Eleventh Quarterly Progress Report
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Effects of Remaining Hair Cells on Cochlear Implant Function

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1 Introduction

In this contract, we are conducting physiological and computational model experiments to assess the effects that functional hair cells have on the auditory nerve's response to electrical stimulation. This work is relevant to a widening pool of cochlear implant candidates as audiological criteria (e.g., pure-tone thresholds) are becoming more relaxed and patients with residual hearing are being implanted. Intact hair cells may interact with or modify electrical stimuli in several ways. Acoustically evoked neural activity may interact or compete with electrically evoked activity. It is also possible that the very presence of viable hair cells - without any exogenous acoustic stimuli - can modify electrically evoked neural responses. For example, electrical stimuli may depolarize hair cell membranes and initiate the release of neurotransmitter, resulting in nerve-fiber activation. It is also possible that the spontaneous release of neurotransmitter may modulate the response characteristics of nerve fibers, thereby changing their responsiveness to electrical stimuli. The experiments of this contract are designed to acquire evoked potential data from sets of experimental animals that have functional and non-functional hair cells. Comparisons will then be performed to assess the effect of functional hair cells on the transduction of electrical stimuli delivered by intracochlear electrodes.

2 Summary of activities in this quarter

In our eleventh quarter (1 January through 31 March, 2002), the following activities related to this contract were completed:

1. We attended and reported on results at the ARO Midwinter meeting in St. Petersburg Beach FL.

2. We have made measures of the time course of hearing loss with ototoxic deafening (kanamycin and ethacrynic acid) and assessed changes in electrical stimulation over that same time course.

3. We have completed measurements of the acoustic-electric interactions in six partially deafened cats. Results of those experiments are summarized in this QPR.

3 Acoustic electric interactions in partially deafened animals

3.1 Introduction

Over the past several years, there has been an increase in the number of individuals with significant hearing that have received cochlear implants. As implant candidate selection criteria are relaxed, the most obvious expansion of the patient cohort would involve individuals with high frequency hearing loss and significant low frequency hearing. Clinical data suggest that patients with residual acoustic sensitivity can retain that sensitivity after implantation and it is evident that perception of speech and non-speech sounds can be enhanced through combined acoustic and electrical stimulation (Kiefer et al. 2001; Turner & Gantz, 2001). Based on animal studies and human audiometric data, a likely pattern of hair cell survival in implanted patients includes a basal region (around the implanted array) generally devoid of functional hair cells and an apical region with a relatively intact sensory epithelium.

The initial experiments conducted under this contract have used "normal-hearing" animals to provide the best means of observing acoustic-electric interactions. Those experiments have demonstrated interaction between acoustic and electric stimulation in measures of the electrically evoked compound action potential (ECAP) and have been reported in previous Quarterly Progress Reports of this contract (QPR 1 and QPR 3). The masking of the ECAP by acoustic stimulation is affected by the spectral characteristics of the acoustic noise (QPR 7). In general, we found that the high frequency components of acoustic noise were more effective in masking the ECAP evoked with basal electrical stimulation. In addition, the temporal characteristics of the acoustic stimulus can affect the degree of masking, as masking is dependent on the phase of an acoustic sinusoidal stimulus (QPR 5). Such data demonstrate important limitations in the combination of acoustic and electric stimulation to acoustically sensitive ears. They also suggest the possibility of a degree of control of these interactions, as the degree of masking can be manipulated by choosing appropriate acoustic and electric stimulation parameters.

Previous experiments addressed the issue of how the presence of acoustic excitation through hair cells can affect the responses of neurons to electrical stimulation. The work described in this QPR uses a different animal model - partially deafened animals – to examine the extent to which the afore-

mentioned results apply to an ear with high-frequency sensorineural hearing loss. This animal model is an attempt to simulate the type of high-frequency hearing loss that may be typical of an individual receiving a cochlear implant. By doing so, we address issues regarding the applicability of the previously reported results to a more clinically relevant situation.

