6th Quarterly Progress Report

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

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Abstract

This Quarterly Progress Report presents our progress in the 6th quarter of this contract. In this period we prepared and presented a poster describing our preliminary current steering and forward masking results at the Midwinter ARO meeting held in Daytona Beach Florida. We have also conducted 4 additional experiments on simultaneous and forward masking using electrical pulses in guinea pigs. In this progress report we describe the acoustic forward masking data as a prelude to the electrical data. We would like to emphasize that these two sets of data are not only unusual (one might even say unique) but also reinforce one another. In these experiments we recorded the responses using the multichannel silicon probes and using high impedance tungsten microelectrodes.

We have also made modifications and extensions to our software which controls our experiments, performs the data acquisition, and does the data analysis. Major changes include:

- adding control of isolated switch modules for multiple channel configurations during a single experimental electrical stimulation run.
- adding capability to interleave multiple probes and/or maskers in a single two-tone acoustic run.
- adding capability to acquire and analyze data from a variable number of electrodes (this was previously fixed at 16).
- adding the ability to subtract spontaneous activity from the displays and adding an Poisson model for spike activity to the analysis/display software to indicate statistical significance of spike count changes.
- creating a utility to correlate spike activity detected on separate channels to determine the level of common activity recorded.

Additional less significant functional changes include:

- updating all files to use a numerical array, channelMap, (rather than a character array).
- modifying all files to use a common routine to open data files; this routine has the ability to look for file names with different formats.
- saving the stimulus matrix file, StimMat, to a Setup file. This Setup file is saved as a Matlab file, which provides more significant digits than the text format file which was previously used to save the stimulus matrix (the added digits are needed for switch channel encoding).
- clearing the Setup variables before each run so that saved information does not included data from previous run(s).

INTRODUCTION:

Contemporary auditory prostheses (APs) are multichannel devices that employ multi-contact intracochlear electrodes to activate the auditory nerve in deaf human subjects. The use of these electrodes is predicated upon the assumption that activation of different contacts in monopolar mode (or pairs of contacts in bipolar mode) at a different locations along the cochlear spiral represent at least partially independent channels of auditory information passing from the external world into the central auditory system of the AP user. However, there is little physiological data available to support this assumption. In these experiments, we examine the spread of activity that individual AP channels evoke in animals as a function of intensity. We describe some spatiotemporal interactions between AP channels, when two or more of them are activated either simultaneously or sequentially.

In these experiments we determine the spatial spread of activation when an AP channel is activated alone and when two-channels are activated sequentially in a forward masking paradigm (masker channel activation followed by probe channel activation). The interactions are indicated by the differences in magnitude and spread of probe evoked activity across the tonotopic organization of the central nucleus of the inferior colliculus (ICC) with and without the preceding masker.

We are conducting these electrical interaction studies in conjunction with acoustic interactions studies using two acoustic tones. We can find no published studies of acoustic forward masking in the ICC and such studies are necessary as a basis of comparison with the AP channel interaction results. Therefore, we have conducted a series of two-tone acoustic experiments, which are designed to mimic two-channel electrical stimulation.

We have chosen to begin our acoustic and electric interaction studies by using a forward masking paradigm. Forward masking was chosen because it avoids two-tone suppression interactions with acoustic stimulation and current summation with electrical stimulation. In our acoustic masking experiments, we have chosen to use pure tones as maskers and probes, since they are the simplest and most selective of all acoustic signals. In our electrical masking experiments, we have employed electrode configurations and stimulation procedures that are as spatially (spectrally) selective as possible in order to make the activity they evoke as comparable as possible to that evoked by pure tones.

In the auditory nerve of normal hearing listeners, the spectral and temporal interactions that occur between two simultaneously presented acoustic signals have been well described. The magnitudes of these interactions are determined by two physiological mechanisms: two-tone suppression (Sachs and Kiang, 1968; Arthur et al, 1971) and adaptation (Harris and Dallos, 1979; Smith, 1977). When the two tones are sequentially presented in a forward masking paradigm, suppression is eliminated as a mechanism of interaction and adaptation accounts for all, or almost all of the interactions of the two tones. This greatly simplifies the interpretation of these interactions..

In the central auditory system, however, inhibitory synaptic mechanisms are concatenated with the peripheral mechanisms of suppression and adaptation. These inhibitory mechanisms greatly complicate both the spectral and temporal consequences of the acoustic interactions. Thus, acoustic interactions in the central auditory system have proven to be more complex than those in the periphery (see Shore, 1995, Calford and Semple, 1995, Brosch and Schreiner, 1997, Sinex et al, 2003a,b; 2003). As we shall demonstrate, some of our ICC forward masking results are dramatically different from those that have been described in the auditory nerve. The frequency/intensity combinations of masker tones producing reduction of

the probe response were often different from those that evoked the strongest masker response and produced the greatest post-masker reduction in spontaneous activity. Therefore, they cannot be explained simply by adaptation.

METHODS:

All procedures were carried out under an approved protocol. Guinea pigs were pre-anesthetized by an IM injection of ketamine/xylazine (4:1). Further IM injections of ketamine/xylazine were used to maintain an areflexic state of anesthesia. The head was shaved and EKG silver wire recording leads were inserted subcutaneously. Another silver wire inserted below the skin in the nape of the neck and served as a recording ground. A rectal probe and temperature-controlled water blanket were used to maintain normal core body temperature. EKG rate and respiratory rate were monitored throughout surgery and during the subsequent experiment. A tube was inserted into the trachea to maintain a patent airway. The scalp was incised down the midline and the tissue overlying the bone was retracted. Two or three bone screws were inserted into the top of the skull and covered with dental acrylic. A large bolt for holding and stabilizing head was fixed to the skull between the screws with more dental acrylic. The bolt was secured in a flexible arm (Noga). The scalp behind each ear was incised and reflected to expose both ear canals. The right tympanic membrane was perforated, the right middle ear bones were disarticulated and the right ear canal was filled with dental acrylic. This effectively deafened the right ear. In addition, in some cases, the right cochlear was destroyed in addition using a dental burr after the middle ear bones were disarticulated.

