7th Quarterly Progress Report
April 1, 2004 to June 30, 2004

Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation: Electrical Forward Masking

Submitted by:

Ben Bonham, Ph.D.

[1]John Middlebrooks, Ph.D.

Russell Snyder, Ph.D.

(in alphabetical order)

University of California, San Francisco

Department of Otolaryngology – Head and Neck Surgery

Epstein Hearing Research Laboratories

533 Parnassus Avenue, Room-U490

San Francisco, CA 94143-0526

[1]Kresge Hearing Research Institute

1301 E. Ann St.

University of Michigan Medical School

Ann Arbor, MI 48109-0506

Abstract

This Quarterly Progress Report presents our progress in the 7th quarter of this contract. In this quarter we conducted 4 experiments on this contract. These experiments focused on forward masking using electrical pulses in guinea pigs. In these and most of the experiments we have conducted in the last two quarters, we completed brief acoustic experiments prior to conducting more extensive electrical stimulation experiments. Thus the acoustic experiments not only "calibrated" our recording probes but also provided comparison data on the forward masking properties of the neurons located at the particular probe sites. In the previous progress report, QPR#6, we briefly described the results of these acoustic forward masking experiments. In this progress report, we describe some of our electrical forward masking results. We would like to emphasize that in many cases both acoustic and electrical forward masking results were collected in the same animal and that the results using both types of stimulation complement and reinforce each other. We have come to feel that a sequential acoustic/electric protocol is advantageous since many of the masking results are unusual (one might even say counterintuitive) and therefore the two sets of results help increase our confidence in the validity of the results. It is also advantageous because some aspects of forward masking vary from animal to animal, and the acoustic and electric results appear to co-vary from animal to animal in parallel. This parallel shift in forward masking suggests either that there are systematic differences in signal processing at different IC locations (we usually record from only one set of 16 locations in each animal) or that there are differences in signal processing between animals.

In addition to conducting these forward masking experiments, we discovered and fixed several "bugs" in our hardware and software. The hardware bugs included problems with our voltage-to-current amplifiers.

Finally, in one experiment we began the examination of stimulation paradigms that we hope will provide lower thresholds and increased activation selectivity. The procedures involve appropriate division of stimulating current between intracochlear electrodes and an extracochlear electrode. By varying the amount of current delivered to intracochlear and extracochlear electrodes, it may be possible to achieve a balance between tripolar and monopolar configurations that maximizes the advantageous properties of each configuration and minimizes the disadvantageous properties. Specifically, we hope that by "morphing" between monopolar and tripolar (or bipolar) stimulation we can combine the low threshold activation of the monopolar configuration with the high selectivity of the tripolar (or bipolar) configuration. Although our first attempt at "morphing" was not completely successful, we plan to conduct further experiments along these lines in the future.

Introduction

Contemporary auditory prostheses (APs) are multichannel devices that employ multi-contact intracochlear electrodes to activate the auditory nerve in deaf human subjects. It is often assumed that each electrode contact (or pair of contacts) in these devices activates a different sector of the auditory nerve array. Thus each AP channel is presumed to represent an independent, albeit over-lapping, channel of information. In these experiments, we examine the spatiotemporal interactions between intracochlear electrode (AP) channels stimulated in sequence. We measure the spread of neural activity evoked across the tonotopic organization of the central nucleus of the inferior colliculus. We compare the spread of activity when an individual AP channel (the probe) is stimulated alone and when it is preceded (forward masked) by stimulation of the same or a different channel. We examine these interactions as a function of the spatial separation between the masking (first-stimulated) and probe (second-stimulated) channels, as a function of the intensity of the stimuli on these channels, and as a function of time. Interactions are indicated by differences in the probe-evoked response either in magnitude or in spatial spread as a function of the masker intensity and channel location. We demonstrate that masking signals that are higher in intensity or that are presented on AP channels which are spatially closer to the probe channel produce more interaction than those presented at lower intensity and further away.

We are conducting these electrical interaction studies in conjunction with acoustic interaction studies using two tones, since we can find no published studies of acoustic masking in the central nucleus of the inferior colliculus (ICC). Such acoustic studies are necessary since they provide a basis of comparison for the electric interaction results. Interactions between acoustic stimuli have been extensively studied in the auditory nerve of normal hearing animals. The primary mechanisms responsible for the production of these interactions have been well described; the two major mechanisms of interaction in the auditory nerve are adaptation and two-tone suppression. Adaptation, the decrement in response amplitude over time during the presentation of a constant stimulus, is often attributed to the depletion of neurotransmitter at the inner hair cell synapse. Two-tone suppression, the decrease in response to one tone when a second tone is presented simultaneously, is often related to the functioning of the cochlear amplifier, its non-linearities, and the production of distortion product otoacoustic emissions (DPOAEs). Since these interactions are present already in the cochleas of normal hearing animals, their effects must be present in some form in the auditory response patterns of central auditory neurons. Thus, for example, the response measured in the IC to a low level probe tone might be decreased when it is preceded by a high level *forward masking* tone at the same frequency, since that is the effect that is seen in the auditory nerve (Smith, 1977, Harris and Dallos, 1979). Likewise, two-tones of different frequencies that are presented *simultaneously* might evoke a response that is less than the sum of the individual responses due to suppression (Sachs and Kiang, 1968). In addition, these two-tone stimuli will produce additional responses corresponding to the quadratic distortion tone at F_2-F_1 and the cubic difference tone at $2F_1$-F_2 (Cooper and Rhode, 1997, Ruggero et al, 1997) in the auditory nerve. These important acoustic interactions cannot occur in the cochlear auditory nerve fibers of deaf animals, since the mechanisms responsible for their production (inner hair cell synapses and the cochlear amplifier) are missing. That is, intracochlear electrical stimulation cannot elicit these interactions. Nevertheless, simultaneous and forward masking (interactions) *can* be observed in the neurons of the inferior colliculus following two-channel electrical stimulation. In this report we describe some of these interactions.

Methods

All procedures were carried out under a protocol approved by the IACUC at the University of California. All surgical, general recording, signal generation, and data analysis procedures have been described previously (see QPR# 6).

