Neurophysiological effects of simulated auditory prosthesis stimulation

12th Quarterly Progress Report

Neural Prosthesis Program
Contract N01-DC-9-2107
(no-cost extension period)

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C.A. Miller, S. Nagase, K. Nourski, P.J. Abbas, B.K. Robinson

Department of Otolaryngology-Head and Neck Surgery
&
Department of Speech Pathology and Audiology

University of Iowa

Iowa City, Iowa, USA

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Effects of Remaining Hair Cells on Cochlear Implant Function
N01-DC-9-2107QPR12

Neural Prosthesis Program

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I. Introduction

The purpose of contract N01-DC-9-2107 was to explore issues involving the transfer of information from implantable auditory prostheses to the central nervous system. While the contract period has expired, we are continuing investigations in some areas that were begun during the contract period and we deemed of significant interest for follow-up work. This activity is being conducted as a no-cost extension of the contract. Areas of investigation will include:

- Evaluation of University of Michigan thin-film recording electrode arrays for auditory-nerve studies.
- Investigation of auditory-nerve adaptation phenomena related to repetitive electrical stimulation.
- Investigation of the effects of recording electrode position, which is the focus of this report.

II. Summary of activities

During this reporting period (concluding March 31, 2003) of our no-cost extension to Contract N01-DC-9-2107, we have continued the following activities:

1. In February 2003, we received a new set of Michigan thin-film electrodes. This new set features the three-shank, 16-contact design that has been used before in our nerve-trunk recordings, but features smaller electrode surface areas. Specifically, the 625 μm^2 electrode sites have been replaced with sites with an area of 133 μm^2, which is the smallest that can be fabricated by the Michigan group. It is our hope that smaller pad sites may translate to improved spatial selectivity, which has been a significant limitation for the application of this approach for field-potential recordings (see Final Report for contract N01-DC-9-2107). Future experiments will perform frequency-selectivity assessments as well as conduction-velocity measures, which are facilitated by the three-shank design.

2. We have continued investigations of the ECAP adaptation and recovery properties, specifically examining the recovery of ECAP amplitude after pulse train stimulation. Some of our results were presented at the ARO Midwinter Meeting in February 2003 (Abstract # 775).

3. We have conducted a series of preliminary experiments designed to assess the effects of recording electrode position on the electrically evoked compound action potentials acquired from feline subjects. Results were reported at the ARO Midwinter Meeting in February 2003 (Abstract #765) and more information is provided on this topic in the following section.

III. Focus topic: Effect of recording electrode position on the electrically evoked compound action potential

A. Introduction

The electrically evoked compound action potential (ECAP) is routinely recorded from both human implant users (equipped with "NRT" or "NRI" systems) and experimental animal subjects. In the case of humans, the ECAP is recorded using the implant's intracochlear electrodes (e.g., Wilson et al., 1994; Abbas et al., 1999). In contrast, animal studies (Stypulkowski & van den Honert, 1984; Killian et al., 1994; Miller et al., 1998; Haenggeli et al., 1998) typically record from extracochlear or nerve-trunk sites. It is possible, however, to use the animal preparations to record intracochlear ECAPs as well, thus providing a means of linking animal and human ECAP findings. Furthermore, Finley et al. (1997) reported intracochlear ECAPs from implantees that demonstrated different sensitivities and rates of growth for different intracochlear recording electrodes. This suggested the possibility of using ECAPs from multiple electrode sites to "map" the base-to-apical extent of neural survival or extent of neural activation. However, interpretation of these intracochlear ECAPs is complicated by unknown degrees of neural survival and poorly understood intracochlear current spread. While animal models provide control over neural survival patterns, the issues of current spread and site-of-excitation remain. We have begun work on this issue by using acute cat preparations to record the ECAP from multiple intracochlear and nerve-trunk recording sites to help interpret the neural contributions to the ECAP.