The temporalis muscle on the right side was reflected and the calvarium exposed. The parietal bone anterior to the transverse sinus was thinned with a dental burr and small rongeur was used to remove the bone and expose the dura overlying the right occipital cortex. A silver wire was inserted between the parietal bone and the dura and fixed in place to serve as a reference for recording probes or tungsten microelectrodes. The dura was excised and a hole in the lateral occipital cortex posterior the posterior horn of the lateral ventricle was aspirated to expose the lateral surface of the inferior colliculus.

Sound stimuli were digitally generated (TDT System III), amplified (Samson) and presented by a super-tweeter (Radio Shack) attached to a custom ear bar that was inserted into the left ear canal. Sound levels were calibrated using a probe microphone (B&K ½”microphone, model 4182) placed through the ear bar near the tympanic membrane. The calibrated acoustic signal was adjusted so that tone transfer function at the ear canal was flat within +/- 2dB over the range between 2 kHz and 41.5 kHz. For multi-channel recording, 16-channel single-shank silicon recording probes (CNCT University of Michigan) were used. The probes had iridium-coated recording sites spaced linearly at 100 micron increments. Prior to insertion, probe sites were immersed in distilled water cleaned by passing anodic and cathodic current through each site until obvious bubbles of hydrolized oxygen or hydrogen appeared. After cleaning, site impedances were typically 300 kOhms. The recording probes were inserted into a custom-built headstage, which was held by a micromanipulator. Using the micromanipulator, the probes were inserted into the IC along a standard trajectory that was in the coronal plane at an angle of 45 º off the sagittal. While the probe was being inserted, response areas were recorded from each recording site by presenting tone bursts over a range of frequencies and intensities. The probe penetration depth was adjusted until probe-site CFs spanned a range from approximately 3 kHz to 25 kHz and the CFs were arrayed monotonically from low frequencies superficially to high frequencies deep in the ICC. This effectively

calibrated the recording probes and ensured that recordings were made from the central nucleus rather than the external nucleus, since the tonotopic gradient reverses at the boundary between these two structures.

To stabilize the calibrated recording probes, a 1% solution of warm liquid agarose was injected into the space formerly occupied by the occipital cortex to cover the exposed nervous tissue. The agarose was allowed to solidify and then the dorsal surface of the agarose, the bone of the calvarium and the distal portion of the probe PC board was covered with dental acrylic. When the acrylic polymerized, the opening in the skull was effectively sealed and the probe was fixed in place. Once the recording probe was fixed in place, it could be removed from its head stage and animal could be freely manipulated.

For recording, the neural signals from the recording probes were passed through a headstage, amplified using a custom-built preamplifier and post-amplifier and bandpass filtered (100 – 6000 Hz). The amplified and filtered signals were digitized and sampled at 20 S/sec/channel (National Instruments, model 6071E). Experiment control, stimulus generation, data acquisition, data analysis and display were carried out using custom software (LabView/Matlab).

For single-unit recording, tungsten electrodes were used. After exposure of the IC (as described above), the IC was covered with a thin layer of 1% agarose to stabilize the IC before recording electrodes were inserted. For these recordings, the electrode was inserted into the IC using a hydraulic microdrive (Kopf) mounted on a micromanipulator. Battery-powered amplifiers (DAM50, WPI) amplified neural signals 10,000x and bandpass filtered them with a bandwidth 300 – 3000 Hz. Sound stimuli were presented either in the free field using an un-mounted super-tweeter (Radio-Shack) speaker or in the closed field (using the ear bars described above). Stimuli consisted of short pure-tone bursts with 2 ms rise/fall times. For determination of frequency response areas (FRAs), 50 ms tones were varied in frequency from 2 to 41.5 kHz in 1/8th octave steps and varied in level across a range of 70 – 80 dB in 5 dB steps. For determination of masked tuning curves, the stimuli usually consisted a variable masking tone followed by a fixed probe tone. The masking tone was varied over the same frequency and level range as that used to record the response areas, The probe tone frequency and intensity was chosen to lie within the response area of as many recording sites as possible, but generally it lay within the response areas of four sites. The probe duration was between 15 and 50 ms. The masking tone duration, except as noted, was 50 ms. Probe tones were presented at 30-50 dB SPL. This level could be as much as 40 dB above the threshold or below threshold for the probe, depending upon the CF of the site.

Data Analysis: For multi-unit activity recorded with 16 channel probes, spike times were determined in real time as threshold-crossing times using custom software. A neuronal waveform was required to cross and then return across a threshold voltage within a preset amount of time (usually 0.4 ms) in order to be counted as a spike. This prevented slow evoked or volume conducted potentials from being counted as a spike. Thresholds for each electrode were determined independently by computing the RMS amplitude of a 90 ms sample of spontaneous activity on each electrode immediately prior to recording a response area, then multiplying that value by a constant (usually between 2.5 and 3.5 RMS). In most, but not all, cases, activity recorded on electrodes on the multi-channel probes were clearly multi-unit, and could not be resolved by spike sorting into single units. For single-unit activity recorded either with the multi-channel probes or with high-impedance tungsten electrodes, a similar procedure was followed. For these recordings, we observed what appeared to be spike activity from a

single neuron that was far above the RMS background level. Similar means were used to identify spike times for these recordings.

RESULTS:

Although results of these acoustic and electrical forward masking studies re-reinforce each other, they are sufficiently unusual that they need a somewhat elaborate description. Therefore, in this initial report on our forward masking studies of channel interaction, we will present a summary of the results using acoustic signals in normal animals. In the next progress report we will summarize the forward masking results using electrical channels as masker and probe.