Following a series of "acoustic calibration" recordings, which calibrate the location of the recording probe, acoustic tone interaction (forward masking) protocols were conducted as a first step in all the described experiments. In the acoustic forward masking phase of these experiments, two forward masking protocols were used. The first was a fixed-masker protocol and the other a fixed probe protocol. These protocols are shown graphically in Figure 1. Each of these protocols has certain advantages in either the analysis of the results or the comparison of the results with those recorded following electrical forward masking. In the fixed-probe protocol, a 20 ms probe tone that was fixed in frequency and level was preceded by a 50 ms variable masking tone. The masking tone was varied in frequency (usually 2 to 32 kHz in eighth octave steps) and level (usually 0 to 80 dB in 5 dB steps). In the fixed-masker protocol, a 50 ms masking tone, which was fixed in frequency and level, was followed by a 20 ms probe tone that was varied across the same range of frequencies and levels. In both protocols, the variable tone was varied randomly in frequency and level with each trial. Each unique masking and probe tone combination was presented an equal number of times (usually four times). The responses to each unique masker/probe combination were summed.

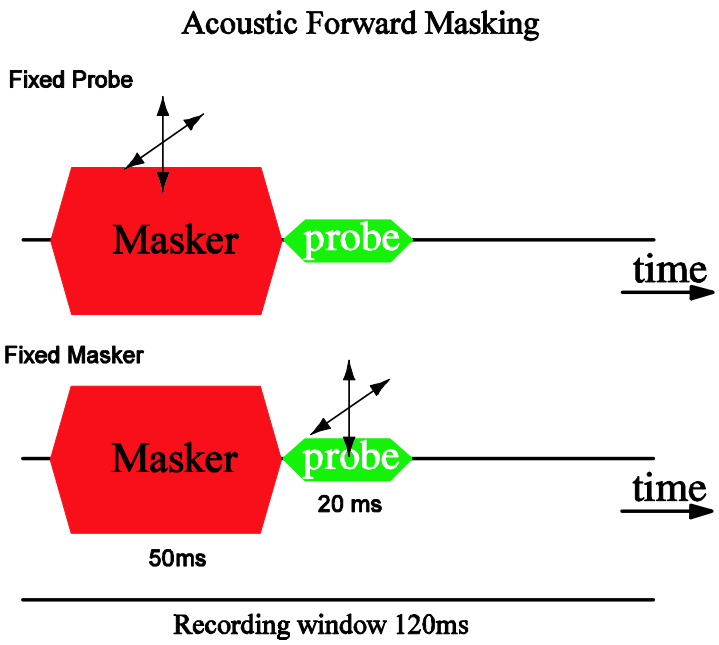

Figure 1. A diagram of the acoustic forward masking protocols used in these studies. In the "fixed probe" protocol (top), a 20 ms probe tone is presented at a fixed frequency and fixed level, but preceded by a 50 ms masking tone of variable frequency and variable level. The frequency and level of the masking tone are randomly varied with each presentation of the probe tone (indicated by the arrows). In the "fixed masker" protocol (bottom), the masking tone is fixed in frequency and level, and the probe tone is varied.

Following the acoustic interaction experiments, animals were deafened as previously described, and an intracochlear stimulating electrode was inserted into the cochlea. Each inserted intracochlear electrode consisted of a series of six to ten platinum/iridium wires embedded in a silicone elastomer carrier (Figure 2). The carrier is designed to fit snugly into

the guinea pig scala tympani. Each wire is terminated as a ball contact, whose outer surface protrudes slightly form the carrier and makes contact with the perilymph of the scala. The contacts are activated either as pairs (bipolar mode with one

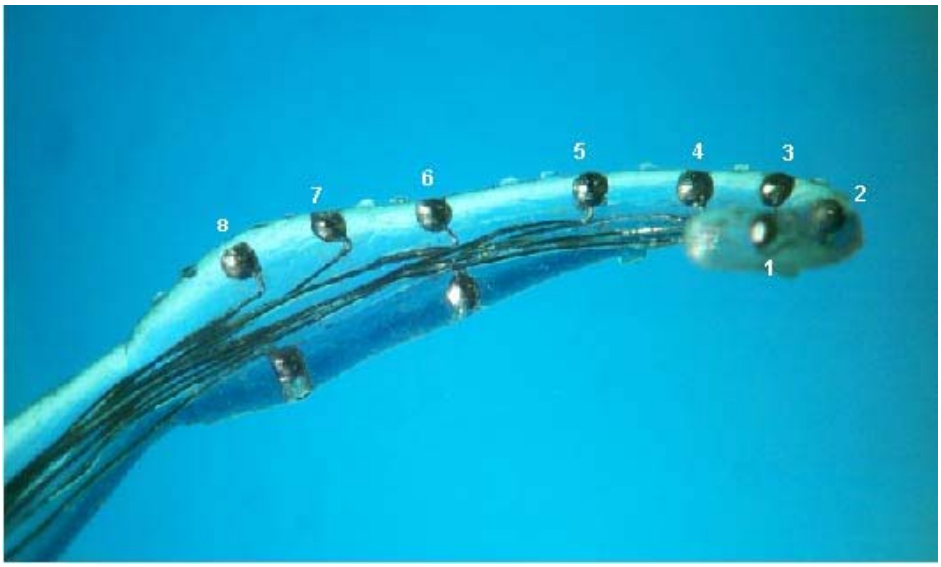

Figure 2. Guinea pig scala tympani intracochlear electrode. This electrode has eight contacts (1-8) arranged along its upper surface and two electrodes (unlabeled) arranged along its lower surface. Electrode contact #1 is the most apical contact and contact #8 is the most basal contact. In these electrical stimulation experiments only the upper surface electrodes were activated. Bipolar channels are designated as follows from apex to base: <1,2.>, <2,3>, <3,4>, <4,5>, <5,6>, <6,7>, <7,8>.

contact as the active and the other the return) or individually (monopolar mode with an extra-cochlear wire acting as the return). Each monopolar or bipolar pair of electrodes constitutes a stimulation channel in these experiments. After the intracochlear electrode has been inserted into the scala, the most apical contact (#1) is located at the beginning of the second turn of the cochlear spiral, whereas the most basal contact (e.g., #8) is located at the junction of the "hook" and the first turn. The cochlear positions of the contacts vary slightly in their radial location and the degree to which they are juxtaposed to the osseous spiral lamina. Documentation of this variation will be the subject of a subsequent progress report. The approximate longitudinal location of each of the contacts is illustrated on a cast of the guinea pig scala tympani (Figure 3).

Figure 3. A cast of the guinea pig scala tympani with the approximate longitudinal location of the eight upper contacts of the electrode illustrated in Figure 2 shown. The location of the habenula, which is the lateral edge of the osseous spiral lamina, is indicated by the white arrows. The location of the round window is indicated by the red dots.

