

Effects of Remaining Hair Cells on Cochlear Implant Function

8th Quarterly Progress Report

Neural Prosthesis Program

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(Quarter spanning April-June, 2004)

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1. Summary of Activities in This Quarter

During the eighth quarter of this contract (April 1 – June 30, 2004), we accomplished the following:

1. Attended the International Conference on Cochlear Implants in Indianapolis.
2. Had two papers accepted for publication in *Hearing Research*. The first paper (Miller et al., 2004a) presented comparisons of the electrically evoked compound action potential (ECAP) as recorded from intracochlear and nerve-trunk recording sites, an issue relevant to the use of animal models in interpreting human ECAP data. The second paper (Miller et al., 2004b) described our experiences with the use of thin-film (Michigan) electrodes for recording from within the auditory nerve.
3. Performed six additional experiments using acute guinea pig preparations following the work described in the previous QPR. These additional data sets were sought to improve the description of overall (group) trends needed for a peer-reviewed report.
4. Completed analysis of the above data sets and completed preparation of a manuscript (to be submitted for peer review) on the effects of acoustic noise on pulse-train evoked ECAPs in guinea pigs.
5. Performed 3 acute cat experiments that paralleled the above-mentioned work with guinea pigs in examining acoustic-electric interactions as revealed by the ECAP. These experiments were conducted to provide direct, within-species, comparisons of ECAP and single-fiber response patterns, as the latter, single-fiber, measures are being obtained from cats. The cat ECAP data will also provide a means of examining how previously reported across-species differences influence the data sets.
6. Collected auditory nerve single-fiber measures from one cat to continue investigation of acoustic-interactions as evidenced in the auditory periphery. Relatively long (100 to 300 ms) bursts of wideband acoustic noise were used to further investigation acoustically driven adaptation and recovery effects that have been observed in the parallel ECAP studies.
7. Began work with acute guinea pig preparations to expose and record from the central nucleus of the inferior colliculus. A total of eight guinea pigs were used in this effort. Four guinea pigs were used to develop the exposure and recording technique. To date, we have recorded single and multi-unit responses from six of the eight guinea pigs, and have recorded responses to combined acoustic and electric stimulation in 3 of those guinea pigs. A preliminary presentation of data recorded using this preparation is the focus topic of this report.
8. Developed new data analysis software (using Matlab) to provide for the simultaneous analysis of the 8 channels of simultaneously recorded single- and multi-unit activity provided by Michigan thin-film probes inserted into the inferior colliculus.

2. Introduction

Our previous reports for this contract have focused on peripheral (auditory nerve) measures of interactions of responses to acoustic and electric stimuli. We have in the past two years described interactions assessed by the electrically evoked compound actions potential in guinea pigs and cat (QPRs 3, 5, & 7) as well as measures of single-fiber responses in cat (QPRs 4 & 6). These measures have described effects of simultaneously presented acoustic noise and electric stimuli, as well as multiple effects (e.g., response recovery and response enhancement) following offset of the acoustic stimulus. As a result, we have adopted as our “standard” stimulus paradigm; one that uses electric pulse trains in order to assess the time course of the effect of acoustic noise. Another standard feature of the combined stimulus is the presentation of the noise burst in the midst of an ongoing electric pulse train, enabling the assessment of onset, adaptation-like, and offset effects caused by the stimuli.

In work under a previous contract (Contract NIH-DC-9-2106, Final Report) we made preliminary measures of binaural interactions between acoustic and electric stimulation. In that work, we developed a novel version of the so-called binaural ABR component that involves both electric and acoustic stimuli. Guinea pigs were used that had normal hearing in the right ear and were implanted with an intracochlear electrode in the chemically deafened left ear. The right ears received acoustic click stimuli, while the left cochleae received electric current pulses. Auditory brainstem responses to right-ear stimulation alone, left-ear stimulation alone, and stimulation of both ears were measured. The binaural ABR component was computed as the difference between the response obtained with simultaneous acoustic and electric binaural stimulation and the sum of the responses to stimuli to each ear alone. This component was assessed as a function of time delay between electric and acoustic stimulation. The largest amplitude of the binaural response occurred for across-ear delays between 1 and 1.5 ms, approximately the latency difference between acoustic and electric responses at the level of the auditory nerve. The amplitudes of these measures varied across subject and were generally small. Nevertheless, they show similar trends, suggesting that there is additional interaction between acoustic and electric stimuli that can take place in the brainstem and CNS.

In the work conducted during this quarter, we have begun to examine acoustic-electric interactions that occur at the level of the inferior colliculus using thin film electrode arrays in order to accomplish multi-unit recordings simultaneously at several locations in the IC. Such an approach was described by Snyder et al. (2001). We have chosen to use a similar stimulus paradigm to that described for measurements of peripheral interactions, i.e., the use of an electric pulse train and an acoustic noise burst of limited duration. With IC recording electrodes we can assess responses to both same ear stimulation (at a more central levels) as well as binaural responses. In these initial experiments we have chosen to use wide-band noise and monopolar electrical stimulation in order to maximize the extent of acoustic-electric interaction. This preparation will, however, also allow us in future experiments to examine the responses to tonal stimuli combined with electric pulse trains to better assess the spatial properties of the interactions.