Furthermore, our standard animal ECAP recordings have used electrodes placed on or near the nerve trunk. This placement provides advantageous signal-to-noise conditions, as the stimulus artifact is greatly reduced relative to the intracochlear recordings. For example, we have been able to record animal ECAPs with little or no need for signal averaging, a significant advantage in our recent efforts to characterize adaptation phenomena (see QPR #8). However, it is plausible that the nerve-trunk placement results in some degree of spatial attenuation that is not constant across the population of excited fibers. Knowledge of the extent and nature of this distortion would help us better interpret ECAPs collected in this manner.

To address these two areas, we have begun a series of experiments examining the effect of recording electrode placement by varying both the intracochlear electrode location and the extracochlear (nerve-trunk) electrode location. The first two cat experiments conducted (in the fall of 2002) established the need to use the forward-masking method of stimulus-artifact reduction (Abbas et al., 1999), as our other method (use of a sub-threshold "template") failed to adequately control stimulus artifacts in the case of intracochlear electrodes. Since then, we have recorded both intra- and extra-cochlear ECAPs from three cats. Data from these cats – forming a preliminary understanding – are presented here.

In analyzing intracochlear ECAPS, we tested two variations of a hypothesis that considers the effect of distance between the neural generators and the recording electrode:

(1) All intracochlear recording electrodes are sufficiently distant from neural generators that the resultant ECAP growth functions will differ by simple constants.

(2) Distance effects are not negligible. ECAP growth functions of electrodes closest to the neural generators will show relatively larger potentials for low-level stimuli.

Our approach considered a two-part problem: First, we compared the intracochlear ECAP growth functions against that obtained using a nerve-trunk recording electrode -- our standard recording site for animal work. We then examined how nerve-to-electrode distance influences ECAP functions obtained by electrodes positioned over and on the nerve trunk.

B. Methods

Three adult cats were used in acute experimental sessions. Subjects were deafened by intracochlear infusions of neomycin sulfate (60 uL, 10% w/v) prior to insertion of a Nucleus 8-band electrode array through the round window. Insertion depth was 5-5.5 mm from the round window. The auditory nerve trunk was exposed by a posterior fossa approach and medialization of the overlying cerebellum. Multiple recording electrodes were placed on and dorsal to the nerve trunk to provide recording sites at several distances from the nerve's surface. In one case, a multiple-ball stalk was used; in the remaining two cases, we used a second Nucleus electrode, coupled with a single-ball electrode, to provide the multiple sites. This set-up is schematized in Figure 1. Stimuli were single 40 µs monophasic pulses presented at a low rate (33 pps) to either a bipolar intracochlear pair I1-I2 or a monopolar electrode (I1 to neck muscle). ECAPs were recorded from either the intracochlear array (electrodes I3 – I8) or one of the nine electrodes (N1-N9) positioned near the exposed nerve trunk. A gain of either 1x or 10x was used. Two techniques were used to reduce stimulus artifact: a subthreshold template subtraction technique or a forward-masking subtraction technique. In most instances, the forward-masking technique was needed to acquire the intracochlear ECAPs.