At the beginning of each electrical stimulation experiment, each electrical channel was activated individually using a biphasic pulse. The channel number and the current level of the pulse was varied randomly across a predetermined range of sites and levels and delivered to each electrode site in random order. Each site-and-level combination was presented 20 times. The sums of the recorded responses as a function stimulus intensity and recording site number were plotted as spatial tuning curves (STCs). These STCs allowed the spatial selectivity of the different sites to be estimated. Once an STC for each stimulus channel was recorded, a forward masked STC was recorded. Forward masking STCs were recorded by first presenting a train of pulses (the maskers) across a range of levels on each of the stimulus channels and then a single pulse (the probe) on the channel to be studied (Figure 3). The current level of the masker pulses and probe pulse were varied randomly across a predetermined range. A null (no masker) condition was included with the masker presentations. Thus probe responses evoked by pulse on a given channel were recorded across a range of probe levels with no preceding masker (the not-masked STC) and with a range of preceding pulse trains (masked STCs). The masking pulse trains varied across stimulus channels and across a range of masking pulse intensities.

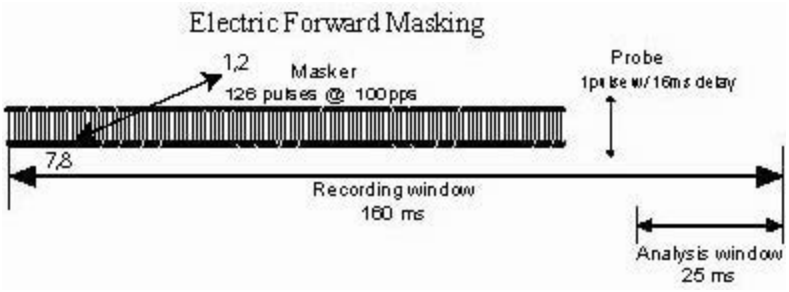

Figure 4. Electric forward masking paradigm. The probe stimulus is a single biphasic pulse delivered on one of seven bipolar channels (<1,2> to <7,8>). The probe stimulus current is varied across a range of levels, from below threshold to several dB above threshold. At each probe level, a train of masking pulses is presented preceding the probe. The masking pulses are presented on any one of the stimulus channels from <1,2> to <7,8> and are varied in current level across a predetermined range of levels. Each of the stimulus parameters -- masker level, masker channel and probe level -- are varied randomly from presentation to presentation until all combinations of these three parameters have been presented 20 times.

Results

Acoustic forward masking:

In all the current studies, acoustic frequency response areas (FRAs) were recorded first. These FRAs were constructed by recording the responses to a large number (2048, i.e., 512 frequency/level combinations presented 4 times) of single 50 ms tones, which were varied across a predetermined range of frequencies and levels and presented in random order (Figure 5). From these FRAs, the characteristic frequency (CF), the frequency to which each recording-probe-site was most sensitive, was estimated and so the position of the recording probe with respect to the tonotopy of the IC was calibrated. Following these calibration recordings, tone interaction (forward masking) experiments were conducted.

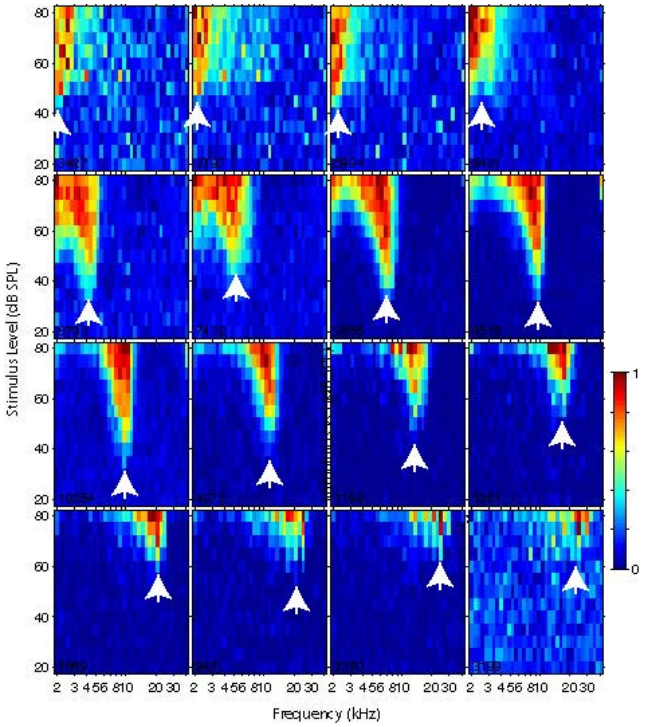

Figure 5. Frequency response areas (FRAs) recorded in animal GP65. Each of the 16 panels represents an FRA recorded from one of the 16 IC probe sites. The FRA in the panel on the upper left was recorded from the most superficial site along the probe; the FRA in the panel on the lower right was recorded from the deepest site. The panels, presented sequentially from left to right then top to bottom, represent FRAs recorded from the intervening sites on the recording probe. Within each panel, stimulus frequency is plotted along the abscissa and stimulus level is plotted along the ordinate. The response to each frequency/level combination of the stimulus is represented by a pixel in each panel with the magnitude of the response color coded on a scale from the maximum recorded response at that probe site (dark red) to no response (dark blue) according to the color scale at the right. The characteristic frequency (CF) and minimum threshold for each site are indicated by the arrow in each panel.

Figure 6 illustrates forward masked probe responses recorded in a "fixed-probe" paradigm. The probe is a 20 ms, 10 kHz tone presented at 60 dB SPL. It is preceded by a variable (in frequency and level) masking tone 50 ms in duration. The analysis window for these FRAs is set so that only the responses to the probe tone are illustrated. Since the probe is a 10 kHz tone only those recording sites (#5 – #11) that are sensitive to this frequency show responses to the probe, as indicated by the greater number of pixels colored yellow to red in these FRAs. The reduction in the probe response produced by the masker is evident as a blue "V" in each FRA recorded from sites 5 – 11. At these sites the frequency producing the maximum suppression (best masker frequency or BmF) and the frequency producing suppression at minimum masker intensity (masking CF, mCF) usually coincide and shift systematically with depth in the IC. At site 5, BmF and mCF are approximately 4 kHz, whereas at site 10 BmF and mCF are approximately 11 kHz. The white arrows, which are copied from the previous figure, indicate the CF and minimum threshold of the responses to

