Effects of Remaining Hair Cells on Cochlear Implant Function

9th Quarterly Progress Report

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1. Summary of activities in this quarter

During the ninth quarter of this contract (July 1 – September 30, 2004), we accomplished the following:

1. The two manuscripts accepted for publication (see QPR 8) now appear in the on-line version of Hearing Research.

2. A manuscript detailing the time course of acoustic-electric interactions as assessed by the electrically evoked compound action potential (ECAP) was accepted for publication (Nourski et al., in press). This manuscript is a formal elaboration of the ECAP work presented in previous QPRs.

3. We performed three additional experiments on acute experiments with guinea pigs examining the recovery properties to both acoustic and electric stimulation.

4. We performed two experiments examining binaural interaction effects between acoustic and electrical stimulation in guinea pigs.

5. We performed 5 experiments with acute cats examining the response of single nerve fibers to combined acoustic noise and electric pulse train stimuli. This report summarizes part of the results from that work.

6. We hosted a site visit by Dr. Roger Miller on 15-16 September to discuss progress on the work of this contract, future plans, and experimental procedures.

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2. Introduction

One primary goal of this contract is to assess the interactions between acoustic and electric stimulation of the auditory nerve in an ear with intact hair cells. The use of acoustically sensitive animals with minimal hearing losses (secondary to surgical procedures) is an appropriate model for assessing acoustic-electric interactions, as it provides a "best case" for possible interactions. It thereby provides "baseline" measures for subsequent comparisons of trends observed in hearing-impaired ears and cochlear implant recipients.

Previous progress reports (QPR's #3, #5 and #7) described the results of acoustic-electric interactions using the electrically evoked compound action potential (ECAP) as the means of assessment. The experimental paradigm presented an acoustic wideband noise in the middle of the presentation of a longer-duration electric pulse train in order to examine both simultaneous and non-simultaneous interaction effects. In those experiments, we reported a decrease in the amplitude of the response during the noise presentation as well as after the noise offset. The temporal pattern of response amplitude to electric pulses over time (during and after acoustic noise stimulation) suggests a relationship to adaptation during the noise burst and recovery from adaptation after noise offset (QPR #5). The time course of these changes during the noise burst have been fit by a two-exponential model consistent with the expected time course of adaptation to the acoustic noise burst (Westerman and Smith, 1984). Such data are consistent with a hypothesis that the increased activity due to the noise results in less synchrony in response to the electric pulse. Consequently, the response to the pulse train mimics the time course of the adaptation to the noise.

The effectiveness of the noise in reducing the amplitude of the response after noise offset suggests a second mechanism. Adaptation of the underlying neurons as a result of acoustic stimulation may affect the responsiveness of neurons to electrical stimulation. One of the more intriguing results of recent work (QPR #7) is the time-course of ECAP recovery immediately after offset of the acoustic noise. This recovery can be quite complex and can demonstrate highly non-monotonic behavior, requiring a three-component exponential model to effectively characterize it. We have previously speculated that the recovery period is characterized by multiple mechanisms including neural response properties including refractoriness, adaptation and changes in spontaneous activity.

As the ECAP amplitude is likely dependent upon (1) the number of action potentials, (2) the amplitudes of action potentials, which are dependent upon refractory effects (Miller et al., 2001), and (3) across-fiber spike synchrony, we have undertaken a series of experiments examining these effects in single auditory nerve fibers. Work described in previous reports (QPR #4 and QPR #6) has demonstrated time course of effects consistent with the ECAP data. In our most recent work (i.e., this reporting period), we have expanded our experimental paradigm to explore a range of noise-burst durations so as to determine the influence of acoustic activity and degree of adaptation on the post-noise recovery process.

3. Methods

The methods used are essentially the same as those described in QPR #4 and they parallel the procedures used in most of our ECAP studies. The electric pulse trains consisted of 40 μs/phase biphasic pulses presented at a period of 4 ms (250 pps). The electric train was presented both by itself ("electric" only condition) as well as with the simultaneous presentation of a noise burst (the "acoustic + electric" condition). The paradigm improvement described in QPR #6, which added a third stimulus condition – that of the acoustic noise presented alone, was used in these single-fiber experiments.