3. Methods

Surgical preparations

Acute experimental sessions were performed using adult guinea pigs. General surgical methods and vital-signs monitoring have been described elsewhere (Miller et al., 1998). Briefly, after induction of general anesthesia, the head was immobilized using a custom head holder. The left cochlea was

surgically accessed and a cochleostomy was made posterior to the round window using a 30 gauge needle and a rotary motion. A platinum-iridium wire was inserted to a depth no greater than 1 mm through the cochleostomy and into the basal aspect of the scala tympani to provide a minimally invasive monopolar electrode for intracochlear stimulation. In most preparations, careful insertion of this electrode provides for a preparation with acoustic sensitivity (as assessed by the click-evoked CAP) maintained to within 20 dB of that measured prior to the cochleostomy. Only preparations with this degree of sensitivity or better were accepted for subsequent electrophysiological data collection.

To expose the right inferior colliculus, 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. After the dura was opened, superficial brain vessels were cauterized with bipolar cautery. 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.

Stimulus and response parameters

Stimuli were generated by a 16-bit digital-to-analog converter (100,000 samples/s) controlled by custom software. Short-duration (40 μ s/phase) biphasic electric pulses were presented in 400-ms pulse trains. Stimuli passed to a custom built isolated current source that was optically isolated from its input and capacitively coupled to the stimulating electrode.

Bursts of broadband acoustic noise were produced by a Grason-Stadler noise generator. The output was fed to an attenuator, an impedance-matching transformer and a Beyer DT-48 earphone coupled to a speculum. Sound pressure in the ear canal was monitored during each experiment using a probe-microphone system described in QPR #4 and overall sound levels were computed by accounting for the system frequency response. Acoustic levels were controlled by an attenuator. Noise bursts were gated using a 1 ms rise-fall time, and presented with a total duration 100 ms.

For multi-site recording along the tonotopic gradient of the central nucleus of the IC, we used the “5mm100 μ m” single-shank probe provided by the University of Michigan Center of Neural Communications Technology. This probe has sixteen 400 μ m² electrode sites arranged linearly with 100 μ m center-to-center spacing and is the same probe that has been used by Snyder et al. (2001) and Bledsoe et al. (2003). Following an approach similar to that described in Snyder et al. (2001), the thin-film probe was inserted perpendicularly to the surface of the inferior colliculus and advanced to a depth of approximately 2 mm with the aid of a Narishige microdrive stage.

Response analysis

Multi-unit activity in the IC was measured using the 16-site probe that was buffered by a custom-built unity-gain headstage. Potentials were then low-pass filtered using 4th order Bessel filters with a 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 initial experiments, we have recorded from 8 of the 16 probe sites (i.e., every other electrode along the array) in order to sample sites along the entire array.

Analysis of spike data was accomplished using a custom program (MatLab) similar to that used in our analyses of single auditory nerve fiber data. The recorded traces were first digitally high-pass filtered. Templates of the electric stimulus artifacts were then computed, based on the response traces with no apparent recorded action potential. Those templates were then subtracted from each individual trace and a spike criterion amplitude was determined on the basis of examining distributions of “events” automatically picked within a selected window. Spike amplitude and latency were then determined and histograms of the responses (based on the aforementioned analysis criteria) were computed. The initial analyses of the data have not attempted to separate individual cells in what could be multi-unit activity from a single recording electrode. Thus, spike counts represent total activity recorded at each site.

Appropriate insertion of the electrode array into the central nucleus of the inferior colliculus was confirmed by using tone-burst stimuli and assessing the channel with the greatest spike activity for each test frequency. Figure 1 shows the result of this assessment for all six guinea pigs from which IC single-unit measures have been obtained. A consistent ordering of the electrode sites can be seen, indicating a tonotopic arrangement of sampled sites, consistent with previous IC data from guinea pigs (Snyder et al., 2001).