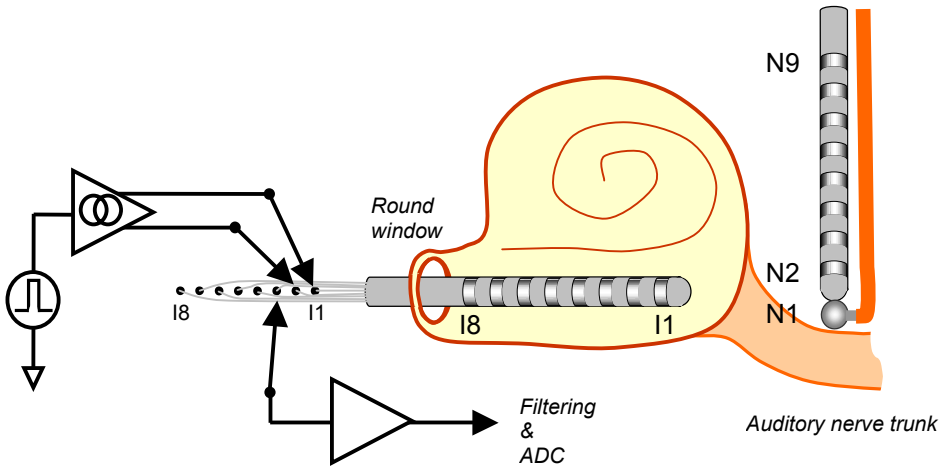

Figure 1
Stimulation and ECAP recording scheme. ECAPs could be recorded from either the intracochlear array or the array positioned dorsal to the nerve trunk. The figure depicts bipolar stimulation (electrodes I1-I2) and recording from intracochlear electrode I3.

C. Results

Part 1: Intracochlear recordings obtained with bipolar stimulation

Figure 2 shows examples of ECAPs evoked by bipolar stimulation (electrodes I1-I2). The left column shows ECAPs recorded by intracochlear electrode I5, while the right column shows ECAPs from nerve-trunk electrode N1. The nerve-trunk waveforms are "raw" traces. The intracochlear waveforms, which suffer more from stimulus artifact, were processed using the template-subtraction method. In both data sets, a level-dependent shift in ECAP latency is evident, although the low-level, long-latency responses from the nerve-trunk electrode are rather small. We ascribe these "jumps" to shorter-latency responses as shifts in the site of action-potential initiation along the length of individual fibers (Miller et al., 1998: Miller et al., 2003).

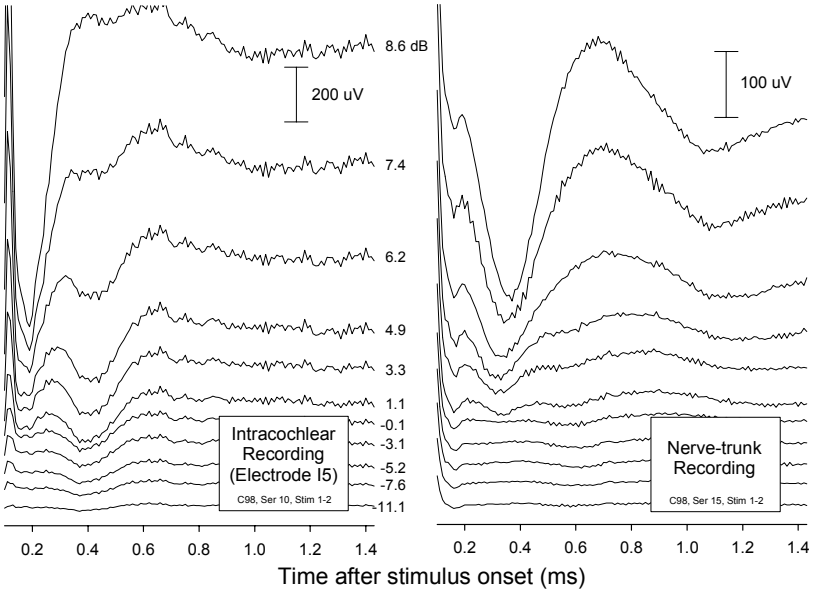

Figure 2
ECAPs recorded from intracochlear electrode I5 (left column) and electrode N1positioned on the nerve (right column). The block arrows indicate the latency of the negative ECAP peak obtained at relatively low stimulus levels. The prominent negative peak shifts to shorter latencies at the higher stimulus levels.

