Assessing the Relationship Between the Electrically Evoked Compound Action Potential and Speech Recognition Abilities in Bilateral Cochlear Implant Recipients

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Abstract

Objectives—The primary objective of the current study was to examine the relationship between suprathreshold ECAP measures and speech recognition abilities in bilateral cochlear implant listeners. We tested the hypothesis that the magnitude of ear differences in ECAP measures within a subject (Right – Left) could predict the difference in speech recognition performance abilities between that subject's ears (Right – Left).

Design—In order to better control for across-subject variables that contribute to speech understanding, the current study used a within-subject design. Subjects were 10 bilaterally implanted adult cochlear implant recipients. We measured ECAP amplitudes and slopes of the amplitude growth function (AGF) in both ears for each subject. We examined how each of these measures changed when increasing the interphase gap of the biphasic pulses. Previous animal studies have shown correlations between these ECAP measures and auditory nerve survival. Speech recognition measures included speech reception thresholds for sentences in background noise, as well as phoneme discrimination in quiet and in noise.

Results—Results showed that the between ear difference (Right-Left) of one specific ECAP measure (increase in AGF slope as the IPG increased from 7 to 30 μs) was significantly related to the between ear difference (Right-Left) in speech recognition. Frequency-specific response patterns for ECAP data and consonant transmission cues support the hypothesis that this particular ECAP measure may represent localized functional acuity.

Conclusions—The results add to a growing body of literature suggesting that, when using a well-controlled research design, there is evidence that underlying neural function is related to post-operative performance with a CI.

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Introduction

The success of cochlear implant (CI) listeners varies widely, and while some of the predictive factors, such as duration of hearing loss, are well-known, the influence of cochlear health on speech recognition outcomes remains somewhat elusive (Holden et al., 2013; Khan et al., 2005; Nadol et al., 2001). Given that the implant stimulates the auditory nerve directly and therefore relies on its integrity to transmit the signal accurately, it stands to reason that cochlear health, primarily spiral ganglion cell (SGN) density and perhaps other attributes of the residual neural population, would be related to post-operative speech recognition abilities in CI recipients.

To date, much of our understanding regarding the relationship between SGN density and speech recognition abilities in CI listeners is derived from post-mortem temporal bone analyses. These studies show a negative correlation or lack of correlation between post-mortem estimates of spiral ganglion neuron (SGN) density and word recognition measured during life when the relationship between these two factors was examined across subjects (Khan et al., 2005; Nadol et al., 2001). However, a more recent post-mortem study analyzing temporal bones of bilaterally implanted adults (Seyyedi, Viana, & Nadol, 2014) showed that ear differences in SGN density were predictive of ear differences in speech recognition abilities within a subject. Similarly, Zhou and Pfingst (2014b) showed that the magnitude of ear difference in multipulse integration (MPI) function slopes predicted the magnitude of ear difference in speech recognition measures (Zhou & Pfingst, 2014b). Within each subject the ear with steeper MPI slope functions averaged across all electrodes was also the ear with better speech recognition scores. Previous studies had shown that MPI slopes correlated with SGN density in cochlear implanted guinea pigs (Kang et al., 2010; Pfingst, Colesa, et al., 2011). Taken together, these studies highlight one confounding factor of earlier temporal bone studies that failed to find a relationship between SGN density and speech recognition performance using data analyzed across subjects. It is known that patient-specific factors, such as cognition (e.g., working memory) influence speech recognition outcomes (Finke, Buchner, Ruigendijk, Meyer, & Sandmann, 2016; Heydebrand, Hale, Potts, Gotter, & Skinner, 2007; Holden et al., 2013). Other factors, such as duration of auditory deprivation and/or age at onset of hearing loss are also important (Holden et al., 2013). However, if the contribution of such individual factors is limited to some degree by comparing ear-differences in bilaterally implanted subjects, then speech recognition measures have been shown to be related to measures of SGN health.

Another confounding variable that arises when comparing post-mortem studies of cochlear health to speech recognition measured before death is the duration of time that elapses between assessment of speech recognition and post-mortem harvesting of temporal bones for analysis. Further variability is introduced by individual health factors or disease processes during the interim that could influence cochlear health or cognition. Studies performed in cochlear implanted guinea pigs demonstrate that both psychophysical and electrophysiological measures relate to cochlear health - primarily, SGN density but possibly also membrane capacitance and/or temporal properties of the remaining neurons (Pfingst, Colesa, et al., 2011; Pfingst et al., 2015; Prado-Guitierrez, Fewster, Heasman, McKay, & Shepherd, 2006; Ramekers et al., 2014). Taken together, a number of studies have shown

that 1) suprathreshold characteristics of the ECAP (or Wave 1 ABR) response such as the peak amplitude, slope of the amplitude growth function (AGF) and N1 latency at a high current stimulus levels are correlated with SGN density; and 2) that the change in suprathreshold ECAP measures resulting from increasing the interphase gap (IPG) of the biphasic stimulus pulses also relates to SGN density and perikaryal area. Specifically pertaining to ECAP measures, these studies show that for a constant IPG the slopes of AGFs are correlated with the number of surviving auditory neurons (Hall, 1990; Pfingst et al., 2015; Smith & Simmons, 1983). Generally speaking, steeper slopes are positively correlated with higher neural survival. Ramekers and colleagues showed that the increase in ECAP AGF slope (sigmoid) as a function of increasing the IPG was positively correlated with SGN density and perikaryal area (Ramekers et al., 2014). The authors reported on several other significant correlations between neural density and how several features of the ECAP (e.g., amplitude) change as a function of increasing the IPG.

While the clinical utility of suprathreshold ECAP measures has been limited to date, the findings reported above warrant further investigation of this measure in human cochlear implant recipients. ECAP measures are advantageous because they are efficient, can be measured using clinically available software, and can be used as an indirect estimate of SGN density in a subject and then compared to speech recognition measures obtained within the same period of time during the life of the subject. Manipulation of the IPG to assess the health of the stimulated SGN population is of particular interest in multichannel CI arrays. One limitation of ECAP measures to assess neural health is that the recordings may be influenced by other variables (e.g., fibrous tissue, new bone or distance of the electrodes from the modiolus) that are not specifically dependent on neural health and which likely vary across individual electrodes in a multichannel array. Some of the effects of these variables might be reflected in individual electrode impedances. Results from a related study showed that significant across-site correlations between electrode impedances and ECAP measures using a constant IPG (ECAP peak amplitude and AGF slope) were found in 37.5% of the ears (Schvartz-Leyzac & Pfingst, 2016). However, ECAP measures for short and long duration IPGs might be affected in similar ways by the conditions near the recording electrode depending on how the resistive and capacitive components contribute to the overall impedance measure. When this is the case, these other underlying factors (e.g., fibrous tissue or new bone) might not contribute to measures based on changes in the ECAP amplitude or slope as the IPG changes. In fact, in the related study mentioned previously (Schvartz-Leyzac & Pfingst, 2016) we found that, in the same subjects, across-site patterns of impedance did not generally correlate with across-site patterns of the changes in ECAP peak amplitude or slope as the IPG was increased from 7 to 30 μs. Thus, assessing how the ECAP changes with increases in IPG to assess neural health is not only supported by animal work, but is also robust to local, site-specific factors that are not related to neural health.

A few studies have examined the relationship between characteristics of the ECAP AGF and speech recognition outcomes in adults with somewhat mixed results (Brown, Abbas, & Gantz, 1990; DeVries, Scheperle, & Bierer, 2016; Kim et al., 2010; C. A. Miller, Brown, Abbas, & Chi, 2008; van Eijl, Buitenhuis, Stegeman, Klis, & Grolman, 2017). In a meta-analysis study, van Eijl and colleagues (van Eijl et al., 2017) identified five studies examining the relationship between ECAP AGF slopes and speech recognition performance.

Among those studies, only one study (Kim et al., 2010) reported significant findings. Kim and colleagues (Kim et al., 2010) measured the ECAP amplitude-growth function using monopolar stimulation on a sample of electrodes within the array in patients with both hybrid and traditional, long-electrode arrays using 8 and 45 μs interphase gaps (IPGs). Within the Hybrid implant recipient group, they reported a significant relationship between the slope of the amplitude-growth function for Hybrid CI (RE) recipients and recognition of both CNC (Consonant-Nucleus-Consonant) words and BKB (Bamford-Kowal-Bench) sentences in noise. Within the traditional, long-electrode array group a positive and significant relationship was noted for the CI24RE but not the CI24M recipients for CNC words. There was no relationship between speech recognition and the shift of the AGF and decreased threshold, as the IPG was decreased, for any group.

A related study by DeVries and colleagues (DeVries et al., 2016) measured ECAP peak amplitudes in ten unilaterally implanted adult subjects with Advanced Bionics implants using monopolar (MP) stimulation. Additional measures included computerized tomography (CT) scans, psychophysical thresholds using steered quadrupolar stimulation and ECAP spread of excitation using MP stimulation. Measures were performed across all electrodes. Results indicated that the amplitude of the ECAP response at a moderately high current stimulation level was positively and significantly correlated with a combined vowel and consonant recognition score when examined across subjects. Results also indicated that positioning of the electrode, primarily distance from the electrode to the modiolus, was positively correlated with psychophysical thresholds. No such relationship was found between distance from the electrode to the modiolus and ECAP peak amplitudes at a moderately high input (current) level. The authors concluded that the condition of the neural population adjacent to the electrode must contribute to the ECAP amplitude more so than distance between the electrode and the excitable tissue.