3.2 Methods

These experiments were designed to accommodate several considerations. First, we wished to use an electrode array appropriate for implantation in an individual with significant low-frequency hearing. Such an experimental array should provide the ability to manipulate the spatial extent and locus of stimulation while at the same time, minimize the extent of insertion trauma. We therefore chose a banded-type, eight-electrode array with a total length of approximately 8 mm in an attempt to meet these opposing needs. Second, to best evaluate electric-acoustic interactions, we chose acoustic stimuli that would maximize the extent of hair-cell activation. Wide-band acoustic noise was therefore chosen. Third, we recognized the need to not only model partial hair-cell loss, but also neural degeneration secondary to such loss. We therefore chose an animal model that was partially deafened and then allowed to survive for a chronic period after deafening. Such an animal model will, in part, simulate limited degeneration of the nerve.

To meet these requirements, our animal model of basal hair-cell loss was produced using cats subjected to a series of daily intramuscular doses of kanamycin, following the protocol of Kiang et al. (1970). After completion of this procedure, tone-burst ABR was assessed to confirm a high-frequency hearing loss contour. Animals were then allowed to survive several months to assure auditory nerve fiber loss and degeneration secondary to the deafening procedure (Spoendlin, 1975; Leake-Jones et al., 1982). A single and terminal experimental session was then conducted to obtain all evoked response measures.

Data are reported here for six cats that demonstrated significant hearing loss after the deafening procedure. Cats (with normal hearing as assessed with ABR measures) were deafened with intramuscular kanamycin injections, according to the procedure outlined in Kiang et al. (1970). Cats were injected daily over a period of 7-10 days. The auditory brainstem response (ABR) was monitored over a period of several weeks after drug administration. Tone-burst stimuli (1, 2, 4, 8 and 16 kHz presented as 5 ms bursts)

were used to obtain threshold responses for the ABR before and after drug treatment. While this model does not simulate damage and/or degeneration typical of all cochlear disease processes, it does have the significant advantage of producing a relatively clear boundary between regions of hair cell loss. The loss of hair cells will result in spiral ganglion cell degeneration in the basal region of the cochlea. We view some degeneration as desirable in that it may better simulate effects in potential cochlear implant candidates. A period of two-to-three months after hearing loss will provide some degeneration of neurons in the basal turn, but will presumably not be long enough to result in complete neuronal loss (Spoendlin, 1975; Kiang et al., 1976; Leake-Jones et al., 1982). Histological evaluations of the cochlea and spiral ganglion cell are not yet completed but will be reported on in subsequent report.

After the 2-3 month waiting period, the animal was anesthetized and prepared for recordings. Methods used were similar to those described in previous QPRs for recordings in normal hearing animals. Initially ABR thresholds were measured for the five stimulus frequencies. A Beyer DT-48 earphone coupled through a speculum was placed into the ear canal. The auditory nerve was exposed and a Pt/Ir ball electrode was placed on the surface of the nerve for compound action potential recordings. CAP thresholds to acoustic stimulation were determined before and after placement of a stimulation electrode in the cochlea through a small opening adjacent to the round window. After electrode placement in the cochlea electrically evoked compound action potentials (ECAP) were measured in quiet as well as in the presence of continuous acoustic white noise. Since we had observed effects of the noise after offset of the noise in previous work, we allowed sufficient time between noise presentations to allow for recovery of the ECAP to pre-exposure response amplitude.

After initial recordings, a Nucleus-type electrode array with 8 banded electrodes was placed into the scala tympani. Typically all 8 electrodes were inserted through the plane of the round window. After insertion, auditory thresholds were measured and then responses assessed for monopolar stimulation of electrode 1 (most apical), electrode 7 or 8 (most basal) and bipolar stimulation between electrodes 1 and 2. After completion of recordings the cochlea was prepared for histological analysis. As of this time, cochlear processing and analyses are not complete; those results be presented in the Final Report.

