# Effects of Remaining Hair Cells on Cochlear Implant Function

## 11th Quarterly Progress Report

Neural Prosthesis Program
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## 1. Summary of Activities in This Quarter

During the tenth quarter of this contract (January 1 - March 31, 2005), we accomplished the following:

1. We attended the ARO Midwinter Meeting in New Orleans, LA. Two presentations related to the work of this contract were given by members of our group (see Section 4, Presentations).

2. We performed 6 acute guinea pig experiments that addressed binaural interactions in response to acoustic and electric stimulation using recordings from the central nucleus of the inferior colliculus. Those data are the focus topic of this QPR.

3. We performed 3 acute cat experiments that addressed the auditory nerve single-unit and ECAP responses to combined acoustic and electric stimuli.

4. We initiated work on developing a computational model (to be implemented on Matlab) to simulate and account for refractory and adaptation effects in acoustically and electrically stimulated auditory nerve fibers (ANF's). Our approach will follow the framework described by Schroeder & Hall (1974), but will expand it for the case of hybrid stimulation. This model will assist us in our efforts to account for the complex effects observed in our ECAP measures (cf. Nourski et al., 2005) and reconcile our ECAP and ANF observations.

The following methodological procedures and improvements were made during this time:

5. We evaluated the use of the Tucker Davis Technology ESD electrostatic driver to extend the high-frequency range of our sound delivery system beyond 25 kHz. While this driver did extend the frequency range, it also created higher levels of radiated (electric) noise that were deemed unacceptable for the electric-train / acoustic-noise ANF experiments.

6. We wrote new Matlab analysis software to increase the efficiency of multi-channel (i.e., Michigan recording electrode array) data analysis.

8. We also wrote new code to perform a more "fine-grained" temporal analysis of ANF responses to our electric pulse train & acoustic noise stimulation paradigm. In contrast to our typical single-fiber analyses that used large (20-50 ms) time analysis bins (see QPR 6), the new code provides analysis of firing statistics (FE, jitter, mean latency, amplitude) with 4 ms bins, allowing us to track ANF responses to each electric pulse in the 250 pps trains used in our standard paradigm. In Q10, we began re-analyzing all fiber data using this new routine.

   Finer temporal analysis will produce ANF measures that parallel the ECAP response measures so that we can make comparable measures of the ANF and ECAP responses and gain insight into the single-fiber response properties that may underlie some of the unusual (non-monotonic) ECAP recovery patterns that we have reported in previous reports.

Finally, we note that the paper by Nourski et al. detailing ECAP acoustic-electric interactions will be published in the April 2005 edition of Hearing Research.

# 2. Focus Topic: Binaural interaction of electric and acoustic stimulation

## 2.1. Introduction

Most of the efforts that we have conducted for this contract have focused on the peripheral assessments of acoustic-electric interactions. The primary focus at this neural location was premised on the notion that knowledge of peripheral processing is essential to appropriate interpretation of the processing by more central sites and that several acoustic/electric interactions are known to occur at the peripheral level. We also reasoned, however, that if cochlear implant users have significant hearing in the implanted ear, they will likely be in a position to take advantage of acoustic stimulation, possibly with amplification, in the ear contralateral to the implanted ear. Our proposed work, therefore, also sought to investigate the degree to which the binaural auditory system may be able to process combinations of acoustic and electric stimulation presented across two ears.

### *Initial work: the binaural ABR*

Our initial experiments in this regard were performed as part of NIH Contract N01-DC-9-2106 and reported in QPR 9 of that contract. To examine acoustic/electric binaural interactions, we chose a paradigm based upon the so-called binaural component of the ABR (Dobie and Berlin, 1979). This paradigm was chosen, in part, as it had the potential of being applied to clinical populations in individuals with significant residual hearing in order to assess the degree of binaural interaction. Consequently we employed a novel means of assessing the binaural ABR component that could be evoked with binaural presentation of electric and acoustic stimuli. Our initial goal was to determine the degree to which this novel measure could be used to assess central (brainstem) interactions. In doing so, we manipulated acoustic and electric stimulus parameters in an attempt to maximize any measurable interaction. Pulsatile acoustic and electric stimuli were employed in order to optimize synchronous neural activity required for robust ABR potentials.

To assess potential effects, we required an animal model that could maximize the difference between each ear's response as well as one that would be flexible enough to examine various degrees of interaction. Thus, guinea pigs were used in which hearing was preserved in the right ear while the left ear was deafened with local administration of neomycin. The deafened ear was then implanted with an intracochlear electrode. The right ear received acoustic click stimuli, while the left cochlea received electric current pulses. Auditory brainstem responses to right-ear stimulation alone, left-ear stimulation alone, and stimulation of both ears were measured. To determine the binaural ABR component, the sum of responses to each ear alone was subtracted from the response to both ears. The derived response amplitude was measured for different time delays between electric and acoustic stimuli. The peak in binaural response was approximately 1.5 ms, which is the approximate latency difference between acoustic and electric responses at the level of the auditory nerve for this species (e.g., Miller et al., 1994). The amplitudes of these measures varied across subject and were generally small. Nevertheless, there were consistent across-subject trends.