The level-dependence of these ECAPs are shown in the plots of Figure 3, in which graph A plots the latency of the negative peak and graph B plots ECAP amplitude (measured from the prominent negative potential to the following positive peak). Latencies of the late, low-level negative peak are plotted using dotted lines, while solid lines delineate the earlier negative peak that occurs at higher levels. The fact that the intracochlear ECAP latencies are shorter than the nerve-trunk latencies suggests that the intracochlear ECAPs arise from generators that are more peripheral than the location of the nerve-trunk recording electrode. Across-electrode comparisons are facilitated by normalizing the amplitude data. In the plots of graph C, the three intracochlear plots are normalized to the ECAP amplitudes obtained by the nerve-trunk electrode. Compared to the nerve-trunk amplitudes, the low-level, long-latency component recorded by the intracochlear electrodes is relatively large, whereas the shorter-latency component is not as large as that recorded by the intracochlear electrodes. Also, the relative amplitudes of the low-level component are

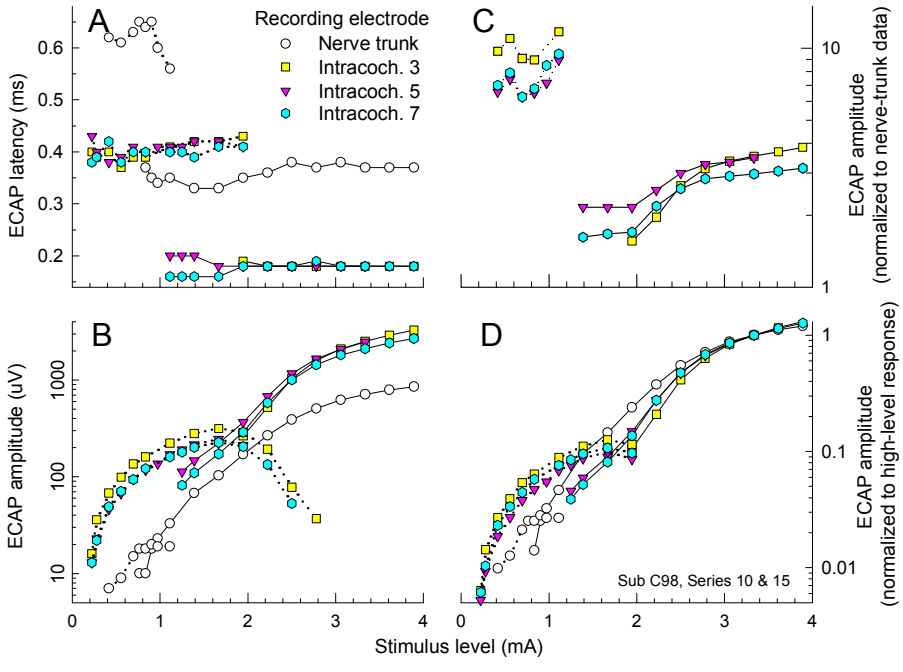

Figure 3
Left column: Latency-vs-level functions (A) and amplitude growth functions (B) for 3 intracochlear electrodes and 1 nerve-trunk electrode. Stimulation mode was again bipolar (I1-I2). Dotted plots describe the long-latency ECAP observed at low stimulus levels while plots using solid lines describe the short-latency ECAP response.
Right column: Amplitude-vs-level functions normalized in two different ways. In (C), amplitudes are normalized to those obtained with the nerve-trunk electrode. In (D), amplitudes are normalized to the amplitude obtained at a high stimulus level (3.4 mA) for each plot.

dependent upon the particular intracochlear electrode. Note that the electrode closest to the stimulating pair (i.e., I3) provides the strongest representation of this ECAP component. These trends are perhaps seen more explicitly in the normalized plots of graph D. Note, in particular, how the relative "strength" of the ECAP recorded by the nerve-trunk electrode varies with level. We presume this trend relates to changes in the sites of neural excitation with level.