The new parameter studied in the experiments of this quarter was the noise duration. Earlier single-fiber work used 100 ms noise bursts; in these cases, we used bursts of 100, 200, and 300 ms duration. The onset of the noise was always 50 ms after onset of the pulse train. The duration of the pulse train was adjusted in accordance with the duration of the noise such that the train persisted 150-200 ms after offset of the noise burst. For example, when a 100 ms noise burst was used, the duration of the electric pulse train was 350 ms. This enabled us to investigate both simultaneous effects and also the nature of the post-noise offset recovery period, in which the pulse train served as a series of probe pulses. In order to avoid cumulative adaptive effects that might occur across stimulus-presentation trials, each electric train presentation was followed by a silent period 1.8 times that of the train duration. Twenty to fifty stimulus repetitions (typically 35) were used in order to collect firing statistics (i.e., firing efficiency, jitter, etc.). It is possible that the inter-train silent period was not sufficiently long to prevent some cumulative processes; however, this period was chosen to meet the time-limitations inherent in single-fiber work.

As in our other animal preparations, electric stimuli were delivered by a monopolar 0.5-mm ball electrode formed by a 3 mil Pt/Ir wire inserted into the basal turn of the cochlea through a small cochleostomy. In at least half of the cases, insertion of this wire (typically to no greater than 1 mm) results in a click-evoked ECAP threshold shift of 10 dB or less. Data collection was terminated if the cat preparation exhibited a click-evoked ECAP threshold shift equal to or greater than 40 dB. Our search stimulus was a low-rate (30 ms IPI) electric pulse train presented at a level corresponding to about the 80% response amplitude on a normalized ECAP growth function. Upon contacting a fiber, the electric and acoustic noise levels were chosen such that high firing efficiencies were evoked at the stimulus onsets.

This stimulus paradigm required a significant amount of fiber-contact time. For example, use of the 300 ms noise burst condition required 3 minutes to collect a single data file. If contact time permitted, we collected responses at different noise and/or electric levels after first collecting a basic noise-duration series at fixed levels. We also attempted to assess best frequency for each fiber using a swept frequency tone. Given the long total duration of the repeated stimulus presentations, our ability to assess many conditions were clearly limited by the "hold" time.

The analysis of the data was performed in a manner similar to that described in our previous progress reports. We used the same artifact templating method in order to extract spike amplitudes and spike times from the electrical artifact. Initial analysis generated histograms such those shown in Figure 1 for each of the three aforementioned stimulus conditions (acoustic alone, electric alone, and the "electric+acoustic" condition). In order to summarize single-fiber response properties and provide the data reduction needed for across-fiber analysis, we re-analyzed all PST histograms using wider analysis windows to characterize several intervals of interest. These analysis windows are described in the table below and are shown in Figure 1. We note that the intervals used in this report are somewhat different than those used in QPR #6.

Windows used to re-analyze and summarize PST histograms		
Analysis interval (window)	Interval duration (ms)	Description of window's occurrence relative to stimulus
1	20	Immediately after electric pulse train onset
2	30	Immediately before onset of acoustic noise
3	20	Immediately after onset of noise
4	30	Immediately before offset of noise
5	30	5-35 ms after noise offset
6	100	Immediately before offset of the pulse train

These intervals – and comparisons of responses between two windows – provided for the assessment of initial adaptation to the pulse train alone (i.e., comparisons of Int 2 and Int 1), adaptation of simultaneous effect of noise (Int 4 vs Int 3), and the recovery process (Int 6 vs Int 5).