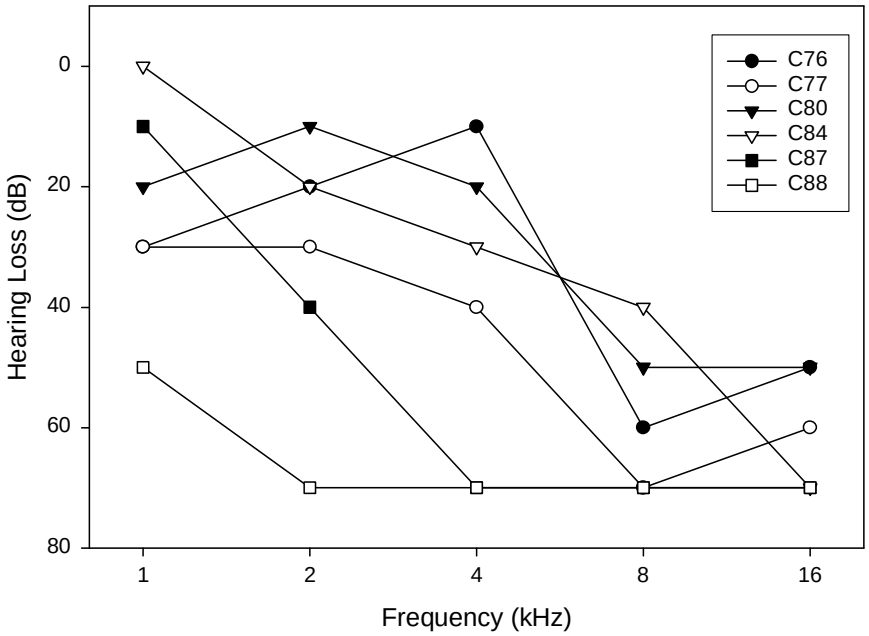

Figure 1: Hearing loss in each of the experimental animals is plotted as a function on stimulus frequency. The loss (in dB) was is the difference in ABR threshold before exposure and the CAP threshold after electrode insertions into the scala tympani.

3.3 Results

Audiometric hearing losses at the time of data collection (i.e., pre-deafening ABR thresholds minus compound action potential thresholds after electrode insertion) are shown for each of the six animals in Figure 1. In all cases there is evidence of high-frequency hearing loss. There is considerable variation in the degree of hearing loss at low frequencies. For this reason, we have elected to present data from individual animals in subsequent figures.

ECAP growth functions in quiet were collected for each stimulating electrode configuration. Typical results are shown in Figure 2 for subject C77. The single-ball electrode and the most basal electrode in the array generally showed similar sensitivity. The more apical electrode produced the lowest threshold, while the bipolar pair typically displayed relatively slow growth and wide dynamic range.

