was not observed (S22, S29, S38, S40, S41, S44, S46).

ECAP Channel Interaction Functions

ECAP amplitudes and the shapes of the CIFs were variable within and across subjects and electrode arrays. ECAP CIF profiles for all subjects are shown in Figure 3, organized by electrode array type (note the different scale on the y-axis for S29, S41, S22, and S42). It should also be noted that for S43, very few CIFs were obtained due to no response on electrodes 8–16. Neither ERBs nor peak amplitudes were calculated for these electrodes, and are considered missing data. For S44, no basal information was available due to non-auditory percepts, and these data are also considered missing. For electrodes with responses, the mean ECAP peak amplitude and ERB were calculated for each subject (Table 2; mean amplitudes also displayed in each panel of Fig. 3). Mean peak amplitudes ranged from .06 to .29 mV ($M = .15$ mV, $SD = .11$), and mean ERB values ranged from 2.55 to 9.20 mm ($M = 5.92$ mm, $SD = 2.86$).

Each CIF is expected to peak when the masker is presented at the probe site; however, in some cases, the peaks were offset from the probe location, as is the case for S29, S40, S46, S47, and S22. For example, for subject S29 (Fig. 3), the peak for probe electrode 1 is located at the peak for electrode 4; however, S29s CIFs are quite broad, and little “noise” would be required to dislocate the peak to an off-masker channel. For S22, the first four electrodes share a peak location; a masker presented to electrode 2 was the most effective for all of these probe sites. For some electrodes, the CIF appears to have a secondary peak (e.g., S41, probe electrode 1). For apical probe electrodes, CIFs with dual peaks have been shown to indicate an electrode array with a tip fold over (Grolman et al., 2009), but this is not observed in the CT data for any of the subjects in the present study.

For all subjects, overlapping excitation patterns across CIFs was observed. Often, the greatest amount of overlap occurred for adjacent probes, as can be seen in Figure 3 for S22's first four electrodes;

FIGURE 1. CT view of cochlea and electrode array along the midmodiolar axis (red and yellow dashed line), organized by electrode array type. The evenly spaced red dots represent electrodes; the outermost dot represents the insertion depth marker. The white line represents the 0° reference point from which insertion

depth is measured, extending from the midmodiolar axis (see Finley et al., 2008 for more details). Rows 1–2: 1J array; Row 3: MidScala; Row 4: 1J Helix and 1J with positioner, respectively.

however, overlaps were also observed for more distant probe electrodes (e.g., S44's electrodes 4, 8, and 9). Additionally, some CIFs completely enveloped others. For instance, S22's probe 5 has a relatively large peak amplitude and a broad spread of excitation across basal electrodes that completely or partially envelops the CIFs associated with probe electrodes 1–10.

Comparisons of ECAP Measures with Focused Thresholds and Electrode-to-Modiolus Distances

Scatterplots between the ECAP data and sQP thresholds (left) and electrode-to-modiolus distance (right) are shown in Figure 4. Mean peak amplitudes are shown in the top panels, and mean ERBs are shown in the bottom panels. Results from the multiple linear regression analysis indicated a significant, negative correlation between ECAP peak amplitude and sQP threshold ($T_{83} = -6.08$, $p < .001$), and a significant, positive correlation between electrode-to-modiolus

distance and ERB ($T_{91} = 2.39$, $p = .02$). The other two comparisons were not significant (sQP threshold and ERB: $T_{83} = 1.73$, $p = .09$ and electrode-to-modiolus distance and ECAP peak amplitude: $T_{91} = -.94$, $p = .35$). Overall, the results show that ECAP peak amplitudes are smaller for channels with high sQP thresholds, and ECAP ERBs are broader for large electrode-to-modiolus distances.