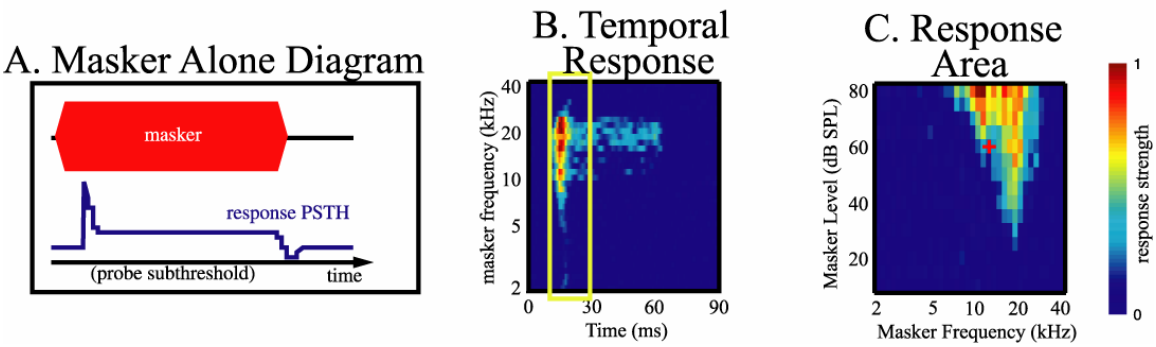

Figure 1. Illustration of recordings from a single multichannel recording probe site when only masking tones at a single intensity, e.g., 50 dB SPL, are presented. A, This diagram illustrates the experimental paradigm with masking tone envelope represented as beginning at time = zero. The tone remains on for 60 ms. An idealized temporal response is shown as post-stimulus time histogram (PSTH) below. B, The actual recorded temporal responses from neurons at this site stimulated with masker tones at 35 frequencies ranging from 2 to 42 kHz. The neurons at this site are tuned to 19 kHz. All the tones are presented at 60 dB SPL. Each row of colored facets represents the responses to one frequency as a function of time. The amplitudes of the responses, the number of spikes summed over each successive 2 ms interval, are scaled relative to the maximum response and color coded (dark red equals the maximum or one; dark blue equal zero). The yellow box indicates the analysis window used to construct the frequency response area in "C". C. A frequency response area (FRA) for the neurons recorded from this probe site. . The minimum threshold is approximately 30 dB SPL. Each facet represents the scaled and color-coded response amplitude evoked by a single tone-frequency/tone-level combination.

We will begin this report by describing the general stimulus paradigm and the procedures used to analyze the responses. Figure 1A illustrates a diagram of the stimulus envelope and response time course of a typical, isolated ICC neuron that responds with a sustained response when it is stimulated with a single tone without any probe stimulus. The neuron responds to the tone after a latency of 7-15 ms with an onset burst of discharges, which decreased to a steady-state response. The steady state response drops below spontaneous activity when the tone is turned off and the spontaneous activity slowly recovers 10 – 50 ms later. Figure 1B illustrates the actual temporal responses of IC neurons recorded at one probe site with a multi-channel silicon probe. The stimulus is a series of tones presented at a constant intensity (50 dB SPL). The tone frequencies are changed in $1/8^{th}$ octave steps from 2 to 42 kHz. These responses are typical of multineuronal cluster recordings made with the silicon probes. The neurons show a sustained response to tone frequencies at and near the CF of the site and display an onset only response to tone frequencies some distant from the CF. At

frequencies even further from CF the neurons show no response at all even at relative high stimulus levels. From the amplitude responses and the relative short latency of the response one can estimate that the neurons at this site are tuned to frequencies near 20 kHz. Figure 1C illustrates a typical frequency response area (FRA) recorded from clusters of neurons at the same probe site as 1B. This response area illustrates that the neurons are indeed tuned to 19 kHz and have a minimum threshold of approximately 30 dB SPL. The responses illustrated in Figure 1 are typical of responses to forward masking tones, i.e., we have seen no evidence of backward masking.

In Figure 2, the stimulus paradigm and responses of typical ICC neurons to a probe tone when the masking tone is below threshold (or when no masking tone is present) are presented. Typically, the probe tone is relative brief (usually 20 ms in duration) and is presented late in the recording cycle. Since there in no masker present in these responses and since the probe tone does not vary in frequency or level both the temporal response and the masked response area (MRA) are relatively uniform. These responses are presented as a basis for comparison with responses illustrated in Figure 3 and subsequent figures when masking tones are present.

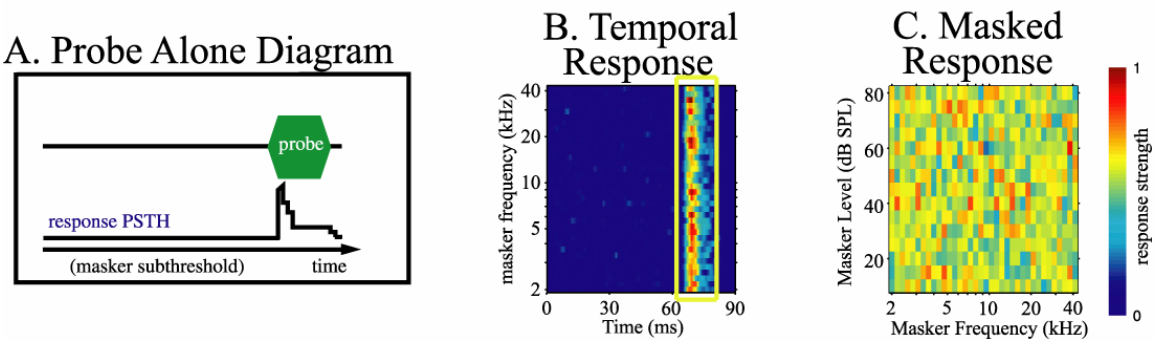

Figure 2. Illustration recordings from a single multi-channel recording probe site when a 19 kHz probe tone is presented at 50 dB and the masking tones are presented at 0 dB, i.e., below threshold. A, This diagram illustrates the stimulus paradigm; the 20 ms probe tone is turned at time = 60 ms. An idealized temporal response shown as post-stimulus time histogram (PSTH) is shown below. B. The actual temporal responses of neurons stimulated with probe tone when all 34 masking tones are presented below threshold. As in figure 1, the masker frequencies varied between 2 and 42 kHz, but since the masking tones are all below threshold, the evoke no response. Each row of colored facets represents responses to the probe tone as a function of time. The continuous vertical column indicates that there is no effect of the subthreshold masking tones, as expected. C. The masked-response area (MRA) of neurons recorded at this site. Since the masker tones were omitted this masked FRA illustrates the response to the probe tone *if there were no forward masking*. This response area should be compared to that shown in the upper.panel of Figure 3C, where significant forward masking is illustrated. Spike counts have been summed over the temporal analysis window indicated by the yellow box in B. Each facet represents the amplitude of the probe response presented by itself. The color variations in these facets, therefore, indicate the variation in the amplitude on the unmasked probe response.