The data described in this report were collected responses from a total of 96 fibers from 7 cats. Of those, contact time was sufficient to collect data across 2 or 3 noise durations in 35 of those cases. Unusual adaptation (some of which is discussed below) or lack of a strong acoustic response further limited this set.
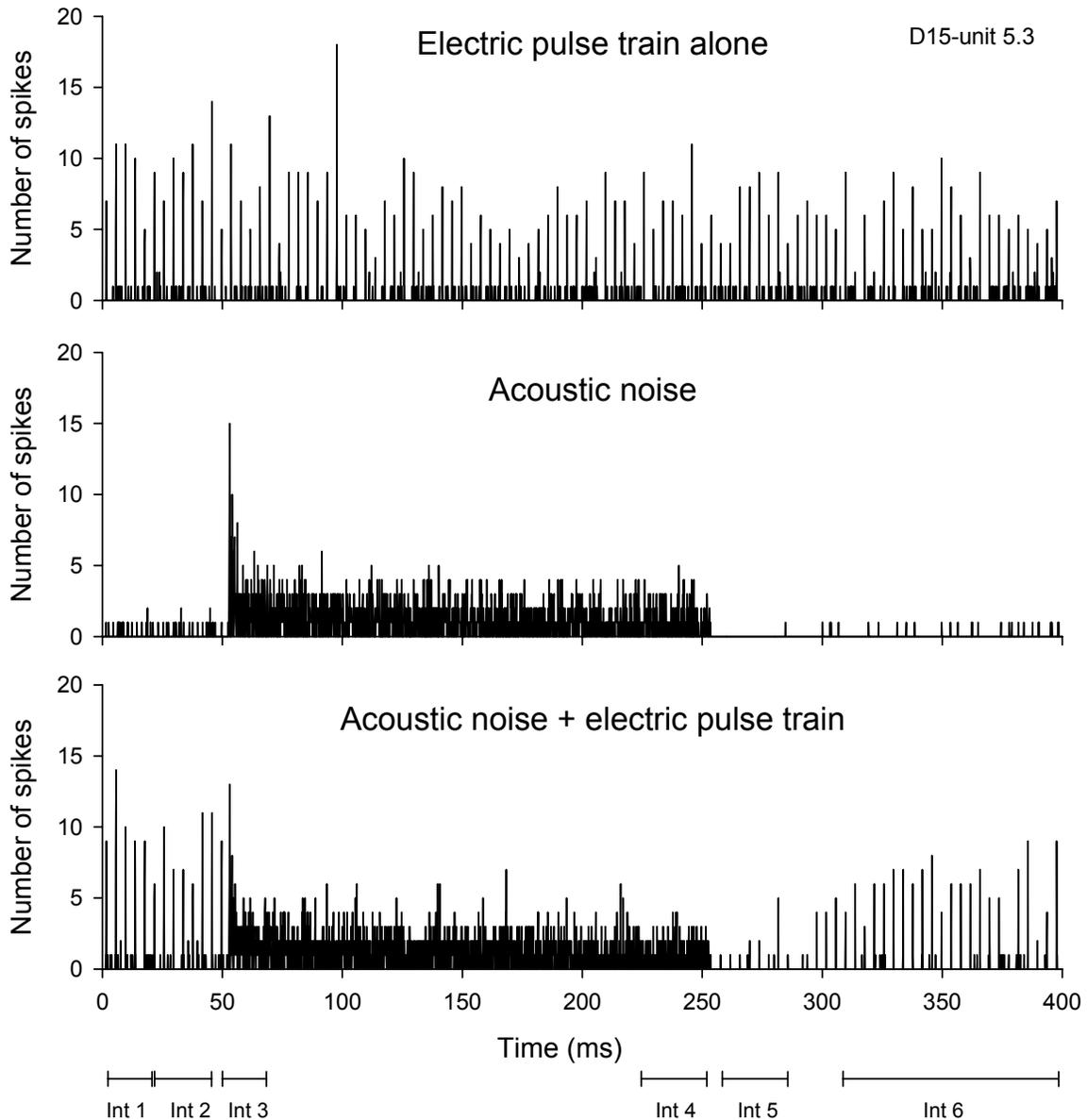
Figure 1: Examples of PST histograms in response to electric pulse trains (400 ms duration, 1.05 mA biphasic pulses) and an acoustic noise (96 dB SPL). The noise onset is at 50 ms and offset is at 250 ms after pulse train onset (duration of 200 ms). The upper panel shows response to pulse train presented alone, the middle panel to noise alone and the bottom panel to the combined stimulus. The intervals for subsequent analysis (1-6) are depicted at the bottom and are explained in further detail in the text.
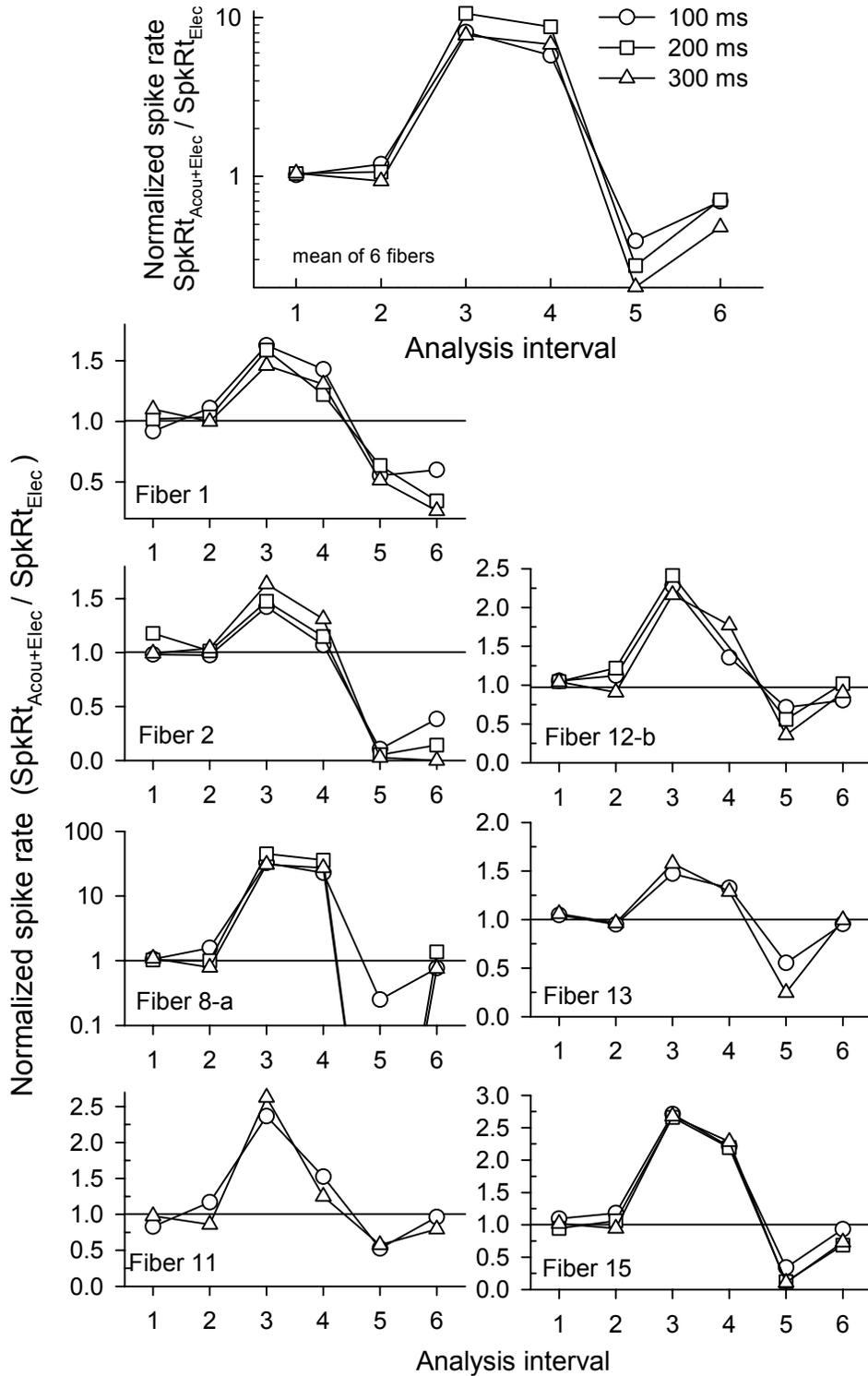
Figure 2: Example data and summary data of the effect of acoustic noise duration on spike rates. As in some of the other presentations of this report, the ordinate value (here, spike rate within each analysis interval) is expressed as a normalized rate, computed as the ratio of the rate obtained to the combined ("acou+elec") stimulus and the electric-alone condition. Thus, a value of one indicates no added effect of the acoustic stimulus. Mean data for 6 of the 7 fibers (one outlier fiber 8-a removed) is shown at the top of this figure. In all but one case, acoustic noise levels used ranged from 84 to 92 dB SPL (overall level). A noise level of 49 dB SPL was used for fiber 12.