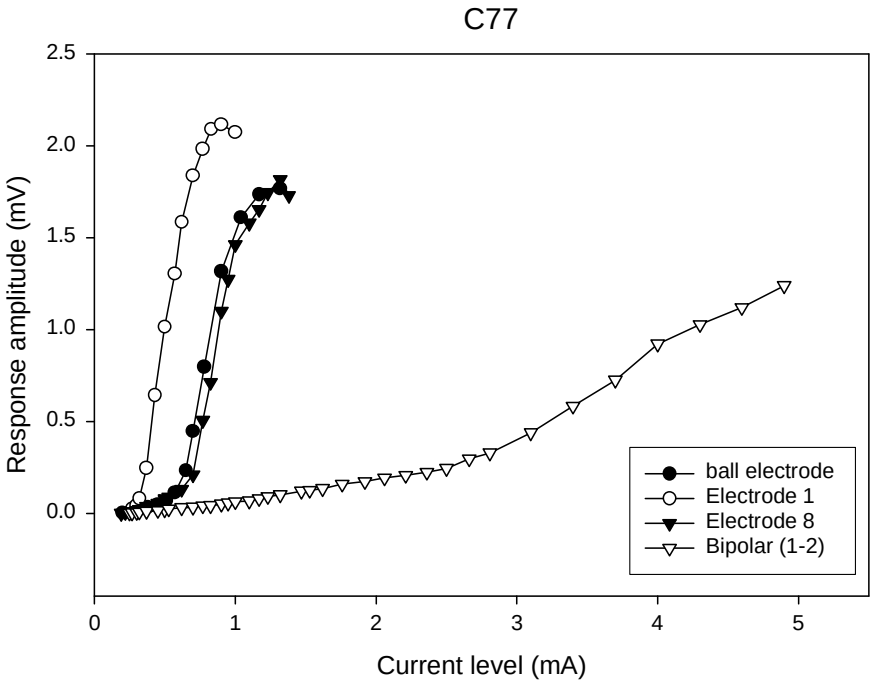

Figure 2: ECAP growth functions (response amplitude vs current level for a 40 us/phase biphasic pulse) are plotted for each of the four stimulating electrode configurations. Ball electrode refers to a single monopolar stimulating electrode placed in the basal turn. Electrode 1 is the most apical electrode in the implanted array. Electrode 8 is the most basal. Both refer to monopolar stimulation configuration.

After detailed growth functions were measured for each electrode configuration (e.g., Figure 2), electric stimulation levels were chosen on a per-subject basis for the acoustic masking study. In each case, we selected 6 to 8 levels spanning the dynamic range for the particular electrode configuration. Responses were then measured across a range of noise levels. In each case, the noise levels were chosen from a level that showed little or no masking up to a maximum of 96 dB SPL overall level. In Figure 3, ECAP growth functions are plotted for each animal for monopolar stimulation of the apical electrode in the array (Electrode 1). Data are plotted for all six subjects in separate graphs. The average hearing loss ("Avg HL"), computed as the mean loss across 5 frequencies, is also indicated in each graph. In each case the parameter is noise level (in dB SPL overall level) as indicated in each legend.

