# Effects of Remaining Hair Cells on Cochlear Implant Function

## Final Report

Neural Prosthesis Program
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P.J. Abbas, C.A. Miller, B.K. Robinson, K.V. Nourski, N. Hu,
F.C. Jeng, J. Woo, H. Noh

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

University of Iowa

Iowa City, Iowa, USA

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# I. Introduction

Cochlear-implant candidates with residual hearing can maintain significant hair-cell integrity after cochlear implantation (von Ilberg et al., 1999), raising the possibility that functional hair cells can influence the response of auditory nerve fibers to electric stimulation. During our previous contract (N01-DC-9-2106) we began investigations using animal models to explore how functional hair cells can interact with the electrical stimulation produced by a cochlear prosthesis. That contract focused exclusively on measures based on the electrically evoked compound action potential (ECAP), a potential that can be routinely recorded from research animal preparations and cochlear implant users equipped with neural response telemetry systems. Work conducted under that contract demonstrated significant effects of functional hair cells on the response of auditory nerve fibers to electrical stimulation. We also demonstrated that the ECAP in response to single pulses or pulses trains could be modified both during and after the presentation of an acoustic noise stimulus.

Research conducted under this contract expanded upon those findings to include more detailed ECAP measures. It also introduced the inclusion of single auditory nerve fiber (ANF) measures to assist in interpretation of gross-potential measures and, it was proposed, to gain insight on underlying mechanisms. By doing so, we sought to provide explanations of activity at the auditory periphery with a long-term goal of contributing to the development of more effective paradigms for stimulation with cochlear implants in individuals with residual hearing. This report summarizes the main findings of that research during the last 5 years. Additional findings can be found in the quarterly progress reports and publications.

# II. Overview of methods

**General approach** For these investigations, we chose wide-band noise as our standard acoustic stimulus so as to maximize the likelihood of evoking acoustic-electric interactions in the response of a typical ANF. For a similar reason, monopolar intracochlear stimulation was used. To maintain acoustic sensitivity, we used what we termed a "minimally invasive" monopolar stimulating electrode. In several cat experiments, both ECAP and ANF measures were obtained. For experiments reliant solely upon ECAP measures, guinea pigs were used, with the notion that the most interesting effects observed from this species would be re-evaluated using the combined ECAP/ANF measures from cats.

**Stimulus and response parameters** For feline ANF experiments, the electrode consisted of a Pt/Ir ball electrode with a diameter of ~0.4 mm (as noted previously, the electrode for guinea pigs was a 5-mil diameter Pt/Ir wire stripped of its Teflon insulation for a length of ~1 mm) . It was inserted approximately 1 mm (from the outer surface of the otic capsule) into the scala tympani via a cochleostomy medial to the round window. The round window was left intact. The return electrode was a needle electrode placed in neck muscle. With the cochleostomy electrode, we could typically maintain hearing sensitivity to within 10 dB of pre-surgical levels, as assessed by measuring acoustically evoked compound action potentials (ACAPs) in response to click stimuli. In cases where threshold losses were greater, the animal was not included in acoustic/electric interaction studies. Wide-band Gaussian noise was presented to the ear canal through a Beyer DT48 earphone and speculum. Electric stimuli were in the form of 40 μs/phase biphasic pulses (cathodic-leading phase) presented either singly (with an inter-stimulus interval of 30 ms) or in short pulse trains. Stimuli were delivered by a constant-current source that was capacitively coupled to the stimulating electrode.

**Recording parameters** Experiments measuring ECAPs were conducted primarily in guinea pigs. In both species, the auditory nerve was exposed using a dorsal approach and a bipolar electrode was placed near the auditory nerve trunk for recording. Standard signal-averaging techniques were then used to record the compound action potential (Miller et al., 1998). In the cat ANF experiments, a standard posterior-fossa surgical approach (Kiang et al., 1965) was used and action potentials were recorded using glass micropipettes filled with a 3 M KCl solution. When searching for responsive fibers, the pipette was advanced in 1 μm steps and a search stimulus, 40 μs/phase pulses presented at a rate of 33 pulse/s, was presented at a level approximately equal to that which evoked an ECAP amplitude 90% of the maximal amplitude. Standard recording techniques were used and a template-subtraction method was used to reduce electrical stimulus artifact. This technique (see Miller et al., 1999) was expanded such that a separate template could be applied to each pulse of the electric pulse train stimulus .

A more detailed treatment of experimental methodology is provided in Miller et al. (2006).

# III. Results

## A. ECAP results

### A. 1. Effects of viable hair cells on the response to electrical stimulation

Our previous contract (N01-DC-9-2106) work showed that chemical deafening applied during the course of acute experiments changed the auditory nerve's responses to electrical stimulation. In this contract work, we systematically studied that effect by exploiting the reversible effect of furosemide on acoustic sensitivity (Pike and Bosher, 1980; Sewell, 1984a,b). Hair cell function was monitored by repetitive measurement of the click-evoked compound action potential. ECAP responses to single biphasic electric pulses and biphasic electric pulse trains were repeatedly measured to assess response properties before, during and after loss of hair cell function. Acute guinea pig preparations were employed.

ECAP growth functions demonstrated increased slope and maximum (saturation) amplitude with loss of acoustic sensitivity. Both trends were reversible and followed post-furosemide hearing recovery. Additional changes were observed using electric pulse-train stimulation:

(1) The magnitude of ECAP amplitude alternation (observed in response to successive stimulus pulses) increased.
(2) The degree of ECAP adaptation (measured 80-100 ms after pulse-train onset) increased, and
(3) the degree of refractoriness (measured by the ratio of ECAP amplitudes to the second and first pulses) tended to increase.

All these trends are consistent with the hypothesis that functional hair cells desynchronize the population of auditory nerve fibers, thereby changing the electrically evoked responses. We conclude that viable hair cells may therefore provide a positive effect on auditory response to electric stimuli delivered to implant patients with residual hearing, as they may enhance stochastic properties of the stimulated nerve. The specific mechanism for this enhancement would most likely be the placement of ANFs in nearly continuous states of partial refractoriness, which is believed to increase ANF membrane "noise" (Rubinstein et al., 1999). Please refer to Hu et al. (2003) for a more detailed treatment of these furosemide-based experiments.

### A. 2. Effects of acoustic noise on ECAP responses to pulse trains

Data from our previous contract had demonstrated effects of the simultaneous presentation of acoustic noise on the auditory nerve's response to electrical stimulation. In this contract work, we assessed the time course of these acoustic-electric interaction effects by using an electric pulse train and measuring the response to individual pulses. At either 50 ms or 100 ms after the onset of the pulse train, we presented a gated white noise burst that had durations of 100-300 ms. We measured the response to electrical stimulation before, during and after the offset of the acoustic noise. We also measured the response to the pulse train without acoustic stimulation as a control condition. During data collection, these stimuli were interleaved to avoid variation due to long-term changes in the preparations.

Biphasic, 40 μs/phase, electric pulses with alternating stimulus polarity were presented in 400-600 ms pulse trains. Interpulse interval (IPI), defined as time between the onsets of adjacent pulses, was set at 4 ms in most experiments. In assessments of the effect of IPI on the ECAP response to pulse trains, IPI was systematically varied from 1 to 6 ms.

The responses to acoustic/electric stimulation generally followed a time course similar to that shown in the example data set of Figure 1, which plots a series of ECAP amplitudes as a function of time for conditions of (1) the electric pulse train presented alone (filled symbols) and (2) the electric pulse train and acoustic noise presented concurrently (open symbols). In the case shown, the duration of the noise stimulus was 300 ms.

The responses to electric stimulation show a decrease in amplitude over time. During the noise presentation (from 50-150 ms) that response underwent further decreases. That decrease in amplitude tended to be greatest immediately after noise onset. After offset of the acoustic noise, there was often a significant residual effect, as is shown in this example. We note that the simultaneous effect of acoustic noise has a time course similar to a PST of a single auditory nerve fiber to a noise stimulus, suggesting that the effect of acoustic noise on electric response amplitude is related to the discharge rate in response to the acoustic stimulation. The residual effects of noise after noise offset, however, indicate the influence of a different mechanism, as background spontaneous activity in individual nerve fibers would be expected to decrease (due to adaptation effects) and result in response amplitudes equal, or transiently greater, than those observed during the "electric alone" condition.

The effect of acoustic-noise level and pulse-train level were systematically studied. Effects of acoustic level are generally consistent with these observations and hypothesis. The decrease in response amplitude due to acoustic stimulation is dependent on both the level of the electric pulses and that of the acoustic noise. In general higher levels of noise produced greater decreases in response amplitude. For a fixed level of noise, the greatest simultaneous effect was evident at high current levels. The "forward-masking" effect, after noise offset was most evident at lower current levels.

We also investigated the effect of interpulse interval (1 to 6 ms) on the degree of acoustic/electric interaction using the same stimulus paradigm. At higher pulse rates, we observed greater decreases in the ECAP response amplitude during the first several milliseconds following onset of the electric train. At high rates, the addition of acoustic noise caused smaller decrements in the electric responses. When the pulses were presented at lower rates, the decrease in the response amplitude for the same level of acoustic noise produced large decreases in the electric response. Such data suggest that the mechanisms producing electrical adaptation and acoustic masking have a common origin.