### *New measure: Invasive IC recordings*

Our work in this contract sought to overcome the relatively low sensitivity of the reported binaural ABR measures. We therefore chose to use a more invasive recording method, placing recording electrodes in the inferior colliculus. Our first experience with thin-film recording arrays within the central nucleus of the IC (QPR #8) demonstrated the presence of a field potential in addition to multi-unit activity. For our first invasive measures of a binaural interaction component, we chose to use the field potential evident in these recordings in response to stimulation of both ears, i.e., a potential analogous to the potential measured non-invasively with surface electrodes. We reasoned that the better signal to noise ratio in these recordings would provide more reliable and global assessment of the binaural component. We note, however, that we also plan to analyze multi-unit activity recorded from the same electrodes to compare the field-potential results with the recorded multi-unit activity. That analysis will be the subject of a future progress report.

As our proposed invasive measures were unique, we deemed it important to also evaluate measured binaural interaction components obtained with acoustic-acoustic binaural stimulation. Such baseline information may prove useful in interpretations of electric-acoustic binaural interactions obtained with invasive CIC electrodes. Thus, in some cases, responses were obtained using acoustic clicks delivered to each ear. These measures were obtained prior to the implantation of one ear with a monopolar stimulating electrode. Our protocol thus consisted of first obtaining acoustic-acoustic measures and then implanting the left ear and obtaining electric (left) –acoustic (right) binaural measures.

## 2.2. Methods

Adult guinea pigs with normal hearing were used in acute experimental sessions. Animal preparation, anesthesia and general surgical methods were similar to those for our experiments described with guinea pigs for auditory nerve recordings. After inducing the surgical level of anesthesia, both left and right ear canals were excised and the left bulla opened. Initial measures of ABR threshold to click stimuli were made in order to assess hearing sensitivity in each ear. Following this, the right inferior colliculus was exposed. First, skin incisions were made from midline, through bregma, and then laterally toward the jugular processes on both sides. Skin flaps were retracted to expose the posterior aspect of the skull. Superior portions of parietal bones and the occipital bone were thinned using a diamond burr and then removed by a rongeur to expose the dura and visualize the sagittal and transverse sinuses. The posterior portion of the occipital lobe of the cerebrum was aspirated to expose the right inferior colliculus, which could be partially visualized, lying between the superior colliculus and cerebellum.

For multi-site recording along the tonotopic gradient of the central nucleus of the IC, we used the “5mm100µm” single-shank probe designed by the University of Michigan Center of Neural Communications Technology and now available from NeuroNexus Technologies (http://www.neuronexustech.com/). This particular electrode configuration has been used by the UCSF group. The thin-film probe was inserted perpendicularly to the surface of the inferior colliculus using an angle of 30-40 degrees from bregma in a coronal plane (Snyder, personal communication). The probe tip was advanced to a depth of approximately 2 mm with the aid of a Narishige microdrive stage. Recordings were made with the 16-site probe through a custom-built 16-channel unity-gain headstage. Potentials were then low-pass filtered using 4th order Bessel filters (3 dB cut-off frequency of 15 kHz) and sampled at 25,000 sample/s/channel. Custom software (LabView) was used that allowed for recording of 8 channels simultaneously using time-division multiplexing. Responses to each stimulus presentation were saved for later off-line analysis. In these experiments, we report data obtained from 8 of the 16 probe sites (i.e., every other electrode along the linear array).

Stimuli were digitally generated by a 16-bit digital-to-analog converter (100,000 samples/s), controlled by custom-written software. Acoustic clicks were produced by driving a BeyerDynamics DT48 earphone with 100 µs/phase biphasic electric pulses, presented using an interstimulus interval (ISI) of 30 ms. Electric stimuli were 40 µs/phase biphasic pulses fed through an isolated current source to an intracochlear stimulating electrode. Sound pressure in the ear canal was monitored during each experiment using a probe-microphone system described in QPR #4.

After placement of the recording array, tonal stimuli were presented and the range of maximum response across electrodes within the recording array were determined. As necessary, the depth of the recording electrode was adjusted to obtain a range of best frequency across the recording electrodes. The final, selected, electrode array depth resulted in best maximum response frequencies that spanned from a range (measuring superficial to deep) from approximately 1 kHz to 16 kHz (J23, J26, J27) or 20 kHz ( J32, J33). Representative best-frequency maps obtained with these procedures were illustrated in QPR 8.

After completing these preliminary measures, binaural responses to click stimuli (delivered to both ears) were assessed; relevant details of this procedure are noted in the Results section. Following the acoustic-acoustic measures, a cochleostomy was performed on the left cochlea at a site medial to the round window and a Pt/Ir wire electrode was inserted into the scala tympani. This electrode provided intracochlear monopolar electric stimulation. ABR measures were obtained and compared to earlier ABR measures to ensure acoustic sensitivity in both ears after this cochlear procedure. In all cases reported here, sensitivity remained upward acoustic threshold shifts were always within 20 dB after the cochleostomy and electrode insertion. Finally, measures of binaural response with an electric pulse in the left ear and an acoustic click in the right ear were performed.