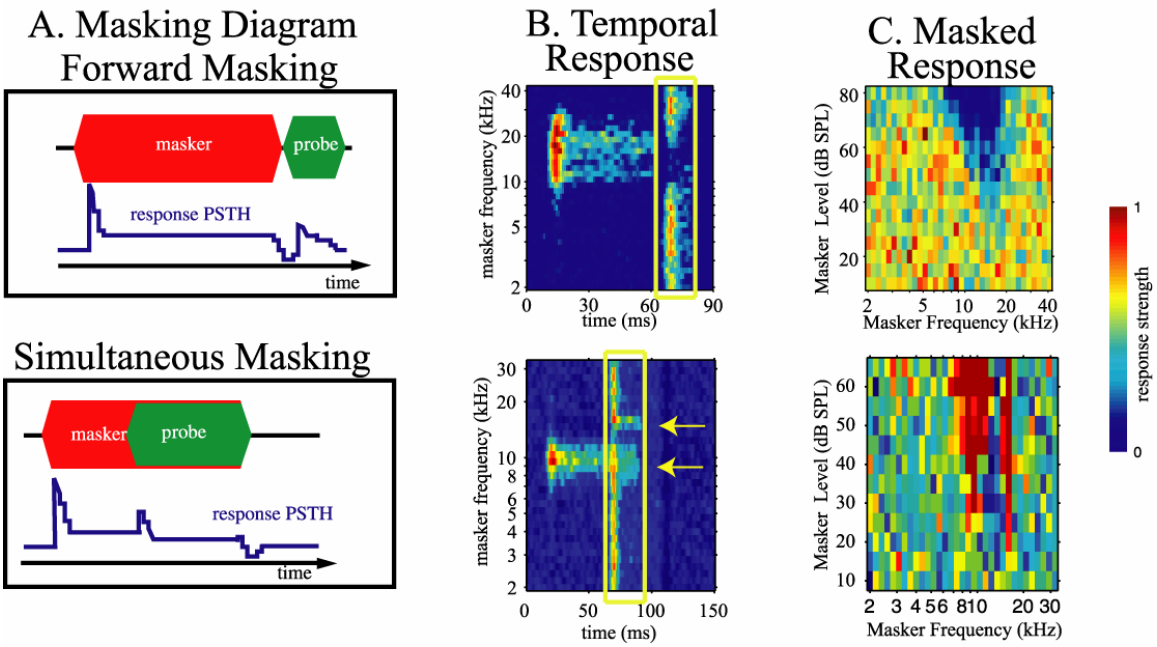

Figure 3. Illustration recordings from two multi-channel recording sites (upper and lower row of panels) of the same 16-channel recording probe illustrated in the previous two figures. The ICC neurons are stimulated with both masker tones and a probe tone in a forward masking paradigm (upper row) and a simultaneous masking paradigm (lower row). A. Diagrams of the stimulus paradigms. The masking tones are turned on with a 2 ms on-ramp at time = 10 ms. In the forward masking paradigm, the masking tones remain on for 60 ms and are ramped off. The masking tones are followed immediately by a 20 ms probe. In the simultaneous masking paradigm, the masking tone is ramped on at 10 ms; they remain on for 80 ms and are ramped off. A 30 ms probe tone is ramped on at 50 ms and ramped off at 80 ms, coincident with the masking tone offset. In each diagram, idealized temporal responses are illustrated as post-stimulus time histograms (PSTHs) at the bottom of the diagram. B. The actual temporal responses of neurons stimulated with a fixed level and frequency (50 dB, 16 kHz) probe tone. In the upper panel, the neurons, which are tuned to 19 kHz, are **forward** masked using tones between 2 and 42 kHz at 60 dB SPL. In the lower panel, the neurons, which were recorded from another recording site and tuned to 10 kHz, are **simultaneously** masked using tones between 2 and 32 kHz. The probe tone in this case is a 12 kHz tone at 50 dB SPL. Note the enhanced response of these neurons when they are stimulated by the probe tone and the "masker" tones at some frequencies (yellow arrows). C. The masked-response areas evoked using the forward masking and simultaneous masking paradigms diagramed in A. These masked-response areas summarize the responses to fixed frequency and level probe tones when they are forward masked (upper panel) or simultaneously masked (lower panel) by a variable frequency and level masking tones. Spike counts for these panels have been summed over the temporal analysis windows indicated by the yellow box in B.

In Figure 3, the stimulus paradigm for forward and simultaneous masking are presented in addition to the ICC neuronal responses typically evoked in these paradigms. The upper panel in Figure 3A diagrams the forward masking paradigm used in our studies and illustrates the typical temporal response or post-stimulus time histogram that is expected from such stimulation when the neurons respond to both the masker and the probe tones. The lower panel of Figure 3A diagrams the simultaneous masking paradigm and the expected PSTH of the

response to this stimulus complex. In Figure 3B the temporal response patterns evoked by presentation of a series of masker tones at one stimulus level (followed by a single probe tone are illustrated. The response to the masking tone looks very similar to the response to the tones seen in Figure 1B, but the response to the probe tone is interrupted (or reduced) at certain masker frequencies in both the forward masking and simultaneous masking paradigms. In addition to reducing the probe response, in the simultaneous masking paradigm, the responses to the probe tone can be enhanced (yellow arrows) at some masker frequencies. The dependence of the response to the probe tone as a function of the masker frequency and level is illustrated for the two masking paradigms in Figure 3C. In the upper panel of Figure 3C, the forward masked-response area for the same neurons illustrated in Figure 1A is shown. The reduction in the probe response produced by the masker is clearly indicated by the blue region in the center of the masker-response area. In this case, the probe tone frequency approximates the CF of the neurons at this site and this masked-response area (MRA) is a negative image of the FRA for the same neurons (see Figure 1C). Although this is the expected result, this does not occur uniformly in ICC neurons, as we shall see later. In the lower panel of Figure 3C, a simultaneous masked-response area is shown. There is a narrow blue region centered at 11 or 12 kHz where the probe response is reduced or masked by the masker. This region is flanked by two red regions where the masker enhances the probe response. This relatively complicated simultaneous masking behavior is one reason why we have delayed our examination of simultaneous masking until after exploring the effects of forward masking.