### A. 3. ECAP adaptation and recovery due to acoustic stimulation

The work described in the above section employed trains of constant-amplitude electric pulses and gated acoustic noise to assess the time course of acoustically induced adaptation and subsequent recovery. That work demonstrated residual effects on the ECAP after noise offset. In many observations, the offset effects had a complex time course that featured a fast recovery component and a slower residual effect. In some cases, we observed an even more complex recovery function, one that included a period of enhanced response amplitude. Careful examination of Figure 1 during the epoch labeled "residual effect" reveals a period over which the ECAP is slightly elevated from that of the control condition.

We hypothesized that the ECAP recovery process was, itself, influenced by the presentation of the electric "probe" pulse train. In effect there could be adaptation due to the electrical stimulation "interfering" with the recovery due to acoustic stimulation. For that reason, we performed a series of follow-up experiments in which we used electric probe pulses that were widely spaced in the time domain (i.e., IPI = 200 ms). Such a low-rate train of probe pulses was used to assess the ECAP before, during and after the presentation of an acoustic noise. A penalty of this approach was, of course, that data collection required much more time (approximately an order of magnitude) to complete.

An example of the ECAP results obtained with such low-rate probe pulses is shown in Figure 2. In this case, the amplitude in response to a probe pulse is plotted relative to various times after onset of the acoustic noise stimulus. The response to the electric-only condition (electric pulses presented without any acoustic noise presentation) is shown by the dashed line. The patterns of amplitudes observed at the noise onset and during the noise stimulus are similar to those observed when the relatively high-rate probe pulses were used (cf., Figure 1). However, the responses observed after noise offset (i.e., the period of recovery from adaptation) demonstrate a markedly nonmonotic time course. Increasing noise level tended to increase the degree of

masking both during noise presentation and after noise offset. Acoustic noise duration tended to increase the post-noise effects and also to enhance the nonmonotonic recovery behavior. We elaborate, in the discussion below, that the nonmonotonic recovery may be the result of two competing processes, one decreasing the amplitude of the ECAP due to adaptation and the other increasing the amplitude due to increased synchronization after noise offset.

### A. 4. ECAP: Adaptation and recovery due to high-rate electrical stimulation

The work described above examined interactions caused by acoustic and electric stimuli, particularly demonstrating a "forward-masking" effect that resulted in a period of post-noise nonmonotonic recovery, as demonstrated in Figure 2. We were interested in determining the extent to which such effects resulted from acoustic stimulation and/or hair cell synaptic mechanisms, i.e., mechanisms unique to acoustic excitation of ANFs. We therefore investigated the effects using a similar stimulus paradigm, but with the use of a high-rate (5000 pulse/s) electric pulse train as the masking stimulus, in place of an acoustic stimulus.

We found that, in general, the effects of recovery were similar for both acoustic and electric stimulation, i.e., electric masking produced similar nonmonotonic recovery over approximately the same time course. We recognized that such a stimulus presented to an acoustically sensitive cochlea could result in responses mediated by hair-cell activity (such as the β and δ responses described by Moxon (1971) and van den Honert and Stypulkowski, (1984)). We therefore conducted parallel sets of experiments in animals that had been deafened, either with a permanent agent (neomycin) or a temporary one (furosemide). While there were some differences evident in the results obtained compared to hearing animals, the basic features of the recovery were evident without hair cell function. These results suggest that the mechanisms of adaptation, at least for electrical stimulation, include properties inherent to the nerve membrane.

## B. Single-fiber results

### B. 1. Effects of acoustic noise on ANF responses to single pulses

Based on ECAP data showing decreased amplitude of the response to electric stimulation with simultaneously presented acoustic noise, we made initial measures from ANFs stimulated by single electric pulses. Our rationale for this basic assessment was that basic measures of ANF temporal and probabilistic response properties were hypothesized to change under the influence of simultaneous acoustic excitation. The (peak-to-peak) amplitude and morphology of the ECAP is dependent on discharge rate (response probability) and response synchrony. Single-fiber measures allow separate assessment of those response variables. One possible cause of electric-acoustic interactions observed in the responses to single-electric pulses could be acoustically induced states of partial refractoriness. For example, our previous work (Miller et al., 2001) had shown that the state of partial refractoriness can alter relative spread (Verveen, 1961), i.e., the fiber's dynamic range to the electric stimulus.

Single-fiber responses were analyzed for threshold (defined as the electric level producing a firing efficiency of 50%), jitter (the standard deviation of spike times) and relative spread (expressed in %). Figure 3 plots these three measures as functions of the spike rate to the acoustic stimulus presented alone. Data from feline subjects D01 and C93 are shown in the graphs. We computed linear regression fits to each fiber's threshold, jitter, and RS plots to determine overall trends (applying linear regression over the combined group data would be inappropriate due to across-fiber differences in driven spike rates). Most fibers demonstrate positive correlations of each of the three measures with increases in the acoustically driven spike rates. We computed the mean changes in each of these measures for an increase in the acoustically driven rate from 0 to 100 spike/s. With that criterion, the mean change in electric threshold was approximately 3 dB and the mean change in jitter was about 0.1 ms. The change in relative spread – in absolute terms – was, on average, about 5%, corresponding to about a doubling of relative spread as measured without acoustic stimulation.

These results suggest that the simultaneous presence of acoustically driven activity may be advantageous for the encoding of electric stimuli from the standpoint of decreasing the degree of determinism in ANF responses to electric stimuli (see Kiang et al., 1965). Additional information about the experimental preparation and results of these experiments can be found in QPR #2. For example, long-term (cumulative) effects of acoustic noise excitation were also observed. Details of the experimental preparation, along with characterizations of electrically evoked responses from acoustically sensitive feline ears, are provided in Miller et al. (2006).

### B. 2. Adaptation and recovery resulting from acoustic stimulation

As noted above, a straightforward hypothesis relative to the effect of noise on the electric response may be that neural activity in response to the noise may reduce or desynchronize the responses to the electric pulse train. The time course of observed ECAP decrements shortly after noise onset is consistent with this hypothesis in that there is initially a large effect of the noise followed by an approximately exponential recovery. The expected activity in response to the noise would show a similar time course. The "overshoot", or increased response, that we have observed after noise offset in some cases is also consistent with this hypothesis, i.e., decreased background activity may result in larger amplitude responses. However, the residual masking effect observed, in many cases, after noise offset is not consistent with that simple hypothesis. This post-noise effect suggests that adaptation caused by an acoustic stimulus can influence later, subsequent, neural responses to electrical stimuli.

The complex pattern of recovery observed in the ECAP findings suggests that there may be multiple mechanisms involved in the masking effects. Detailed descriptions of auditory nerve fiber response properties such as spike rate, jitter, and synchronization index would therefore be helpful in providing a better understanding of the observed influence of acoustic noise. Experiments described in this section examine single-fiber responses using an acoustic-noise / electric-train stimulus paradigm similar to that used in our previously reported ECAP experiments.

Data from a typical fiber are presented in Figure 4. The upper panel illustrates the stimulus paradigm showing the relative timing of the acoustic noise and electric pulse train stimulation. As in the case of previously described ECAP work, the electric pulse rate was fixed at 250 pulse/s. The histograms of the responses to each of three interleaved presentations (electric train presented alone, acoustic noise alone, and combined electric and acoustic stimuli) are shown below that diagram, with each histogram covering the entire duration of the acoustic and electric stimuli. Typically, such histograms were based on 30-100 repeated presentations, with the number of sweeps dependent on ANF response rate to the electric train. The peaks in the histogram in response to the electrical pulse train represent phase-locked responses to the electric pulses separated by 4 ms. The variability in the peak amplitudes across pulse presentations are likely due, in part, to the moderate number of stimulus presentations (50). However, as noted later, there is a general trend of reduced spike probability over the pulse train. The middle panel plots the response to the noise burst presented alone. A clear onset effect is noted, typical of acoustic responses, decaying to a steady-state response rate. The response to the "noise + pulse train" (bottom panel) demonstrates a lack of clear peaks in the response during the noise burst and a decrease in the magnitude of the electrically induced peaks during the period after noise onset.

These example histograms demonstrate several features characteristic of ANF responses. The acoustic noise can significantly decrease the responses locked to the pulse train. That effect is in some way analogous to the acoustic masking of noise on tone-burst responses that was described by Kiang et al. (1965). In the "acoustic alone" condition, a transient reduction of spontaneous activity is seen after offset of the noise (Figure 4, middle panel). In addition, after offset of the acoustic noise, we observe decreases in the response to the electric pulses (bottom panel), presumably due to adaptation of the neurons to the acoustic stimulation. This clear decrease may be analogous to post-stimulus acoustic effects reported by Smith (1977). We note,

however, that both the simultaneous and post-noise offset effects observed here affected the direct-electrical responses which are not hair-cell or synaptically mediated.

In order to summarize response properties from a number of fibers, we analyzed the responses over six time intervals relative to stimulus onset, as shown at the bottom of Figure 4. Intervals 1 and 2 characterize the response to the pulse train before noise onset. Intervals 3 and 4 characterize the response to the electric pulse train during the acoustic noise. Intervals 5 and 6 characterize the effect on the electric pulse train immediately after noise offset and during the subsequent recovery period. Total spike count, vector strength relative to the period of the pulse train stimulus, and spike jitter were assessed over each interval. In each case, we characterized the effect of the acoustic noise (on the electric responses) by plotting measures (e.g., spike count, vector strength, spike amplitude) as ratios of the response obtained in the electric+noise condition to the response obtained in the electric-alone condition. Spike-count ratio characterizes the change in overall activity due to the combined acoustic+electric stimulus. Vector strength and jitter ratios were calculated in order to assess the degree to which noise presentation has an effect on the response to the electric pulses.