### 2.3. Results

Both field potential and unit activity were evident in our recordings evoked in response to clicks or electric current pulses. We used signal averaging techniques to extract the field potential and attenuate the neural spikes. Analyses of the field potentials are presented in this report. Analyses of unit activity will be presented in a later report. Averaged evoked potentials were measured in response to three different stimuli: (1) stimulation of the right ear alone, (2) stimulation of the left ear alone, and (3) stimulation of both ears.

Figure 1a plots averaged IC responses to click stimuli presented in each of the three stimulus conditions. The evoked potential represents an average waveform computed both across sweeps and across the eight selected recording electrodes so as to obtain an overall response analogous to more far-field (i.e., ABR) measures. In general, the response from the ear contralateral to the recorded IC shows relatively larger response amplitudes. When we sum the responses from stimulation of the individual left and right ears, that response is clearly different than the response obtained with bilateral stimulation. This is illustrated in the traces of Figure 1b. The binaural interaction component is then measured as the difference between these two conditions (i.e., [Binaural response] – [Sum of monaural responses]) and is plotted in Figure 1c.

Analogous responses obtained using a click stimulus presented to the right ear and an electric current pulse presented to the left ear are shown in Figure 2. In this case of “hybrid” stimulation, we delayed the presentation of the electric pulse by 2 ms relative to the onset of the click to account for differences in propagation time. As a result, the responses to the two stimuli overlap in time. The resulting binaural interaction component has a morphology similar to that obtained with the presentation of acoustic stimuli to both ears (see Figure 1).

In our previous measures of the binaural interaction component of the ABR, we observed that the response was highly dependent on the relative delay of stimulation between the two ears. The maximum response occurred when the electric pulse was delayed approximately 2 ms relative to the acoustic click in the opposite ear. This delay coincided approximately with the relative response latency of the compound action potential for the two stimuli. For our new IC measures, we conducted additional experiments to evaluate the effect of delay between the two ears for the combined acoustic and electric stimulation. In performing this evaluation, we noted that both the amplitude and morphology of the binaural interaction response varied with changes in the relative electric-acoustic time delay. Thus, we chose to characterize the interaction responses by using a root-mean-squared measure of amplitude, using a 16 ms analysis window beginning 2 ms after onset of the earlier stimulus. This approach allowed us to take into account differences in latency and morphology and characterize the overall amplitude of the response, rather than a selected feature (such as a peak-to-trough measure).

Figure 3 summarizes data on the effect of interaural time delay for several subjects. The rms amplitude of the binaural interaction component is plotted as a function of the delay of the left-ear stimulus (relative to the timing of the stimulus presented to the right ear). Data for four subjects are shown for both acoustic-acoustic interactions (plots of the left column) and electric-acoustic interations (plots of the right column). In all cases, the right ears were presented with the acoustic click. In producing these data sets, electric current levels or sound pressure levels were selected so that each stimulus (acoustic and electric) elicited a response of comparable amplitude when presented monaurally.

In all cases, the plotted binaural interaction amplitudes demonstrate non-monotonic functions of time delay. For acoustic-acoustic stimulation (Figure 3, left column) these functions typically achieved a peak value for a relative delay of approximately zero. For electric-acoustic stimulation (Figure 3, right column), the maximum response was elicited with an electric time delay of approximately 2 ms. The form of the function (e.g., the peaked and asymmetric function) and the amplitude of the interaction components were similar for the two combinations of stimuli.

In the experiment summarized by the data of Figure 3, the level of both acoustic and electric stimuli were chosen to be clearly above threshold, but well below levels resulting in a saturated (maximal) response. It is of interest to determine the extent to which levels of stimulation may affect the form of the functions such as those shown in Figure 3. Additional measures were obtained by varying the level of the acoustic clicks while determining interaction functions for acoustic-acoustic stimulation. In the data shown in Figure 4, the click level was the same in each ear and overall level was varied. Data are shown for two subjects. As the level increased, the amplitude of the binaural interaction component increased, but the shape of the functions were similar across the levels tested.

Similar functions are shown in Figure 5 where binaural interaction components are shown for electric pulses in the left ear and acoustic clicks in the right ear. In these cases, the level of acoustic stimulation was varied and the current level of electrical stimulation was fixed. Again, the amplitude of the binaural interaction component increased with stimulus level; however, the general shape of these delay functions is similar across levels.