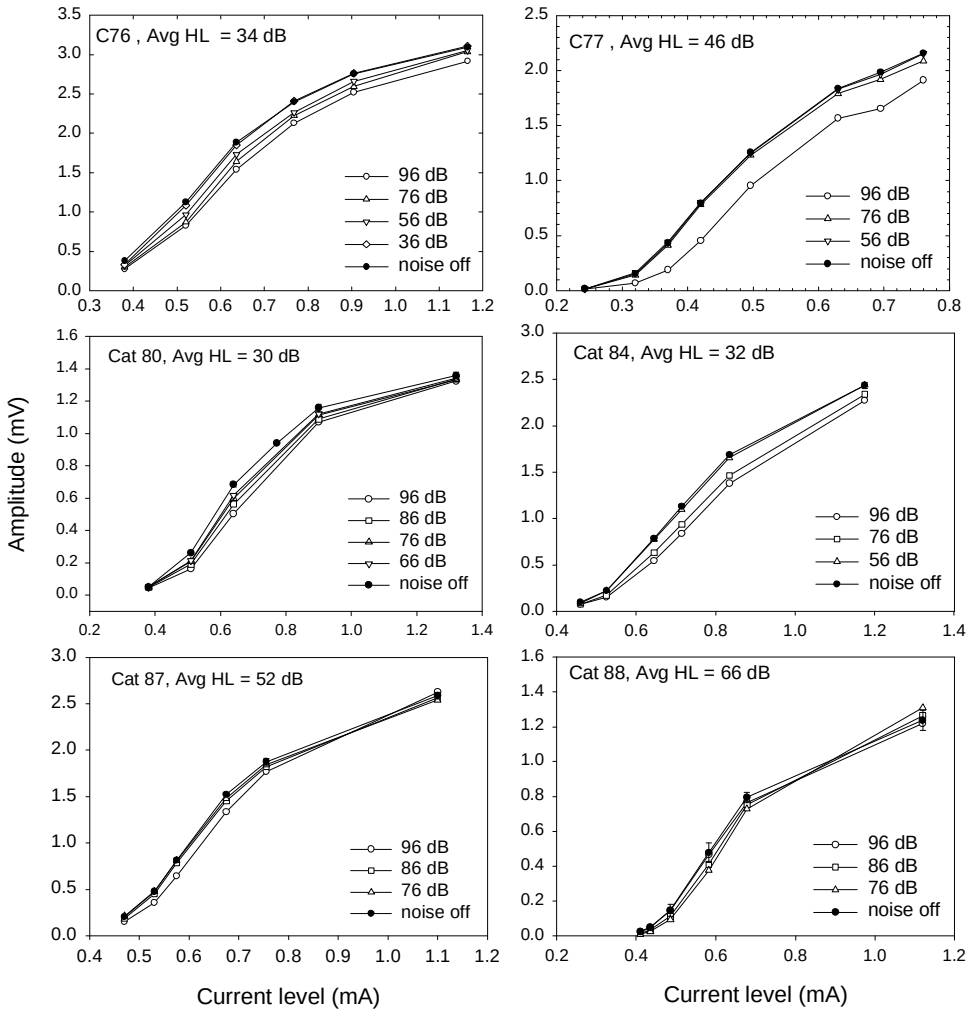

Figure 3: ECAP growth functions with and without a background of continuous white noise. Overall noise level in dB SPL is indicated in the legend.

Several trends are evident in the data of Figure 3. First, there is generally a decrease in response amplitude in the presence of noise. We have observed no enhancement, or increase, in response amplitude in the presence of noise. This is consistent with previous observations in animals with more normal hearing (QPR 5). The decrease in response is most evident at high noise levels and the effect tends to be smaller (i.e., response amplitude increases) at lower noise levels. The effect is evident over a wide range of current levels, i.e., over a wide portion of the dynamic range. Finally, considered as a group, a trend may be evident that subjects with the most hearing loss display the least masking effects (Subjects C87 and C88).

In Figure 4, we present the acoustically masked ECAP data in another way to highlight the effect of the level of the acoustic noise. This figure presents ECAP amplitude as "average normalized amplitude". For this measure, we first computed, for each current level, the response amplitude with noise divided by the amplitude to the same electrical stimulus in quiet. These normalized amplitudes were then averaged across the 6-8 current levels (see Figure 3) and plotted as a function of acoustic noise level for each of the six subjects. With this manipulation, lower values on the ordinate scale correspond to greater degrees of masking. The parameter of each graph of Figure 4 is the stimulus electrode configuration. As noted for the data of Figure 3, there is a general trend that amplitude decreases with increasing noise level. The subjects with more residual hearing tend to show a decrease in response at lower stimulus levels (particularly C80 and C84). Finally there is a clear trend that the apical stimulating electrode shows the greatest masking effect and the bipolar stimulating configuration shows the least. Those trends are all consistent with those expected in terms of overlap of the acoustic and electrical responses with high-frequency hearing loss.

Finally, we wished to examine the trends in masking as a function of electric stimulus level. Since the ECAP growth functions have different sensitivity and slope, we represented stimulus level as the percentage of the saturated response amplitude in order to compare the masking effectiveness across level and across stimulating conditions. Data for the 96 dB SPL noise is plotted in Figure 5 for the six subjects. In each case the parameter is the electrode configuration. In general, as indicated in Figure 4, the effectiveness of the noise was least for the bipolar stimulation condition. We also note that for the monopolar stimulation conditions, the apical electrode tends to show a minimum (greatest masking) at a point lower in the growth func-