Group results for 27 fibers are shown in Figure 5. The data were selected for initial firing efficiencies (FE) to electric stimuli between 50 and 100 %. Acoustic noise increases spike rate (intervals 3, 4) during its presentation and results in reduced, or adapted, rates afterward (interval 5). During noise presentation, temporal jitter is increased as vector strength is decreased. After noise offset however, the electric response becomes more synchronous than in the electric alone condition.

Several mechanisms may contribute to these response properties. Refractoriness of fibers during the noise presentation would clearly decrease their responsiveness to electrical stimulation and consequently affect the response timing. The reduced responsiveness to electric stimulation 50-100 ms after noise offset suggests additional mechanisms may also contribute to these effects. Adaptation effects could decrease responsiveness to electric stimulation both during and after the noise presentation. Further, suppression of spontaneous activity after noise offset, possibly due to the same adaptation effect, could enhance the temporal precision (reduce jitter) in response to electric stimulation.

### B. 3. Adaptation and recovery resulting from electrical stimulation

ECAP amplitude recovery from prior acoustic excitation was characterized by a nonmonotonic function, suggesting both adaptation (reduced responsiveness) and, possibly, increased synchrony in the response to electrical stimulation. As noted above, single-fiber responses to electric stimulation during the presentation of an acoustic noise exhibited significantly reduced synchrony. The group-ANF analysis indicated that responses to electrical stimulation after noise offset demonstrated decreased jitter in many cases, along with reduced firing probability. These two effects could demonstrate different time courses, and thus account for the non-monotonic ECAP recovery functions that we have reported. Thus, our working hypothesis has been that adaptation recovery and recovery of suppression of spontaneous activity determine the time course of ECAP recovery.

In a manner analogous to the efforts directed toward ECAP measures, we sought to distinguish stimulus-interaction effects that were due to hair-cell activity *per se*, as opposed to activity-driven effects. Toward the end of this contract work, we conducted a series of experiments to evaluate the degree to which these response properties are unique to acoustic/electric interactions at the level of the auditory nerve. To that end, we adopted a paradigm that replaced the acoustic stimulus with a high-rate (5000 pulse/s) electric pulse train. ECAP measures showed a similar nonmonotonic recovery; this section outlines the analogous ANF measures that we collected. As in the ECAP experiments, the probe stimulus was a 250 pulse/s electric pulse that followed an electric masking stimulus consisting of a high-rate (5000 pulse/s) pulse train.

Figure 6 shows a typical example of the responses of an ANF to the electric pulse train stimuli described above. The upper graph plots the PST histogram of the response to a 200 ms high-rate (5000 pulse/s) masker. The response rate is initially high and adapts to a steady state by approximately 100 ms, similar to the general response pattern reported with acoustic stimulation. The temporal pattern of the high-rate response undergoes a significant transition within the first 50 ms of high-rate presentation. Within the first 20 ms, an oscillating pattern is observed that is presumably driven by the refractory properties of the fiber. After that initial period, no clear peaks are observed in the histogram, suggesting a less deterministic, more stochastic, pattern of the underlying response. The second plot of Figure 2 is a PST histogram of the response to the probe (i.e., a 250 pulse/s train starting at 200 ms with a duration of 300 ms). The responses show clear phase-locking to the stimulus period. The third plot is a histogram of the responses to the combined stimulus, the high-rate masker followed by the low-rate probe. As expected, the response to the high-rate masker is similar to that shown in the top plot. The response to the probe pulse train still shows clear phase-locking to the 250 pulse/s stimulus, but the rate is significantly decreased, presumably due to the effects of the masker. The decrease in responsiveness and the time course of subsequent recovery over the duration of the 300 ms probe pulse train are of primary interest in this study.

To quantify these interaction effects, we have analyzed the data for six different 20-ms long windows across the stimulus presentation, as indicated in Figure 6. Results of such analyses are shown in Figure 7. Each of the six graphs of the figure presents responses from a different fiber and they show the generally consistent pattern of activity that is evident in our data. The open circles in each plot represent the discharge rates over each 20 ms analysis window to the high-rate masker stimulus alone. The filled circles indicate responses to the low-rate probe, and the filled triangles show the responses to the combined stimuli. The effect of the masker on the probe pulses can be appreciated by comparing the triangles to filled circles at each analysis interval. The masker effect is greatest at probe onset (200 ms) and decreases over the probe interval. In general we see clear effects of the masker over the first 100 ms but in most cases the effects are diminished by end of the probe pulse train (300 ms after masker offset, corresponding to the 500 ms point of Figure 7).

The results with electric maskers are similar in many ways to those described above with acoustic maskers. The time course of recovery, assessed by discharge rate, was typically on the order of 100 to 300 ms. This range is similar to that observed using acoustic noise stimuli in our previous work (Miller et al., 2005). Increasing the high-rate (masker) current level generally resulted in greater decrease in probe discharge rate and longer times of recovery. Increasing probe level, with a fixed masker level, generally resulted in smaller decrease in discharge rate. ECAP measures have demonstrated that the relationship between masker and probe is a primary determinant of effectiveness of the electrical adapter on the response. Masker/probe ratios greater than one result in maximum masking; ratios of less than 0.5 result in little or no masking. Single-fiber responses show more variability. For instance, in comparing responses across fibers, each stimulated with equal masker and probe level, we observe considerable variability in the rate decrement.

### B. 4. Effects of electrical stimulation on the acoustic responses

The results described above suggest that the adaptation and masking effects of acoustic stimulation on the electrical responses occur, to a significant degree, at the level of the nerve membrane. Those observations further suggest that the effects of electrical stimulation on the acoustic response that are clearly mediated through hair cells may result in different response patterns. Accordingly, we conducted ANF measures to examining the response to acoustic probes after offset of an electrical adapting stimulus.

The stimulus for these experiments: the masker was a 300 ms electrical pulse train, immediately followed by a 200 ms acoustic noise burst. The masker pulse rate was, in some case, parametrically varied. In addition to recording the responses to this combination, responses were measured to presentation of the noise burst alone, facilitating the evaluation of the effect of the electrical stimulation on the acoustic response.

We analyzed data from over 80 fibers across six animals and observed instances where there was a significant decrease in the acoustic response after electrical stimulus offset. In many cases, however, we observed a significant response to the electrical stimulus, but with essentially no effect on the acoustic response. Two examples, obtained from two fibers, are shown in Figure 8. In this case, the masker rate was 1000 pulse/s. Responses to the electrical pulse train are similar in both cases, but the effect on acoustic discharge rate was quite different. Our analyses show little or no effect of electrical stimulation in approximately 50% of the fibers. We do note an important caveat: not all fibers yielded complete data sets across their electric and acoustic dynamic range; it is possible that a larger proportion of fibers were capable of demonstrating masking of acoustic responses. Nonetheless, it is clear that such effects are dependent upon stimulus levels.

Several fibers provided long contact times that enabled us to investigate the effects of several stimulus parameters over a wide range of values. Figure 9 provides an example such detailed data sets obtained from one ANF. This figure plots the response to the acoustic noise stimulus (presented immediately after electric train onset), both with and without a preceding electric pulse train. We characterized the effect of electric stimulation by dividing the response (number of spikes per bin) to acoustic stimulation with the preceding masker by the response to acoustic stimuli without the preceding stimulus. This normalized response is expressed as “percent adaptation.

Figure 9A plots these responses as functions of electric stimulus level, with electrical pulse rate as the parameter. Greater adaptation is observed with increasing electrical stimulus level. Electric pulse rate was varied as a parameter and was found to have little effect on the degree of adaptation. Figure 9B and 9C demonstrate the effects of acoustic noise level on adaptation. In these graphs, percent adaptation is again plotted as a function of electrical current level, with acoustic noise level as a parameter. High levels of acoustic noise generally resulted in smaller decreases in the response. As can be seen by comparing the two plots of Figure 9C, the effect of noise level is clear at high electric levels where adaptation is greatest; the effect of noise level tends to be smaller at lower electric levels. In examining trends across animals, the effects of both acoustic noise and electric level are evident, in that fibers stimulated with high levels of noise and/or low levels of electric current tend to show little or no effect on the acoustic response. Fibers in which we had chosen low levels of noise or high levels of electric stimulation tended to show clearer effects.

We conclude that while adaptation to electrical stimulation can affect responses to acoustic stimulation, the effects are not as consistent as the effects of acoustic noise on electrical stimulation. These differences likely are related to the mechanism of neural excitation, synaptic vs direct electrical stimulation, as well as the location of action potential initiation using the different modes.

## C. Modeling of responses

To provide quantitative descriptions of the time courses of acoustic-electric interactions, we performed nonlinear regression analyses of the simultaneous and forward-masking functions. Such fits were applied to the ECAP functions, such as those shown in the first two figures of this report. As simultaneous masking appeared to follow a negative exponential time course, we first attempted to describe it using a single exponential equation with three free variables (time constant, asymptote to account for steady-state masking effect, and a time offset to account for the latency of the masking effect). However, systematic errors in the residuals pointed to the need for a second exponential component. ECAP forward-masking recovery functions often had a non-monotonic shape (see Figures 1 and 2). To account for this, we used two exponential components to describe the recovery of the ECAP, and introduced a third component with an opposite sign. The model for the description of forward masking of the ECAP therefore included two recovery components and one enhancement component. Model parameters were fit using the Marquardt-Levenberg least-squared error algorithm with SigmaPlot version 7.101 software.