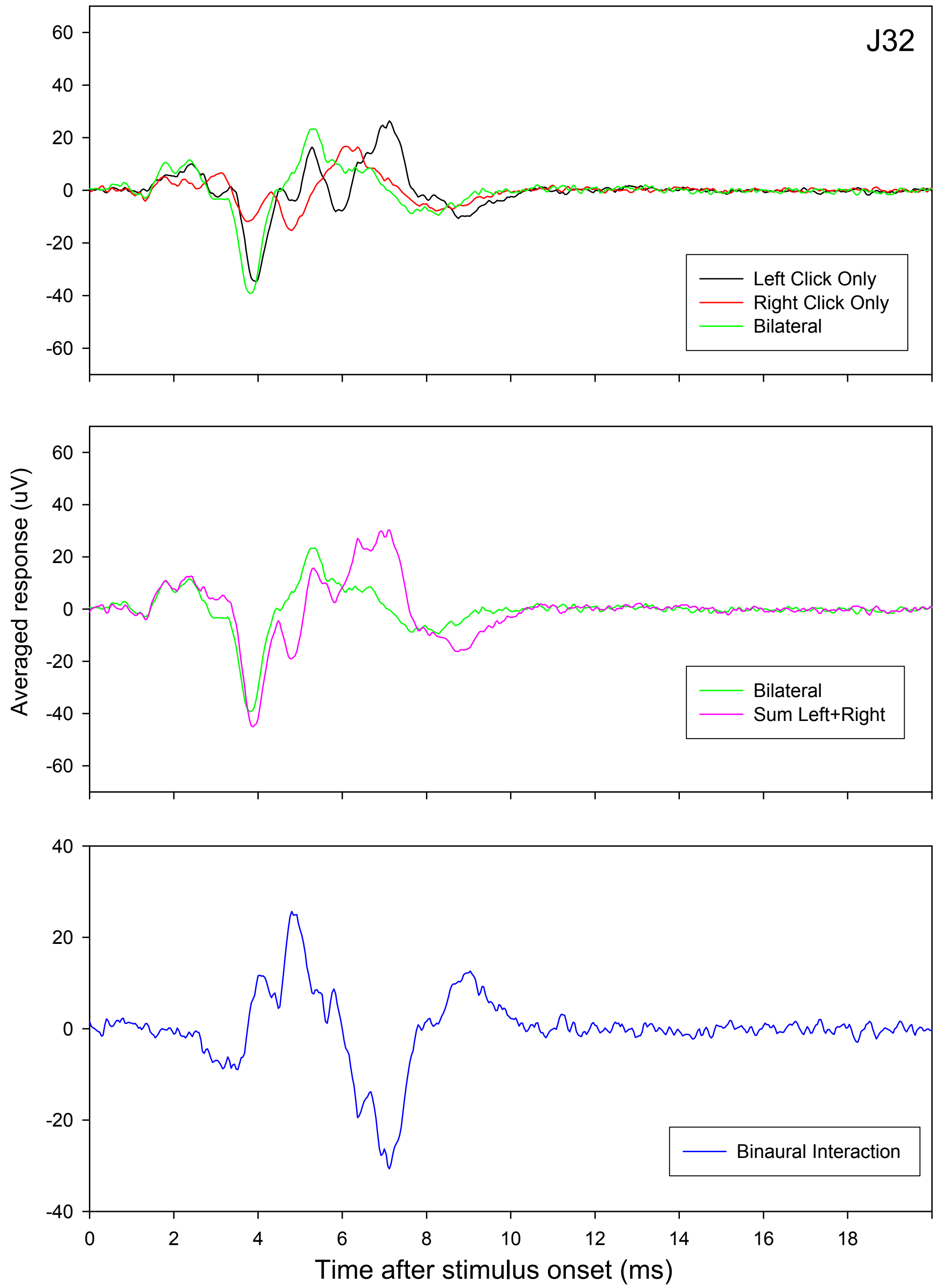


**Figure 1.** Plots of the recorded waveforms averaged across the eight recording sites in the inferior colliculus. Top: Response to left ear stimulation, right ear stimulation and simultaneous stimulation to both ears. Middle: Response to bilateral stimulus presentation is plotted as well as the summed responses to left and right ear alone. Bottom: The binaural interaction component is the difference between the two waveforms plotted in middle graph. Acoustic click level in both ears: 76 dB SPL pe.