We have also noted other ECAP latency-vs-level patterns that vary from those shown in the previous case. Figure 4 shows latency-level plots for a second animal stimulated in the same manner as before (i.e., I1-I2 bipolar stimulation) which vary in multiple ways. First, there are no discrete shifts to shorter latencies with increasing level. Second, the intracochlear electrode closest to the stimulating pair (I3, squares) recorded unusually long N1 latencies. The ECAP amplitudes of this animal exhibit some similarities and differences relative to those of the first subject. Again, electrode I3 produced the largest ECAP amplitudes, but only at relatively low stimulus levels. We do not know what underlies these across-subject differences, but note that small differences in electrode position can result in large changes in fiber recruitment (e.g., Shepherd et al., 1993; Miller et al., 1993). Although we have observed such variations, we also see a consistent trend of relatively large ECAP amplitudes recorded by intracochlear electrode I3 at low stimulus levels. This is shown for all 3 animals in Figure 5, which plots the normalized ECAP growth functions from three subjects. We speculate that this greater representation by electrode I3 is due to its relative proximity to the subset of fibers excited by the bipolar stimulating pair at those low levels. As fiber recruitment increases at higher levels, this electrode advantage disappears.

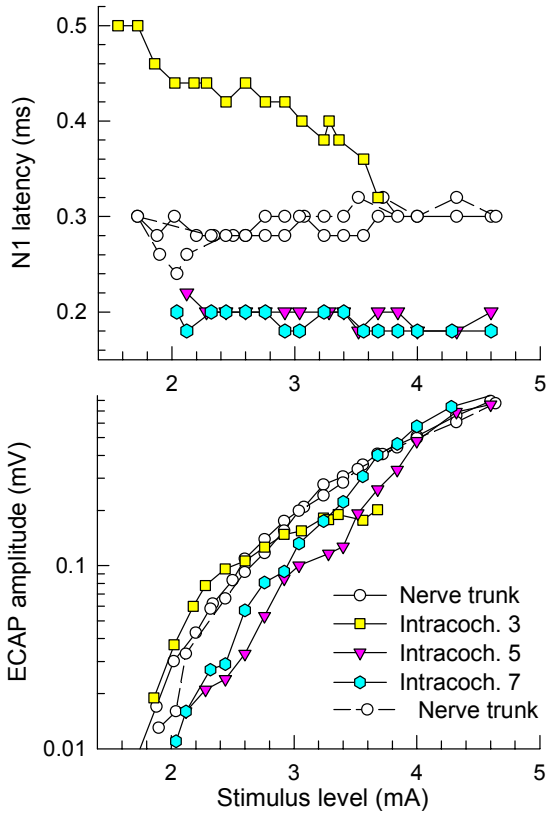

Figure 4
ECAP input-output functions from a second subject with somewhat different level- and electrode dependent trends.