Figure 10 presents a summary of time constants that describe simultaneous and forward masking functions obtained by a regression analysis. Panel A shows time constant fits for simultaneous acoustic stimulation, panel B for recovery after acoustic noise stimulation and panel C for recovery after high-rate electric stimulation). Also plotted (using vertical bars) are the ranges of time constants of single-fiber response adaptation to and recovery from acoustic stimulation, obtained in the gerbil by Westerman and Smith (1984) and Smith (1977). The two time constants that described simultaneous masking of the ECAP with noise were comparable to the ranges of time constants of rapid- and short-term single-fiber response adaptation (Westerman & Smith, 1984). The short-term recovery time constant obtained by the regression analysis of our ECAP forward-masking data was consistent with the range of single-fiber recovery time constants (40–310 ms) reported by Smith (1977). Further, the fits to electrical forward masking recovery are similar to those observed for acoustic forward masking.

We note further that one of the recovery time constants and the enhancement time constants tend to have similar values. These terms, under some conditions, can then effectively cancel, resulting in a monotonic recovery pattern. Such effects are consistent with the variability reported in the patterns of ECAP recovery for both acoustic and electrical stimulation.

## D. Additional results and observations

The above results summarize major findings of the studies conducted under this contract. Most of these findings have been, or will be, published in peer-reviewed journals (see List of Publications, below). However, across the five-year period of this contract, several other findings of potential interest were recorded and reported. The following lists topics of interest and the quarterly progress reports (QPRs) in which they are reported.

**ECAP response characteristics**

| | |
|---|---|
| Effects of acoustic stimulus duration on the ECAP recovery | QPR 5 |
| Detailed report of ECAP masking at the onset of acoustic noise | QPR 7 |
| Details of model of ECAP responses to combined acoustic and electrical stimulation | QPR 15 |

**Single-fiber response characteristics**

| | |
|---|---|
| Effects of acoustic noise on ANF responses to single electric pulses (threshold, relative spread, and jitter) | QPR 4 |
| Changes in ANF action potential amplitude due to prior stimulation | QPR 6 |
| Differential rates $\alpha$ (direct) and $\beta$ (electrophonic) rate adaptation (and level effects) | QPR 6, 12 |
| ANF characteristics in cats implanted with “minimally invasive” electrodes (acoustic thresholds, acoustic CFs, $\beta$ response incidence, spontaneous activity) | QPR 12 |
| Effects of acoustic stimulus duration on recovery of electric responses | QPR 12 |
| Examples of fibers with “build-up” responses at onset of electric pulse train | QPR 12 |

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# IV. Discussion

Overview

The data presented in this Final Report extend and complement earlier findings of research conducted under our previous contract. The addition of single-fiber measures provided insight into neural mechanisms suggested in the ECAP responses obtained from guinea pigs of the previous contract. Effort was made to make ANF stimulus paradigms similar to those used in the ECAP studies. Single-fiber measures provided unique information. For example, the $\alpha$ and $\beta$ responses that occur in response to electric stimulation of acoustically sensitive ears were found to have different rates of adaptation and both were dependent upon stimulus level. Such differential rates may have implications for speech stimulus encoding. As another example, ANF measures of jitter and spike rate provided evidence that some of the ECAP enhancement observed after offset of an acoustic masker (see Fig. 2) is likely due to differential rates of jitter and rate recovery.

The data sets yielded by this work therefore provide means of ascribing single-fiber response properties to aspects of ECAP response patterns. We also quantified effects such as the time course of adaptation and recovery of both the ECAP and single-fiber responses. Additional studies using electric forward masking of electrically evoked responses provided a means of dissociating some response patterns from those that might otherwise be attributed to hair-cell mediated activity.

Adaptation

The decrease in response to electric stimulation both during and after presentation of an acoustic noise is a complex function of time and highly dependent on stimulation parameters such as pulse rate, acoustic and electric stimulus levels, and stimulus duration. In our previous reports, we hypothesized that the observed effects of noise on ECAP may arise -- at least in part -- from acoustically-driven neural activity that desynchronizes the population response of the auditory nerve. Regression analysis of the time course of post-onset decay in the effect of acoustic noise demonstrated that it may be described as a process that has a distinct fast (rapid) and slower (short-term) component. Changes in the ECAP amplitudes and ANF discharge rate during the presentation of the noise burst (i.e., the onset effect and recovery to a steady state – see Figure 1) have a morphology similar to the shape of PST histograms in response to acoustic stimuli (Kiang et al., 1965). Westerman and Smith (1984) demonstrated that rapid and short-term adaptation in the auditory nerve responses can be mathematically described by a double exponential function, with the two time constants corresponding to rapid and short-term components, and the asymptote corresponding to the steady-state. The time constants of the post-onset decay in the effect of acoustic noise determined in the present work are comparable with the time constants of rapid and short-term adaptation reported by Westerman and Smith (1984). This indicates that the partial recovery of the pulse-train ECAP that follows the onset of the noise burst to some extent may reflect the adaptation of the auditory nerve response to the acoustic stimulus.

Our working hypothesis has been that there are at least two possible mechanisms by which acoustic stimulation can affect the response to electrical stimulation. One may be, as noted above, the result of ongoing activity in response to the acoustic stimulus that desynchronizes and modifies (through refractoriness) the response to the electric pulses. A second mechanism may be due to the adaptation of the neuron due to acoustic stimulation. The large effect at noise onset observed in these data suggests that the first mechanism may be important in simultaneous noise-electric pulse interactions.

We have hypothesized that the observed effects were driven by neural activity (specifically, discharge rate) rather than stimulus level, per se. Also, as acoustic stimulation affected the response to electric-current

induced depolarization of auditory nerve fibers, we attributed this effect to a mechanism at the level of the neural membrane. This view is also consistent with the post noise-offset effects noted above. The observation of adaptation effects produced by acoustic stimulus demonstrated a previously unreported type of acoustic/electric interaction. Such interaction could be relevant to the design of cochlear implants (and associated hearing aids) in cases where individual fibers are responsive to both modes of stimulation.

Recovery pattern

After noise offset, the background activity would be expected to decrease (i.e., decreased spontaneous activity after stimulus offset) and therefore the effect of the noise may be expected to recover immediately or even produce an enhanced amplitude response. The consistent residual effect (decreased ECAP amplitude and decreased single-fiber discharge rate) suggests that some type of adaptation mechanism affects the responsiveness to electrical stimulation after noise offset. We suggest that a transient increase in firing synchrony in the post-noise interval, combined with recovery from adaptation, gives rise to the complex, nonmonotonic, time course of ECAP recovery that has been detailed in previous progress reports (see QPR #10, for example). These two effects may offset one another to some extent, i.e., increased synchrony enhancing ECAP amplitude and decreased response rate lowering ECAP amplitude after noise offset.

Our single-fiber studies have shown that at least some ANFs demonstrate differential rates of recovery of spontaneous activity and electrically driven activity. Two examples are shown in Figure 11. In each case both the response rate to electrical stimulation and jitter are plotted as a function of time – before, during and after acoustic noise presentation. Both discharge rate and jitter are decreased after noise offset but the time course of recovery (filled diamonds) is faster for jitter than for response rate. Since decreased jitter would tend to increase synchrony and ECAP amplitude, while decreased discharge rate would decrease ECAP amplitude, the differential rates of recovery can explain at least the nonmonotonic pattern of recovery.

Finally, based on such observations, we might hypothesize that post-offset increases in fiber synchrony are due to the cessation and recovery of spontaneous activity. Data from QPR #12 suggest that while post-stimulus recovery of spontaneous activity likely plays a role, it does not completely account for our observations (i.e., ANF jitter is not solely dependent on the degree of spontaneous activity of fibers). We also note that ECAP recovery data showed nonmonotonic recovery in deafened ears. This observation further suggests that if changes in fiber synchrony are the source of nonmonotonic recovery, then changes in spontaneous activity are not inherently responsible for such changes in fiber synchrony or jitter.

Mechanisms

A number of observations suggest that the mechanisms for adaptation and recovery reported here are primarily at the nerve membrane. While responses to acoustic stimulation clearly depend on the hair-cell neuron synapse, the electrical responses described here are, for the most part, mediated through direct stimulation of the auditory nerve (based on latency of response). Models of acoustic/electric interaction must then take into account the relatively long-term effects (on the order of 100 ms) at the level of the neural membrane. Those effects are not simply refractory properties. There may be several mechanisms that could produce such changes; one may be related to potassium gating and/or changes in potassium concentration with neural activity (Baylor and Nicholls, 1969; Woo, 2007).

Other mechanisms relevant to electrical stimulation of acoustically sensitive ears include those that give rise to the $\beta$ (electrophonic) and $\delta$ responses (van den Honert & Stypulkowski, 1984), with the former ascribed to electromechanical induction of a traveling wave and the latter hypothesized to be generated by direct depolarization of the inner hair cell. Although the $\delta$ response is relatively infrequent (van den Honert & Stypulkowski, 1984), we found that a significant number of fibers from implanted cochleae demonstrated the electrophonic response. The degree to which this response is relevant to the population of persons with

"hybrid" hearing is unknown and it could be speculated that cochleae with "corner" audiograms may not be able to generate this response. However, in a collaboration with Dr. Bryan Pfingst, we have noted that an electrophonic response can be recorded from guinea pigs chronically implanted (for several weeks) with a short, but invasive, intracochlear electrode array. This response was recorded using the intracochlear array and represented a gross, ensemble, response.

## Clinical Applications

The results described in this report were all derived from animals in which a minimally invasive electrode was placed in the cochlea to minimize damage to hair cells. This choice was made to maximize the degree of overlap between acoustic and electric stimulation in individual neurons of the auditory nerve. That preparation has allowed us to examine the interactions at the level of auditory nerve.