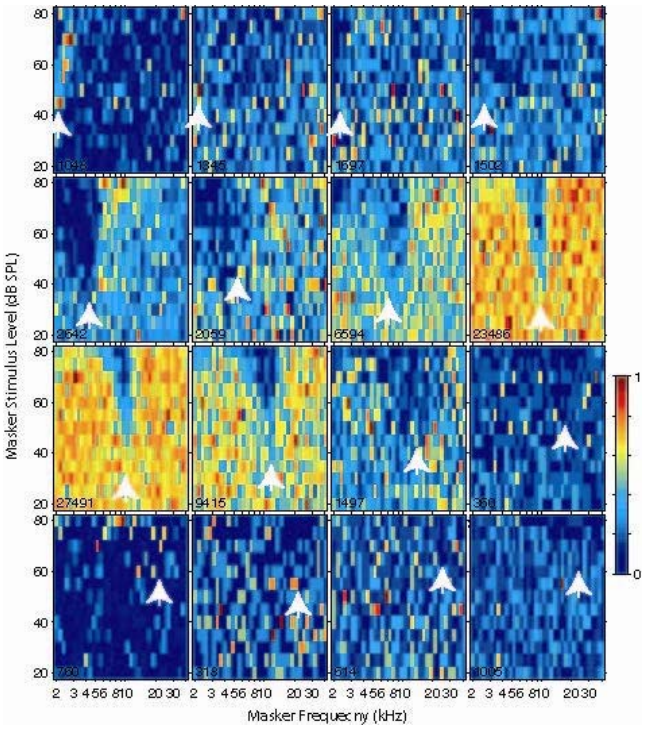

Figure 6. Forward masked FRAs recorded from GP65. The probe is a 10 kHz tone presented at 60 dB SPL. It is preceded by a masking tone that was varied in frequency (indicated along the abscissa) and level (indicated along the ordinate). The recording window was adjusted so that only the response to the probe is illustrated. The arrow in each panel indicates the CF and minimum threshold of the responses to the preceding masking tones (see Figure 5).

the masking tones. These arrows closely match the mCF of the suppression areas. Comparison of the masker evoked excitatory regions (Figure 5) with the masker evoked suppression areas in Figure 6 indicates a close correspondence between the two. Thus the region of probe response suppression closely matches the masker excitatory regions. This indicates that the frequency and level of the forward masking tone that evokes the greatest excitation at each site prior to the onset of the probe tone are the same as those that produce the greatest suppression (forward masking) of the subsequent probe response. This result is consistent with the masking patterns that would be predicted in auditory nerve fibers, and is consistent with an adaptation model of forward masking. In those neurons, the amount of masking produced by a forward masking tone is directly dependent upon the magnitude of the excitation that it evokes (Harris and Dallos, 1979). Moreover, for each neuron the best masker at any given stimulus level corresponds to the best frequency (the frequency that evokes the largest response) at that level. Thus the area of probe response suppression in the FmFRA has the same shape and the same CF as the excitatory region in the FRA regardless of the frequency of the probe tone.

The forward masking pattern illustrated in Figure 6 is typical of the results of some, but not all, of our experiments. Figure 7 illustrates a different pattern of forward masking that is also often observed. In this experiment, the stimulus paradigm used is similar to that used in the previous experiment, although there are some differences. For example, the probe is a 15 kHz tone presented at 45 dB SPL, but the most important difference it that it was conducted in a different animal. As in the previous experiment, the regions of probe response suppression are

evident as blue "Vs" in the response areas of neurons located at sites that respond to the probe (#3–12). However, unlike the previous response-suppression areas seen in Figure 6, these suppression areas are often offset in frequency from the CF of the masker-evoked excitatory regions (indicated by the white arrows). This offset is greatest for recording sites in which the CFs of those sites are different from the probe frequency; i.e., regions of the IC that are less responsive to the probe (sites 3 – 6 and sites 10-12). Moreover, the BmF and mCF appear to be relatively constant and correspond closely to the probe frequency rather than shifting with the CF of the recording sites. Thus, the difference between site excitatory CF (white arrows) and site BmF or mCF increases progressively in sites that are progressively less sensitive to the probe.

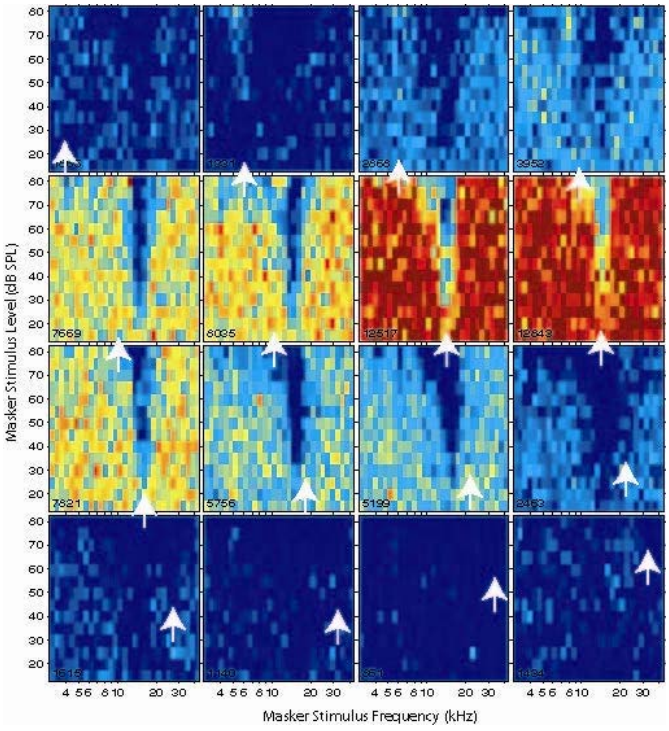

Figure 7. Forward masked FRAs recorded from GP24. The probe is a 15 kHz tone presented at 45 dB SPL. It is preceded by a masking tone that was varied in frequency (indicated along the abscissa) and level (indicated along the ordinate). As in Figure 6, the recording window was adjusted so that only the response to the probe is illustrated. The arrow in each FRA indicates the CF and minimum threshold of the responses to the forward masking tones (not shown). Note the frequency offset between the areas of probe response suppression and the tips of the arrows.

Electrical forward masking:

The forward masking results described above resulted from acoustic stimulation in normal hearing animals, but similar results can be obtained using intracochlear electrical stimulation in deafened animals. Figure 8 illustrates three types of responses recorded in a electrical fixed-masker experiments in one animal using a fixed masker paradigm: the responses to acoustic tones presented alone (acoustic calibration), the responses to electric probe stimuli presented alone; and the responses to the same electrical probes when they are forward masked by an electrical pulse train delivered on one channel at a fixed current level.