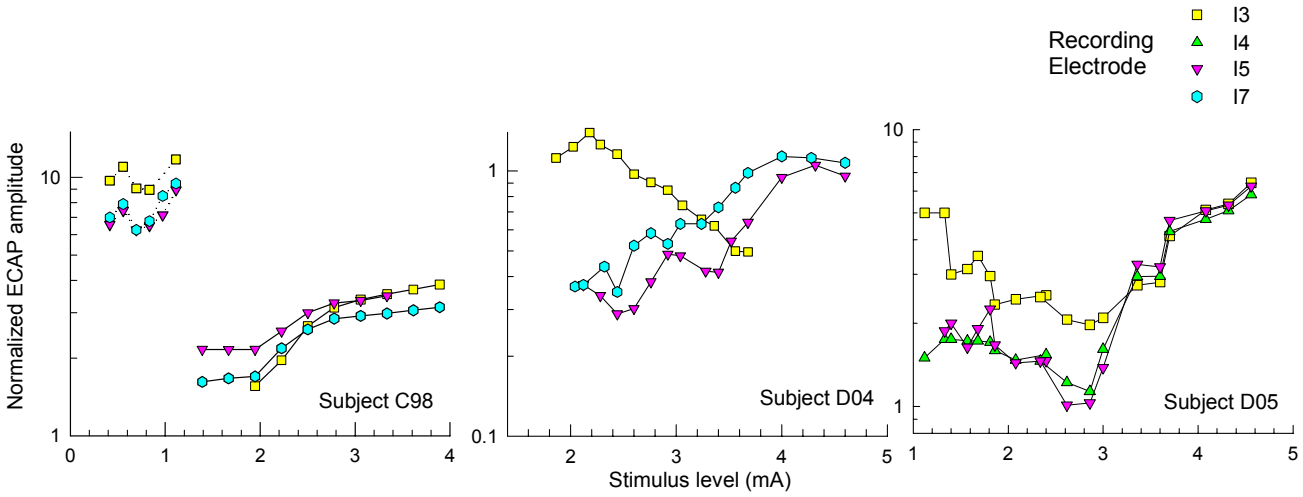

Figure 5 Normalized ECAP growth functions from 3 subjects for different intra-cochlear recording electrodes. In all cases, stimuli were presented to intra-cochlear electrodes I1 and I2. Amplitudes recorded from the other electrodes have been normalized to those obtained from the nerve-trunk electrode (N1)

Part 2: Intracochlear recordings obtained with monopolar stimulation

Given the differences between the way monopolar and bipolar stimulation recruit fibers of the auditory nerve (van den Honert & Stypulkowski, 1987; Miller et al., 2003), we hypothesized that monopolar stimulation will produce different patterns than those seen in Figure 5, namely, fewer differences among the intracochlear curves and less dependence upon stimulus level. We have just begun to examine this issue using intracochlear electrode I1 for monopolar stimulation. We have found it necessary to use the forward-masking technique to obtain usable ECAP waveforms under this stimulation condition, as stimulus artifacts are much larger. Figure 6 compares the normalized intracochlear ECAP functions obtained with bipolar (left panel) and monopolar (right panel) stimulation. Note that, relative to the bipolar curves, the plots obtained with monopolar stimulation show less systematic variation across electrodes and, particularly at the low stimulus levels where bipolar effects were observed.

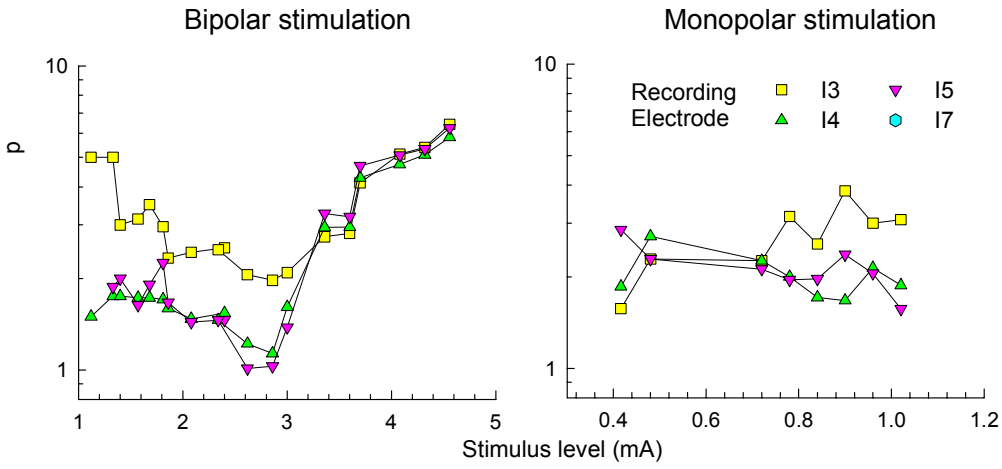

Figure 6 Normalized ECAP growth functions for 3 intracochlear electrodes for both bipolar stimulation (left panel) and monopolar stimulation (right panel).

Part 3: Effect of electrode position on the nerve-trunk recordings

The above examination of intracochlear electrode recordings was based upon comparisons relative to ECAPs recorded using an electrode positioned directly on the surgically exposed nerve trunk. It is reasonable to assume that such a position will produce a distance-weighted representation of the excited neural population, as the fiber-to-electrode distance varies substantially across the nerve population.