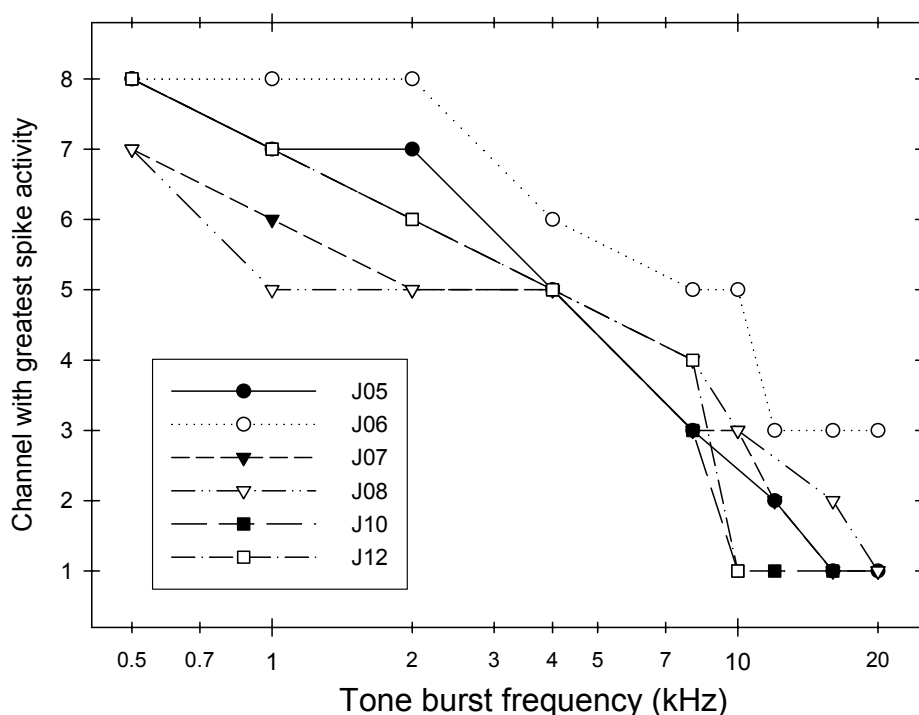


Figure 1: Demonstration of the distribution of maximum spike activity across the array of thin-film electrode sites as a function of stimulus frequency. Data are shown for six guinea pigs from which inferior colliculus unit activity were collected in this reporting quarter.

An example of recorded spikes obtained from one channel as a result of combined electric and acoustic stimulation is shown in Figure 2. In this case, electric pulses were presented at an interpulse interval of 40 ms. Both stimuli are presented to the ear contralateral to the IC under investigation. As is typical for the data reported in this QPR, the wideband acoustic noise stimulus was presented during the interval from 50 to 150 ms. These stimuli are shown schematically at the top of the figure. The small inset figure shows a spikes on an expanded time axis. Note that the spikes appear as triphasic waveforms as a result of high-pass filtering. In the case shown here, the response appears to be dominated by spikes from a single unit. We also observed instances of multi-unit responses.

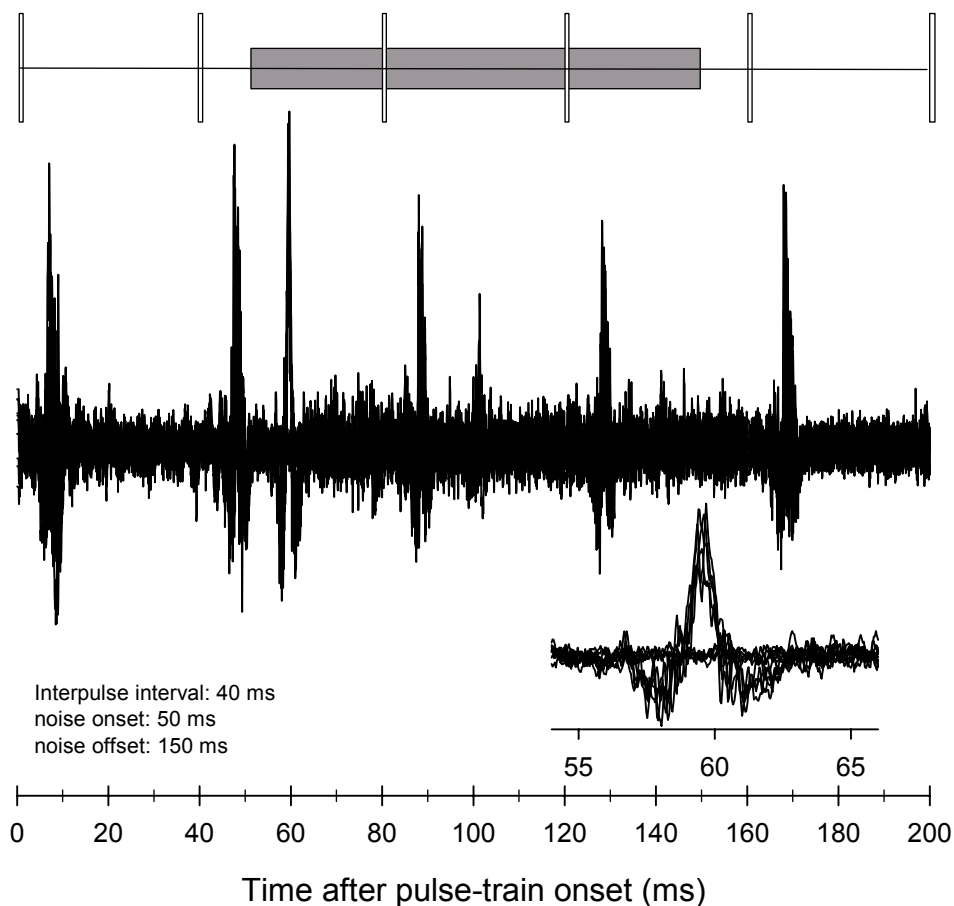


Figure 2: Example of recorded waveforms obtained with a Michigan thin-film electrode array inserted into the central nucleus of a guinea pig inferior colliculus. Shown schematically at the top of the figure is the timing of the acoustic noise (grey bar) and electric pulses. The small inset figure at the bottom shows temporal detail of the spikes occurring in response to the noise onset. Waveforms have been high-pass filtered.