Acoustic calibration (Fig. 8A) shows that the recording probe sites in this experiment measured activity in ICC neurons that were originally tuned to frequencies ranging from 1.8 kHz (upper row, left-most column) to 25 kHz (bottom row, right-most column). After these acoustic calibration responses were recorded, the contralateral cochlea was surgically exposed and deafened using an intracochlear injection of neomycin. After deafening, an 8-electrode implant like that illustrated in Figure 2 was inserted into the scala tympani and an electrical forward masking experiment begun. In random trials, masked-probe or the probe-alone stimuli were presented to the cochlea. The responses to electric probe pulses presented by themselves (probe-alone responses) are presented in Figure 8B. In the masked-probe trials, the masking pulses were fixed on one implant channel at one level. Probe pulses were delivered on each of seven different implant channels located at seven intracochlear locations (frequencies). Probe pulses were also varied in level from below threshold to near or above saturation on at least one channel. The probe-alone ERAs shown in Figure 8B illustrate the "tuning" of the electric probe-alone responses as a function of location within the IC. Superficial recording sites in the IC that are tuned to low acoustic frequencies, i.e., sites #3 & 4 (top row), are responsive only to stimulation of the most apically located intracochlear electrode channel, pair <1,2>. At progressively deeper sites, the neurons are most sensitive to more basal (higher frequency) electrode channels, until at IC sites #13 & 14, the neurons are sensitive only to stimulation of channels <6,7> and <7,8>, the most basal (highest frequency) channels. There is a progressive shift in the best stimulating channel from apical to basal as the recording site shifts from low to high frequency. At high current levels, electrodes located more basally or more apically to these best stimulating channels begin to excite the neurons at each recording site. Thus, these IC electrical response areas can be interpreted in the same manner as the acoustic FRAs (Figs. 5 & Fig 8A), although the frequency resolution is much poorer with electrical stimulation -- an issue that we are currently addressing.

The forward masked ERAs seen in Figure 8C illustrate the responses of the same neurons to the same probe stimuli when they are preceded by a forward masking pulse train. In this case, the masking stimulus was delivered on channel <5,6> at 251 μA (42 dB attenuation re. 1 mA). Based on the probe alone responses (Fig 8B), if forward masking were dependent primarily upon adaptation mechanisms, this masker should suppress activity recorded only on those sites that are strongly excited by the masker -- sites #10–13 (third row). This, indeed, appears to be the case. The responses recorded at sites #10-13 are strongly suppressed by the forward masker and the responses on the other channels are unaffected or only weakly affected by the masker (Fig 8C). As suggested above, this result is completely consistent with adaptation mechanisms operating to produce this masking.

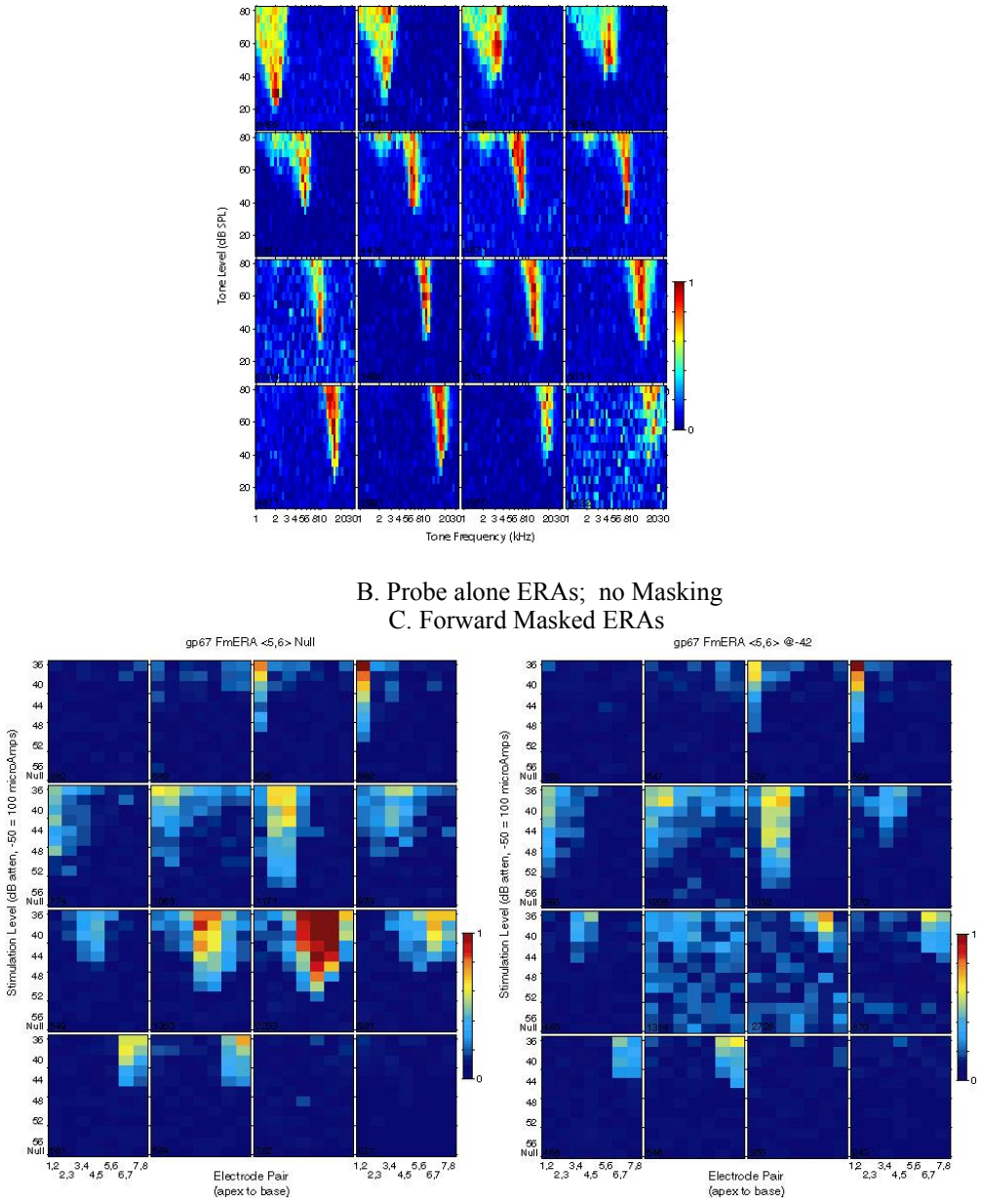

Figure 8. A. Acoustic FRAs. B. Probe alone / electric response areas (ERAs). C. Forward masked electric response areas (FmERAs). Each panel in B and C is an ERA showing the response to electrical pulses recorded at one of 16 recording-probe sites. The panels are arranged as in previous figures with ERA at the lowest frequency (most superficial) site in the upper left and the ERA at the deepest (highest frequency) site in the lower right. Both masked and not-masked responses were evoked by probe pulses delivered on one of 7 adjacent bipolar (BP+0) electrode pairs, <1,2>, …, <7,8>. The probe stimulus was a single pulse whose intensity was varied and is plotted on the ordinate of each panel. For both sets of responses, the analysis window was adjusted so that only the probe response (masked or not-masked) was recorded. All stimuli were presented 20 times and delivered as randomly interlaced trials in a large stimulus matrix. The forward masker was a train of 250 pulses on channel <5,6> (a BP+0 channel). The masker amplitude was fixed a 251 μA (42 dB attenuation, 50 dB = 100 μA) approximately 10 dB above its threshold. The not-masked responses were preceded by the same masker with masker attenuation maintained at 120 dB. GP323.