While many individuals receiving cochlear implants have significant residual hearing at low frequencies, high frequency hearing is generally compromised. Implantation of such individuals can provide a significant effect on their perception abilities by supplementing acoustic hearing with electric stimulation through a cochlear implant. The effect of implantation on hearing is likely significantly determined by the length of the implanted array. Longer arrays may provide more channels of stimulation and consequently more effective electrical stimulation; shorter arrays may result in less chance of hearing loss. Thus, different length arrays have been used to provide electrical stimulation, and obviously individuals vary in the extent of residual hearing. Consequently there are likely large variations in the degree of overlap between acoustic and electric stimulation in the auditory nerve of individuals receiving cochlear implants.

At the University of Iowa we have implanted a number of individuals with a Nucleus "hybrid" implant (acoustic and electric stimulation). This implant uses an 8 mm electrode array with 6 channels that has been successful in preserving significant hearing in individuals. The implant is equipped with a telemetry system (Neural Response Telemetry, Abbas et al 1999), to measure the ECAP using intracochlear electrodes. As part of the Iowa Cochlear Implant Clinical Center, we have made such measures in 14 individuals. In all cases ECAPs are clearly evident across the electrode array. We have made similar measurements in the presence of acoustic wideband noise and have not observed any decrease in the amplitude of the response. These measures suggest that there is not a significant overlap between neurons responding to acoustic and electric stimulation in these individuals. We note that these individuals have a limited hearing range and the electrode array is shorter than that of a normal implant. Consequently, while these individual have not shown clear interactions, it is certainly possible that future implantees with more extensive hearing and/or longer electrode arrays will display the types of interactions that we have observed in animals. In those cases, an understanding of possible acoustic-electric interactions such as those demonstrated in this report may provide insight into the optimal processing of both electric and acoustic stimuli delivered to such individuals.

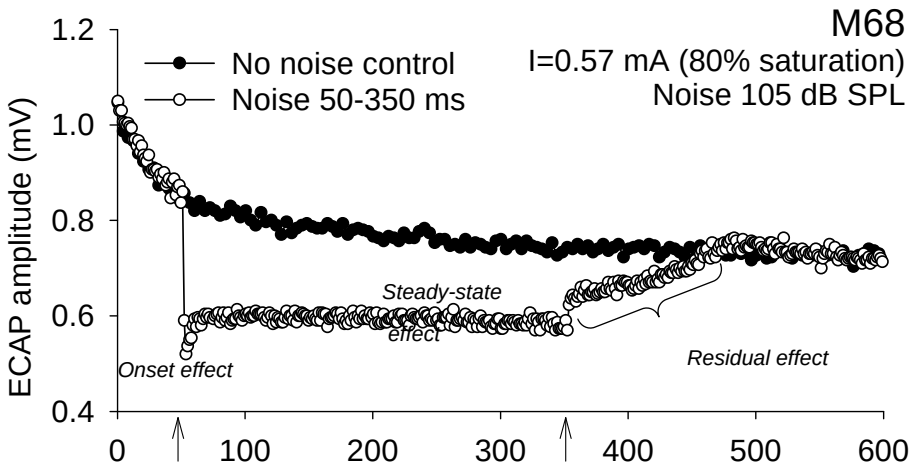


**Figure 1** Example of the time-course of the effects of wideband acoustic noise on the ECAP responses evoked by a train of pulses. ECAP response amplitudes to individual pulses are plotted as a function of time after first pulse onset. Electric pulses were presented at a level of 0.57 mA (80% saturation of the single-pulse ECAP growth function), with or without simultaneous acoustic noise (open and filled circles, respectively). Acoustic noise was presented at a level of 105 dB SPL during the period from 50 to 350 ms after first pulse onset. Arrows indicate noise onset and offset time. The interpulse interval was 4 ms. Phenomena of interest are labeled in the graph.

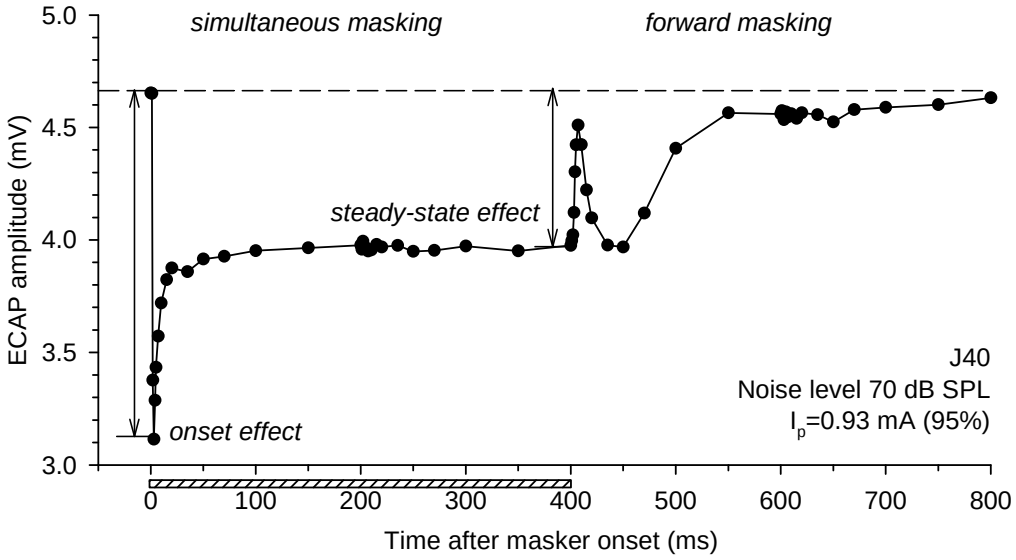


**Figure 2** Simultaneous and post-stimulatory effects of acoustic noise on the ECAP. In this case (and in contrast to the results of Figure 1), the time course of the post-noise recovery period was assessed using low-rate (200 ms IPI) electric pulses to avoid a confounding effect of higher-rate electric trains on the acoustically driven phenomena.

ECAP amplitudes in response to probe electric pulses are plotted as functions of time after the masker onset. The dashed line corresponds to the probe-alone (control) response. The horizontal bar indicates the presentation time of the acoustic masker. Acoustic masker level 70 dB SPL, electric probe level 0.93 mA (corresponding to 95% of the maximum single-pulse ECAP amplitude)

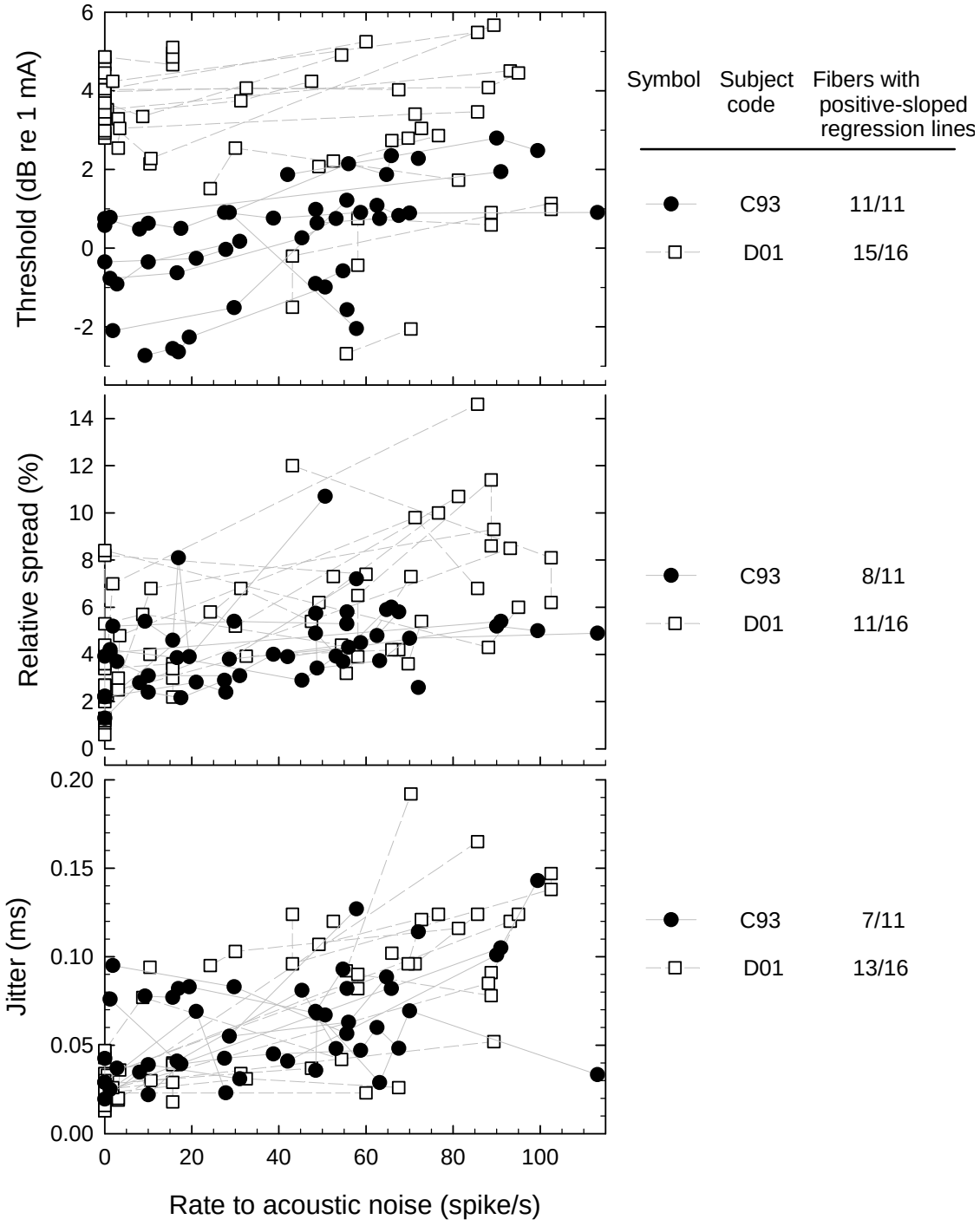


**Figure 3** Summary of single-fiber data from two cats showing the effect of acoustically driven spike activity on three measures of the spike activity elicited in response to a single, 40 us/phase biphasic, electric pulses. The fractions shown along the rightmost column indicate the number of fibers that demonstrated a positive correlation between the two plotted variables, as assessed by linear regression.