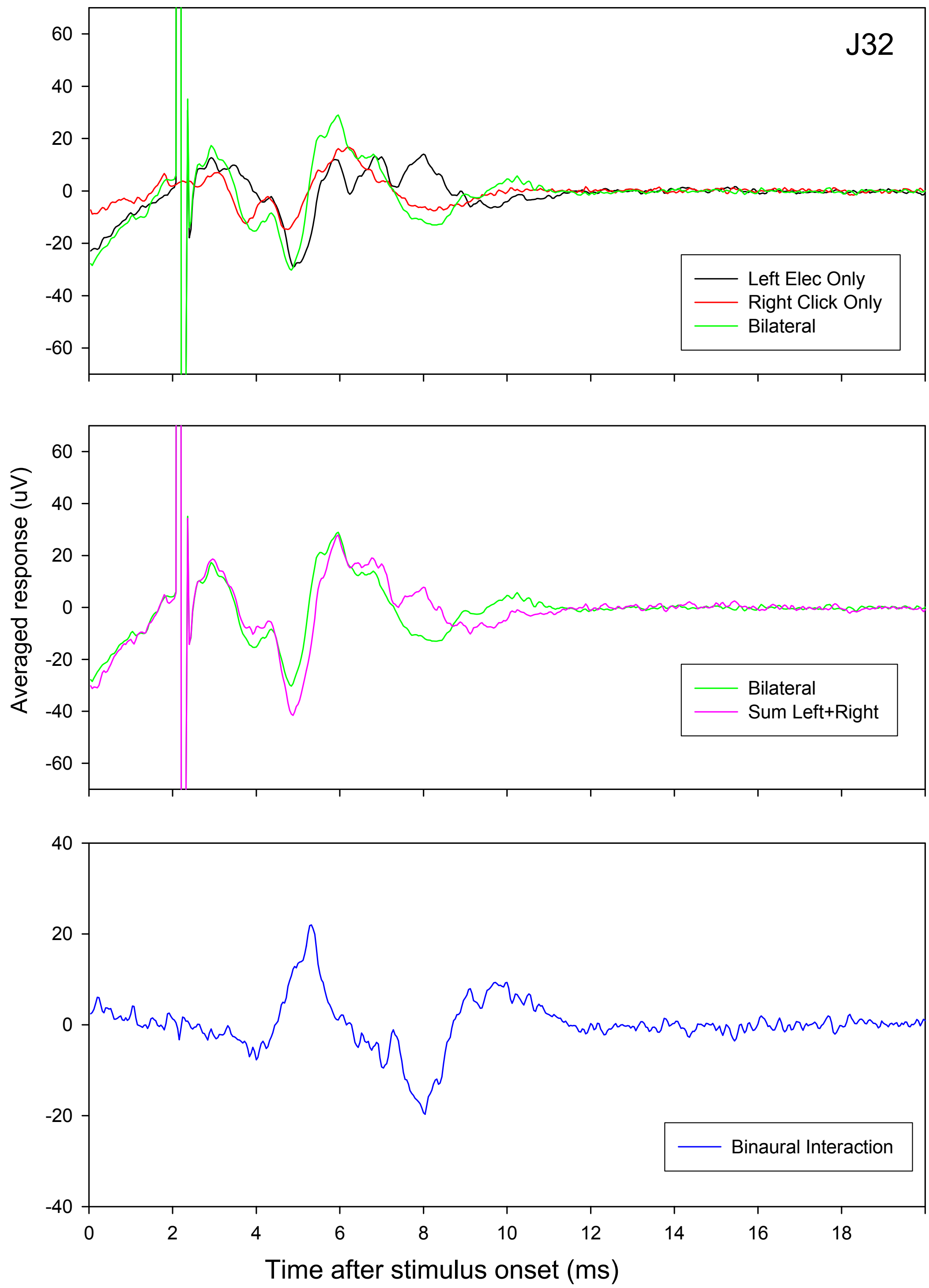


**Figure 2** Plots of the recorded waveforms averaged across the eight recording sites in the inferior colliculus. See Figure 1 legend for details. In this case acoustic click level in right ear was 76 dB SPL pe and electrical pulse current level in left ear was 0.6 mA.