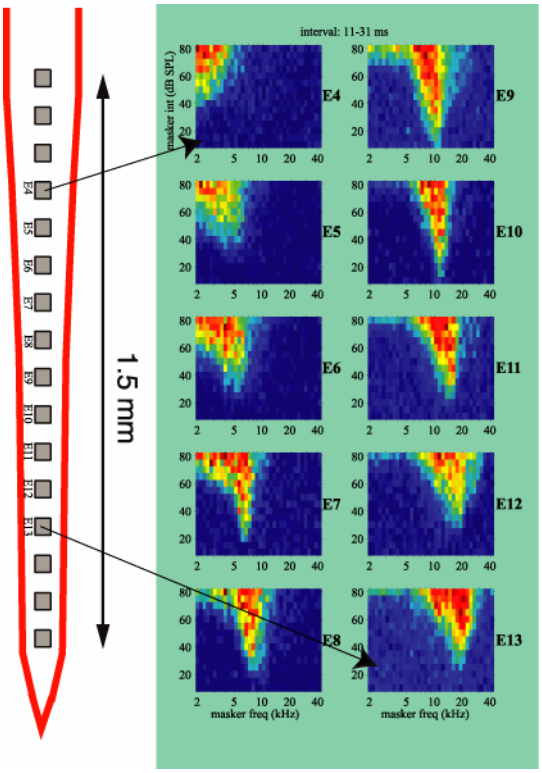

Figure 4. Illustration of the frequency response areas (FRAs) recorded from the 10 probes sites illustrated in Figure 4. The analysis window used to construct these FRAs is indicated by the yellow box in Figure 4. These FRAs summarize the responses to forward masking tones. The tones varied in frequency from 2 to 42 kHz and were presented at levels that ranged from 10 to 80 dB SPL. GP46_4.

In these experiments, we are using multi-channel recording probes. These probes allow us to examine the responses of 16 ICC locations simultaneously while the neurons are being stimulated.. In Figure 4, FRAs evoked by the forward masking tones at 10 probe locations (#4 - #13) are illustrated. The CFs of the neurons at these locations vary systematically with location. Neurons at superficial locations are tuned to relatively low frequencies. For example in Figure 4, the neurons at site E4, the most superficial site are tuned to approximately 3 kHz. In contrast, the neurons at site E13 (the deepest site) are tuned to approximately 20 kHz. The minimum threshold for these sites varies from approximately 40 dB SPL (E4) to approximately 10 dB SPL (E9).

The temporal response patterns of neurons at these locations are illustrated in Figure 5. These patterns illustrate the response to masking and probe tones in a forward masking paradigm like that diagramed in Figure 3A. The activity pattern evoked by the variable frequency but constant intensity masking tones varies with the neurons' CF. Neurons located at sites tuned to low frequencies (e.g., E4) respond strongly to relatively low frequency (below 5 kHz) masking tones, whereas they response poorly or not at all to masking tones above 10 kHz. Conversely, neurons at sites tuned to high frequencies (e.g., E14) respond poorly to low frequency masking tones and strongly to high frequency tones. Thus there is masker evoked activity at all 10 sites but frequency location of the activity varies systematically among the sites. Likewise, the activity pattern evoked by the fixed frequency and level (16 kHz, 50 dB SPL) probe tone varies from site to site. It evokes little or no activity at sites tuned to low frequency (E4, 5, 6 & 7), but evokes strong activity at higher frequency sites (E10, 11 &12). Nevertheless,

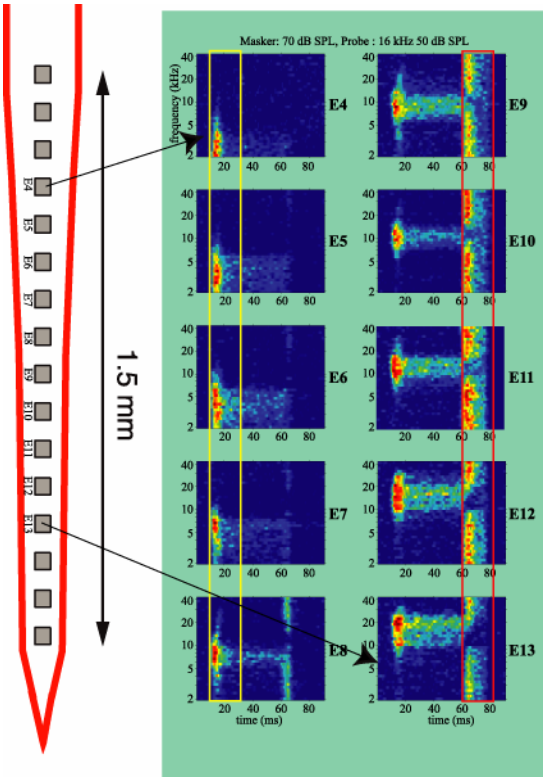

Figure 5. Illustration of the temporal responses of ICC neurons evoked by forward masking tone and probe tones. These responses were recorded simultaneously from 10 multi-channel-recording-probe sites. The locations of the sites are indicated in the diagram of the probe shank at the far left. The masker tones, which varies in frequency from 2 to 42 kHz, were presented at 70 dB SPL. The 12 kHz probe tone was presented at 60 dB SPL for 15ms. The yellow and red boxes indicate the temporal analysis windows used to calculate the frequency response areas (Figure 4) and the masked response areas (Figure 6). GP46_4

strong masking effects (i.e., reduction in the response to the probe) can be seen at all the sites except that tuned to the lowest frequencies, E4. Significantly, the masking effects are centered on approximately the same masker frequencies regardless of the CF of the site. Moreover, probe masking occurs whether or not there is a sustained response (or any response) to the masking tone. Thus the magnitude of the masking effects appear to be only weakly related to the magnitude of the activity evoked by either the masking tone or the probe tone.