4. Results

Data collected this quarter is the first that our laboratory has collected from the inferior colliculus. Initial analysis has been completed on one animal and representative data are presented here. The results presented are, hence, preliminary. Insufficient data exist to characterize general trends; however, we present findings that will form the basis of further analyses and illustrate interesting observations. In most cases, IC responses were obtained from the presentation of contralateral electric and acoustic stimulation in order to assess “same ear” acoustic-electric interactions. In noted cases, however, the electric stimulation was delivered to the contralateral cochlea and acoustic stimulation was delivered to the ear ipsilateral to the recorded IC in order to examine binaural effects.

One basic goal is to quantify adaptation-like phenomena in the IC, as our ECAP data has demonstrated that electric-acoustic interactions are strongly dependent upon the degree of adaptation to the ongoing electric pulse-train stimulus. Figure 3 shows a dot-raster display obtained from the deepest of the eight recorded channels in response to the presentation of an electric pulse train without presentation of the acoustic stimulus. Panel A shows the response patterns obtained using an interpulse interval (IPI) of 4 ms; panel B shows the response pattern from the same channel for an IPI of 40 ms. In both instances, the total train duration was 400 ms and the stimulus current level was 0.76 mA, the level at which the single-pulse ECAP amplitude was approximately 50% of its saturation (maximum) amplitude. This stimulus clearly resulted in an initially high probability of discharge for the units recorded with this electrode. The responses for the 4 ms IP show a high degree of adaptation. Compared with that typically seen in our laboratory from either deafened or acoustically sensitive auditory nerves (Matsuoka et al., 2000; Hu et al., 2003), a greater degree of adaptation is evident from these IC cells and is consistent with data from deafened feline preparations that demonstrate relatively strong adaptation in the inferior colliculus (Snyder et al., 1995). Even at the 40 ms IPI, a slight degree of adaptation can be seen.

Figure 4 summarizes IC unit adaptation patterns observed with electric pulse-train stimuli across IPI values ranging from 4 to 100 ms.. In each case, the number of spikes was evaluated in the interval following the stimulus pulse using spike analysis windows corresponding to the IPI used in each case. Total spike counts have been normalized to that obtained in response to the first pulse. Adaptation can be observed at the longest IPI, with the degree of adaptation increasing with decreasing IPI.

Turning to combined electric and acoustic stimulation, Figure 5 presents an example of the effect of acoustic noise on the response to pulse trains. In this case, IPI was chosen to be 20 ms to achieve a moderate degree of adaptation to the pulse train. In this case, the noise was presented to the same (contralateral) ear as the electric stimulus. Acoustic noise was presented over the interval 50–150 ms after pulse train onset. There are clearly fewer spikes over the duration of the noise. In addition, after onset of the acoustic stimulus (i.e., after 50 ms on the abscissa), the response pattern is transiently altered, with shorter response intervals.

Figure 6 presents acoustic-electric interaction data from the IC using monaural presentation of the stimuli (i.e., electric and acoustic presented to the contralateral ear) and binaural presentation of the stimuli. The top panel shows normalized spike counts as a function of time for monaural presentation while the bottom panel shows the binaural data. The effects of acoustic noise on spike counts are shown for different noise levels. As in the case of Figure 4, normalized spike counts are plotted as a function of time after onset of the electric train. Again, the noise was presented in the interval from 50 to 150 ms.. For both the monaural and binaural presentation, the response of the IC undergoes a decrement during noise presentation that is proportional to the noise level. Compared with the binaural data, the monaural data reveal larger decrements during the noise presentation.