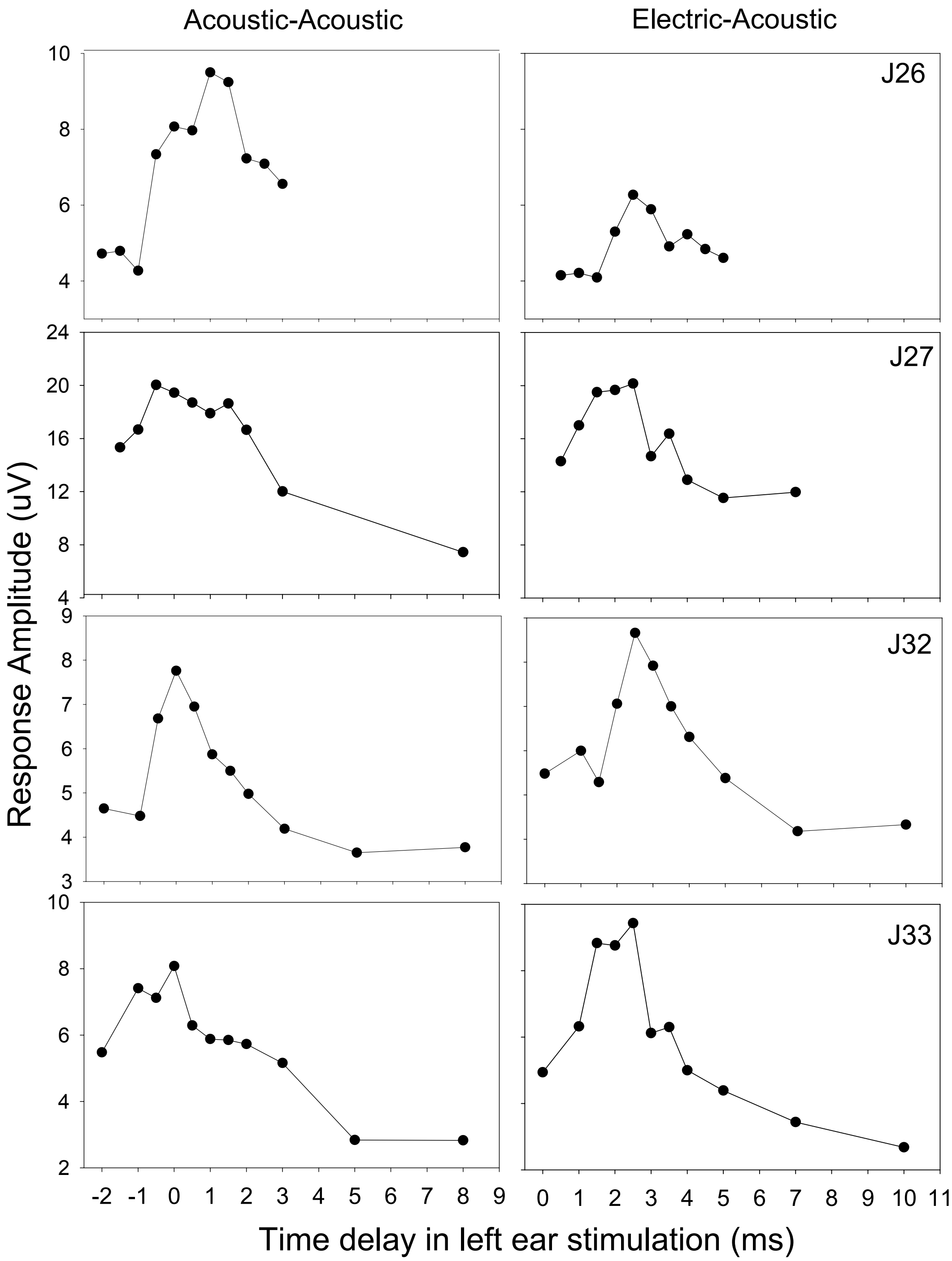


Figure 3. Response amplitude calculated as an rms value over an 18 ms window is plotted as a function of the time delay between right ear (acoustic click) stimulation and left ear stimulation. In column 1 the left ear stimulus was an acoustic click. In column 2 the left ear stimulus was an electric pulse (see text).