The masking effect magnitude is related, however, to the intensity of the masker. This relationship is illustrated in Figure 6. This figure illustrates the masked response areas for the 10 sites shown in Figures 4 & 5. In this figure the magnitude of the probe response is plotted as a function of the masking tone frequency and level. If there were no effect of the masking tones, these response areas would all look like the one illustrated in Figure 2C. If there were forward masking effects comparable to those seen in the auditory nerve, these masked response areas would look like negative image of the FRAs illustrated in Figure 4. They would have blue areas of reduced excitation on orange to red backgrounds and *the reduced response regions at each site would be tuned to a different frequency, and that frequency would correspond to the CF at that site*. Instead, the areas of reduced activity are tuned to nearly the same frequencies at all 10 sites. Although the unusual result is not always seen, it is commonly seen and, as we will document in the next progress report, it is seen after forward masking of electrically evoked responses.

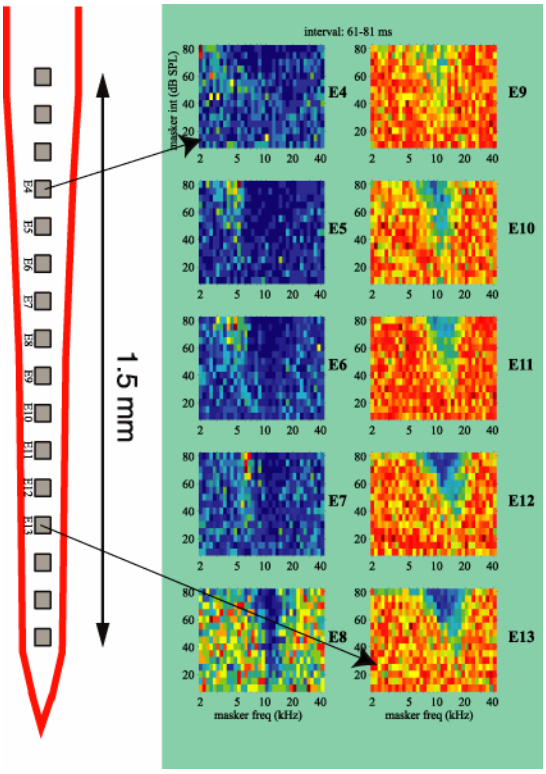

Figure 6. Forward masked response areas of neurons recorded at the same 10 sites as illustrated in the previous two figures. These masked FRAs summarize the masking effects that the variable frequency/level masking tones have on the fixed frequency/level probe tone (12 kHz at 60dB). The masking tones vary in frequency from 2 to 42 kHz and level from 10 to 80 dB SPL. Spike counts for these panels have been summed over the temporal analysis windows indicated by the red box in Figure 5.
GP46_4

Meanwhile, we will examine this phenomenon with acoustic stimulation in more detail. In Figure 7, a series of response areas from another animal are presented. In this illustration, the response areas were constructed for 3 probe sites (horizontal rows) using 4 time windows (vertical columns). The probe sites (E1, E5 and E10) represent sites tuned to frequencies well below the probe frequency , E1, to sites tuned to frequencies well above the probe frequency, E10. Using the first time window, the recording at each site is centered on the onset response to the masking-tone. Using the second time window, the recording is centered near the end of the masking tone steady state response. Just as is seen in the previous figure, the onset response is more broadly tuned than the steady-state response. The third window straddles the masking tone offset and the probe tone onset responses. In two of these FRAs (E1 & E5) a remnant of the master response can be seen in conjunction with the reduction of the probe response. The final window is centered on the probe onset response and excluding the masking tone offset. In these FRAs only the region of response reduction can be seen. It should be noted that these areas of reduction are tuned, that their tuning width is different from the masking tone excitatory response and that their best masker frequency is the same for all three sites and is approximately equal to the equal probe frequency. Thus the region of probe-response reduction incompletely overlaps the region of masker excitation. This indicates that the FRAs must be composed of multiple frequency specific channels.

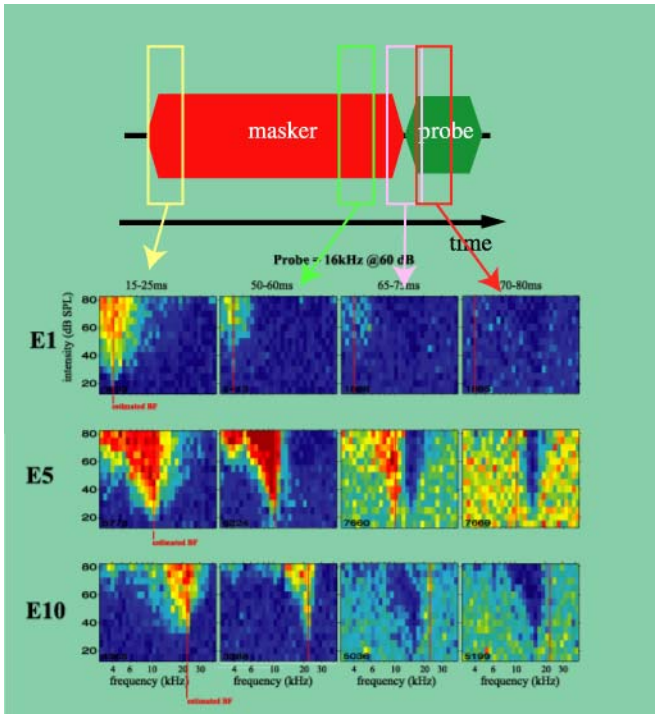

Figure 7. Frequency response areas illustrating the response areas at 3 recording-probe sites (E1, E5 and E10) constructed using four different 10 ms time windows during a single forward masking sequence. The neurons at these sites were stimulated with the same forward masking tones , which ranged in frequency from 3 – 38 kHz and varied in level from 10 – 80 dB SPL. The probe tone was held constant at 15 kHz @ 45 dB SPL. The analysis windows are indicated by the colored rectangles in the diagram at the top. The vertical red line in each panel indicates the estimated CF of the neurons at each probe site. Note that the area of probe response reduction is greatly above (E1), just above (E5) and just below the CF estimated from the response to the masking tone at successively deeper sites. GP24_7

In addition to examining these normalized responses, we have quantified the results of these masking experiments in absolute terms. In Figure 8A, for example, absolute discharges rates recorded at each of the sites illustrated in Figures 4 – 6 are plotted as a function of masker frequency for 70 dB SPL masking tones. The peak in each of these iso-intensity functions

shifts to higher frequencies as the recording locations moves deeper in the ICC. This shift matches the progressive shift CF (the blue vertical line) that was estimated from the FRAs illustrated in Figure 4. In Figure 8B, the absolutes discharges rates evoked at each recording site by the 12 kHz, 45 dB SPL probe tone is plotted as a function of the forward masking tone frequency. The frequency of the probe tone is indicated by the vertical red line in each plot. Two features of these masking plots should be noted. First, the probe evoked discharge rates increase progressively from E1 to E6 as the CF of the neurons at these locations approaches the 12 kHz probe frequency. At deeper locations (E7 – 10) the overall discharge rate declines as the CF of these neurons progresses above the probe frequency (vertical red line). Second, the magnitude of the reduction in probe response increases as the site CF increases. Third, the masking tone frequency at which maximum reduction was produced varies little from site to site. It more closely approximates the probe frequency than site CF. Thus CF shifts to the left from E4 –E10 (A), while maximum masking remains relatively fixed (B).