Figure 9 illustrates a different type of forward masking response using a fixed probe paradigm. In this figure, the panels are ordered in the same sequence as those illustrated previously. The most superficial site -- the site that was tuned to the lowest acoustic frequency, in this case 3 kHz (not shown) -- is located at the upper left. Successively deeper sites are arrayed from left to right and from top to bottom so that the deepest site -- the site that was tuned to the highest frequency, in this case approximately 25 kHz -- is located on the lower right. In Figure 9A, each panel illustrates the responses evoked by activating a different bipolar pair of intracochlear electrodes (abscissa) with biphasic pulses at a range of intensities (ordinate). As illustrated in the previous figure, activation of the most apically placed (low frequency) electrode pair, <1,2>, preferentially excites neurons tuned to low frequencies, i.e., those located superficially in the IC (the upper row of panels). It produces the strongest response from these neurons at these locations at the lowest stimulus current levels. . Conversely, activation of the most basally placed (high frequency) electrode pair, <5,6>, of this six-electrode implant preferentially excites (produces the strongest response in) neurons tuned to the high frequencies, i.e., those located deep in the IC (the lowest row of panels) at the lowest current levels. Activation of the intermediate three electrode pairs preferentially excite neurons located at sites between these two extremes. As seen in Figure 8B, there is a progressive shift in the best channel from apical to basal as the recording site shifts from low frequency to high frequency. At high current levels, electrodes located more basally or more apically to these best channels begin to excite the neurons at each recording site.

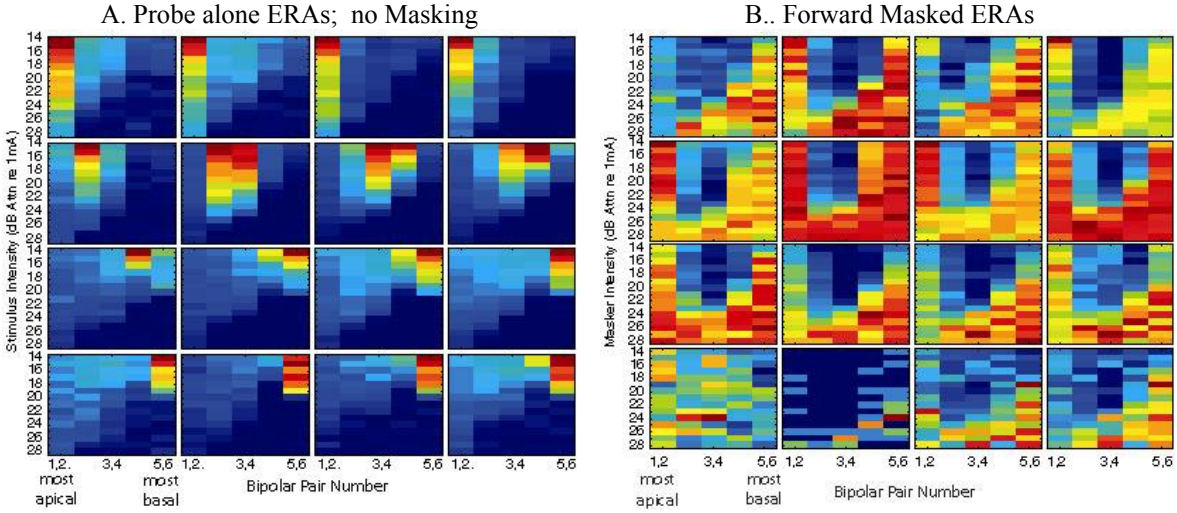

Figure 9. A. Electric response areas. Each panel illustrates the response recorded on one of the 16 sites of a silicon recording probe. The response recorded from the most superficial probe site (#1) is shown at the upper left, and that recorded from the deepest site (#16) is shown in the panel on the lower right. Arrayed along the abscissa of each panel are the responses evoked by successive channels of the intracochlear stimulating electrode. Responses evoked by activation of electrode sites located apically, e.g., <1,2> , are plotted on the left of each panel, those evoked by electrode sites located basally, e.g., pair <5,6>, are plotted on the right. B. Forward masked electric response areas evoked by stimulation with a fixed probe pulse. The probe was a pulse on channel <3,4>, at 100 μA (20 dB attenuation re 1 mA), approximately 6 dB above its threshold. The forward masker was a train of pulses; the intensity of the masker is used as the ordinate of each panel. The channel on which the masker train was presented is used as the abscissa of

each panel. Masking sites are arranged as previously with apically located sites on the left and basal sites on the right of each panel. GP230.

Just as ERAs can be recorded which are comparable to acoustic FRAs, forward masked ERAs can be recorded which are comparable to the masked fixed-probe acoustic response areas shown in Figure 6 & 7. Figure 9B illustrates an example of one set of electric forward masked ERAs that were evoked by a fixed electrical probe stimulus presented on an adjacent pair of cochlear electrodes, channel <3,4>, at 6 dB above threshold, i.e., at 100 μA (20 dB attenuation re. 1 mA). In this example, the probe stimulus evoked responses at all the recording sites (except site #13 in the lower left corner) of this recording electrode. The forward masking signal suppressed the amplitude of these probe responses (blue regions), and the magnitude of this suppression was dependent upon the amplitude of the masking signal (the ordinate in each panel) and the location of the stimulating channel along the cochlear spiral (the abscissa in each panel). The masker produced clear areas of suppression that were roughly "V" shaped at all responding sites but the nature of this suppression varied with the recording site. At high frequency sites (sites #7 -16, ignoring site 13), the suppression area is more or less centered on channel <3,4> and the the region of greatest masking, the deepest blue region, occurs when the masker is presented on channel <3,4>. This indicates that the best masking channel or BmCh (corresponding to the BmF of acoustic masking) is channel <3,4>, i.e., the same channel as the probe signal channel. Presenting the masking stimulus on channel <3,4> produced more masking than that produced by presenting the same masker on any other channel despite the fact that maskers on these other channels evoked greater responses at these sites (see Fig 9A). This result is similar to the acoustic masking results shown in Figure 7 and is **in**consistent with adaptation within the IC as mechanism for IC forward masking. An adaptation mechanism would predict that the probe responses of neurons at site #16, a site tuned to 25 kHz and most sensitive to stimulation on channel <5,6>, should be most strongly suppressed by a masker presented channel <5,6>, not one presented on channel <3,4>.