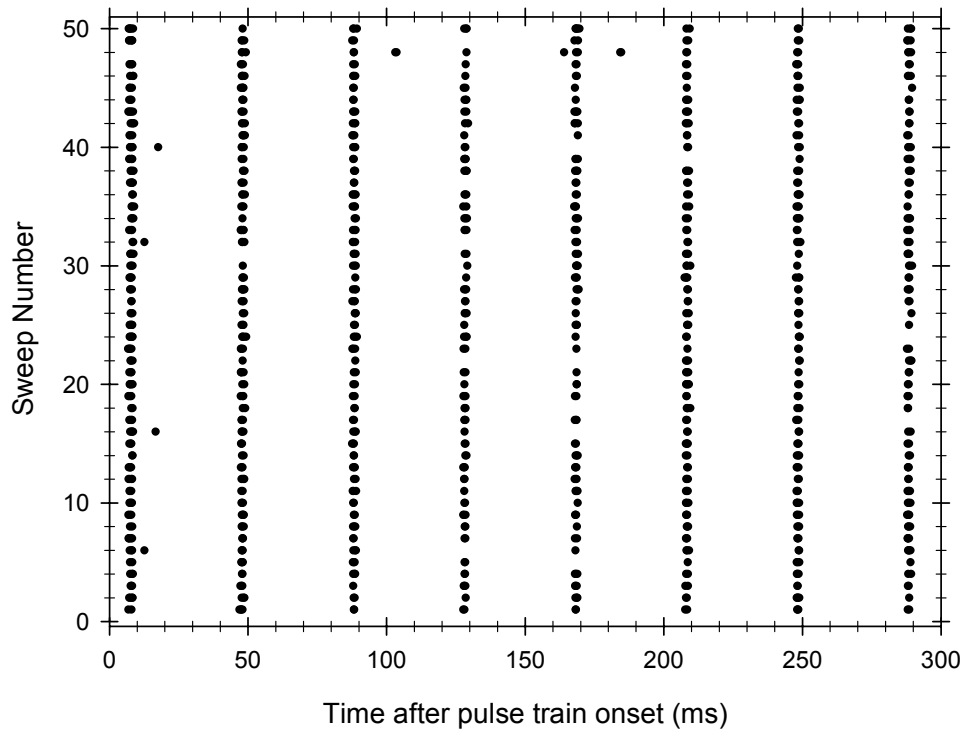
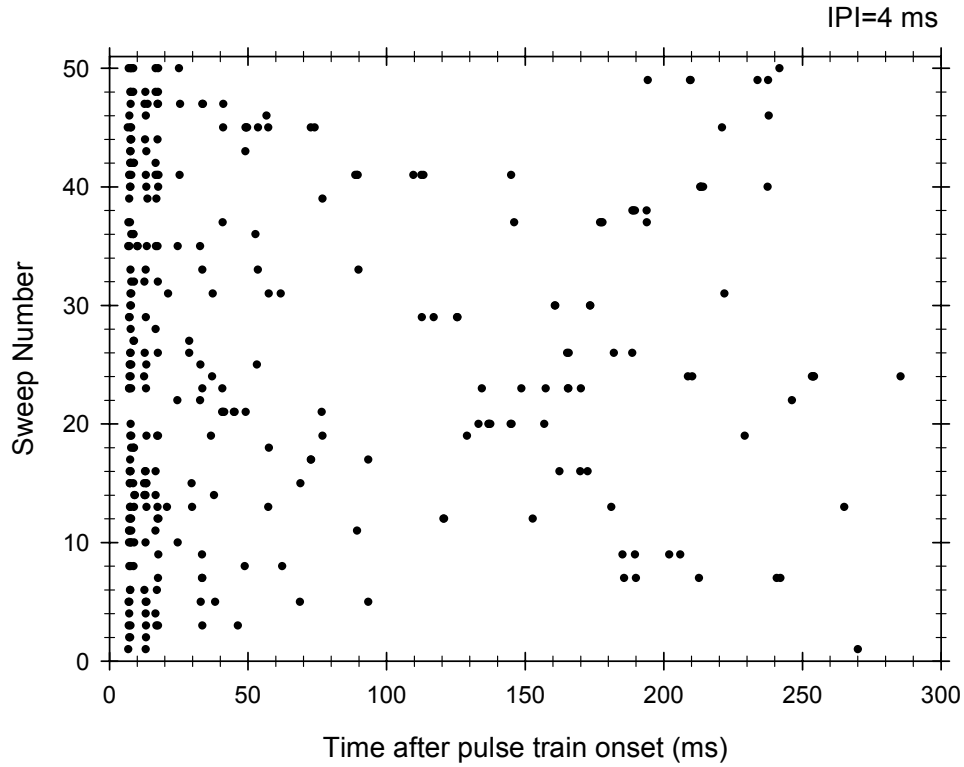


Figure 3: Dot-raster displays of unit responses recorded from the central nucleus of the guinea pig inferior colliculus. The stimuli were electric pulse trains having a total duration of 400 ms and a level of 0.76mA. Data were recorded from the deepest electrode site of the a 16-channel “5mm100 μ m” thin-film recording array. The interpulse interval (IPI) for each panel is indicated.