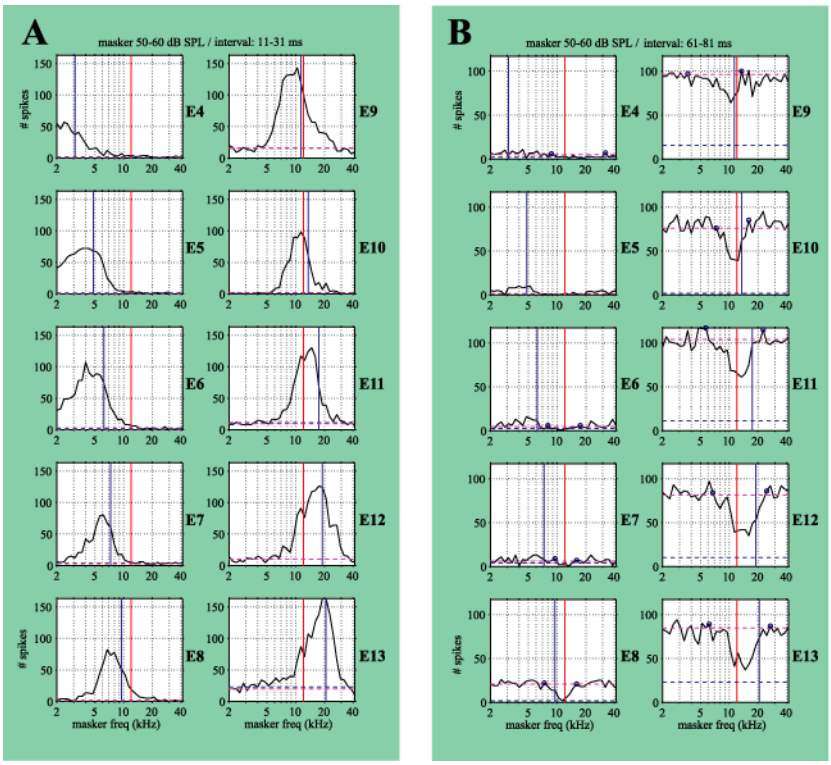

Figure 8. A. Iso-intensity contours for masking tone frequencies. Evoked discharge rate as a function of masker frequency measured during the forward masking tone onset (A, left) and during the probe tone onset (B, right). Each panel in A and B represents the discharge rate at 10 recording sites measured as a function of the masking tone frequency. The solid blue lines indicate the CF estimated for each site based on the FRAs evoked by the masking tone. The vertical red lines indicate the fixed probe frequency, 12 kHz. The dashed blue lines indicate the spontaneous discharge rate. The magenta lines indicate the expected response rate to the probe tone without the masking tones

The results illustrated so far were recorded using a probe tone that immediately followed the masking tones, i.e., with zero time delay between them. In an additional series of experiments, we have examined the time course of recovery from forward masking by introducing a time delay (Δt) between the offset of a masking tone at the most effective frequency and the onset of the probe tone. This paradigm is shown in the diagram at the top of Figure 9. In Figure 9A - F, the difference in masked and unmasked discharge rates in response to the probe tone are plotted as a function of masking tone intensity. In each panel, each masking function represents the reduction in probe response amplitude as a function of masking tone intensity at a different recording site. Thus parameter in each panel is recording site location. The plots in different panels illustrate the effects of different probe delays (increasing from A - F) on these masking functions. These plots illustrates that the effects of the forward masking tone increases monotonically with masker intensity and that these effects have dramatically within 30 ms of the offset of the masking tone, but is still present at this time.

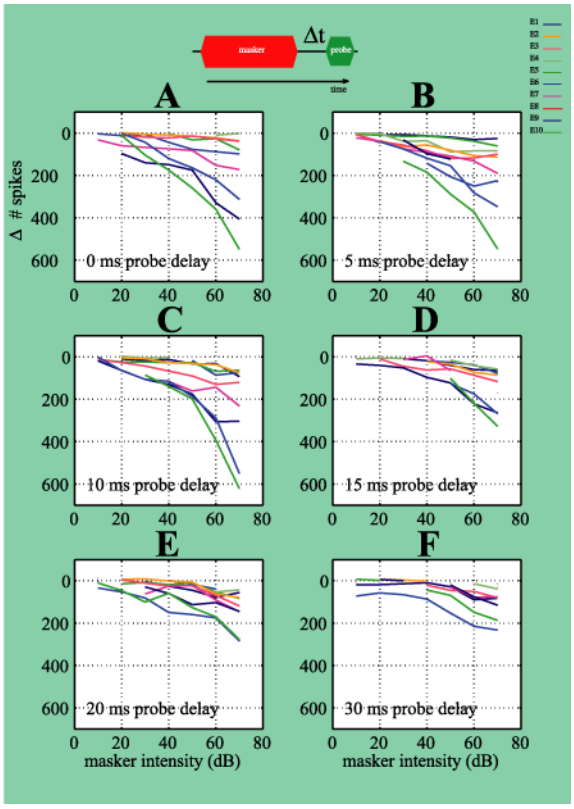

Figure 9. Masking functions, difference in probe-evoked discharge rates (masked – unmasked) as a function of masking tone intensity, recorded at each of the 10 sites illustrated in Figure 8. Each panel illustrates the masking functions for these sites at one probe delay (Δt in diagram at the top) between the offset of the masking tone and the onset of the probe tone. The changes in the recovery functions as Δt increases (A – F, upper left to lower right) illustrate the time-course of recovery of the probe response from the most effective forward masking tone.