Scalar Location

Scalar location was estimated for all subjects and electrodes. Fifty-two percent of all electrodes were located in the ST, which is the target location during surgical implantation. Most of the other electrodes were estimated to be in the intermediate position (37 %), with the remaining electrodes in the SV (11 %). Figure 5 presents histograms relating scalar location data to sQP threshold (Fig. 5A), electrode-to-modiolus distance (Fig. 5B), and ECAP peak ampli-

TABLE 2

Means and SDs for distance, threshold, ECAP measures, threshold variability, and mean speech scores

ID	Electrode-modiolus distance (mm) Mean (SD)	sQP threshold (dB) Mean (SD)	sQP threshold variability (dB)	ECAP peak amplitude (mV) Mean (SD)	ERB (mm) Mean (SD)	Mean speech scores (% correct)
S22	1.12 (.37)	42.72 (6.92)	5.49	.24 (.12)	5.78 (1.51)	74
S29	1.52 (.23)	47.15 (3.32)	3.77	.18 (.06)	9.20 (3.16)	82
S38	1.30 (.25)	45.16 (3.00)	3.29	.08 (.02)	4.89 (1.67)	46
S40	1.79 (.22)	54.27 (1.30)	2.02	.07 (.02)	5.22 (2.30)	30
S41	1.56 (.37)	45.14 (.89)	1.13	.29 (.10)	7.54 (1.99)	88
S42	.64 (.33)	36.96 (4.80)	2.03	.23 (.13)	5.28 (3.04)	95
S43	.84 (.44)	44.69 (3.95)	3.22	.07 (.02)	2.55 (.01)	60
S44	.85 (.49)	50.67 (1.58)	1.86	.11 (.07)	2.57 (.40)	73
S46	1.80 (.32)	51.69 (1.53)	.91	.06 (.02)	6.60 (1.73)	39
S47	.87 (.46)	38.39 (5.91)	4.08	.09 (.03)	3.11 (.52)	94
Summary	1.23 (.53)	45.43 (6.54)	2.85 (1.39)	.15 (.11)	5.92 (2.86)	67.69 (23.24)

Shows means and standard deviations for electrode-to-modiolus distance, sQP threshold, ECAP peak amplitude, and ECAP equivalent rectangular bandwidth (ERB). Channel-to-channel sQP threshold variability and mean speech scores are also listed. The “summary” line indicates means and standard deviations across subjects

tude (Fig. 5C) and ERB (Fig. 5D). Results from the ANOVA show a main effect of scalar location, wherein sQP threshold was lower for electrodes in ST compared to those in an intermediate position; however, this was not significant after Bonferroni adjustment ($F(2,129)=3.54$, $p=.03$). Electrodes located in either the intermediate position or in SV were further from the modiolus ($F(2,157)=19.38$, $p<.001$), which was shown previously to correlate with higher thresholds. An unexpected finding was that ECAP peak amplitude was significantly smaller for electrodes in ST ($F(2,131)=5.97$, $p=.003$), with no effect for SV ($p>.05$). Electrodes in ST had a narrower spread of excitation than those in the intermediate position, but electrodes in the SV did not differ from ST or those in the intermediate position ($F(2,101)=14.00$, $p<.001$) (Fig. 5D). It is possible that for some measures, electrodes in SV did not differ significantly from the other scala due to the low number of SV electrodes available for analysis.

Speech Performance

Figure 6 shows mean speech performance (the average of medial vowel and consonant discrimination scores) in relation to sQP threshold (Fig. 6A), electrode-to-modiolus distance (Fig. 6B), ECAP peak amplitude (Fig. 6C), and ERB (Fig. 6D). Simple linear regression analyses reveal a positive correlation between mean speech score and ECAP peak amplitude ($T_8=2.50$, $p=.04$), and a negative correlation with sQP threshold ($T_8=-2.84$, $p=.02$). However, no association was observed with ERB ($T_8=0.31$, $p=.76$) or electrode-to-modiolus distance ($T_8=-2.11$, $p=.07$). Finally, results show no relationship between mean speech performance and number of electrodes in the SV

($F(4,5)=.75$, $p=.60$), or with angular insertion depth ($F(1,8)=.15$, $p=.71$).

DISCUSSION

The present study sought to assess the relationship between the ECAP and other metrics related to the electrode-neuron interface: sQP thresholds, electrode-to-modiolus distance, and scalar location using estimates from CT imaging. Results support the hypothesis that electrodes further from the modiolus are associated with higher behavioral thresholds and broader ECAP CIFs, and electrodes with lower behavioral thresholds are associated with larger ECAP amplitudes. However, channels with lower thresholds did not yield narrower ECAP CIFs, nor were electrodes far from the modiolus associated with smaller ECAP peak amplitudes. From these results and those showing that ECAP peak amplitude was predictive of speech performance, we infer that ECAP peak amplitude may be more sensitive to neural status than electrode position. Likewise, we infer that ECAP CIF width is more sensitive to electrode-to-modiolus distance and scalar location than neural status, as the ERB measure was not correlated with behavioral threshold or speech performance. Thus, ECAP peak amplitude and CIF widths appear differentially sensitive to two important aspects of the electrode-neuron interface.