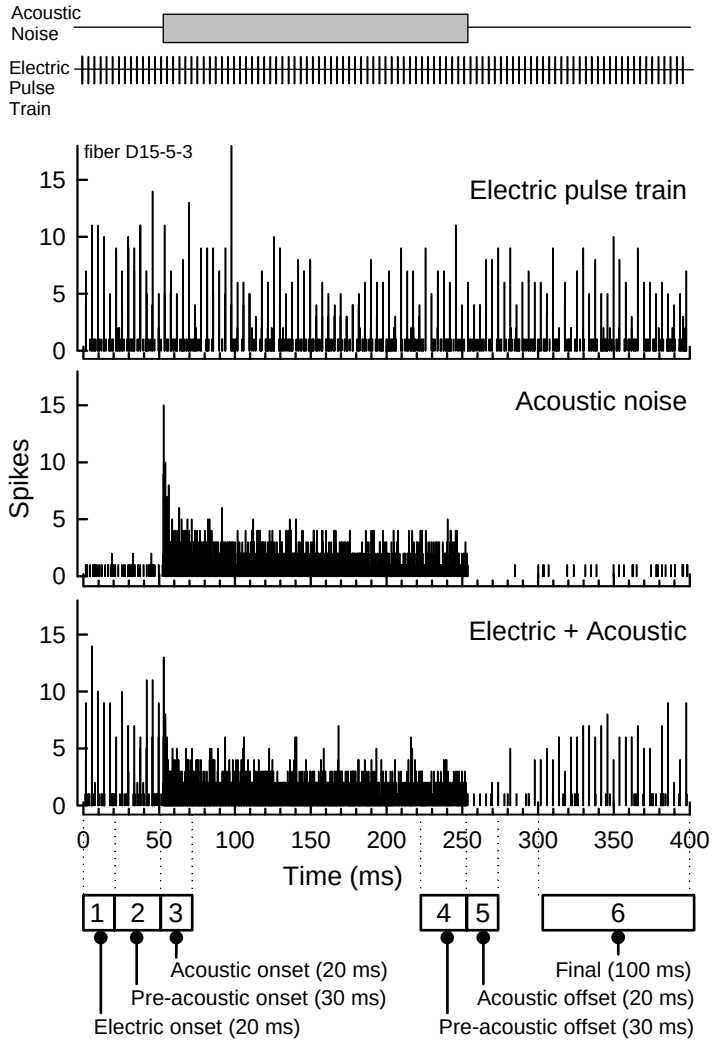


**Figure 4** Overview of the stimulus paradigm and response histograms obtained from a feline ANF in response to combined acoustic noise and electric pulse-train stimulation. The top schematic shows the timing of the wideband acoustic noise (gray bar) and 250 pulse/s electric train (vertical line segments). In histograms shown below (with time=0 beginning at the pulse train onset), a 200 ms duration acoustic noise burst was presented 50 ms after the onset of an electric train that had a duration of 400 ms. Responses to the interleaved presentations of the (1) electric train alone, (2) acoustic burst alone, and (3) combined stimuli are shown in the three graphs. Six temporal analysis windows that covered regions of interest are labeled at the bottom of the figure. Scalar ANF response statistics obtained for each of those windows provided for data reduction and subsequent group-fiber analysis, as described in the text.

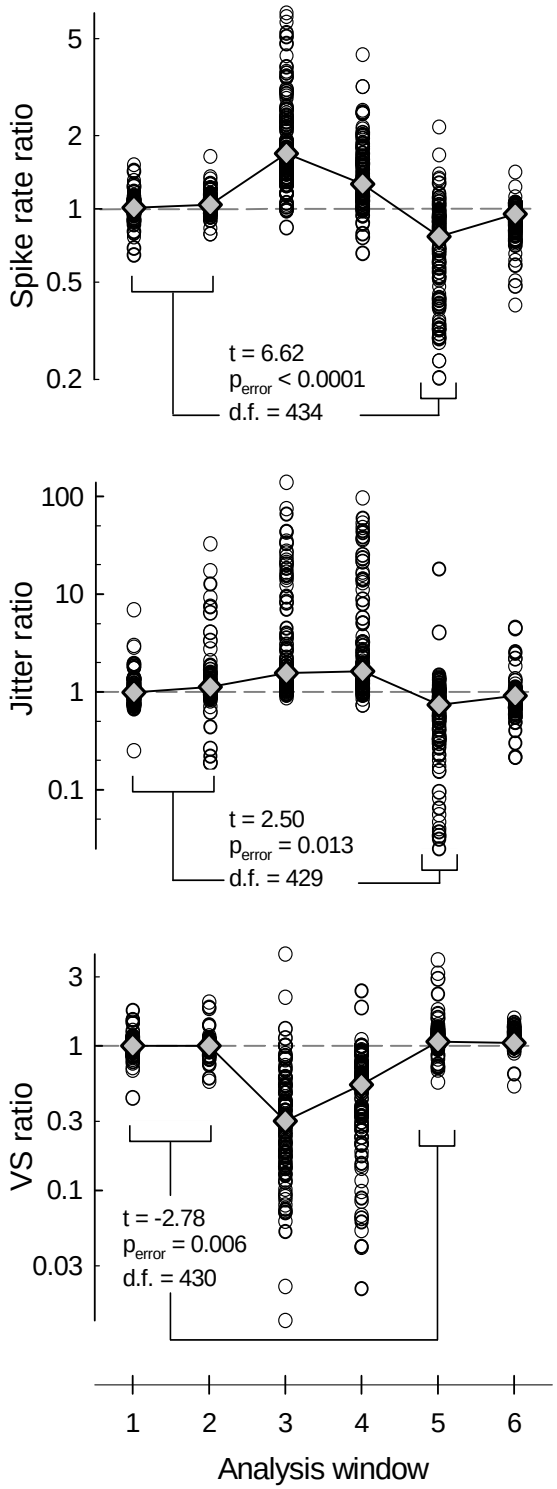


**Figure 5** Summary of single-fiber responses obtained from 27 fibers. To assess the influence of the acoustic noise on the response to the electric pulse train, each of the dependent variables is computed as a ratio of the value obtained under the combined (acoustic + electric) stimuli and the electric-alone condition. The six analysis windows are those defined in Figure 4. Mean values are shown by solid symbols connected by line segments.

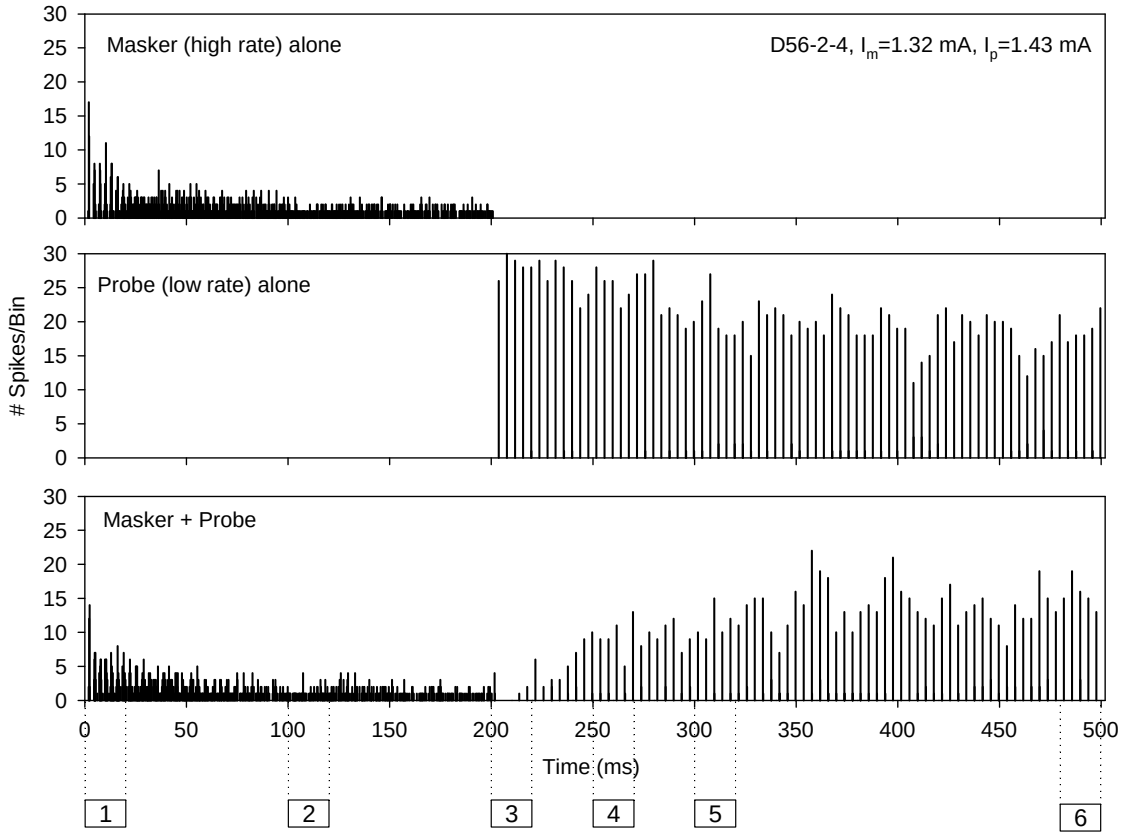


**Figure 6** Example ANF PST histograms in response to the (1) high-rate (5000 pulse/s) electric pulse-train masker, (2) low-rate (250 pulse/s) electric train, and (3) the above two stimuli combined. The number of spikes in each 100 μs bin are plotted as a function of time after the masker stimulus onset. Several 20-ms intervals for defined for further analysis (labeled 1 through 6,) are indicated below the lowest abscissa.