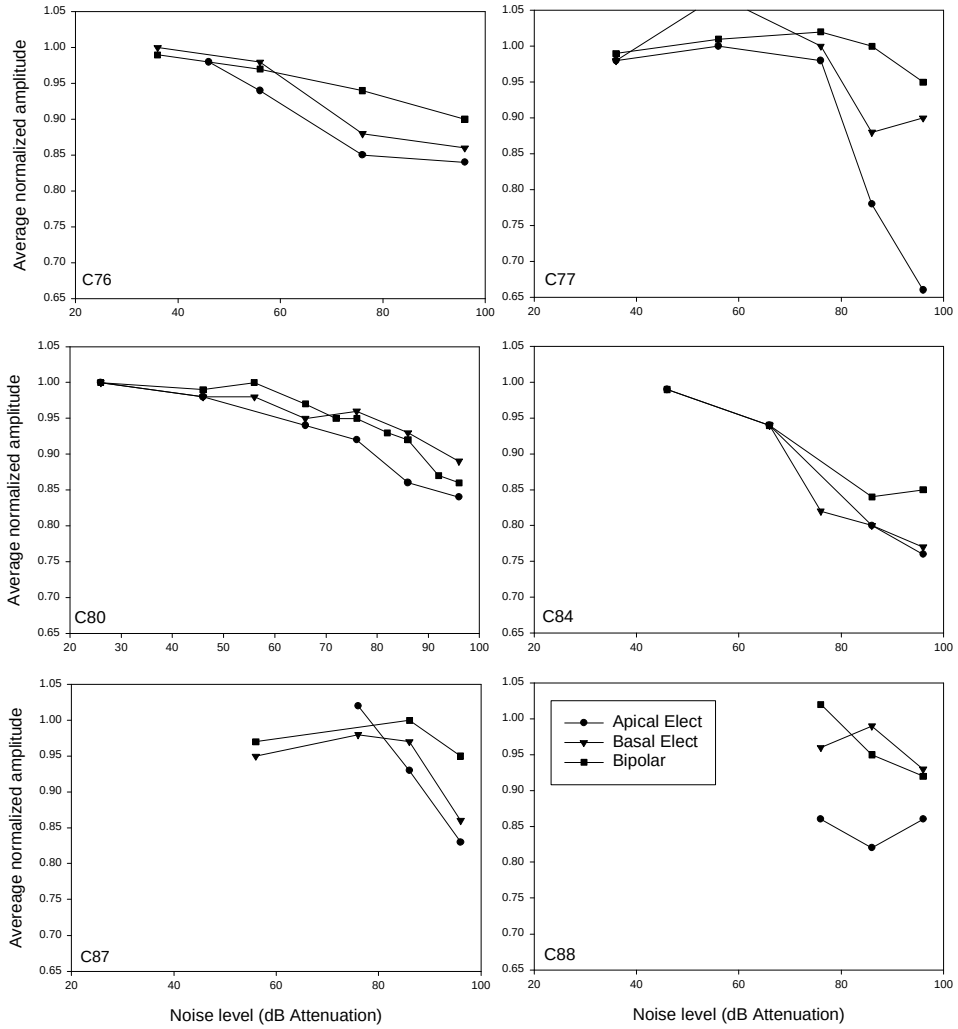

Figure 4: Average normalized amplitude is plotted as a function of noise level. Normalized amplitude is calculated as amplitude of the ECAP with noise divided by the amplitude of response in quiet. In each subject, the stimulus current levels were chosen to span the dynamic range. The average normalized amplitude is the average decrease across stimulus current levels. Values of 1 indicate no effect of noise. Values less than one indicate a decrease in the response in the presence of noise.

tion. Or alternatively, at low levels the apical monopolar electrode shows the greatest interaction. This trend is consistent with a simple model of apical stimulation with acoustic noise and more basal electrical stimulation. If the more apical stimulation electrode (1) is chosen, then one might predict more overlap in the acoustic and electric stimulation at low stimulus levels. Further, the smaller effects observed with bipolar stimulation are also consistent with such a model.

3.4 Summary

These data demonstrate that in subjects with high-frequency hearing loss and an electrode array implanted in the basal turn of the cochlea, there is still significant interaction between electric and acoustic stimulation at the level of the auditory nerve. Those interactions tend to be greatest at high acoustic noise levels (Figure 4) but the interactions are evident at relatively low electric current levels as evidenced in Figure 3. The interactions tend to be less in subjects with greater hearing loss. Finally, with a relatively short electrode array (8 mm), there are clear variations in the interactions for stimulation of different electrode configurations.

4 Plans for the next quarter

In the eleventh quarter, we plan to do the following:

- We will conduct further analysis of the data collected on these animals to assess the changes in interactions with stimulus level. That analysis will be described in the final report for this contract. In addition, the histological analysis will be complete and in that report comparisons between physiologic and histologic data will be reported.