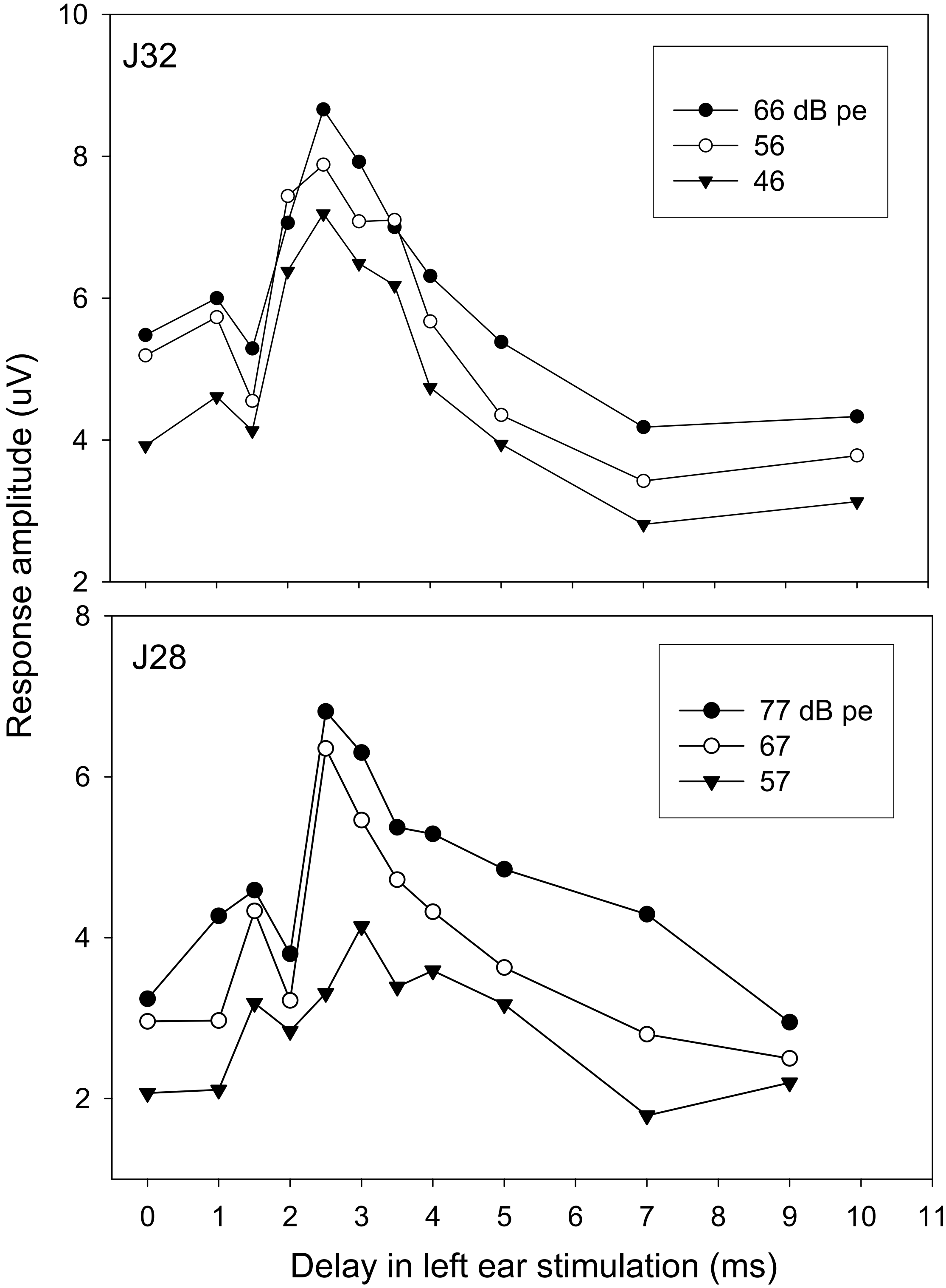


**Figure 4.** Response amplitude calculated as an rms value over an 18 ms window is plotted as a function of the time delay between right ear stimulation and left ear stimulation. In these cases, acoustic clicks were presented to both ears. Parameter is level of the clicks in both ears.

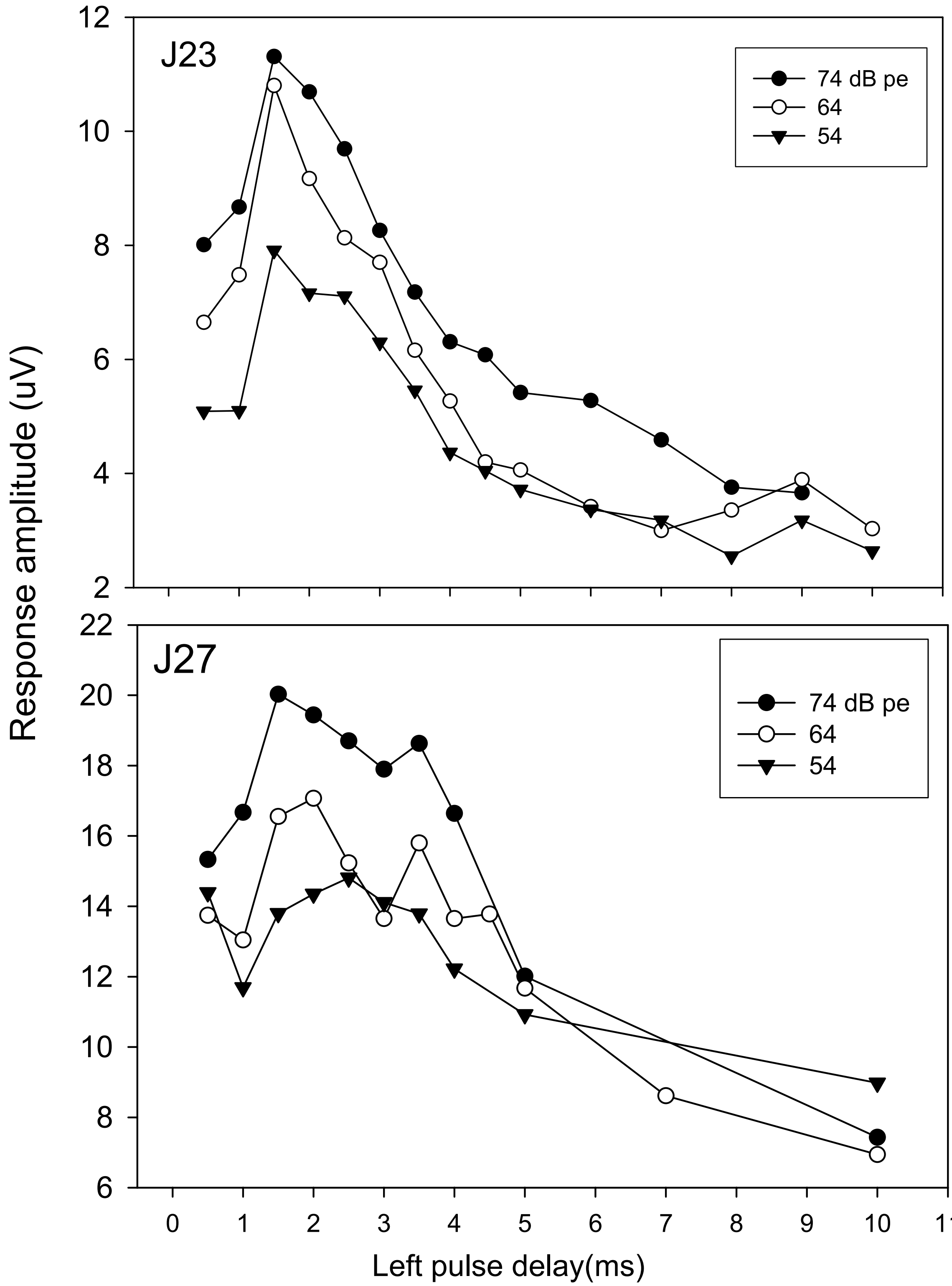


**Figure 5** Response amplitude calculated as an rms value over an 18 ms window is plotted as a function of the time delay between right ear stimulation and left ear stimulation. In these cases, acoustic clicks were presented to the right ear and electric pulses at 0.6 mA were presented to the left ear. Parameter is level of the clicks in right ear.