In a previous, related study we examined how two suprathreshold ECAP measures (linear slope of the AGF and peak amplitude of the AGF) varied across stimulation sites in the electrode array, how they related to one another, and how they changed as a function of increasing the IPG in 10 bilaterally implanted subjects (Schvartz-Leyzac & Pfingst, 2016). Results showed that patterns of performance varied across subjects, and across ears, and were measure-dependent. Generally, peak amplitudes and AGF linear slopes were correlated, as were 7 and 30 μs IPG conditions for each ECAP measure. It was noted that increasing the IPG on average resulted in an increase in the slope and peak amplitude for most electrodes tested. The current study extends these findings by examining how these ECAP measures compare across two ears within a subject, and also how they relate to speech recognition abilities both within and across subjects. Specifically, in the present study we attempt to control for characteristics that differ across subjects and are known to contribute to speech understanding by measuring ECAPs in bilaterally implanted subjects and then comparing those measures across the two ears within a subject. We also examined the relationship between ECAP measures and speech recognition across subjects. The key variables of interest for each ECAP input-output function were: (1) linear slope of the AGF, and (2) peak amplitude of the AGF. We also examined the relationship between speech recognition and how each of these three measures changed when the IPG was increased (the "IPG effect").

We tested several hypotheses about the utility of ECAP measurers to for diagnosis of conditions near individual stimulation sites in the implanted cochlea. First, we hypothesized that, using a well-controlled within-subject design, suprathreshold ECAP measures previously shown to reflect neural density in animals, would relate to speech recognition. Specifically, we hypothesized that within each subject, the ear with better-estimated neural density based on ECAP responses would also provide better speech understanding. Second, for reasons previously stated, we hypothesized that, rather than using an ECAP measure with a constant IPG, examining the change in each ECAP measure with increasing in IPG would provide a stronger measure of the relationship between site-specific neural health and speech understanding in CI patients. Third, we hypothesized that, because each suprathreshold ECAP measure studied here has been shown to significantly correlate to neural density in cochlear implanted animals, then theoretically for any given subject, each ECAP measure should point to the same ear within that subject as estimated to have better neural density. Based on patterns reported by Ramekers and colleagues (Ramekers et al., 2014), the ear that showed larger ECAP amplitudes or AGF slopes should also be the ear that demonstrated a larger change in each ECAP measure as the IPG increased from 7 to 30 μs.

In the present study we chose to measure speech recognition abilities using various stimuli: Vowels and consonants in quiet and in noise as well as speech recognition in steady-state or a fluctuating masker. The rationale for doing so is based on previous literature which has cited that different characteristics of the ECAP measure have correlated with a combined vowel-consonant recognition score (DeVries et al., 2016) or sentence recognition using a 4-talker babble (Kim et al., 2010). Additionally, Zhou & Pfingst (2014b) reported that ear differences in speech recognition using sentences in a modulated noise and consonants were correlated with between ear differences in MPI in bilaterally implanted human subjects, but this relationship did not hold true for vowel stimuli.

Materials and Methods

Subjects

Subjects were 10 bilateral cochlear implant users with peri- or post-lingual sensorineural hearing loss. The subjects who participated in the current study are identical to those who participated in a previous, related study (Schvartz-Leyzac & Pfingst, 2016). None of the subjects tested had residual hearing post operatively at the limits of the audiometer. The ears were implanted with Nucleus CI24R(CA), CI512 or CI24RE(CA) devices, all of which used a contour-advance precurved electrode array. All subjects used the ACE speech-processing strategy in their everyday/clinic MAP. Demographic information for the subjects is shown in Table 1. All subjects were native speakers of American English. The use of human subjects in the study was reviewed and approved by the University of Michigan Medical School Institutional Review Board.

Speech recognition test procedure

All speech recognition tests were administered in a double-walled sound-attenuated booth (Acoustic Systems Model RE 242 S; Applied Acoustic Systems, Montreal, Quebec).

Consonant and vowel tests were administered via a graphical user interface programmed in MATLAB (Mathworks, Natick, MA). Speech materials were delivered from the computer to a Rane ME60 graphic equalizer, a Rolls RA235 35W power amplifier, and presented via a loudspeaker positioned 1 m from subjects at 0° azimuth. All stimuli were calibrated at 60 dB (A) SPL with a sound-level meter (type 2231; B & K, Naerum, Denmark) using the slow time setting. For speech stimuli presented in the presence of background noise, the mixed signal (speech + noise) was presented at a constant level of 60 dB (A) SPL and the signal to noise ratio was adaptively changed from trial to trial. During calibration sessions, the sound-level meter was positioned 1 m away from the loudspeaker at 0° azimuth.

Speech recognition testing was completed by each subject using laboratory owned speech processors (CP810) and the subjects' preferred settings and was completed before collecting electrophysiologic data. Processor settings were kept constant across all test conditions. Nearly all subjects used the 'Everyday' program which consists of the following default settings: Standard microphone mode (Directional), Adaptive Dynamic Range Optimization (ADRO) and Autosensitivity (ASC). The exception to this was s81 who did not use ASC in her speech processor program for either ear, so this was not used in the study either. Prior to testing, the clinic owned speech processor was examined and a listening check was performed. Each subject used their most recent clinical MAP (programmed within the past 6 months).

Six speech tests were completed in total: CUNY sentences in steady-state and modulated noise, vowels in quiet and noise, and consonants in quiet and in noise. Specific details are provided below. Three repetitions of each speech condition (consonants or vowels in noise or quiet and CUNY sentences with two noise conditions) were tested in each ear and were then averaged together and used in the analyses. Subjects first listened to one presentation of the six speech tests (CUNY in steady-state noise, CUNY in modulated noise, Vowels in quiet, Vowels in +10 dB SNR, Consonants in quiet, and Consonants in +10 dB SNR) in one ear, presented in a random order. Then, the subject listened to a second round of the six speech tests in the other ear, presented in a random order. The testing continued in this manner, alternating between ears, until six repetitions of each of the six speech tests referenced above were completed. Half of the subjects began testing in the right ear, and half of the subjects began testing in the left ear. Subject s108 did not complete the Vowels +10 dB SNR condition due to time constraints.

Speech stimuli

Sentence recognition in noise—CUNY sentences (Boothroyd, Hanin, & Hnath, 1985) were presented in a white noise amplitude modulated at 100% modulation depth with a 4Hz sinusoid (similar to speech envelope modulations) or using steady-state (SS) speech weighted noise. The CUNY sentences are meaningful utterances with contextual cues spoken by a male speaker. Four sentence lists (each containing 12 sentences) randomly chosen from a total of 72 lists were used for measuring one SRT. A different set of sentences was used for each condition/repetition. For this task, the background noise was presented alone for 1.5 seconds before the target, during presentation of the target, and for 0.5 second after the target sentence was completed. Raised cosine ramps were applied at the onset and

offset of the stimulus with the onset and offset each measuring 5% of the entire stimulus duration. Signal to noise ratio (SNR) was calculated for the time period when the target and noise overlapped. The mixed signal (target + noise) was normalized to its peak amplitude. Therefore, the level of the masker plus sentence was similar from trial to trial. This method should be advantageous since a fixed masker and adaptive noise (or vice versa) could lead to potential, unpredictable interactions with the adaptive gain control (AGC) present in the speech processor. The SNR started at 20 dB at the beginning of the test and was adapted in a one-down one-up procedure using a step size of 2 dB. The sentence was presented in the noise background one time and the subject was instructed to repeat the sentence to the experimenter. The experimenter lowered the SNR by 2 dB if the subject repeated all words in the sentence correctly, or increased the SNR by 2 dB if any of the response words were incorrect. However, we did not count errors in verb tense, plurality, or pronouns as incorrect. The one-down one-up procedure estimated a 50% correct point on the psychometric function. The SRT was taken as the mean of the SNRs at the last six reversals out of a total of 12 reversals.

Vowel recognition—Vowel stimuli were taken from materials recorded by Hillenbrand et al. (1995) and were presented to the listeners with custom software. Four presentations (2 females, 2 males) of each vowel were tested for two conditions (Quiet and +10 dB SNR, steady-state speech weighted noise). Each of the 12 medial vowels (i, ɔ, ɛ, u, ɪ, ʊ, ʌ, æ, ɝ, o ɑ, e) was presented in a/h/-vowel-/d/context [heed, hawed, head, who'd, hid, hood, hud, had, heard, hoed, hod, and haid]. Chance level was equal to 8.33% correct. Each calculated percent correct for one repetition for each condition tested was based on discrimination of 48 speech tokens (4 speakers × 12 speech tokens).

Consonant recognition—Consonant stimuli were taken from Shannon et al. (1999) and were presented with custom software. Four presentations (2 females, 2 males) of each consonant were tested for two conditions (Quiet and +10 dB SNR, steady-state speech weighted noise). Stimuli consisted of 20 consonants,/b, d, g, p, t, k, m, n, f, s, ʃ, v, z, Θ, l, dʒ, tʃ, w, j, r/, presented in a consonant-/a/- context (ba, da, ga, pa, etc.). Chance level was equal to 5%. Each calculated percent correct for one repetition for each condition tested was based on discrimination of 80 speech tokens (4 speakers × 20 speech tokens).

Electrically evoked compound action potentials (ECAPs)

ECAP AGFs were measured on each available electrode, within each ear, for all subjects. ECAPs were not measured on electrodes that were deactivated in the subjects' everyday clinical MAP. Of the electrodes for which ECAPs were measured, the AGF could not be assessed on 11% of the total number of electrodes and conditions (7 or 30 μs IPG) tested across subjects due to compliance limitations, restricted dynamic range, or poor morphology of the waveform. Most commonly, these electrodes consisted of the two or three most basal electrodes within the array for each ear (electrodes 1–3).

Method—ECAPs were measured with CustomSound EP Versions 4.2 and 4.3 software using Neural Response Telemetry. A laboratory owned CP910 speech processor connected to a desktop computer through a commercially available programming pod was used for data

collection. Prior to measuring AGFs, the maximum tolerable stimulation level was determined on each electrode for each subject using the 'stimulate only' feature in the software. The measured maximum stimulation level for each electrode was used as the upper limit of stimulation when measuring the AGFs. Typically, subjects reported the maximum stimulation level as very loud but tolerable. Because manipulation of the IPG can affect loudness, the maximum stimulation level was measured for both 7 and 30 μs IPG conditions.