- We will also continue recordings with ethacrynic acid/kanamycin as well as experiments with furosemide discussed in the previous QPR to further assess recovery patterns.

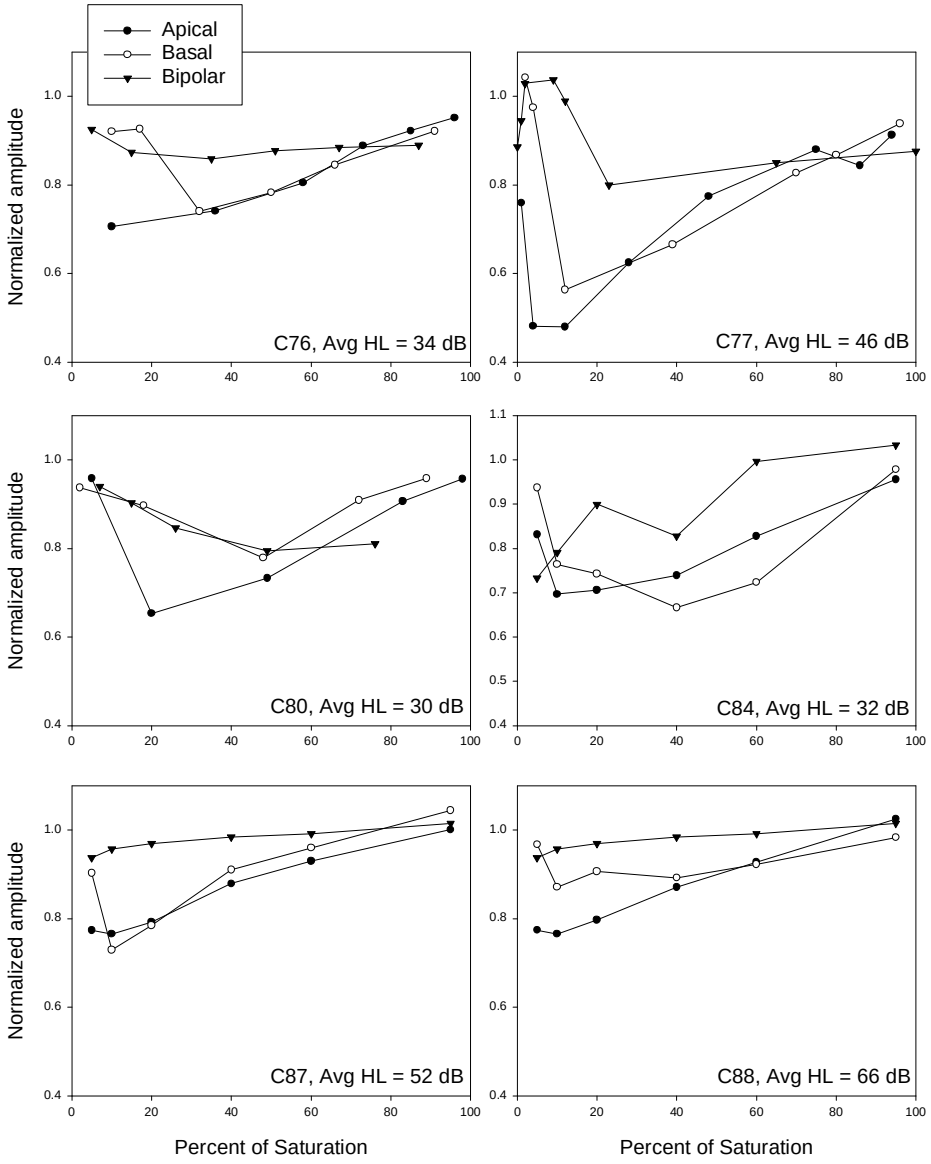

Figure 5: Normalized amplitude is plotteed as a function of stimulus level expressed as the percent of the saturated ECAP response produced by that level. Data are plotted for each of the six subjects. In each graph the parameter is electrode configuration as indicated in the legend.

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