Focused Single Channel Thresholds and Electrode-to-Modiolus Distance

Previous physical measurements in animals (e.g., Jolly and Spelman 1996) and computational modeling

FIGURE 2. A sQP threshold in decibels (green line) and electrode position in millimeters (blue line) profiles for all subjects, organized by electrode array type. Scalar information is represented by symbol along the electrode position line: ST (circles), intermediate (diamonds), and SV (triangles). B Scatter plot comparing electrode position with sQP threshold for individual subjects (colored lines;

see legend) and group data (black line). The circles represent electrodes in ST, the diamonds electrodes in the intermediate position, and the triangles electrodes in SV. Regression analysis reveals a significant, positive correlation between sQP threshold and electrode position.

studies of human cochleae (e.g., Goldwyn et al. 2010) demonstrate that voltage decreases with distance from the electrodes; therefore, electrodes that are farther from the modiolus require more current to drive neural responses. Consistent with modeling expectations and other studies (Cohen et al., 2003; Goldwyn et al. 2010; Long et al., 2014), focused thresholds (measured with sQP configuration in the present study) were highly correlated with electrode-to-modiolus distance, such that increased thresholds were indicative of greater electrode-to-modiolus distances. Despite the significant correlation, however,

distance did not account for all of the variability in focused thresholds, particularly within subjects (Fig. 2B). Long et al. (2014) suggested that the remaining variability may be presumed to reflect variable neural health, though factors such as local variations in tissue impedance may play a role as well. They explored this hypothesis by correlating the RMS error of the threshold-distance model with speech perception scores and found that subjects for whom threshold was well predicted by distance tended to have better speech perception. However, we were unable to replicate those findings with the data

FIGURE 3. CIFs for all subjects, organized by electrode array type. The x-axis represents masker electrode (millimeters from the apical electrode). The y-axis represents ECAP amplitude (mV). For subjects with overall low amplitudes, the y-axis ranges from 0 to 0.3 mV; for the others, it ranges from 0 to 0.6 mV. Note that this is reflected in the

scales on the y-axis. Mean ECAP peak amplitude (mV) is indicated at the *top right* of each panel. The *numbered lines* inside the plot are probe electrodes, labeled at the peak amplitude of the CIF.

obtained in the present study ($r^2=.14$, $F(1,8)=.16$, $p=.70$).

The results presented in Figure 6A show a significant correlation between mean speech performance and sQP threshold. These results also differ from the Long et al. (2014) study, which found that mean phased array threshold was not correlated with logit-transformed speech performance on CNC words. However, they did observe that the within-subject variance ($V=34.8 \text{ dB}^2$) of phased array threshold was negatively correlated with speech performance. Similarly, Bierer (2010) showed a negative correlation between channel-to-channel threshold variability (based on the difference in standard deviation) and CNC words, such that greater variability in thresholds resulted in poorer speech performance. The present results did not replicate the correlation between either measure of threshold variability and speech performance ($V=42.8 \text{ dB}^2$, $r^2=.42$, $p=.22$; $F(1,6)=.07$, $p=.80$; $r^2=-.12$, for individual data, see Table 2), likely due to the small sample size.

ECAP Amplitude and Channel Interaction

Peak Amplitude. Most previous ECAP studies have related evoked potential thresholds to behavioral threshold and comfort levels (reviewed in Miller et al. 2008; Jeon et al. 2010). To our knowledge, studies specifically evaluating the relationship between peak amplitude at a suprathreshold level (MCL) and behavioral thresholds have not been conducted. In the present study, ECAP peak amplitudes were small for electrodes with high focused behavioral thresholds (Fig. 4A). In animal studies, the amplitude of evoked responses has been correlated with neural status, such that longer deafened animals had smaller amplitudes and fewer surviving auditory neurons (Hall 1990; Shepherd and Javel 1997; Ramekers et al. 2014; Smith and Simmons 1983).