The 'amplitude-growth function' protocol available within the clinical software was used to obtain each input-output function. The limits of the dynamic range of stimulation for the AGFs differed in absolute current level for each electrode. The lower limit of the dynamic range of stimulation was always a current level below the level required to elicit an ECAP response (Noise floor = 20 μV for CI24R; 5μV for CI24RECA and CI512). The upper limit of the dynamic range of stimulation was equal to the maximum stimulation level, as defined in the previous paragraph. The current level step sizes varied from 3–5 clinical units (CUs) depending on dynamic range (smaller step sizes used for a smaller dynamic range) in order to obtain a sufficient number of data points for curve fitting. The step size calculated in μA depended on the specific current levels used. For CI24RE(CA) and CI512 devices, IμA = 17.5 uA* (100^(CU/255)). For CI24R devices, IμA = 10*175^(CU/255). Three data points were required to fit the slope function. For each recording, the peak-to-peak ECAP amplitudes were measured from the leading negative peak (N1) to the following positive peak (P2) using the CustomSound EP software. The input-output function for each electrode was measured 2–3 times for each condition (7 and 30 μs IPGs, as outlined below).

ECAP recording parameters—For most recording parameters, the default settings of the software were used: 80 Hz rate, MP1 (extracochlear monopolar ball electrode) served as the probe & masker indifferent electrode, and the MP2 (extracochlear monopolar plate electrode) served as the recording indifferent electrode. The sampling rate was 20 kHz (one sample every 50 μs). The probe and masker active electrodes were always co-located; the masker level was always 10 CUs higher than the probe level. The masker probe interval was 400μs. The recording indifferent electrode was almost always located two electrodes apical to the probe electrode (e.g., if probe = electrode 10, then recording = electrode 12) when the probe electrode varied between electrodes 1–20. When the probe electrode was 21, then the recording electrode was 22. When the probe electrode was 22, then the recording electrode was 21. However, slightly alternative configurations were used for cases in which this default recording electrode was a deactivated electrode not used in the current study. For example, for s81 (L) electrodes 19–20 were deactivated and therefore the recording electrode was 18 or 21 when the probe electrode was 17 or 18, respectively. In any case, the recording electrode was never located more than three electrodes from the probe electrode. A forward-masking technique was used for artifact cancellation (Abbas et al., 1999; Abbas, Hughes, Brown, Miller, & South, 2004). The number of sweeps for one recording varied from 50–200. The leading phase of the biphasic pulse for both the probe and the masker was always cathodic. The default gain and delay for both CI512 and CI24RE(CA) electrodes are 50 dB and 122 μs, respectively. The default gain and delay for the CI24R(CA) electrode are 60 dB and 55 μs, respectively. For most electrodes, these default gain settings were used, however, in some cases these parameters were adapted in order to improve the visibility of

the N1 peak or morphology of the signal. For most subjects, the default pulse phase duration of 25 μs was used. For two subjects (s106 and s100) the phase duration was increased to 37 μs in order to achieve levels adequate for recording the ECAP response. Regardless, the pulse phase duration remained constant within a subject, across ears and across all electrodes. As noted above, the IPG of the biphasic pulse was either 7 or 30 μs, depending on the condition.

Examples of ECAP recordings are shown in Figure 1 for two ears, and are identical to those examples provided in a related study (Schvartz-Leyzac & Pfingst, 2016). The first figure on the left of Figure 1 shows an ECAP AGF for one electrode [s103 (R), Electrode 6] which demonstrated very robust, clean responses with a large dynamic range, while the second figure on the right of Figure 1 [s99 (L), Electrode 18] shows an ECAP AGF with acceptable morphology and a narrower dynamic range. Note that in both cases both an N1 and P2 response are present, with no indication of significant artifact. For the current study, all ECAP AGFs were required to show similar morphology with no indication of significant artifact (particularly affecting the N1 response).

Statistical analysis

All data were analyzed using Sigmaplot Version 10.0, SPSS Version 22, and/or R Version 3.3.2 (R, 2016; SPSS, 2013). The key variables of interest for each ECAP input-output function were the peak amplitude and AGF slope. The linear slope ($y=y0 +ax$) was derived by determining a best-fit line through all data points that increased as a function of current level, recorded above the noise floor of the system. For electrodes which showed a non-monotonic response at high levels, the linear slope was derived by including all data points above the noise floor, which increased in output value (μA) up to, but not including, the level which produced a decrease in the N1-P2 amplitude relative to that produced by the next lower stimulus level. At least three points were required to fit the linear slope function. Figure 2 provides an example of two AGFs obtained for one subject (s104) in the current study and shows how linear slopes were fit for cases in which the function was non-monotonic (e.g., electrode 21). It was found that most AGFs were monotonic and therefore could be fit with a linear slope equation. In many of these cases, a non-linear equation (e.g., sigmoidal) did not provide a good fit. Therefore, a linear equation was used for all electrodes. In all cases the linear fit was statistically significant and produced an R^2 of 0.95 or higher. For each electrode, the peak amplitude was defined as the maximum value of the N1-P2 amplitude in the AGF. Typically, the peak amplitude occurred at the highest stimulation level. However, in cases of non-monotonicity (as previously discussed), the peak amplitude occurred at a stimulation level lower than the highest stimulation level.

For each variable of interest, the average value was calculated across the entire electrode array to derive an across-site mean (ASM). These values were also averaged over specific frequency regions to derive regional means which correspond to frequency characteristics of vowel and consonant stimuli. For each variable, the ear difference in across-site means (right ear minus left ear) were calculated. The change (increase or decrease) in slope and amplitude as a function of the IPG was also calculated (30–7 μs) for each electrode, and an ASM was calculated. For peak amplitude measures, the change in amplitude as function of

the IPG for each electrode was calculated using equal stimulus current levels across the two IPG conditions, within an ear.

For correlating magnitudes of ear differences in the ECAP measure with those in the speech recognition measures, linear regressions were performed to force through the origin such that the intercept was excluded in the linear model (Casella, 1983). Prior to all linear regression analyses, Normal P-P Plots and histograms were plotted to ensure that residuals were normally distributed. A linear mixed model approach was also used to evaluate how ECAP measures compared to speech recognition performance when analyzed across subjects.

Results

Comparison of ECAP measures across ears within a subject

Figure 3 shows the ear difference (Right – Left) for the ASM for each ECAP measure for each condition, for each subject. Each row represents results from one subject. The two columns on the left represent the ear difference for peak amplitude values (μV) and the two columns on the right represent ear difference for linear slope values (μA/μV). Within each pair of columns, the left bar graph represents the ECAP measure for the 7 and the 30 μs IPG conditions separately, and the right bar graph represents the change in the ECAP measure when the IPG was increased from 7 to 30 μs.

In order to determine if, for each ECAP measure, the ASM values for each ear were statistically significantly different from one another, paired t-tests were calculated (two-tailed Pearson's product moment correlation, *p<0.05*). The results of the across-ear t-tests are color coded in Figure 3. A red bar reflects cases in which the ASM values were significantly higher (*p<0.05*) in the right ear (positive value on y-axis); a blue bar reflects cases in which the ASM values were significantly higher (*p<0.05*) in the left ear (negative value on y-axis); a gray bar reflects a non-significant finding (*p 0.05*). Note that the y-axis values differ on each bar graph in order to improve visualization of the graphs. Based on our hypothesis stated in the introduction and based on the results of Ramekers et al. (2014), in only a few cases (s 81, s89 and s104) did we observe the expected pattern; specifically, in these subjects all ECAP measures showed larger values in one ear. Two other subjects (s107 and s100) showed results somewhat consistent with this pattern, with the exception that not all between ear comparisons reached statistical significance. Other subjects showed various other patterns. It is also worth noting, that, in most cases the ear difference in peak amplitude or AGF slope was greater in the same ear for both IPG durations.

Correlational analyses across speech stimuli

Multiple speech stimulus conditions were tested in order to assess how various aspects of speech recognition potentially related to the ECAP measures obtained for each subject (refer to introduction for rationale). However, it was observed that the across-ear difference (R-L) in performance on various speech recognition tasks tended to be related to each other. The study design provides a multitude of potential variables to consider when performing additional statistical analyses related to the ECAP measures including the specific ECAP

dependent variable (peak amplitude or AGF slope) as well as the IPG effect, which leads to potential issues regarding multiple comparisons during statistical analyses. For this reason, multiple correlational analyses (Pearson's product correlations, 2-tailed) were performed between the speech recognition measures to derive a correlational matrix and parse speech variables considered for further analysis in the paper. The results of the analyses are shown in Table 2. Bonferroni correction was applied ($p=0.05/15$), and significant correlations are noted with an asterisk ($p<0.003$). It can be observed that 1) Within each speech stimulus, performance with the two types of background conditions were always highly correlated with one another; 2) Scores for sentence and consonant stimuli were significantly correlated with one another; 3) Scores for vowel stimuli were not significantly correlated with those for sentence and consonant stimuli.

Comparison of ECAP measure to speech recognition abilities

Results provided in Table II showed that, for sentence stimuli, speech recognition abilities in a steady-state background noise were highly correlated with abilities in a modulated background noise. Additionally, within vowel and consonant stimuli, performance in quiet was highly correlated with performance in a steady-state background noise. In an effort to limit the perils of multiple comparisons and adjustments to significance levels, the remainder of speech recognition analyses will examine performance using sentences in a steady-state background noise and vowels and consonants in a quiet background.