To date, we have examined this in one subject using the combination of nerve-trunk electrodes shown in Figure 1. This consisted of a ball electrode positioned directly above the nerve trunk and a dorsally oriented 8-band array. ECAP growth functions obtained from the four electrodes closest to the nerve trunk are shown in the upper graph of Figure 7. Stimuli were presented through bipolar pair I1-I2. The resultant ECAP growth functions are shown in Figure 6. ECAP amplitudes are predictably smaller for the more distant electrode sites. Note that the functions from electrodes N3 and N4 are quite similar.

By normalizing the functions of N1, N2, and N3 by the N4 data, we can arrive at estimates of how electrode distance results in weighted functions (lower graph). Two observations can be made from these normalized functions. First, the degree of distortion increases as electrode-to-nerve distance decreases. Second, the low-level responses have the greatest weight. These patterns may arise from the fact that, at low stimulus levels, our bipolar stimulation likely excites a basal locus of fibers that are located toward the edge of the nerve trunk's cross section.

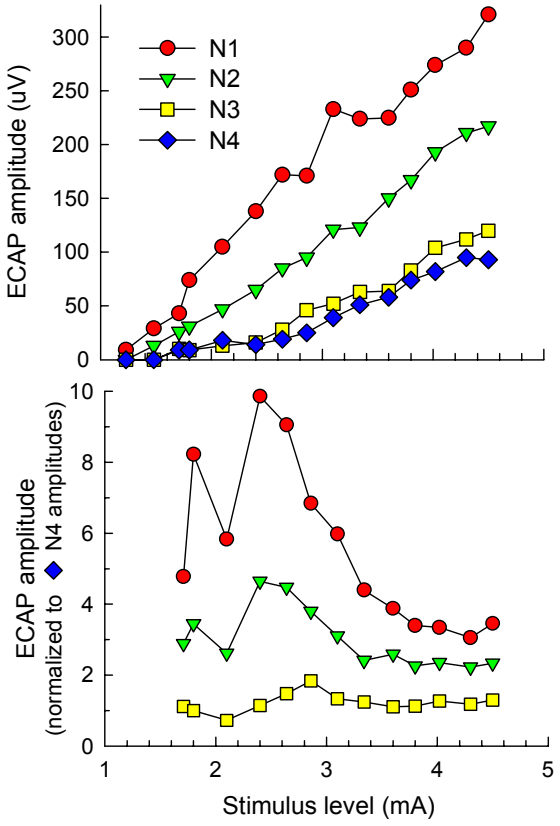

Figure 7
Upper panel: ECAP growth functions obtained from four recording electrode positions on or near the surgically exposed auditory nerve trunk. **Lower panel**: Growth functions of electrodes N1, N2, and N3 normalized to the amplitudes obtained using electrode N4. Stimulation mode was bipolar, through electrodes I1 and I2.

D. Comments

The results presented here are preliminary and part of an ongoing investigation. We observed significant across-subject variations that require further scrutiny; however, some trends are evident. The data suggest that intracochlear electrodes can indeed record spatially restricted neural activity. Furthermore, the patterns of normalized recruitment are consistent with the generally accepted notions of restricted excitation with bipolar intracochlear stimulation and wide excitation with monopolar stimulation. Our comparisons of ECAP recordings from electrode positions on and near the nerve trunk indicate the need to account for spatially weighted neural responses, at least when attempting to use the ECAP in a quantitative way to assess fiber recruitment. Finally, although the weighting of intracochlear ECAPs consistently shows spatially restricted measures (Figure 4), analysis of latency patterns suggests that fiber recruitment is strongly affected by the position of the electrode array within the cross-section of the scala tympani. Not only are these results relevant to research with animal models, but also suggest that the choice of the intracochlear electrode used to record human ECAPs (with "NRT" and "NRI" systems) may affect results. Specifically, by choosing a recording electrode close to the stimulating electrode(s), one might obtain ECAPs weighted toward a local subpopulation. In contrast, use of a more distant electrode may be the appropriate choice for more "global" ECAP measures.

VI. References

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