4. Results

Figure 2 (above) illustrates individual and group single-fiber data for 7 of 15 fibers collected to date assessing the effects of noise duration. These 7 fibers were chosen on the basis of spike-rate stability across all three noise-duration conditions. The smaller graphs of Figure 2 show individual data across the six analysis windows. The mean data for the three durations are plotted at the top of Figure 2. Note that the analysis windows are adjusted relative to the noise onset and offset so that the time of the windows relative to pulse train onset varies with noise duration. In each case, spike counts are plotted as a ratio comparing the acoustic+electric condition to electric alone. In this way we can compare the effectiveness of the acoustic signal in across fibers and across conditions. As the signals are interleaved, effects of long-term changes are minimized with this paradigm.

Effects of noise are evident. During presentation (intervals 3 and 4), there are elevations in spike rate. The rates during interval 4 are relatively smaller, reflecting adaptation to the noise. There are also some effects of noise duration. The individual and mean data indicate a decrease in the response during the intervals immediately after noise offset (intervals 5) that is graded by noise duration. Consistent with a hypothesis of increased adaptation with longer acoustic excitation, the post-noise reduction in firing rate is greatest for the 300 ms noise burst. We also note that the spike-rate decrement following the noise offset can persist for at least 100 ms, as is evident in "interval 6" data of Fiber 1.