Linear regression analyses were calculated between the performance within each speech stimulus (CUNY sentences in steady-state noise, vowels in quiet, and consonants in quiet) and each of the six ECAP measures. The results of the analyses are shown in Table III. Bonferroni correction was applied ($p=0.05/6$), and significant correlations are noted with an asterisk ($p<0.008$). Results show that, in most cases, linear regression analyses between ECAP measures and speech recognition were not statistically significant. However, the proportion of variance in CUNY sentences and consonant recognition explained by the slope change as a function of increasing the IPG was significant ($p<0.008$). In both cases, results of the Durbin-Watson statistic (1.72 for CUNY sentences and 2.41 for consonants) revealed observations were independent. Results of the significant linear regression analyses are shown in Figures 4 (CUNY sentences) and 5 (Consonants). Figure 4 shows that the magnitude of ear difference on a sentence recognition task is significantly correlated with the magnitude of ear difference on the ASM change in the linear slope as the IPG is increased from 7 to 30 µs. Note that, for Figure 4, the y-axis represents the SNR, so a lower value (negative value) on this axis represents better performance in the right ear. Raw data for each subject's speech recognition performance are provided in Table IV. Likewise, Figure 5 shows a similar relationship but with consonant recognition in quiet (percent correct). Raw data for each subject's consonant recognition performance are provided in Table V. Raw data for all other speech recognition testing performed is provided as a supplement (Supplemental Digital Content 1, http://links.lww.com/EANDH/A380). Given these significant findings, all further analyses in the paper will only examine results using the ECAP AGF slope increase that results from increasing the IPG from 7 to 30 µs, henceforth, referred to as *primary ECAP measure.*

Further analysis was performed to determine if this primary ECAP measure also relates to speech recognition differences *across subjects*. A linear regression analysis was performed to determine the extent to which the primary ECAP measure explained the variance on a sentence recognition test in noise when examined across all ears tested in the study (N=20). Results showed that, when analyzed across all tested ears, the relationship between speech recognition performance (SRT for CUNY sentences with steady-state noise) was not significantly related to the primary ECAP measure (R^2 = 0.14, p= 0.10).

An alternative approach, and more appropriate method, to examine how the primary ECAP measure relates to speech understanding across subjects was performed using a generalized linear mixed model in the lme4 package (Bates, Maechler, Boker, & Walker, 2015) in the R environment (R, 2016). Models were constructed to better account for random subject variability in the data. Fixed factors were the primary ECAP measure and the SRT (dB) for CUNY Sentences in steady-state noise. The first model also incorporated a random slope, while the second model incorporated a random slope and intercept. In both cases, basic assumptions of linear regression were analyzed using the lmer package. The relative qualities of these statistical models were assessed by the Likelihood Ratio Test and examining the Akaike information criterion (AIC). Analysis showed that the best fit model incorporated effects of both random subject slope and intercept ($\chi^2(2)$ = 10.72, p=0.004). This model predicts that speech recognition [SRT (dB) CUNY steady state noise] decreases by 25.63 dB SRT $\pm$ 7.38 (standard errors) for every 1 unit of the primary ECAP measure (e.g., 1.0 µV/µA). Note that the largest value of the primary ECAP measure in the present study was 0.36 µV/µA. See x-axis in Figure 6.

In order to better visualize the individual subject variability present in the data, and the significance of the model described above (random intercept and slope), results of the across-subject analyses are displayed in Figure 6. Here, individual linear regression lines are displayed within each subject, and symbols color reflects test ear (Right = Red; Blue = Left). This figure highlights the intersubject variability in the data, showing variance in both slopes (and y-intercepts) across subjects. It can be observed that, in nearly all cases, a negative relationship exists between the primary ECAP measure and the SRT (dB) score suggesting that, within each subject, the ear with poorer performance on the speech task (higher value on y-axis) had a lower value for the primary ECAP measure (smaller change in ECAP slope when IPG increased; x-axis). This general pattern highlights the importance of across-ear, within-subject comparisons (as shown in Figures 4 and 5).

Information transmission analysis

Responses on the consonant recognition task (20 phonemes) were analyzed for transmission of voicing, manner and place cues for each ear tested (G. A. Miller & Nicely, 1955). Within each subject, the ear difference (R-L) in the transmission of each of these consonant cues in quiet was calculated and compared with the ear difference (R-L) for the primary ECAP measure. Linear regression analyses were performed for all three comparisons, resulting in a Bonferroni adjusted criterion of p<0.016. Results are shown in Figure 7. While a general trend in the data can be observed, none of the regression analyses reached statistical significance after Bonferroni adjustments. We hypothesized that, consistent with previous

literature (Zhou & Pfingst, 2014b), place cues would show a significant relationship with the primary ECAP measure whereas other consonant features would not show the same relationship. Place cues require the transmission and perception of spectral peak information which should theoretically relate to a localized measure of cochlear health, such as the one proposed in the current study (e.g., suprathreshold ECAP measures). The p-value noted for consonant place regression (0.022) is nearly, but not quite significant.

Further analyses were performed for the consonant recognition in quiet task to determine if site-specific regions of ECAP patterns correlated with the transmission of specific acoustic cues which correspond in frequency based on frequency-to-place assignment of the subject's clinical speech processor MAP. The analysis is similar to the approach used previously (Zhou & Pfingst, 2014b). We hypothesized that ear differences in regionally-specific ECAP data should predict ear differences in recognition of specific place of articulation cues that were based on corresponding frequencies. Ear differences in regional ASMs of the primary ECAP measure were calculated for each ear and compared to ear differences in the transmission of articulatory features of consonant sounds that were spectrally specific. For each ear, the frequency table (e.g., frequency band to electrode assignment) programmed in the speech processor MAP was analyzed. Note that the frequency tables are altered if any electrodes are deactivated in the speech processor MAP, so we were careful to analyze results with the correct frequency MAPs based on each subject's programming. Table VI provides the approximate frequency ranges associated with different electrodes assuming that all 22 electrodes are activated in the speech processor MAP. As noted in the table, these frequency ranges correspond to the approximate spectral peak characteristics of each articulatory category depending on the placement of the constriction along the supralaryngeal vocal tract (Stevens & Blumstein, 1978). It should be noted that regional means for the alveolar frequency range could only be achieved in 3 of the 10 subjects. This is because often, when ECAP AGFs cannot be recorded or an insufficient number of points obtained to fit a slope function, this occurs in the lower-numbered, higher-frequency electrodes. For the regional mean calculation, we required ECAP measures for at least two electrodes for each ear within the specific frequency range in order to calculate a reliable value. For velar place of articulation, we were able to calculate between-ear differences regional means for 8/10 subjects. For all other articulatory features, we were able to calculate regional means for all subjects tested (10/10).

A regression analysis was performed and showed that a small, but significant proportion of the ear difference in the transmission of frequency-specific place cues ($R^2 = 0.15$) could be accounted for by the ear difference in regional across-site means of the primary ECAP measure. Results are shown in Figure 8. Note that, unlike those results observed in previous graphs (Figures 4 and 5), more variability is noted. Regardless, these results collective support a significant trend between place of articulation features and corresponding regional means for the primary ECAP measure.

Discussion

Relationship between speech recognition and ECAP measures

Several ECAP (or Wave I ABR) measures have been shown to correlate with SGN density in animal models (Hall, 1990; Pfingst et al., 2015; Ramekers et al., 2014; Smith & Simmons, 1983; van den Honert & Mortimer, 1979). We assume that those same ECAP measures reflect neural health in human subjects. The current study found that one specific ECAP measure which for convenience we referred to as the primary ECAP measure (AGF slope increase caused by increasing the IPG) significantly predicted the ear with better speech understanding in bilateral cochlear implant users. It can be observed in Figure 4 that, for subjects who had very similar speech understanding across their two ears as shown on the y-axis (e.g., s103 and s100) this ECAP measure did not technically predict the correct ear as having better speech understanding. However, the magnitude of difference between this primary ECAP measure across ears (R-L) predicted the magnitude of difference between speech recognition performance across ears (R-L).

Based on previous data showing that ECAP measures are related to neural density and/or function and based on previous results (Zhou & Pfingst, 2014b) we hypothesized that place but not manner or voicing cues would be related to the primary ECAP measure. Certain consonants such as stop-consonants are comprised of spectral peaks which are determined by tongue placement and/or location of restriction along the supralaryngeal vocal tract (Johnson, 2004; Stevens & Blumstein, 1978). While effects of coarticulation can lead to acoustic variance, these spectral cues remain dominant in stop-consonant identification (Blumstein & Stevens, 1979). Spectral cues play less of a role in the transmission of manner and voicing cues (Johnson, 2004; Pickett, 1999). The multichannel CI is designed to take advantage of the tonotopic organization of the cochlea. Results shown in Figure 7 show that none of the three articulatory features was significantly related to our primary ECAP measure after correcting for multiple comparisons. However, it remains interesting that a nearly significant relationship was present for the place of articulation feature.

In order to further study the predictive value of our primary ECAP measure and how it relates to place of articulation, we examined the relationship between the spectral cues typically present for each manner classification of stop consonants (Table VI) and the results of the primary ECAP measure for electrodes corresponding to the matching frequency ranges for each stop-consonant cue. As stated previously, spectral peak cues are particularly dominant in perception and discrimination of stop consonants. This is in contrast to Figure 7, which considers place of articulation cues for all consonants. Similar to previous analyses, results were examined within each listener comparing findings across ears, and results are shown in Figure 8. These results showed a weak, but significant correlation between the ear difference in regional means of the primary ECAP measure (R-L) and the ear difference in the transmission of distinct stop-consonant cues with corresponding spectral-peak content. These results are consistent with the idea that the primary ECAP measure reflects conditions at a localized population of neuronal fibers that affect speech perception.

While these results largely showed the between ear difference in the primary ECAP measure was related to the between ear difference in most speech recognition measures, further

analysis using a simple regression model revealed that the primary ECAP measure is not significantly related to speech recognition skills when analyzed across all subjects. Results of the linear mixed model analysis and the patterns present in Figure 6 complement the results obtained in Figures 4 and 5 (between ear analyses); specifically, these results emphasize the importance of individual subject factors when comparing speech recognition with ECAP measures.

Comparison of ECAP measures across ears

We hypothesized that within each subject there would typically be an ear which demonstrated larger values for ECAP measures using a constant IPG. Additionally, based on the data reported by Ramekers and colleagues (Ramekers et al., 2014) one might expect that the same ear would demonstrate a larger change in ECAP peak amplitude or AGF slope when the IPG was increased. Therefore, we predicted that if for example the right ear had higher ECAP peak amplitude and AGF slope values, then the right ear would show a greater change in both features as the IPG was increased. As shown in Figure 3 this was not necessarily the case. Only three subjects (s81, s89, s104) showed a clear pattern consistent with this prediction. In the remaining subjects, there were not clear patterns across ECAP measures or ears tested. As a reminder, gray bars shown in these graphs represent a non-significant difference across the two ears for the measures shown.