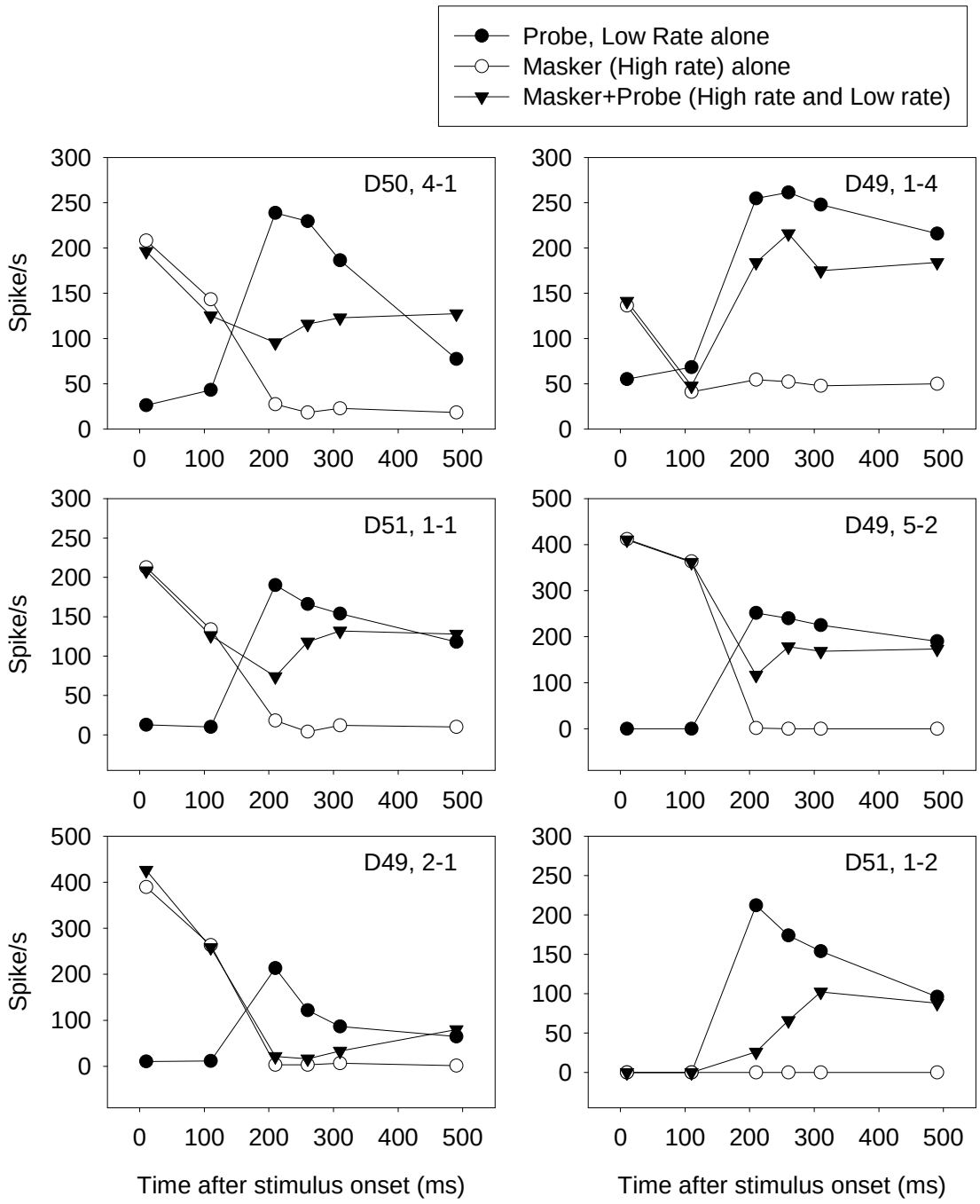


**Figure 7** Temporal changes in ANF responsiveness in response to high-rate electric masking of a low-rate series of electric probe pulses. Data are shown for 6 ANFs from 3 cats. Spike rate is plotted for each of six analysis windows (as indicated in Figure 6). Each panel presents data from a different fiber (animal number and fiber number are indicated). In each plot, the response to the probe alone, masker alone and combined stimuli are plotted separately (See legend at the top of the figure).

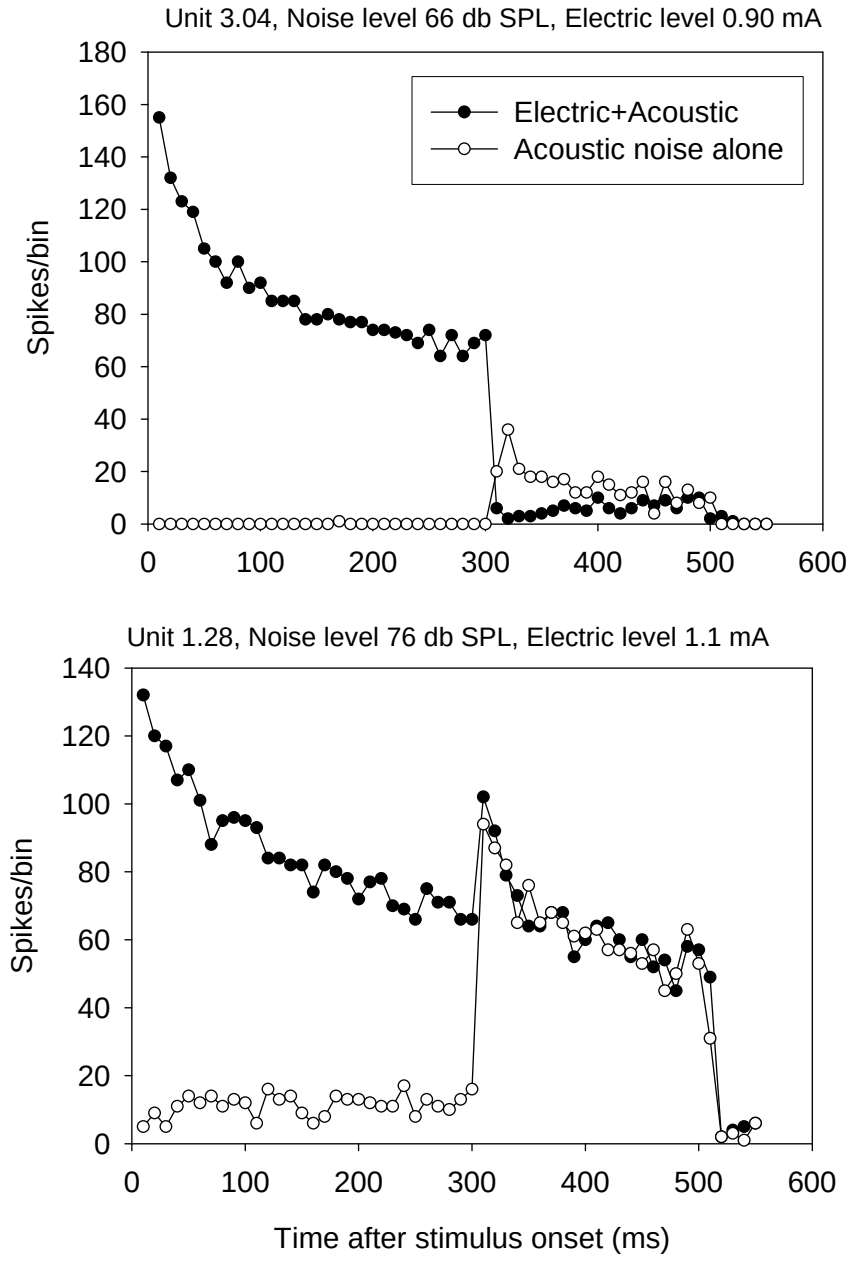


**Figure 8** PST histograms from two fibers in response to a 1000 pulse/s electric train followed by an acoustic noise stimulus (filled symbols). The two examples provide contrasts in the effect of electric masking. For evaluating the effect of the electric masker, the response to the acoustic stimulus presented alone is also shown (open symbols). Electric pulse train was 300 ms in duration and used 40 us/phase biphasic pulses. The wideband acoustic noise was 200 ms in duration with its onset at 300 ms (i.e., immediately after pulse-train offset).