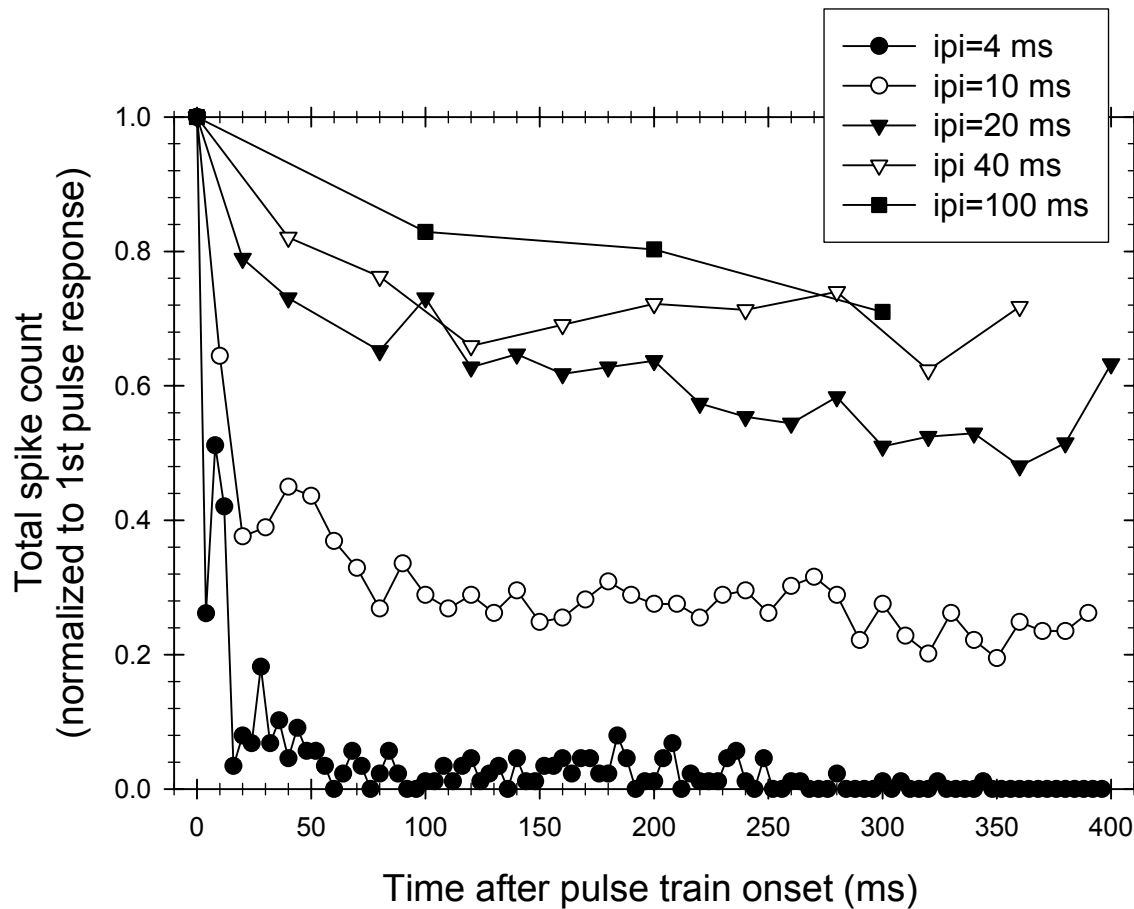


Figure 4: Effect of electric interpulse interval (IPI) on the IC unit responses as recorded by the Michigan thin-film electrode. Spike counts were obtained by analyzing total spike activity in windows corresponding to each IPI. Stimulus level was the same as in the previous figure.

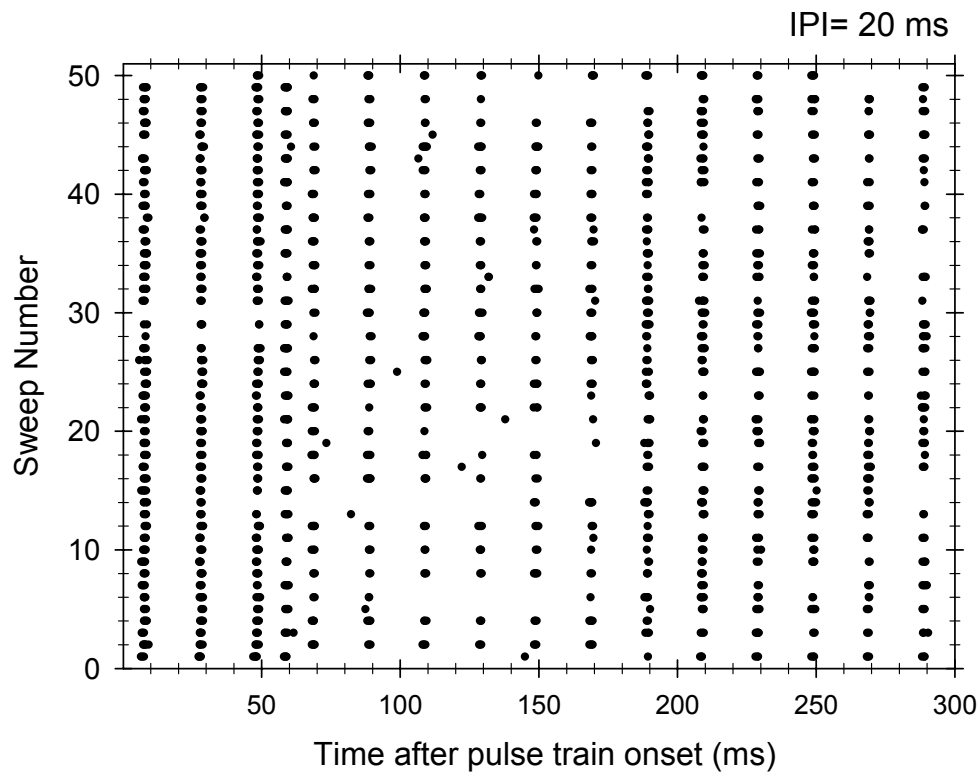


Figure 5: Dot-raster plot showing the effect of the presentation of wideband acoustic noise on the electric pulse train response. A 400 ms long train of electric pulses was presented at an interpulse interval of 20 ms. Acoustic noise was presented in the interval from 50 to 150 ms.