While the reason for these results is not exactly clear, one could speculate that there are a number of possible explanations. For example, the effective stimulus polarity might differ across species and/or as a function of neural survival. Results obtained by Ramekers and colleagues were collected using an alternating phase polarity (Ramekers et al., 2014) while the phase polarity in the current study was always cathodic first. Ramekers and colleagues (Ramekers et al., 2014) included three groups of animals that underwent different deafening procedures to create diverse neural health including one group that received an implant in a normal-hearing ear. The SGN density of the groups, on average, spanned a wide range from approximately 600 to 1600 cells/mm^2. While human temporal bone analyses reveal that the range of SGN survival is broad and overlaps significantly across cadavers of normal hearing and deafened humans, the average SGN count is greater among the former compared to the latter group (Pfingst, Bowling, et al., 2011). Therefore, studies using animals that encompass a wide range of neural density may not necessarily accurately reflect the average neural density of human CI recipients. This broader range of neural health of the animals used by Ramekers and colleagues and others (Prado-Guitierrez et al., 2006; Ramekers et al., 2014), accompanied by anatomical differences across species, are particularly important to consider given that both variables have been postulated to effect the excitatory phase of a biphasic pulse. For example, the effect of IPG manipulation on increasing excitability may be minimal if the excitatory phase of the biphasic pulse is the leading phase. It has been reasoned that there are three possible factors that may influence polarity sensitivity to electrical stimulation including position of the electrode relative to the neuron, properties of the neurons (e.g., health of the neurons), and stimulus level (Macherey, Carlyon, van Wieringen, Deeks, & Wouters, 2008). There is evidence in guinea pigs and cats showing that either a cathodic or anodic phase can drive the ECAP response (Matsuoka, Abbas, Rubinstein, & Miller, 2000; C. A. Miller et al., 1998; C. A. Miller, Robinson, Rubinstein,

Abbas, & Runge-Samuelson, 2001). Some have hypothesized that these differences in animals might be caused by species-dependent differences such as cochlear anatomy and/or physical distance/relationship between the electrodes and stimulated neurons (Matsuoka et al., 2000; C. A. Miller et al., 1998). The excitatory phase might also depend on neural health and anatomy; specifically, if the peripheral process is present and/or myelinated (Rattay, 1999; Rattay, Lutter, & Felix, 2001).

Much evidence to date using both ECAP and psychophysical measures shows that the anodic phase of the biphasic stimulus pulses contribute most towards the ECAP response in human subjects (Macherey et al., 2008; Schvartz-Leyzac & Pfingst, 2016; Undurraga, van Wieringen, Carlyon, Macherey, & Wouters, 2010). Ramekers and colleagues (Ramekers et al., 2014) used an alternating polarity when measuring ECAPs but post-measurement analysis revealed a trend that the cathodic phase was the excitatory phase for implanted animals with normal hearing; and there was evidence that the anodic phase was the excitatory phase for the deafened animals. Given this trend, one must consider how increasing the IPG would affect ECAP amplitudes and slopes in deafened cochlear implanted humans, whose responses are primarily driven by the anodic phase and how that might relate to SGN density. In such cases, the leading phase of the cathodic-first pulse would hyperpolarize the cell. The IPG would allow for the membrane potential to achieve a resting state before being depolarized by the anodic phase. It is hypothesized that, in a deafened human with lower SGN density a shorter IPG duration is sufficient to allow all or nearly all of the fibers hyperpolarized by the first state to reach a resting state before being excited (depolarized) by the second, anodic phase. In cases of higher neural density, increasing the IPG would allow more time for a greater proportion of fibers to reach a resting state prior to excitation by the second phase. This reasoning would help to explain the fact that, in our population of bilaterally-implanted, deafened human subjects where it is likely that ECAP responses were primarily driven by the anodic phase, speech understanding was better in the ear with the larger IPG effect.

Further, ECAP measurements obtained using animals can be difficult to apply directly to human subjects when there are differences in the dynamic range used for testing. Specifically, clean and systematic ECAP data obtained in previous studies in animals were typically collected when the animals were anesthetized (Ramekers et al., 2014). In studies which we have done in awake animals the upper limit of stimulation has been determined by the onset of facial nerve stimulation (Colesa et al., 2016; Pfingst et al., 2015). In this study and nearly all those performed in human subjects, participants are tested in the awake state and the upper limit of stimulation is based on perceptions of loudness. As mentioned previously, this perception of loudness is highly subjective and likely varies across subjects and electrodes. In animal studies, SGN dendity has been shown to correlate with ECAP measures such as the peak amplitude measured at high stimulation levels near the upper limit of the neural dynamic range, i.e., the level at which the input-output function saturates. In awake human subjects, there is no way of knowing at which point along the neural dynamic range these measures are being collected/analyzed. This could lead to inconsistencies when comparing across animal and human data and also across ECAP measures (e.g., peak amplitudes and AGF slope).

Primary ECAP measure

We hypothesize that this primary ECAP measure is unique in two specific ways, which could perhaps explain its significant predictive relationship with speech recognition in human subjects, whereas other measures performed here did not significantly correlate with speech recognition. First, we suggest that the slope of the ECAP AGF is the a better measure to use in CI users who are tested in an awake state than are measures at a peak current because the upper limit of stimulation on each electrode is subjective and depends on each listeners' tolerance for loud sounds. It is clear that this tolerance differs across subjects and across electrodes. For example, based on anecdotal evidence when working in clinical settings, it is often observed that CI listeners are more sensitive to higher pitched, basal electrodes even if they report that the perception is not truly "loud". Much of the data in animals showing a relationship between ECAP peak amplitude to SGN density have been collected in sedated animals and therefore these ECAP measures can be collected at very high stimulus current levels, certainly at the peak of the neural dynamic range. Therefore in human listeners, measures such as the ECAP peak amplitude are somewhat ambiguous as the maximum tolerance level for each electrode could be confounding these results. Indeed, among most listeners tested we found that the AGFs were fairly linear and only a minority of electrodes showed a sigmoidal function (or, saturation of the response). Alternatively, data collected in our lab to date shows that the slope of the ECAP AGF can be typically, accurately estimated (e.g., goodness of fit, correlation coefficients and significance levels) based on 3–4 points above the ECAP threshold even when the dynamic range is limited.

Second, we propose that one potential advantage of using the change in ECAP AGF slope with increased IPG as opposed to using slope alone is that the slope change may be less influenced by across-channel characteristics of the electrode-neural interface such as impedances that affect ECAP amplitudes and by extension AGFs. ECAP measures should be inherently affected by conditions between the neurons and the electrode, such as fibrous tissue or osseous growth which also likely vary across the electrode array. That is, ECAP AGF slopes might reflect biophysical attributes other than, or in addition to, neural health such as those reflected in impedance values. In fact, in a related paper we found that in nearly 40% of cases across-site variations in common ground impedances at the sites of the recording electrodes were significantly negatively correlated with across-site variations in ECAP peak amplitude and AGF slope values for a stimulus with 7 μs IPG. In contrast, it was observed that a similar significant correlation was found in only 2.5% of cases when impedance values were compared with the proportional increase in peak amplitude or AGF slope as the IPG was increased from 7 to 30 μs (Schvartz-Leyzac & Pfingst, 2016). At any given stimulation site, across-site variances for factors other than neural health might be strong enough to mask effects of neural health on the AFG slopes. Examining how ECAP measures change as the IPG increases might provide a method of estimating neural health that is less affected by conditions between the neurons and the electrodes. ECAP AGFs for two IPG durations should theoretically be affected in similar ways by other conditions (unrelated to neural health) near the recording electrode site. These effects might cancel out when examining the differences between two AGFs (at two IPGs)\at a single recording site, thus providing a "within-channel" measure of neural health.

Comparison with previous results

The results reported in the present study are very comparable to those reported by Zhou and Pfingst (2014b), which used a psychophysical measure to estimate neural density. The authors reported that between ear differences in MPI slope were related to between ear differences in an adaptive sentence recognition in noise task and a consonant recognition task but, similar to the current study, no such relationship was found on a vowel recognition task. They also found a similar pattern of results when examining the information transmission analyses for consonant recognition (Zhou & Pfingst, 2014b). It should be noted that only two subjects who participated in the Zhou & Pfingst (2014b) study also participated in the current study. Therefore, this pattern of performance relating a given measure of neural health to speech recognition appears to be present across a larger cohort of participants. Taken together, these findings further support the hypothesis that regionally specific measures of neural density and/or function are important for the transmission of speech cues conveyed through spectral peaks.

The findings reported in this study generally support our hypotheses and previous research that the IPG effect reflects neural density to some extent. Ramekers and colleagues demonstrated that animals with greater neural density also showed greater/larger effects of increasing the IPG on ECAP slope measures (Ramekers et al., 2014). In our study, we found that the ear which scored better on sentence recognition in noise and consonant recognition tasks was also the ear which demonstrated greater increases in AGF slope as the IPG was increased from 7 to 30 μs. It is also important to keep in mind that the underlying mechanisms of IPG sensitivity are not fully understood. It is logical that IPG sensitivity also reflects temporal integration mechanisms of the auditory nerve, and perhaps this is true regardless of how many fibers remain.