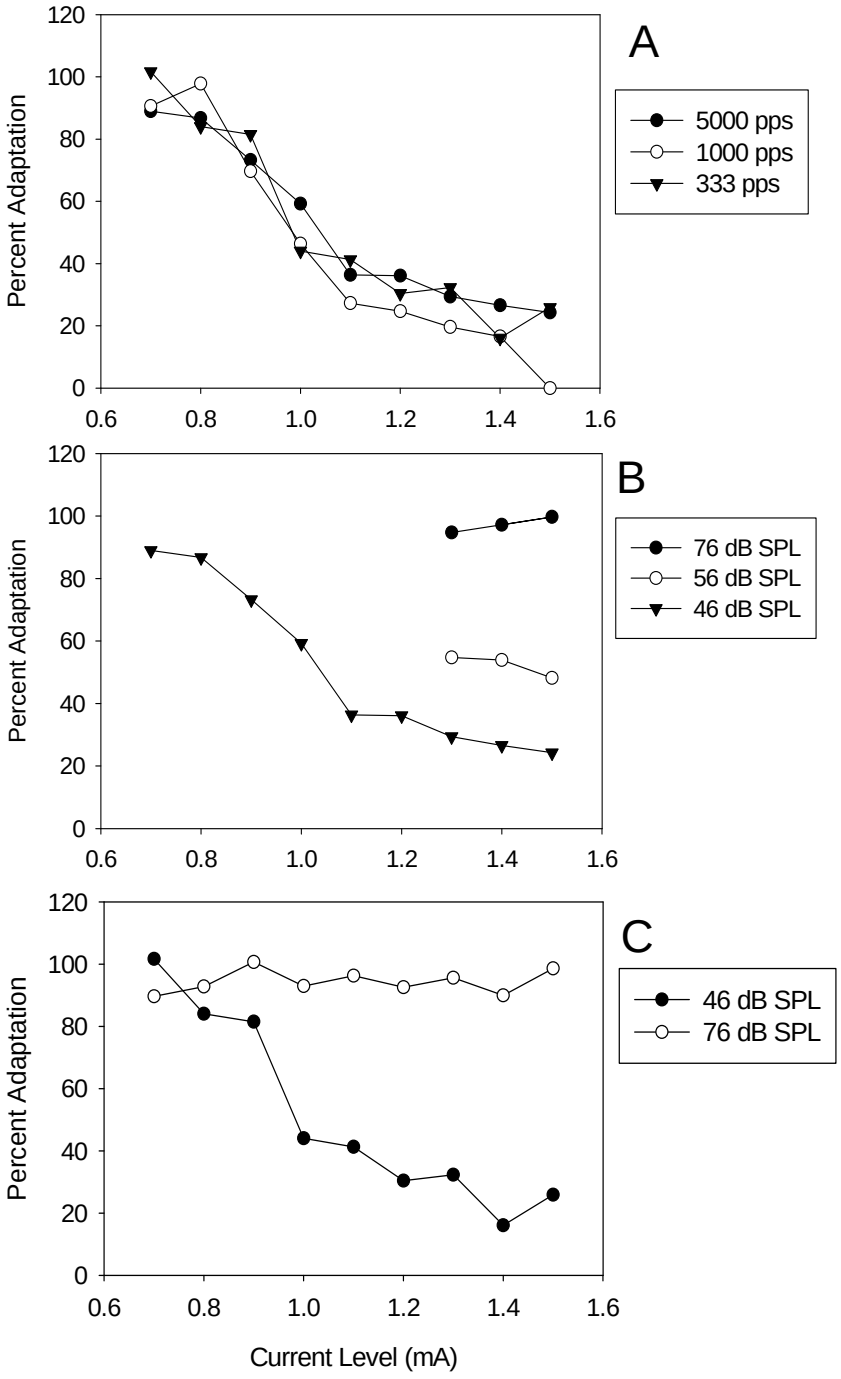


**Figure 9** A. Percent adaptation (see text) plotted as a function of electric current level, with electric pulse rate as a parameter. In all cases, the acoustic level was fixed at 46 dB SPL. B. Similar functions, but with acoustic noise level fixed and the masker pulse rate at 5000 pulse/s. C. Similar data as in B, only with the masker pulse rate reduced to 1000 pulse/s.

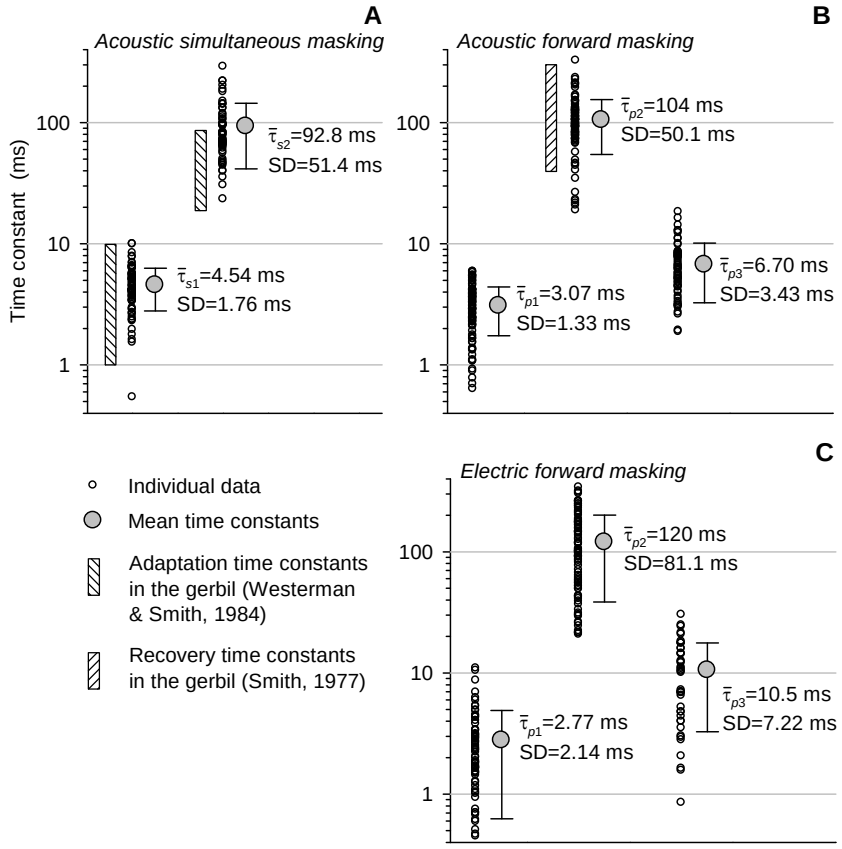


**Figure 10** Summary of time constants that described the time course of simultaneous (A) and forward (B, C) masking of the ECAP. Regression analysis of acoustic (A, B) and electric (C) masking was performed on data obtained from twelve and nine subjects, respectively. Small open circles represent time constants obtained from individual masking functions. Large filled circles indicate mean values of the time constants. Vertical shaded bars correspond to the ranges of adaptation and recovery time constants, obtained in the gerbil by Westerman and Smith (1984) and Smith (1977), respectively.

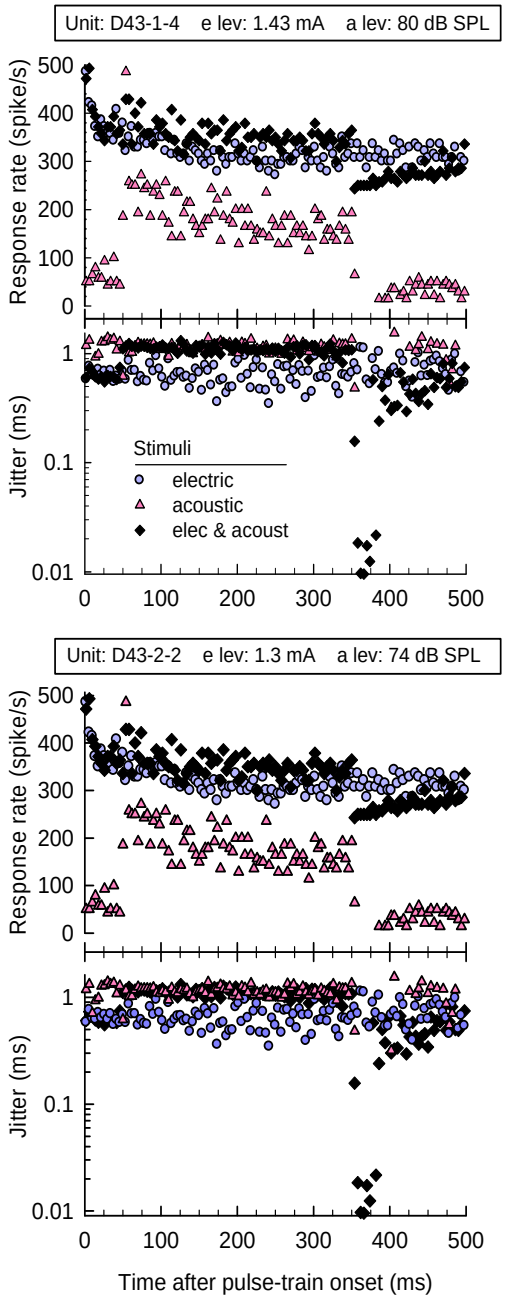


**Figure 11** Response rate and jitter is plotted for 3 stimulus condition in two example fibers. The stimulus in each case is a 250 pps electric pulse train over the interval 0-500 ms and an acoustic noise presented over the interval 50-350 ms. The response after noise offset shows a differential rate of recovery for jitter and discharge rate (filled triangles).

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Miller, C.A., Abbas, P.J. Robinson, B.K., Nourski, K.V., Zhang, F., Jeng, F-C. (in preparation) Electrical excitation of the acoustically sensitive auditory nerve: Effects of acoustic stimulation

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