This trend is further examined in Figure 3 where normalized spike rates for interval 5 are plotted as a function of noise duration for the same fibers of the previous figure. For each case shown, the noise level and current level was held constant while noise duration was varied. There is a clear trend showing a decrease in responsiveness following the noise with increasing noise duration. The rate of this effect with duration is not necessarily the same for each fiber.
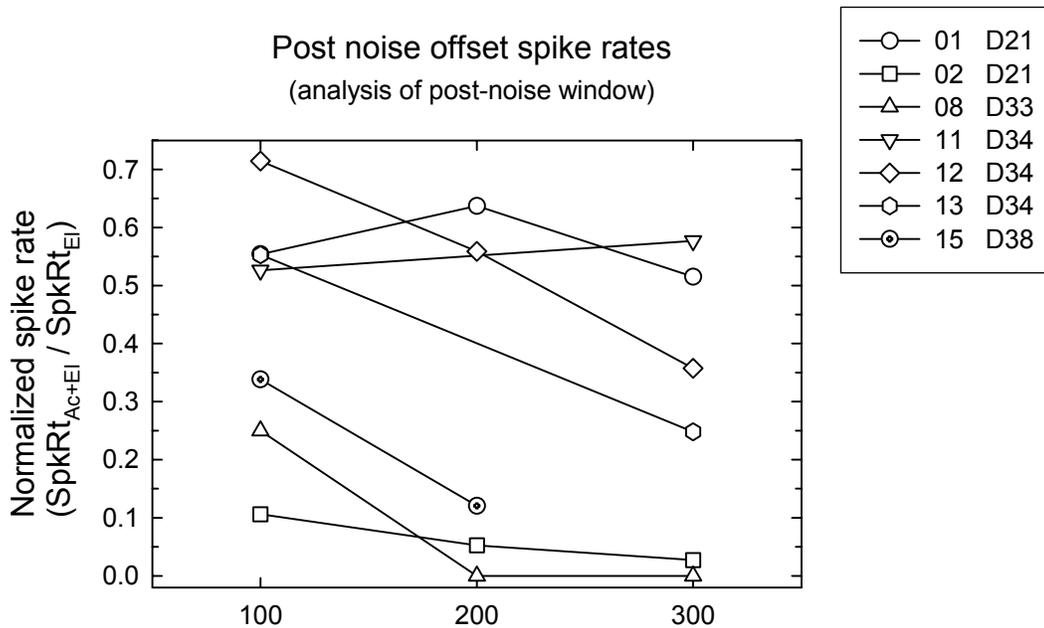
Figure 3: The effect of noise burst duration on normalized spike rate during the post-noise interval (i.e., interval 5). Data are shown for the same fibers illustrated in Figure 2.

As both our guinea pig and feline ECAP amplitude measures have demonstrated non-monotonic (post-noise) recovery functions, we have hypothesized that they may be the result of at least two physiologic factors: (1) an enhancement of synchrony in the post-noise period and (2) decreased responsiveness in this interval. Consequently, in addition to the rate measures, we have assessed the temporal measures of jitter (i.e., the standard deviation of spike times) and vector strength for analysis interval 5.