In contrast to the masking pattern observed at the high frequency sites, the patterns observed at the low frequency sites (#1–6) in B, are shifted to the left, to lower frequency channels. Compare for example the masking patterns evoked at sites #1-4 with those evoked at sites #5-8 directly below them. At the upper sites (with the exception of site #2), the area of suppression appears to be shifted to the left. Thus activation of channels located at more apical cochlear locations produces activation of IC neurons tuned to lower frequencies. Moreover, activation of these channels masks responses evoked by the probe channel more strongly than maskers presented at the probe channel. This result is consistent with the results following acoustic forward masking in Figure 7 and is consistent with a local adaptation mechanism for forward masking.

A second example of masking that is inconsistent with local adaptation as a mechanism for forward masking in shown in Figure 10. This figure illustrates the forward masked probe response areas, FmERA, evoked in animal GP323 by activation using a more widely spaced probe channel, one consisting of two non-adjacent (BP+1) electrode contacts (pair <4,6>). Activation of the cochlea with this more widely spaced electrode pair produced activation that was more broadly distributed across more recording sites than the activation seen in Figure 9, where an adjacent pair of electrode contacts, <3,4>, were used. This broad activation is forward masked by pulse trains on narrowly spaced adjacent (BP+0) bipolar contacts (<1,2>, …, <5,6>). As in Figure 9B, the masking channels are arrayed along the abscissa and the masking levels are arrayed along the ordinate. The acoustic tuning measured during calibration (not shown) was comparable to that illustrated in Figure 5 and 8A and the acoustic forward masking was comparable to that illustrated in Figure 7. In this extreme example of electric

forward masking, suppression of the probe response is restricted to a narrow range of masker channels. The most effective masking channel is the most basal channel of this implant, pair <5,6>, although some masking is produced by other channels, most notably channel <4,5>, especially at lowest and highest frequency sites. This is a clear example of masking in which the BmCh does not vary across the recording sites despite their differences in acoustic and electric tuning. This masking cannot be accounted for using local mechanisms of adaptation.

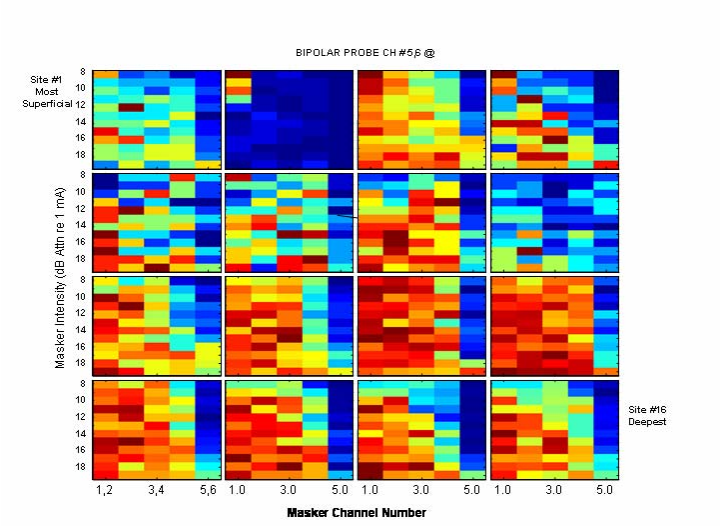

Figure 10. Forward masked electric response areas recorded GP323. Each panel shows the forward masked probe responses to a fixed-level probe on a fixed channel. The probe channel was electrode pair <4,6>, electrodes separated by one electrode (a BP+1 channel). The probe amplitude was a 200 μA (14 dB attenuation re 1 mA), approximately 8 dB above its threshold for this channel. The probe stimulus was preceded by a masking train of pulses delivered on adjacent bipolar pairs (BP+0), the intensity of which is plotted on the ordinate of each panel. The channel on which the masker train was presented is plotted along the abscissa of each panel. Masking sites located apically, e.g., <1,2> , are plotted on the left of each panel, and those sites located basally, e.g., pair <5,6>, are plotted on the right. GP323.

Discussion

The acoustic and electric forward masking results present here suggest three general conclusions regarding non-simultaneous channel interactions in the auditory CNS: First, adaptation is not the only mechanism that underlies non-simultaneous channel interactions. Although adaptation at the inner hair cell synapse can account quantitatively for all, or almost all, acoustic non-simultaneous interactions (forward masking) observed in auditory nerve fibers (Harris and Dallos, 1979), adaptation cannot account for some of the forward masking results presented here or seen in other central auditory areas (e.g., Shore, 1998). Moreover, although peripheral adaptation can account qualitatively for psychophysical forward masking results in the normal-hearing humans (e.g., Houtgast, 1972; Moore, 1978; Shannon, 1977), it cannot account for these results quantitatively (Relkin and Turner, 1988, Turner et al, 1994). Moreover, psychophysical forward masking is observed in profoundly deaf human users of cochlear implants (Shannon, 1990; Chatterjee and Shannon, 1998; Chatterjee et al, 1998;

Chatterjee, 1999), who presumably have no, or very few, inner hair cells. Finally, electrical stimulation paradigms, which produce no physiological forward masking in the auditory nerve, can produce profound forward masking in the IC (see Figures 9C and 8B).

Second, non-simultaneous channel interactions in the auditory periphery represent only subset of the non-simultaneous interactions present in the auditory system as a whole. It has always been obvious that forward masking observed in first order neurons of the auditory nerve must influence the response patterns evoked in the second and higher order neurons of the central auditory system. What is obvious now also is that certain classes of acoustic and electrical signals can evoke dramatically different responses in central auditory system than they evoke in the auditory periphery (Sinex et al 2002a,b; Sinex et al 2003; Biebel and Langner, 2002; Shore, 1998). These signal-evoked interactions are different both in the spectral (spatial) domain (Beibel and Langner, 2002) and in the temporal domain (Sinex et al 2002).