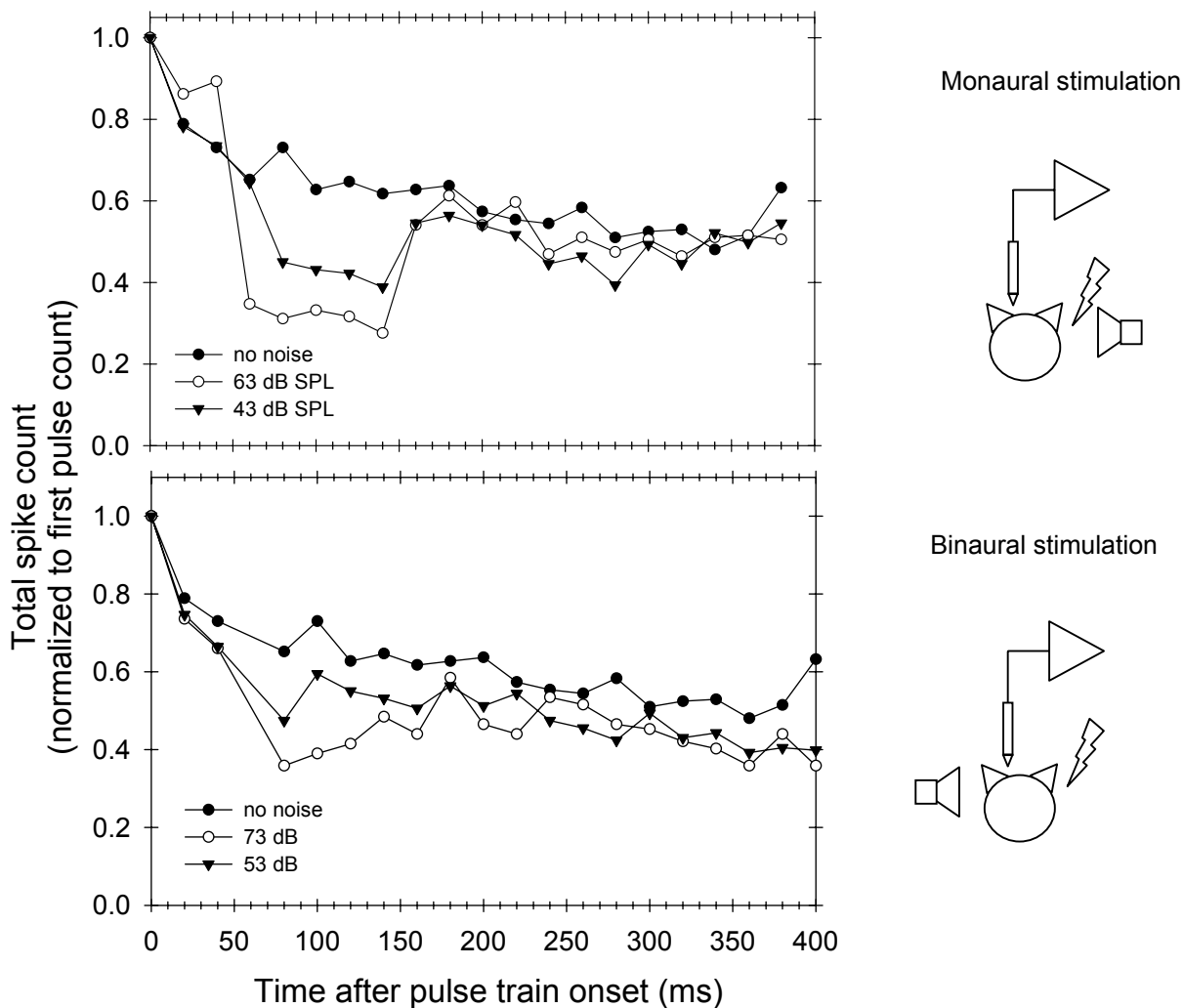


Figure 6: Effects of combined acoustic-electric stimulation on IC responses using two stimulus delivery schemes. In the case of the top plot (“monaural stimulation”), the acoustic and electric stimuli were presented to the same ear while recording from the contralateral IC. In the case of the bottom plot (“binaural stimulation”), the acoustic stimulus was applied to the opposite ear, providing an evaluation of binaural effects.