Examples of normalized spike rate and jitter as a function of the six analysis intervals are shown in Figure 4. As in the previous cases, the normalization of the dependent variables was done using the data from the "electric only" stimulus condition. Data from two fibers are shown. In both cases, fiber "hold" times were sufficiently long (> 30 m) to provide for data collection at several levels. In one case (fiber 15, left column), several electric levels were examined; in the other (fiber 16, right column), acoustic noise level was explored. Note the decreased fiber responsiveness in the post-noise interval (interval 5). Also, jitter is reduced during this interval (and somewhat less so in interval 6). It is important to note that the interval spike rate and jitter values are also lower relative to the values in interval 1, i.e., when no acoustic stimulus was present. This finding is particularly intriguing in that a general property of electrically stimulated fibers is increased jitter at lower firing efficiencies (Miller et al., 1999). We note further that at some stimulus levels (e.g. 1.0 and 1.05 mA for fiber D38-2-1), there is little change in rate with a decrease in spike jitter.
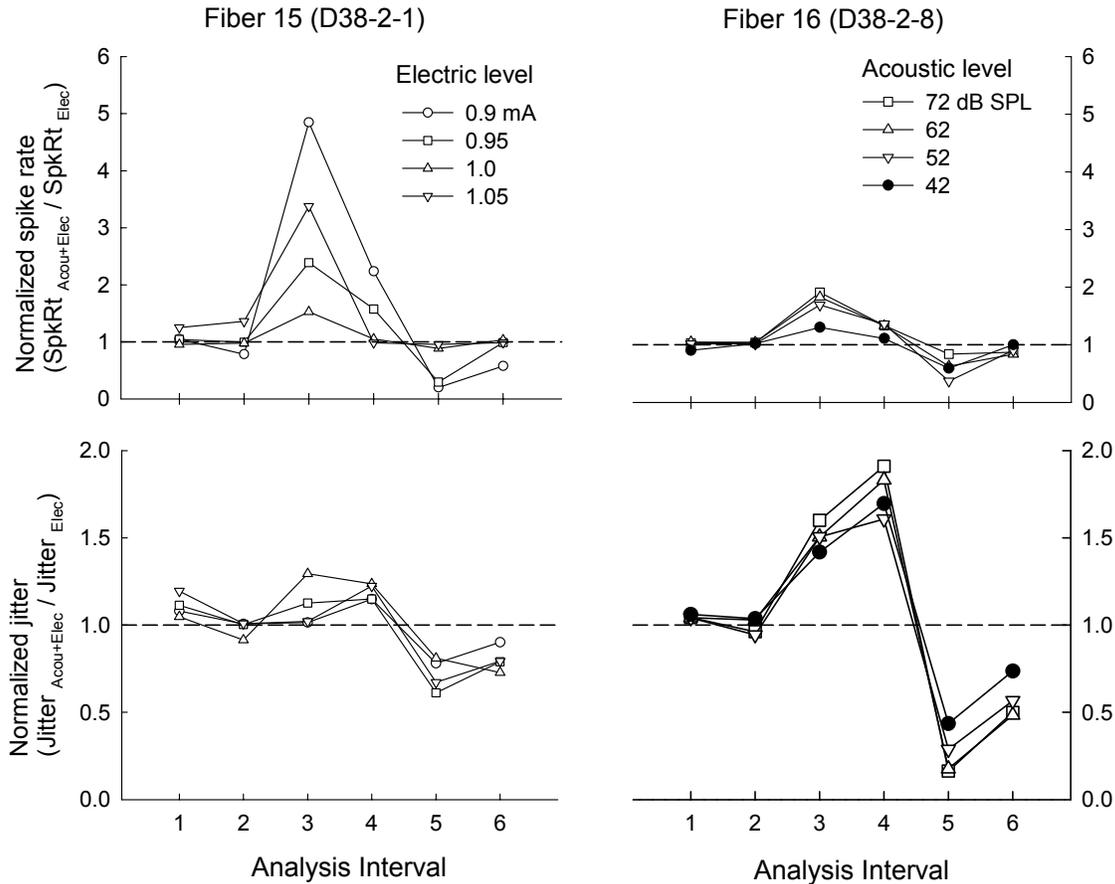
Figure 4: Effect of combined acoustic and electric stimulus presentation on spike rate (top panels) and spike jitter measures. Both the spike rate and jitter measures are normalized in a manner described earlier in the text. Acoustic noise level for fiber 15 was 82 dB SPL. Electric pulse level for fiber 16 1.0 mA.
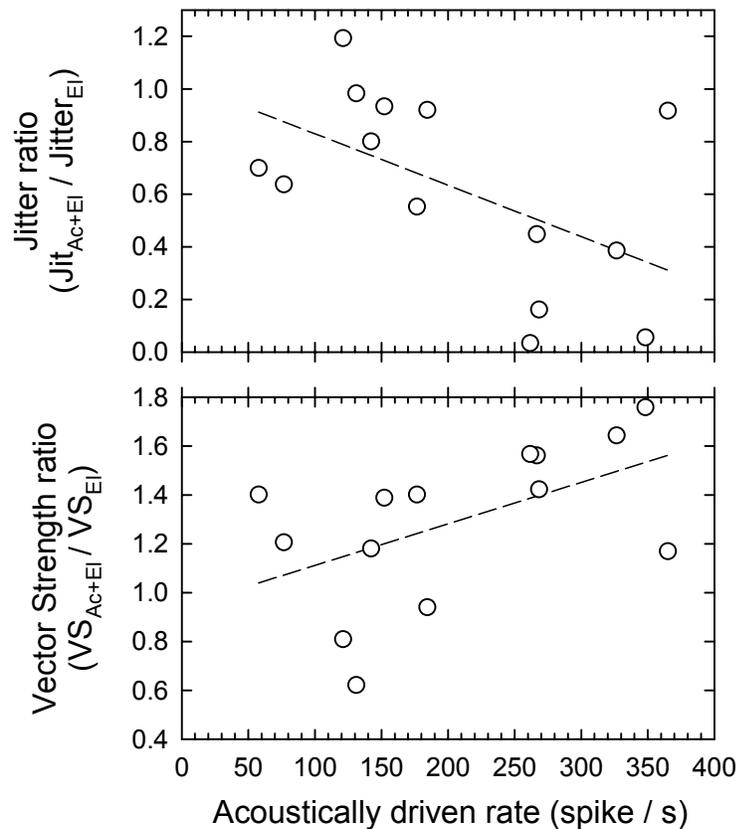
Figure 5: An examination of the effect of the acoustically driven spike rate on post-acoustic (interval 5) changes in spike synchrony. Data are shown for the same 6 fibers used in the group-fiber analysis presented in Figure 2. The "acoustically driven rate" was computed using spike rates measured within analysis interval 4 (i.e., the interval immediately before noise offset). The temporal measures were obtained in interval 5 (i.e., the post-acoustic interval, immediately after offset of the noise). Both temporal measures were normalized in the same manner used in previous plots. Dashed lines show linear-regression fits.