When comparing ECAP measures to speech recognition, the results of the current study are somewhat in contrast with previous studies (DeVries et al., 2016; Kim et al., 2010), granted there is not overwhelming evidence of a clear relationship between ECAP measures and speech recognition abilities (van Eijl et al., 2017). DeVries and colleagues (DeVries et al., 2016), found that the ECAP amplitude using monopolar stimulation was significantly correlated with a combined vowel and consonant recognition score analyzed across subjects. In the present study, we did not find that the between ear difference in the ECAP maximum amplitude was significantly correlated with the between ear difference on any speech recognition measures. Of note, in the experiment by DeVries and colleagues, the ECAP amplitude was derived from a current stimulus level corresponding to a loudness rating of "most comfortable" on each electrode, and then a loudness balancing procedure was performed across all electrodes within the array (similar to a procedure used in a clinical setting). It is possible that differences in methodology or stimuli could help to account for the incongruent findings. While Kim and colleagues (Kim et al., 2010) did find a significant correlation between the slope of the ECAP AGF and speech recognition abilities for both hybrid and traditional cochlear implants, they did not find that the magnitude of change in ECAP sensitivity at various points along the psychometric curve of the AGF as a function of increasing the IPG related to speech understanding. However, results by reported by Ramekers and colleagues (Ramekers et al., 2014) noted that this particular measure (shift at

50% of the dynamic range) produced a weaker correlation with neural health than examining the change in the AGF slope as a function of the IPG. Additionally, as reported in a related study (Schvartz-Leyzac & Pfingst, 2016) we found that this measure becomes difficult to accurately estimate in human subjects. Often within the same electrode changing the IPG completely shifted the input dynamic range and that of the output AGF. In some cases, the shift in current stimulus produced very little overlap in current level values across two IPG conditions, thereby making it difficult or impossible to apply this measure (shift at 50% of the AGF dynamic range).

Clinical application

In the current study, we showed that the between ear difference of the primary ECAP measure was predictive of speech understanding differences across ears within a subject. Previous studies have shown that within a subject, speech understanding can be improved by using a "site-selection" approach in which specific electrodes are activated or deactivated based on performance measured on a psychophysical task or based on estimates of channel interaction obtained from CT scans (Garadat, Zwolan, & Pfingst, 2012, 2013; Noble, Gifford, Hedley-Williams, Dawant, & Labadie, 2014; Noble et al., 2016; Noble, Labadie, Gifford, & Dawant, 2013; Zhou & Pfingst, 2014a; Zwolan, Collins, & Wakefield, 1997). Likewise, the current primary measure, which is assumed to reflect underlying, localized neural status could also be implemented in a site-selection approach in an effort to improve speech recognition by processor-MAP programming based on individual characteristics of the impaired, implanted cochlea near each electrode in the cochlear-implant electrode array. One advantage of using ECAP measures instead of data obtained from a psychophysical task or CT imaging is that the hardware and software required for testing are already available in all cochlear implant clinics. While currently used in a different capacity, ECAP measures are familiar to clinical audiologists and therefore implementation of such measures would be easier than implementation of a psychophysical task. Furthermore, with further development of protocol and slight modification to programming software, ECAP measures could be obtained rather efficiently compared to psychophysical tasks. Lastly, ECAP measures are a low-risk assessment of neural function to use for a site-selection approach whereas the use of CT scans to manipulate speech processor MAPs carries increased cost and exposure to radiation. Future studies will work toward applying ECAP measures to select electrode sites for activation, deactivation, or modification to ultimately improve performance with a CI in individual subjects.

Acknowledgments

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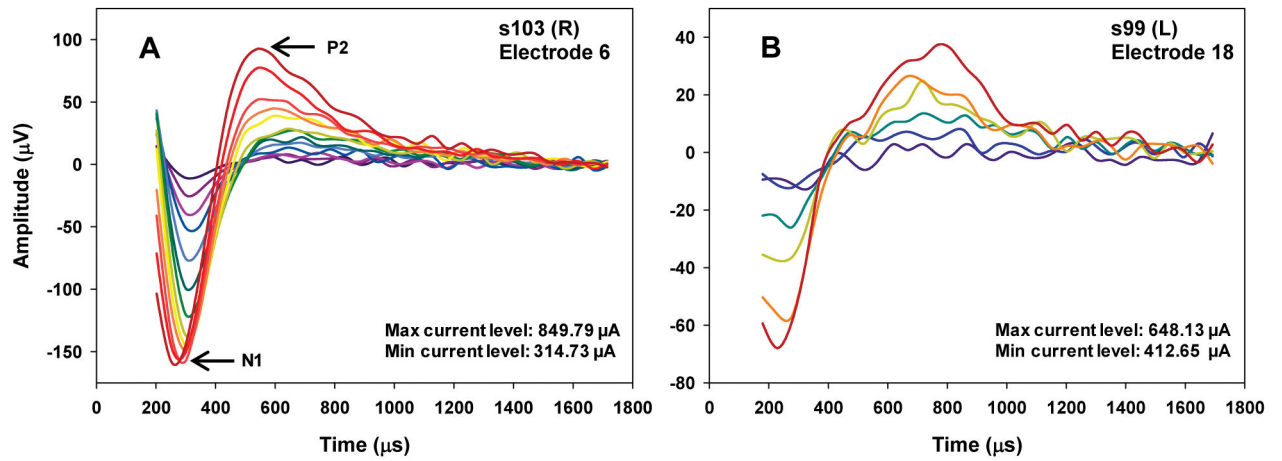
Figure 1.