## 2.4. Discussion

The data presented here demonstrate that the binaural interaction component, measured using the nearly simultaneous presentation of acoustic and electric stimulation, shows similar characteristics and functional dependencies to those obtained using purely acoustic stimuli routed to both ears. The data presented here suggest, to the extent that can be inferred from the far-field potentials elicited by our stimuli, that the binaural auditory system processes acoustic and electric stimulation in similar manners. In addition, the shapes of the amplitude vs. delay functions are not sensitive to level of stimulation, either overall level or relative level between ears. These observations suggest that measurements of these responses may be relatively robust in that if binaural interactions are evident, the pattern of response with delay is not exquisitely sensitive to a specific combination of stimulus parameters.

We previously reported on similar measures using surface electrodes and measuring the binaural EABR in the guinea pig (Final Report, Contract NO1-DC-9-2106). The present measurements in the inferior colliculus generally showed a greater response amplitude and, at least qualitatively, the peak in the responses were more consistent across subjects. Also, in comparing the two sets of data, the peak in the response with delay tended to be slightly earlier than that observed with the earlier ABR measures. Nevertheless, the similarity of the measures however suggests that a major component of the binaural ABR in these cases may be from the inferior colliculus. These data then suggest that it may be worthwhile to explore the use of such measures in cochlear implant users. Firszt et al. (2003), have reported measurements of a binaural ABR in response to bilateral stimulation through two cochlear implants, demonstrating the feasibility of such measures in human cochlear implant users.

The degree to which individuals with residual hearing in one ear may effectively take advantage of binaural cues likely varies across individuals. These data suggest that in the "intact" auditory system some binaural interaction is evident. Measures such as these in human populations may indicate the degree to which such interactions are evident in those populations with possible neural degeneration.

The binaural interaction measures obtained either with scalp electrodes or the invasive technique described here are logical steps in assessing how central nuclei process combined acoustic and electric stimuli in a binaural system. There are, of course, significant limitations, to these particular measures. First, they require the generation of a significant level of across-unit synchrony to elicit recordable responses; registration of more subtle response patterns elicited by ongoing or continuous stimuli may be more problematic. Second, at least as presented to date (i.e., using response amplitudes summed across recording sites), the reported IC measures represent a global measure of activity.

We have begun IC measures based upon multi-unit activity to address some of these concerns. By measuring spike activity at several IC sites along its tonotopic axis (together with the use of other, more place-specific acoustic stimuli), we hope to assess issues related to the place specificity of interactions highlighted by our present measures. Finally, developing an understanding of the degree to which the global measures reflect more spatially restricted activity is clearly useful for efforts to establish the clinical meaning of far-field binaural interaction measures.

## 3. Plans for the Next Quarter

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

1. Conduct additional acute cat ANF experiments using our standard low-rate (250 pps) electric train and wideband acoustic noise stimuli. The focus of these experiments, however, will shift somewhat in that determination of characteristic frequency will be given higher priority. This will be done to address questions regarding possible relationships between CF and ANF responses under hybrid stimulation.

2. Continue re-analyses of existing ANF response data using the new, aforementioned, analysis software that enables us to examine the time courses of adaptation and recovery phenomenon associated with our hybrid (acoustic & electric) stimulus protocol.

3. Submit a manuscript detailing a method to reduce asynchronous noise “signals” (related to power-line harmonics) from single-unit recordings. This method uses cross-correlation and template subtraction techniques to accomplish this.

4. We plan additional experiments to investigate the effect of site of electrical stimulation on properties of adaptation.

## 4. Presentations and Publications

The following two presentations were given at the 28th Midwinter Meeting of the ARO, held in New Orleans from Feb 19 to Feb 24. The content of these presentations was related directly to the work performed under this contract.

Kirill Nourski, Paul Abbas, Heil Noh, Charles Miller, Barbara Robinson. (2005) Acoustic-Electric Interactions in the Auditory Nerve: Simultaneous and Forward Masking of the Electrically-Evoked Compound Action Potential. Abstract # 75.

Charles Miller, Heil Noh, Paul Abbas, Barbara Robinson, Kirill Nourski, Fuh-Cherng Jeng (2005) Effects of Combined Acoustic and Electric Stimuli: Single Auditory Nerve Fiber Responses. Abstract #1020.

We were informed that our accepted paper (Nourski et al., 2005) will be published in the April 2005 edition of *Hearing Research*.

# 4. References

**Dobie, R.A., Berlin, C.I. (1979).** Binaural interaction in brainstem-evoked responses. Arch. Otolaryngol. 105, 391-398.

**Firszt, J.B., Gaggl, w., Runge-Samuelson, C., Wackym, P.A. (2003).** Electrophysiologic measures of binaural interaction in bilateral cochlear implant recipients. 2003 Conference on Implantable Auditory Prostheses.

**Miller, C.A., Abbas, P.J., Robinson, B.K. (1994).** The use of long-duration current pulses to assess nerve survival. Hear. Res. 78, 11-26.

**Nourski K.V., Abbas P.J., Miller C.A., Robinson B.K., Jeng F.C. (2005).** Effects of acoustic noise on the auditory nerve compound action potentials evoked by electric pulse trains. Hear. Res. 202:141-153.