There was no observed relationship between electrode-to-modiolus distance and ECAP peak amplitude. In this study, peak amplitudes were measured using masker and probe stimulus levels that were

FIGURE 4. Comparisons between sQP threshold, electrode position, and the ECAP variables of interest for individual subjects and group data (black line). All *p* values are from the multiple linear regression analysis. The circles represent electrodes in ST, the diamonds electrodes in the intermediate position, and the triangles electrodes in SV. **A** Comparison between sQP threshold and ECAP peak amplitude. **B** Comparison between electrode position and ECAP peak amplitude. **C** Comparison between sQP threshold and ERB. **D** Comparison between electrode position and ERB.

FIGURE 5. Histograms of scalar counts for all variables of interest. Black, green, and blue bars represent ST, intermediate, and SV, respectively. It is important to note that panels for sQP threshold and ERB have a different y-axis from the other panels, for ease of viewing the distributions. **A** sQP threshold (dB rel. to 1 μ A). **B** electrode distance (mm). **C** ECAP peak amplitude (mV). and **D** ECAP ERB (mm).

FIGURE 6. Relationships between the variables of interest and mean speech scores (from aCA and hVd stimuli). **A** mean sQP threshold (dB rel. to 1 μ A), **B** mean ECAP peak amplitude (mV), **C** mean ECAP ERB (mm), and **D** mean electrode distance (mm).

loudness-balanced at MCL, as opposed to a fixed stimulation level. For a fixed stimulus level, smaller ECAP amplitudes would be expected for electrodes with a more lateral placement because the stimulus decays as a function of distance. By adjusting stimulus level for each electrode, electrodes farther away from the modiolus were presumably stimulated with greater current than electrodes close to the modiolus; however, the stimulus reaching the neurons was comparable.

The significant correlation between ECAP peak amplitudes and speech-perception scores (Fig. 6B) has, to our knowledge, not been observed previously. Brown et al. (1990) evaluated the relationship between ECAP amplitude of a single electrode stimulated at a high level and speech-perception scores but did not observe a correlation. The different outcomes may be due to the fact that ECAP amplitudes were averaged across electrode sites in the present study, and a smaller sample size was used, among other factors. If smaller amplitudes are indicative of poor neural survival (Hall 1990; Smith and Simmons 1983), poorer speech outcomes may be reasonably expected for those listeners.

Given that ECAP peak amplitudes were not correlated with electrode-to-modiolus distance, we speculate that amplitude, evoked using stimulus levels equated for loudness, primarily reflected the number and health of the neurons contributing to the response. This speculation is further supported by the significant correlation with speech perception scores, though this result should be interpreted with caution because of the small sample size. Another element to consider is that if neural health

is poor near the stimulating electrode, the distribution of responding neurons will be broad and less synchronous than a more tightly bunched group of neurons. Synchrony, not just the number of activated neurons, is essential to measurable evoked potentials, and at least one animal study has shown that with neural degeneration, neural synchrony is reduced (Shepherd and Javel 1997).

Channel Interaction. ECAP CIFs were sensitive to electrode position. The ERB was moderately correlated with electrode-to-modiolus distance, such that electrodes further away from the modiolus showed a greater degree of channel interaction (Fig. 4D). Additionally, electrodes in the ST had narrower ERB widths compared to electrodes in the intermediate position. These results are consistent with observations from previous studies that spread of the excitation pattern is primarily affected by electrode position (Cohen et al., 2003; Hughes and Abbas, 2006b; Miller et al., 2008).

Furthermore, consistent with previous studies, the present results did not show a correlation between channel interaction width (mean ERB) and mean speech performance (Brown et al. 1990; Cohen et al. 2003; Hughes and Abbas 2006a); in fact, the results across subjects were quite variable (Fig. 6D). This suggests that previous null results were not solely due to sampling CIFs for a limited number of electrodes. Scheperle and Abbas (2015) found a similar result across subjects; however, within subjects, ECAP channel-separation indices (used as a novel measure of peripheral spatial selectivity) were correlated with speech perception. Though interaction width was

estimated differently in the present study, the general results are similar. The evidence suggests that while CIF width may be predictive of electrode-to-modiolus distance, it does not appear to extend to speech performance across subjects; however, more data is needed to support this result.