Examples of typical acceptable waveforms recorded in the current study. The figure on the left shows an example of a robust response with a larger amplitude and dynamic range. The figure on the right shows an acceptable tracing, but with a lower overall amplitude and narrower dynamic range. Various colors corresponding with the color spectrum represent different input current levels; both the maximum (red) and minimum (violet) levels used to achieve these tracings are provided within each panel.
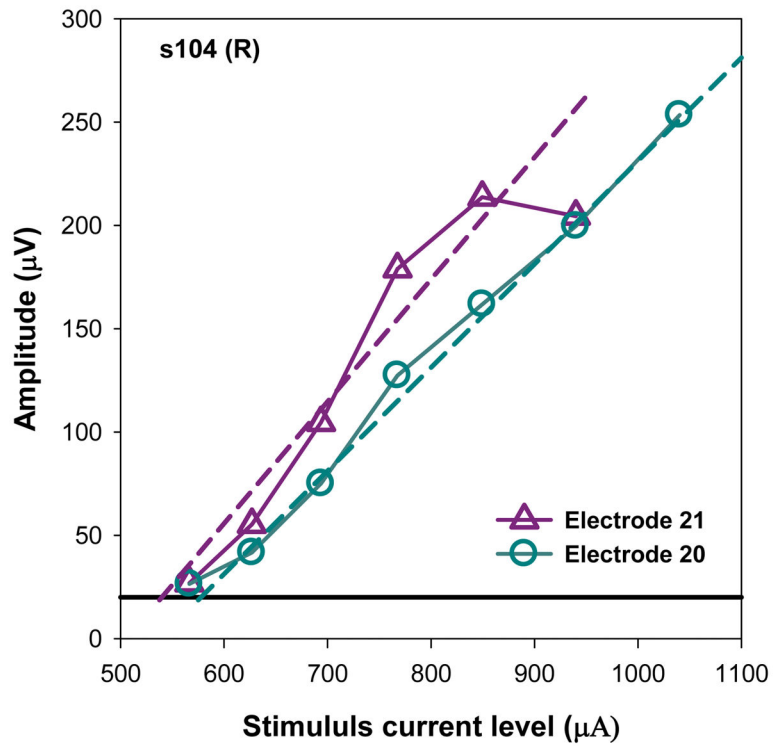
Figure 2.
Examples of ECAP AGF functions for two electrodes within one subject (s104) evaluated in the current study. In both examples shown, the IPG was equal to 7 μs.
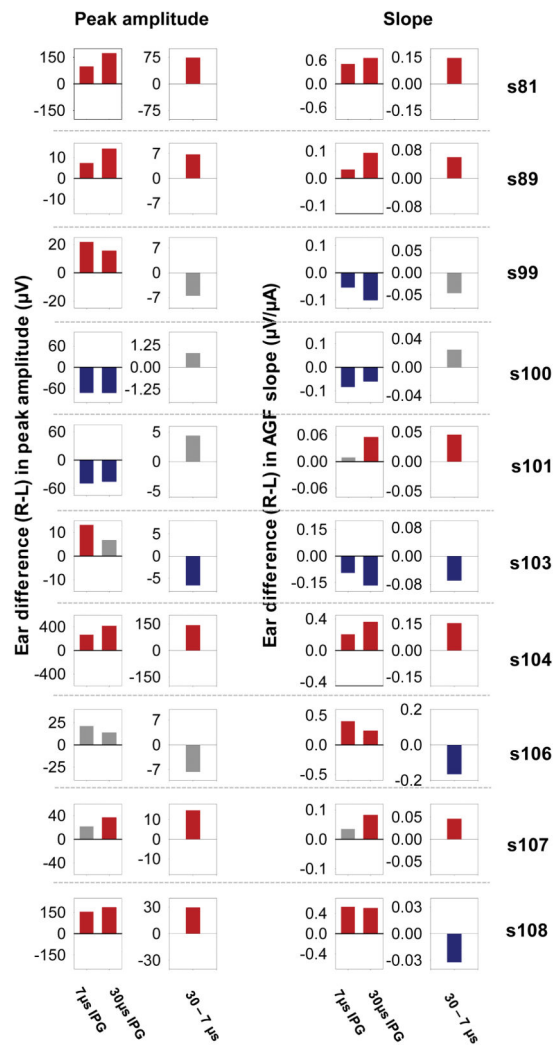
Figure 3.
Individual bar graphs for each subject (identified at far right column) showing the magnitude of ear difference (R-L) for each ECAP measure (identified by column title). The IPG condition is provided at the bottom of the graphs for each column/ECAP measure. For each ECAP measure and IPG condition shown, red bars indicate a significantly higher value in the right ear and blue bars indicate a significantly higher value in the left ear. Gray bars represent non-significant findings (p>0.05).
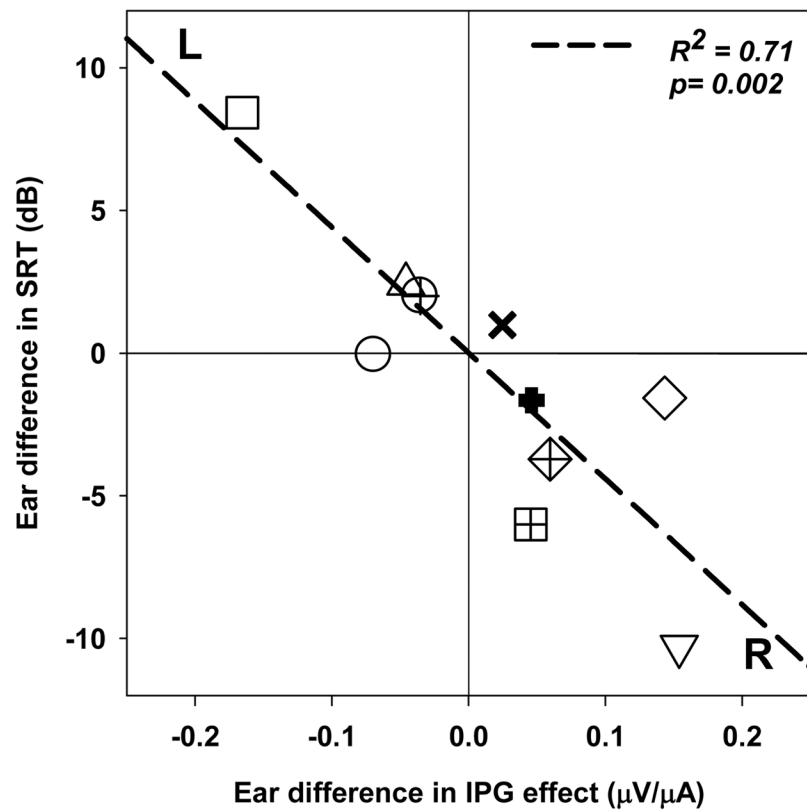
Figure 4.
Scatterplot of ear differences (R-L) in the speech recognition thresholds (SRTs) on the y-axis compared to the across-site mean ear differences (R-L) of the primary ECAP measure [IPG Effect = AGF slope (μV/μA) increase as the IPG was increased from 7 to 30 μs] on the x-axis. Each data point corresponds to one of ten subjects tested, and symbols are identified in Table I. The dashed line shows the fitted linear function of the regression analysis, and statistics (regression coefficient and p-value) are also provided.
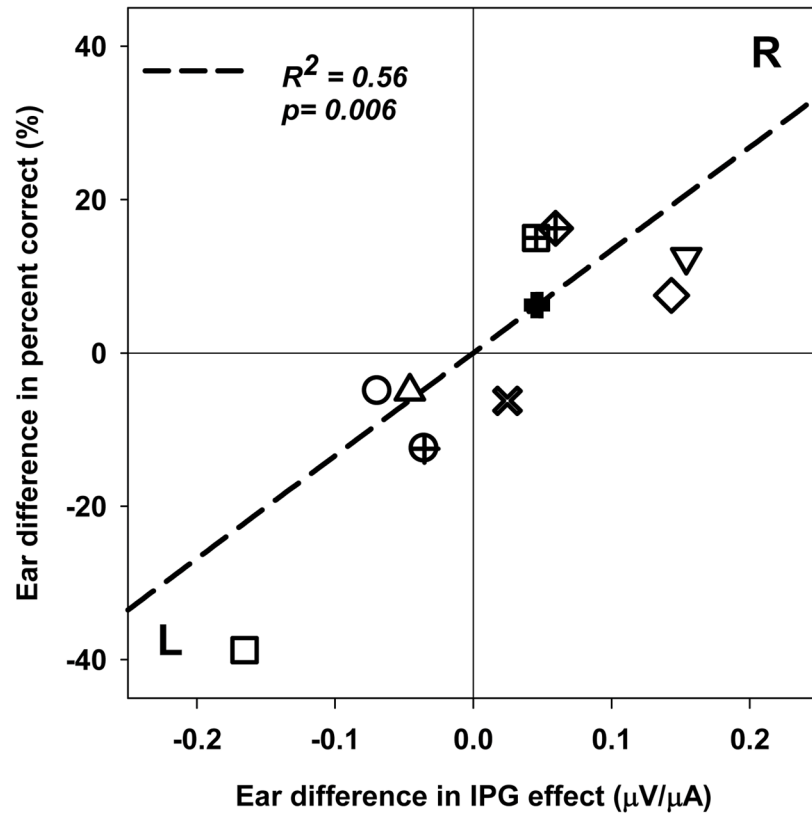
Figure 5.
Same as Figure 4, with the exception that the y-axis represents the ear difference (R-L; percent correct) on a consonant recognition in quiet task.
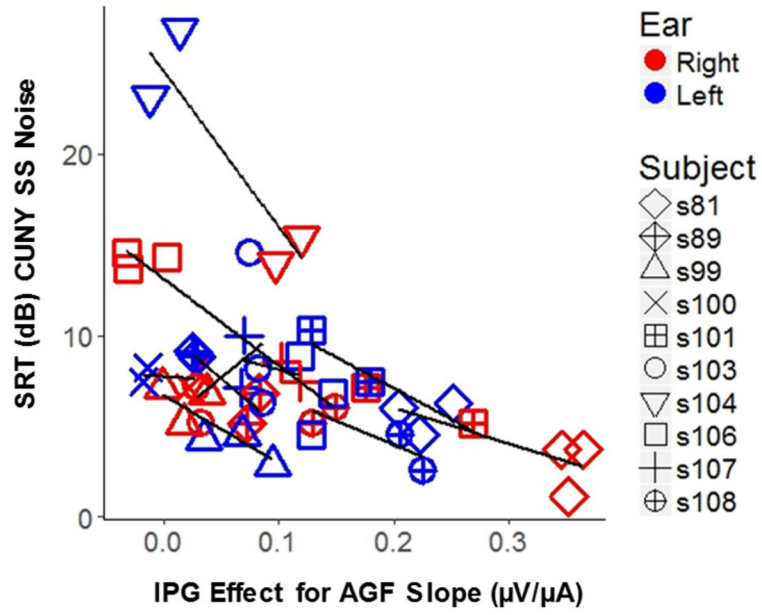
Figure 6.
Scatterplot showing the across-subject relationship between the across-site mean of the primary ECAP measure (e.g., relative AGF slope increase as the IPG was increased from 7 to 30 μs) on the x-axis and speech recognition thresholds (SRTs) for each ear on the y-axis. Data points include all data for each repetition in each ear. Individual subjects' data points are identified using various symbol shape (see Table I), and test ear is represented by color (Right Ear = Red; Left Ear = Blue). Individual regression lines are shown for each subject.
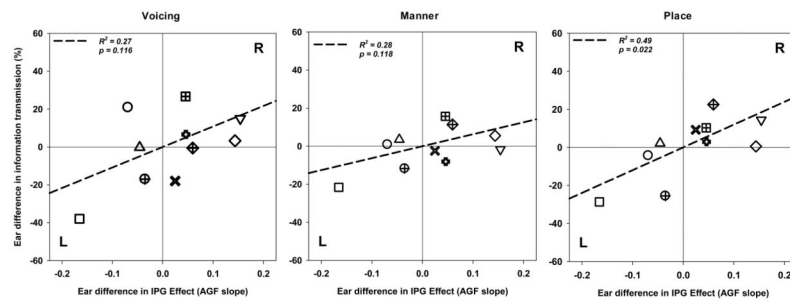
Figure 7.

Three scatterplots representing transmission of voicing, manner, and place cues for the consonant identification in quiet task. Each plot shows the ear differences (R-L) in the transmission of the consonant feature on the y-axis, and the ear difference (R-L) in the across-site mean of the primary ECAP measure (e.g., AGF slope increase as the IPG was increased from 7 to 30 μs) on the x-axis. Each data point corresponds to one of ten subjects tested, and symbols are identified in Table I. The dashed line shows the fitted linear function of the regression analysis forced through the origin, and statistics (regression coefficient and p-value) are also provided.
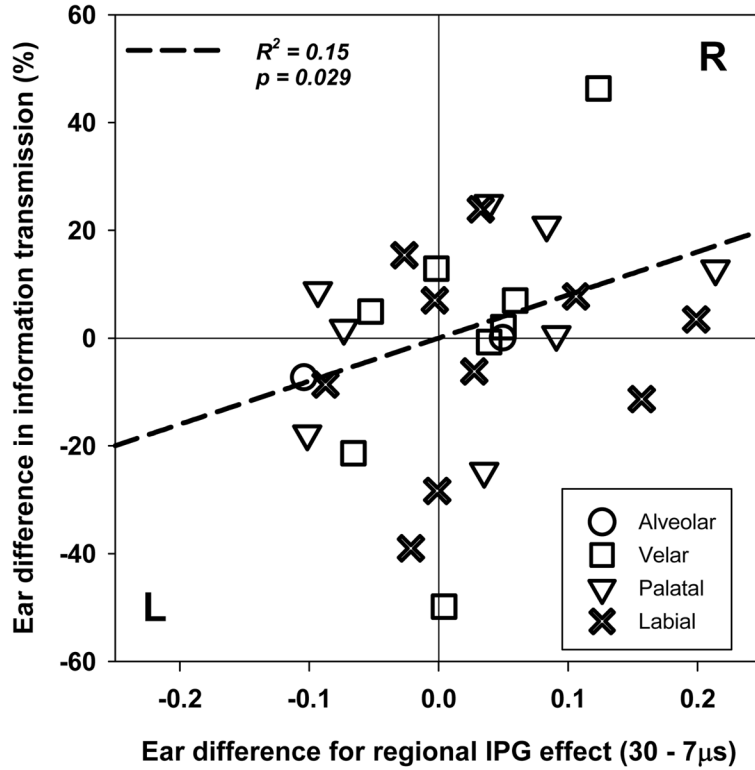
Figure 8.
Scatterplot of ear differences (R-L) in the transmission of frequency-specific place of articulation cues on the y-axis and the ear differences (R-L) in the across-site mean of the primary ECAP measure (e.g., AGF slope increase as the IPG was increased from 7 to 30 μs) on the x-axis. Each symbol represents place of articulation (alveolar, velar, palatal, and labial) as shown within the figure legend. Each data point represents a between-ear comparison for each subject, for each place articulatory feature. The dashed line shows the fitted linear function of the regression analysis forced through the origin, and statistics (regression coefficient and p-value) are also provided.