Third, the patterns of interactions between information channels vary both for acoustic and electric stimuli. In some cases, the best masking frequency (or channel) shifts with the CF(probe site #, ICC depth) as in Figure. 6 and in other cases it is fixed at the probe frequency (or channel) regardless of site CF or channel sensitivity as in Figures 7 & 10. This variation in masking pattern is consistent with at least two possible interpretations. The first is that ICC neurons vary in their masking patterns from animal to animal. The second is that ICC neurons vary systematically in their masking patterns within an animal and that we insert our recording probes into different ICC locations, and consequently into different neuronal populations, in successive experiments. If, for example, ICC neurons varied in their masking patterns along the rostrocaudal dimension of the IC (in the same way that they vary in CF with depth), we might see this variation in successive experiments, despite our best efforts to sample the same ICC regions for experiment to experiment. We try to insert the recording probes into the same location, the center of the ICC, and to the same depth (covering the same range of CFs, 2-32 kHz) in successive experiments. We are convinced that acoustic calibration controls penetration depth within acceptable limits. Nevertheless, we observe clear differences in the patterns of forward masking. However, we estimate that our initial probe insertions procedures allow variations of as much as 500 μm or more along the rostral-to-caudal and medial-to-lateral dimensions of the IC. Therefore, we have recently adopted a stereotaxic approach to probe insertions. We believe that this approach should minimize this variation in probe location. In addition, stereotaxic probe insertions allow us to sample the masking patterns of IC neurons along multiple penetrations at defined rostral-to-caudal and medial-to-lateral locations.

Literature Cited

Biebel UW, Langner G. 2002. Evidence for interactions across frequency channels in the inferior colliculus of awake chinchilla. Hear Res. 2002 Jul;169(1-2):151-68.

Chatterjee, M, Shannon, RV (1998) Forward masked excitation patterns in multielectrode electrical stimulation. J. Acoust. Soc. Am. 103:2565-72.

Chatterjee, M, Fu, QJ, Shannon, RV (1998) Within-channel gap detection using dissimilar markers in auditory prosthesis listeners. J. Acoust. Soc. Am. 103:2515-9.

Chatterjee, M. (1999) Temporal mechanisms underlying recovery from forward masking in multielectrode-implant listeners. J. Acoust.Soc. Am. 105:1853-1863.

Cooper, N.P., Rhode, W.S., 1997. Mechanical responses to two-tone distortion products in the apical and basal turns of the mammalian cochlea. J. Neurophysiol. 78, 261-270.

Hanekom JJ, Shannon RV. (1998) Gap detection as a measure of electrode interaction in auditory prostheses. J. Acoust. Soc. Am. 104:2372-84.

Harris DM, Dallos P. 1980. Forward masking of auditory nerve fiber responses. J. Neurophysiol. 41:1083-1107.

Houtgast, T. 1972. Psychophysical evidence for lateral inhibition in hearing. J. Acoust. Soc. Am. 51: 1885-1894.

Moore, BCJ. 1978. Psychophysical tuning curves measured in simultaneous and forward masking. J. Acoust. Soc. Am. 63:524-532.

Relkin, EM, Smith, RL. 1991. Forward masking of the compound actions potential: thresholds for detection of the N_1 peak. Hear. Res. 53:131-140.

Relkin, EM, Turner, CW. (1988) A reexamination of forward masking in the auditory nerve. J.Acoust. Soc. Am. 84:584-91.

Rhode, W.S., Greenberg, S., 1991. Physiology of the cochlear nuclei. In: Popper, A.N., Fay, R.R. (Eds.), The Mammalian Auditory Pathway, Neurophysiology. Springer, New York, pp. 94-152.

Ruggero, M.A., Rich, N.C., Recio, A., Narayan, S.S., Robles, L., 1997. Basilar-membrane responses to tones at the base of the chinchilla cochlea. J. Acoust. Soc. Am. 101, 2151-2163.

Sachs MB, Kiang NY. 1968. Two-tone inhibition in auditory-nerve fibers. J Acoust Soc Am. 43(5):1120-8

Shannon, RV (1983) Multi-channel electrical stimulation of the auditory nerve in man. I. Basic psychophysics. Hear. Res. 11:157-189.

Shannon, RV. (1990) Forward masking in patients with auditory prostheses. J. Acoust. Soc. Am. 88:741-744.

Shannon, RV. (1991) Temporal modulation transfer functions in patients with auditory prostheses, J.Acoust. Soc.Am, 91:1974-1982

Shore SE. 1998. Recovery of forward-masked responses in ventral cochlear nucleus neurons. Hear Res. 82:31-43.

Sinex DG, Henderson J, Li H, Chen GD. 2002a. Responses of chinchilla inferior colliculus neurons to amplitude-modulated tones with different envelopes. Assoc Res Otolaryngol. 3(4):390-402.

Sinex DG, Sabes JH, Li H. 2002b. Responses of inferior colliculus neurons to harmonic and mistuned complex tones. Hear Res. 168(1-2):150-62.

Sinex DG, Guzik H, Li H, Henderson Sabes J. 2003. Responses of auditory nerve fibers to harmonic and mistuned complex tones. Hear Res. 182(1-2):130-9

Smith, RL (1977) Short term adaptation in single auditory nerve fibers: some post-stimulatory effects. J Neurophysiol. 40:1098-1112.

Smith, RL. (1979) Adaptation, saturation and physiological masking in single auditory-nerve fibers. J. Acoust. Soc. Am. 65, 166–178.

Smith, RL, Brachman, ML. (1982) Adaptation in auditory-nerve fibers: a revised model. Biol. Cybern. 44:207-120.

Turner CW, Relkin EM, Doucet J. 1994. Psychophysical and physiological forward masking studies: probe duration and rise-time effects. J Acoust Soc Am. 96:795-800

Work Planned for the Next Quarter

1) We plan to continue to examine the forward masking patterns of IC neurons using both acoustic and electric stimuli in order to increase our sample statistics.

2) We plan to examine the effects of various electrode configurations and stimulus waveforms on the spread and location of excitation. Preliminary studies suggest that small adjustments in electrode configuration and/or changes in stimulus waveform (small changes of waveform from equal phase-duration biphasic waveforms to asymmetric biphasic (pseudomonopolar) waveforms 1) can change the spread of excitation an produced more selective excitation patterns, 2) can lower the minimum threshold at with a give electrode pair produces excitation, and 3) can adjust the location (frequency) of the minimum threshold and center of gravity of the excitation pattern evoked by a given pair of electrodes.

3) We plan to begin to examine the effects of the simultaneous presentation of acoustic and electric stimuli on the response patterns in the IC.

4) We plan to implement stereotaxic procedures for the insertion of the recording probes. This includes devising a way to connect our speakers and their connecting tubes to the stereotaxic earbars

5) We plan to attempt to record electrically evoked compound action potentials (ECAPs) using one or more of the unstimulated sites of our intracochlear electrode. Recording such ECAPs would allow us to estimate the spread of excitation of stimulation in our guinea pigs in a manner that is comparable to similar measurements conducted in CI users. Recording these ECAPs requires building or acquiring a fast recovery amplifier -- one that can recover from the electrical artifact in time to capture the ECAP.