Further insight into the post-noise changes in spike synchrony is provided by Figure 5, which plots both normalized jitter and normalized vector strength for six fibers. The "acoustically driven rates" were computed for the "acoustic only" stimulus condition using interval 4 data (i.e., the analysis interval corresponding to the latter part of the noise presentation). The temporal measures were obtained from the following interval (interval 5) so as to determine the effect of the acoustic spike activity on the length of the recovery period. Note that data are included from the three different acoustic noise durations; thus, each fiber contributes more than one datum. The two temporal measures indicate a consistent trend – an increase in spike synchrony proportional to the degree of acoustically driven activity. More generally, note that in most cases, temporal uncertainty in interval 5 is less than that occurring in response to the electric pulses alone.

We speculate that the two identified post-noise effects, (1) reduced spike rate and (2) increased synchrony, may be the countervailing factors that result in our previously reported non-monotonic ECAP recovery functions. While the decreased responsiveness is a general property of refractoriness and adaptation, it is not clear what biophysical mechanisms underlie the increased spike synchrony.

We note, however, that we have previously observed reduced jitter in electrically stimulated fibers of deaf ears stimulated to states of partial refractoriness (Miller et al., 2001).

Finally, we note that while we observe adaptation of the neuronal response to both acoustic and electric stimulation, the pattern of adaptation can differ considerably between the two modes of stimulation as well as across single auditory nerve fibers. Examples from two fibers are illustrated in Figure 6. The histograms in Figure 6 differ from those in Figure 1 in that the bin width is set to 4 ms, the period of electrical stimulation. Consequently, the phase-locking of the spikes to the individual electrical pulses is not evident, but the time course of adaptation across the duration of the pulse train and/or noise burst are more evident.

The adaptation to electrical stimulation is minimal for fiber D33-4-4 plotted on the left; the adaptation to acoustic noise is typical of that observed with acoustic stimulation. The response to the combined acoustic-electric stimulation still shows a clear onset response to the noise. The pattern of electrical adaptation is clearly different for fiber D33-4-3. This particular fiber shows a rapid pattern of adaptation to electrical stimulation while the response to acoustic noise still shows the typical response over time. We note that the stimuli in all cases are interleaved, i.e., the response to noise alone stimuli are interspersed with the electric alone and combined stimulation. In that way we attempt to avoid any sequential adaptation effects that could be influencing these response patterns.