Table I

Demographic table showing relevant data for each subject, for each ear. The asterisk (*) indicates that, this particular subject received her first implant in the left ear 13 years ago, then subsequently underwent explantation/reimplantation of the device 10 years ago. The number symbol (#) indicates this subject received her first implant in the right ear 6 years ago and underwent explantation/reimplantation of the device 5 years ago.

	Age	Symbol	Ear	Implant	Age at onset of hearing loss	Years implantation	Etiology
S81	64	∘	R	CI24RE(CA)	39 years old	10	Hereditary
			L	CI24RE(CA)	39 years old	8	Hereditary
S89	70	⊕	R	CI24RE(CA)	5 years old	3	Measles
			L	CI24RE(CA)	5 years old	2	Measles
S99	48	△	R	CI24R(CA)	8 years old	11	Hereditary
			L	CI24RE(CA)	8 years old	6	Hereditary
S100	75	×	R	CI512	5 years old	5	Unknown
			L	CI24RE(CA)	5 years old	3	Unknown
S101	63	⊞	R	CI512	35 years old	5	Autoimmune
			L	CI24RE(CA)	35 years old	9	Autoimmune
S103	73	○	R	CI24RE(CA)	40 years old	.5	Hereditary/Noise Exposure
			L	CI24RE(CA)	40 years old	1	Hereditary/Noise Exposure
S104	48	▷	R	CI24R(CA)	3 years old	11	Hereditary
			L	CI512	3 years old	6#	Hereditary
s106	23	□	R	CI24RE(CA)	4 years old	3	Meningitis
			L	CI24RE(CA)	4 years old	13*	Meningitis
s107	64	+	R	CI24RE(CA)	5 years old	9	Hereditary
			L	CI512	5 years old	5	Hereditary
s108	25	⊕	R	CI24R(CA)	Congenital	1	Connexin 26
			L	CI24RE(CA)	Congenital	11	Connexin 26

Table II

Correlational analyses between all speech recognition measures performed in this study, when analyzed across subjects. Significant correlation coefficients following Bonferroni corrections are indicated with an asterisk (*).

	CUNY Sentences (SS Noise)	CUNY Sentences (Modulated Noise)	Vowels (Quiet)	Vowels (+10 dB SNR)	Consonants (Quiet)	Consonants (+10 dB SNR)
CUNY Sentences (SS Noise)	---	*r = 0.93** *p < 0.003*	*r=−0.63* *p = 0.07*	*r=−0.56* *p = 0.11*	*r= 0.85** *p < 0.003*	*r= −0.79** *p < 0.003*
CUNY Sentences (Modulated Noise)		---	*r=−0.48* *p = 0.15*	*r=−0.49* *p = 0.17*	*r=−0.80** *p < 0.003*	*r= −0.78** *p < 0.003*
Vowels (Quiet)			---	*r= 0.89** *p < 0.003*	*r= 0.65* *p = 0.03*	*r= 0.62* *p = 0.08*
Vowels (+10 dB SNR)				---	*r= 0.67* *p = 0.05*	*r= 0.68* *p = 0.04*
Consonants (Quiet)					---	*r= 0.98** *p < 0.003*
Consonants (+10 dB SNR)						---

Table III

Correlational analyses between three speech recognition measures performed in this study, and all ECAP measures. Significant correlation coefficients following Bonferroni corrections are indicated with an asterisk (*).

	CUNY Sentences (SS Noise)	Vowels (Quiet)	Consonants (Quiet)
Peak amplitude (7 μs IPG)	$R^2 = 0.33$ $p= 0.08$	$R^2 = 0.03$ $p= 0.61$	$R^2 = 0.00$ $p= 0.91$
Peak amplitude (30 μs IPG)	$R^2 = 0.40$ $p= 0.04$	$R^2 = 0.01$ $p= 0.74$	$R^2 = 0.01$ $p= 0.72$
Peak amplitude change (30-7 μs)	$R^2 = 0.50$ $p= 0.02$	$R^2 = 0.00$ $p= 0.94$	$R^2 = 0.08$ $p= 0.40$
Linear slope (7 μs IPG)	$R^2 = 0.00$ $p= 0.82$	$R^2 = 0.30$ $p= 0.09$	$R^2 =0.19$ $p= 0.20$
Linear slope (30 μs IPG)	$R^2 = 0.05$ $p= 0.50$	$R^2 = 0.13$ $p= 0.29$	$R^2 = 0.10$ $p= 0.77$
Linear slope change (30-7 μs)	**$R^2 = 0.71$ $p<0.008$***	$R^2 = 0.09$ $p= 0.39$	**$R^2 = 0.56$ $p<0.008$***

Table IV

Individual raw scores (dB SNR) for each subject and ear on the CUNY Sentences in Steady- State Noise speech recognition task. Numbers in parenthesis indicate the standard deviation. The raw value of the difference scores is also shown in the last row (dB SRT, R-L).

	S81	S89	S99	S100	S101	S103	S104	S106	S107	S108
Right	3.71 (0.42)	6.28 (0.80)	6.14 (1.41)	7.98 (1.22)	5.28 (0.19)	7.14 (0.00)	14.71 (1.00)	14.14 (0.60)	6.77 (0.91)	5.57 (0.60)
Left	5.28 (1.01)	9.99 (1.20)	3.71 (1.21)	6.99 (0.60)	11.28 (1.41)	7.21 (1.31)	24.99 (2.62)	5.71 (1.61)	8.42 (2.22)	3.57 (1.14)
Difference (R-L)	−1.57	−4.14	2.43	0.99	−6.00	−0.07	−10.28	8.43	−1.65	2

Table V

Individual raw scores (percent correct) for each subject and ear on the consonant recognition in quiet speech recognition task. Numbers in parenthesis indicate the standard deviation. The raw value of the difference scores is also shown in the last row (percent correct, R-L).

	S81	S89	S99	S100	S101	S103	S104	S106	S107	S108
Right	90.00 (3.53)	82.5 (0.00)	80.00 (3.53)	58.75 (1.76)	68.75 (1.76)	73.75 (5.30)	41.25 (5.30)	53.75 (5.30)	72.5 (3.53)	52.5 (3.53)
Left	82.5 (0.00)	66.25 (12.37)	75.00 (3.53)	65.00 (0.00)	48.75 (1.76)	71.25 (1.76)	28.75 (15.90)	92.5 (1.76)	66.25 (5.30)	65 (10.60)
Difference (R-L)	7.5	16.25	5	−6.25	20	2.5	12.5	−38.75	6.25	−12.5

Table VI

Frequency allocations associated with electrodes which were selected for regional slopes. Corresponding place of articulation features are also shown for each frequency allocation. The frequency allocation shown here is for a standard speech processor map using default settings with all electrodes activated and is therefore provided to provide approximate allocation used for each ear. However, actual frequency allocation differed if electrodes were deactivated in the speech processor map and analyses were adjusted accordingly.

Electrodes	Frequency allocation (Hz)	Articulatory Feature (Place)
1–3	5313–7938	Alveolar
4–6	3563–5413	Velar
7–16	938–3563	Palatal
15–22	188–1063	Labial

Table VII

Individual raw scores (dB SNR) for each subject and ear on the CUNY Sentences in Modulated Noise, Vowel recognition in quiet and in noise (+10 dB SNR), and Consonant Recognition in noise tasks. Numbers in parenthesis indicate the standard deviation. The raw value of the difference scores is also shown in the last row (R-L).

	S81	S89	S99	S100	S101	S103	S104	S106	S107	S108
CUNY Sentences (Modulated Noise)										
Right	1.71 (1.61)	7.85 (1.14)	7.28 (1.81)	15.71 (1.61)	8.71 (1.00)	10.57 (2.02)	16.42 (1.81)	16.85 (0.80)	8.99 (0.20)	9.28 (1.01)
Left	3.21 (0.09)	11.99 (1.61)	5.71 (0.41)	11.85 (0.60)	11.57 (1.41)	10.57 (0.00)	27.71 (0.40)	5.71 (1.61)	8.71 (0.60)	10.21 (4.14)
Difference (R-L)	−1.5	−4.41	1.57	3.86	−2.86	0	−11	11.14	0.28	−0.92
Vowel Recognition (Quiet)										
Right	90.62 (4.41)	89.58 (8.83)	82.29 (4.41)	91.67 (0.86)	89.58 (2.94)	93.75 (0.00)	43.75 (0.00)	50.14 (5.91)	72.92 (8.83)	65.52 (1.47)
Left	90.62 (1.47)	89.58 (5.89)	89.45 (0.17)	84.37 (4.41)	54.16 (11.78)	53.12 (4.41)	34.37 (4.41)	83.33 (2.94)	79.16 (5.89)	76.04 (4.42)
Difference (R-L)	0	0.00	−7.16	7.29	35.42	40.62	9.375	−33.31	−6.24	−10.41
Vowel Recognition (+10 dB SNR)										
Right	86.46 (1.47)	76.04 (1.47)	75.00 (5.89)	71.87 (4.41)	70.83 (2.94)	79.17 (1.61)	28.12 (10.31)	51.04 (1.47)	76.04 (1.47)	DNT
Left	77.04 (0.05)	69.79 (1.47)	86.45 (4.41)	70.83 (5.89)	50 (2.94)	48.96 (1.47)	27.08 (8.83)	76.04 (1.47)	66.66 (8.83)	DNT
Difference (R-L)	9.42	6.25	−11.45	1.04	20.83	30.21	1.04	−25.00	9.38	DNT
Consonant Recognition (+10 dB SNR)										
Right	66.25 (5.30)	62.5 (3.53)	61.25 (5.83)	13.75 (5.30)	58.75 (5.30)	50.00 (7.07)	10.00 (0.00)	28.75 (5.83)	53.75 (8.83)	16.25 (1.76)
Left	62.5 (3.53)	56.25 (6.83)	58.75 (5.30)	21.25 (6.37)	43.75 (5.30)	52.5 (1.76)	6.25 (5.30)	60 (1.76)	48.75 (5.30)	52.25 (1.76)
Difference (R-L)	3.75	6.25	2.5	−7.5	15	−1.25	3.75	−31.25	5	−35