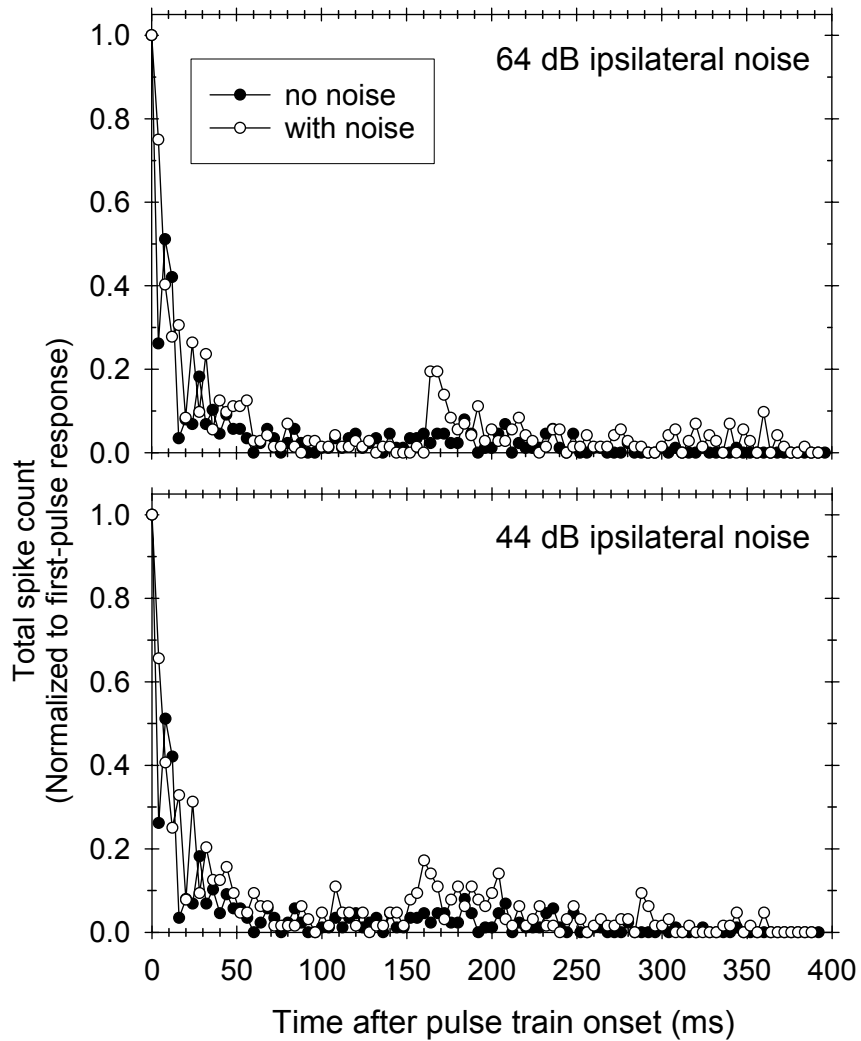


Figure 7: Normalized spike counts as a function of time for combined acoustic-electric stimulation. In these cases, the acoustic noise stimulus was presented to the ear opposite to that receiving the electric pulse train. The electric interpulse interval was set at 4 ms, producing large amount of adaptation. The acoustic noise was presented over the interval between 50 and 150 ms. Note the enhanced responses that occur after offset of the noise.

Although the binaural effect is relatively small and noisy, the data may suggest an onset-type response as opposed to the more steady-state effect observed in the monaural data. In addition to the decrease in response during the acoustic stimulus, we have observed other effects of acoustic noise. Figure 7 illustrates an example in which the response to the pulse train is enhanced after offset of the acoustic noise. In this example, the pulse-train IPI is 4 ms, so that there is considerable adaptation to the pulse train presented alone. While there is not a clear effect of the acoustic noise during its interval of its presentation (50-150 ms), there is a clear increase in spike count at the offset. One interpretation of this response pattern is that there is a decrease in response at the level of the system that results in a recovery from adaptation. After offset of the noise, the less adapted system then results in an increased response.

The results presented here indicate that acoustic-electric interactions can occur for both within-ear (monaural) stimulation or across-ear (binaural) stimulation, although the nature of these interactions is not the same for the two stimulation modes. We note that the binaural interactions occurred for moderate and low levels of acoustic stimulation. Unpublished work in our laboratory indicate that interaural attenuation of the wideband noise (as assessed by click-evoked CAP) is at least 35 dB for stimulation of guinea pigs with our sound delivery system. This suggests that the noise offset effects reported here (Figure 7) are not due to acoustic cross-talk. Cross-talk, however, is a factor in our assessments and future work will be done to provide such measures when investigating binaural effects.

The data presented here were recorded from the deepest electrode of the Michigan array, with a best frequency of approximately 10 kHz. We have observed decreases in response similar to those described here for other recording electrodes, but we have not yet assessed any systematic trends with electrode positions. That analysis is ongoing. While the data represents preliminary findings, they demonstrate several effects of acoustic noise, both ipsilateral and contralateral, on the response at the level of the inferior colliculus. One fundamental difference between the IC and auditory nerve response patterns is that the former demonstrated decreased responsiveness during presentation of the combined electric and acoustic stimulus while that latter demonstrated increased spike rates. Future work will systematically evaluate these effects with both tonal and broadband stimuli across best frequency of neurons.

5. Plans for the Next Quarter

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

1. Continue measures of acoustic-electric stimulation at the level of the auditory nerve using acute guinea pig preparations, with a focus on examining the contribution of adaptation to the electric stimulus to the nature of interaction effects.
2. Conduct additional experiments using acute cat preparations to access acoustic-electric interactions using ECAP measures with a focus on post-stimulatory effects, as well as perform intra-subject comparisons of ECAP and single-unit data.
3. Continue developing the model of inferior colliculus recordings, which will allow us to assess interactions to binaural stimulation as well as to make comparisons between interactions at the peripheral and central levels of the auditory system. This will

involve some adjustment of surgical procedures that involve exposure of the inferior colliculus.

6. References

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