Any underlying anatomical correlates of these differences in adaptation properties are not known at present. We do note, however, that in the case of these two fibers, they were quite close in position along the electrode track and were therefore likely innervating similar sites within the cochlea. At present, we do not have a sufficient sample of fibers with "best frequency" information to make any meaningful assessments of cochlear point-of-origin (or position relative to the basal stimulating electrode) and fiber response properties. Well will continue to collect such data in future experiments.
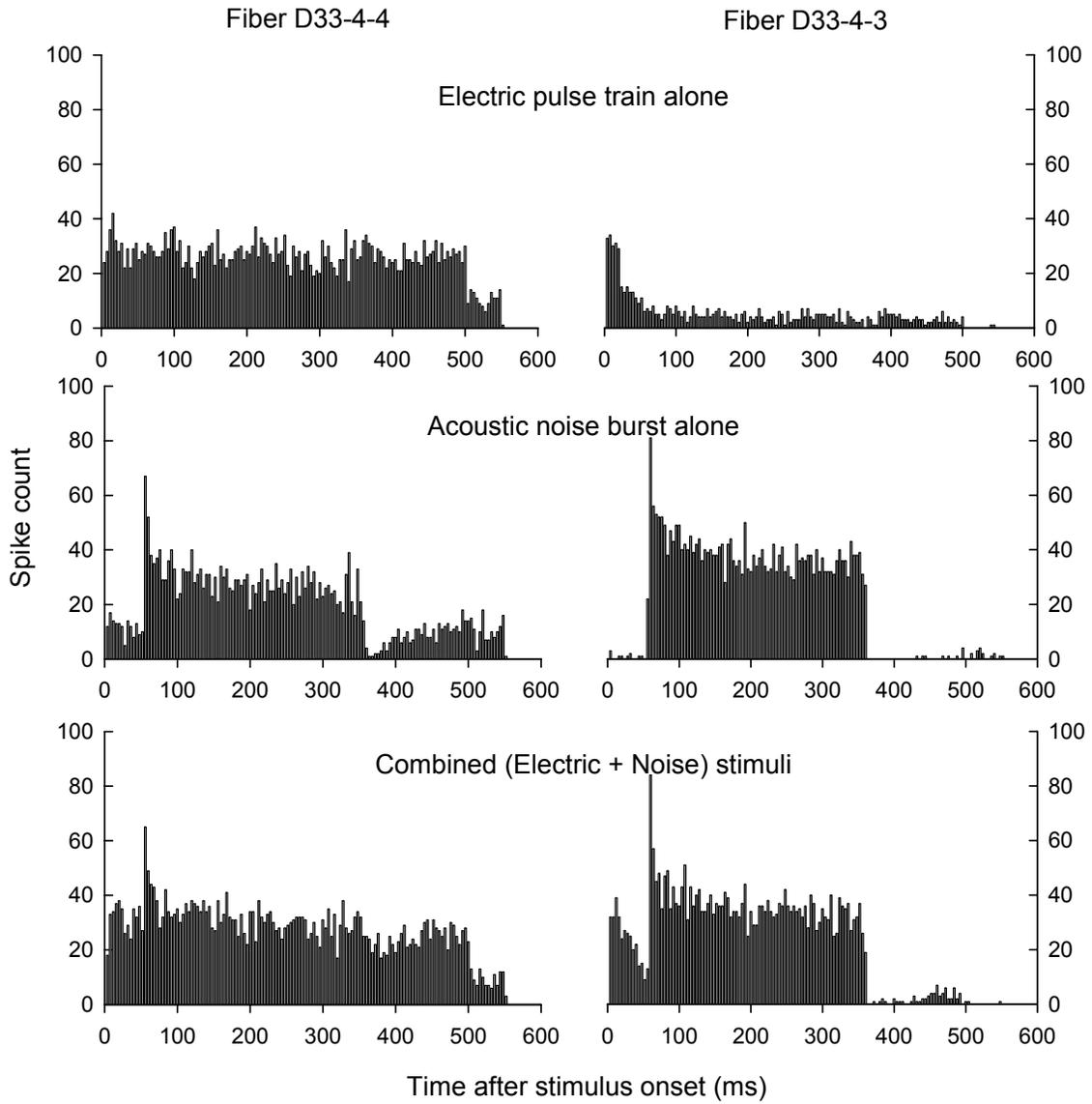
Figure 6: PST histograms illustrating differential rates of electrically and acoustically induced adaptation. PSTH's for the three stimulus conditions are shown for two different fibers from one cat. Fiber D33-4-4: Noise level=82 dB SPL, Current level=2.4 mA. Fiber D33-4-3: Noise level=82 dB SPL, Current level=1.3 mA.

5. Plans for the next quarter

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

1. Continue measures of the single fiber responses to combined electrical and acoustic stimulation. Prepare a manuscript for publication on work to date.

2. Continue ECAP measures of acoustic-electric stimulation in acute guinea pig preparations, with a focus on examining the comparison between recovery from acoustic and electric adaptation and their contribution to the nature of the observed interaction effects.

3. Continue 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.

4. Continue experiments recording in the inferior colliculus to assess interactions to binaural stimulation.

5. Attend Neural Interfaces Workshop in November and present report on progress of contract work.

6. References

Miller, C.A., Abbas, P.J., Robinson, B.K., Rubinstein, J.T., Matsuoka, A.J. (1999). Electrically evoked single-fiber action potentials from cat: responses to monopolar, monophasic stimulation. Hear Res 130, 197-218.

Miller, C.A., Abbas, P.J., Robinson, B.K. 2001. Response properties of the refractory auditory nerve fiber. J Assoc Res Otolaryngol 2, 216-32.

Nourski, K.V., Abbas, P.J., Miller, C.A., Robinson, B.K., Jeng, F.C. (in press). Effects of acoustic noise on the auditory nerve compound action potentials evoked by electric pulse trains. Hear. Res.

Westerman, L.A., Smith, R.L. (1984). Rapid and short-term adaptation in auditory nerve responses. Hear Res. 15(1-2): 249-260.