The data suggest that although a laterally placed electrode may have a direct effect on the degree of channel interaction, channel interaction may not be the most sensitive measure of neural status. If ECAP peak amplitude is taken as an indirect measure of neural status, as suggested previously, and ECAP channel interaction width as a measure of electrode position, combining these measures may yield a comprehensive assessment of the electrode-neuron interface.

Scalar Location and Insertion Depth

In the present study, electrode positions outside of ST were primarily located in an intermediate position, with a much smaller percentage of electrodes in the SV (about 10.6 %). Finley et al. (2008) also categorized translocations into SV, finding that the number of electrodes in SV was correlated with greater insertion depth and decreased speech perception. Holden et al. (2013) also reported that across 114 subjects with either Advanced Bionics or Cochlear Corporation implants, 23.2 % of all contacts were located in the SV, and that those translocations were more common for individuals with decreased speech performance. In the present study, no correlation was found between mean speech performance and the number of electrodes located in the SV; however, the sample size in this study was small compared to Holden et al. (2013), and there were very few electrodes in SV in this population.

To further compare with previous studies, angular insertion depth of the basal-most electrode was evaluated relative to mean speech performance. A correlation was not observed in the present data set, which does not replicate the findings of Finley et al. (2008) or Holden et al. (2013), who observed poorer speech scores associated with deeper angular insertions. However, the present results are consistent with the findings of a recent study evaluating six position-related variables; neither angular insertion depth nor electrode-to-modiolus distances were related to speech outcomes (van der Marel et al. 2015). Though these comparisons are interesting, they should be interpreted with caution, primarily due to the small sample size in the present study. Additionally, in the present study, a closed set task was used and subjects were relatively good performers, whereas in the study by Holden and colleagues (2013), open-set monosyllabic words were used and a wider range of speech perception scores was observed.

Clinical Implications

A recent study used CT imaging data and a computational model as a basis for deactivating electrodes (Noble et al. 2013). When a subset of channels that were estimated to be highly interactive were deactivated, significant improvements on both objective and subjective tasks were observed. The results of the present study suggest that similar programming manipulations should be explored to determine if recommendations could be made based on sQP thresholds or ECAP measures. The ECAP measures may be advantageous over the behavioral and/or CT measures in that peak amplitude, and channel interaction functions appear to be differentially sensitive to electrode position and neural status. With this combined information, perhaps clinical management strategies could be tailored to the underlying cause of a poor electrode-neuron interface. For instance, if an electrode is located far from the modiolus, current focusing may aid in increasing its effectiveness. If an electrode is located near a dead region, frequency reallocation or channel deactivation may be the best method for optimal stimulation. Future studies are needed to examine the relationship between ECAP peak amplitude, CIF overlap, and speech perception, using programs tailored in this manner.

CONCLUSIONS

The electrode-neuron interface likely contributes to the variability observed in speech performance in cochlear implant listeners, and thus should be explored with the aim of improving current programming techniques. Current clinical approaches are time-consuming, potentially costly, or expose listeners to radiation. The ECAP may serve as an alternative to these approaches and has the benefit of measurement without the active engagement of the listener.

The present study showed a moderate association between focused behavioral thresholds and the peak amplitude of the ECAP, which may be useful if small peak amplitude is related to a degraded neural status. Large electrode-to-modiolus distance and wide ECAP ERB were also correlated, indicating that electrodes far away from the neurons are likely to have more channel interaction. Those findings suggest that the placement of the electrode array may have an effect on the degree of spread of excitation that occurs and that ECAP CIFs may be a tool to assess those factors. Additionally, scalar location may be an important causal influence on these relationships, with electrodes in the ST more likely to have smaller electrode-to-modiolus distances, which can lead to lower thresholds and narrower CIFs. Speech performance was also associated with focused thresh-

olds and ECAP peak amplitude. If ECAP peak amplitude is taken as a proxy for neural health, this highlights the potential utility of this measure as a predictor of implant outcomes.

In conclusion, different aspects of ECAP measures relate to different aspects of the electrode-neuron interface, and specifically, ECAP peak amplitude may be sensitive to neural status. It is possible that examining both ECAP peak amplitude and spatial extent of channel interaction may provide a more efficient and holistic approach to evaluating the electrode-neuron interface than the current clinical methods.

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Compliance with Ethical Standards

Conflict of Interest

The authors declare that they have no conflict of interest.

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