Finally, the data that has been so far consists of multi-unit data recorded from multichannel silicon recording probes. No similar data has ever been reported. Therefore, we were concerned that our results might be an artifact of our recording techniques. To test whether this might be the case, we have conducted a series of experiments recording the forward masked responses of well isolated single neurons in the ICC using high impedance tungsten microelectrodes. An example of the results of these experiments is illustrated in

Figure 10. This figure illustrates the responses of one neuron's responses to a series of forward masking tones and three probe tones. The CF of this neuron is approximately 5 kHz. The probe tone frequencies vary from above this neuron's CF (Top row, 6.5 kHz), at its CF (middle row, 5 kHz) and below it CF (bottom row, 3.5 kHz). The left column of panels illustrate this neuron's temporal response patterns to a series fixed intensity masking tones the frequencies of which vary from 2 to 20 kHz. In these temporal responses the masking tone intensities are fixed at 70 dB SPL. These temporal response patterns indicate that this neuron is an onset neuron and responds with only an onset burst of discharges at all tone frequencies. This onset response can be seen at 15 – 20 ms in all three panels. The responses to all three probe tones are also onset responses and occur at approximately 70 ms. Clear gaps in the probe responses can be seen in all three panels, but the gaps are centered at progressively lower masker frequencies as the probe tone frequencies are decreased from 6.5 to 3.5 kHz.

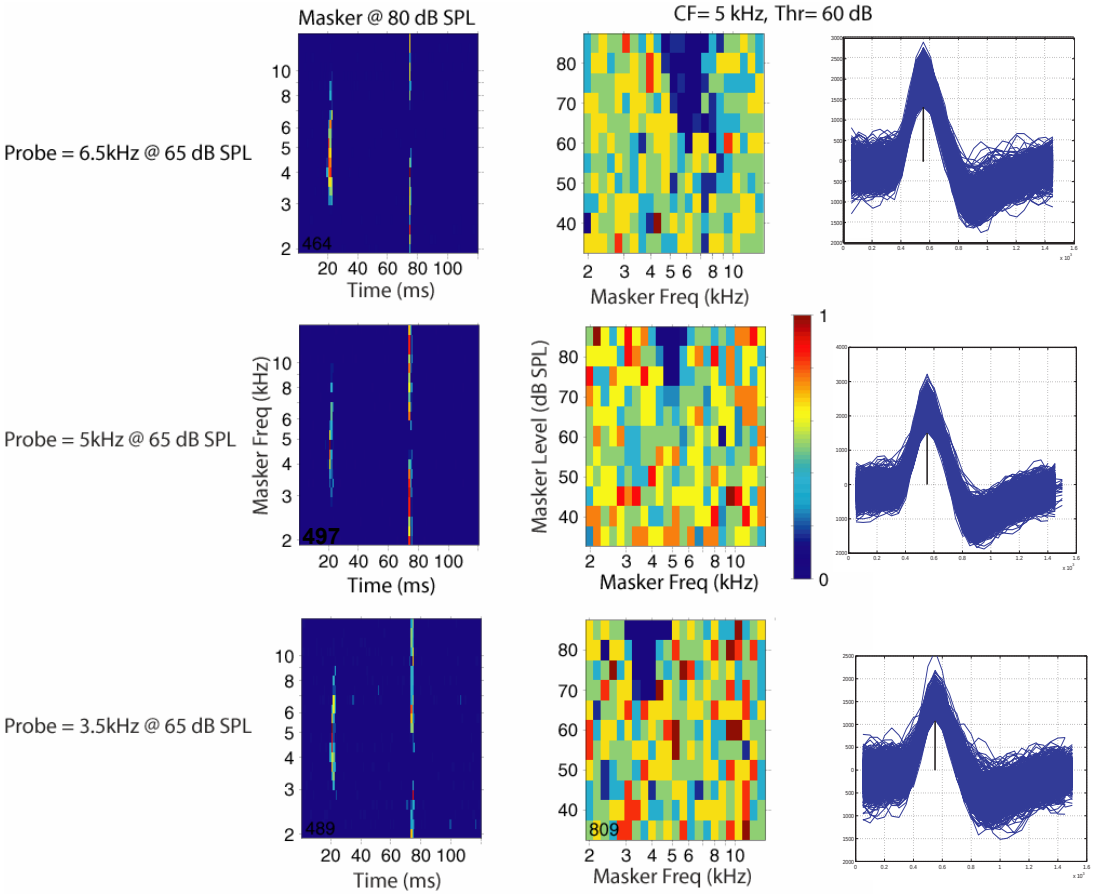

Figure 10. A single neuron's responses to forward masking using three different probe frequencies. Each row of panels represents the response to a different probe frequency. The column of panels in the left illustrated the temporal response pattern. The central column illustrates the forward masked frequency response areas. The column on the right illustrate the spike wavefoms, whose post-stimulus times were used to construct the other two panels.

In the middle column of panels of Figure 10, the forward masked probe response areas of this neuron are illustrated. The analysis window for these response area is centered on the onset response to the probe tone. The probe tone is fixed in frequency and level within each panel, but the masking tone varies in frequency and level from 2 – 20 kHz and from 35 – 85 dB SPL respectively. The areas of reduced probe response are clearly visible as a blue region of facets within a background of orange to green facets. This blue region is tuned in each panel, but the frequency at which the minimum masker intensity is seen varies with the probe frequency. When a probe frequency at 6.5 kHz is used the blue regions is centered at approximately 6.5 kHz. When a probe frequency of 3.5 kHz is used the blue region of reduced response is shifted and centered on that frequency. The panels on the right of this figure illustrate all the spike waveforms that were used to construct the temporal response patterns and masked response area on their left.

DISCUSSION:

Despite the complexities, forward masking has proven to be a useful toot for measuring spectral and temporal interactions among acoustic signals. The spectral interactions have been measured by constructing forward masked physiological tuning curves (see Abbas and Gorga, 1981; Snyder and Schreiner, 1987; Relkin and Smith, 1991; and Calford and Semple, 1995 among others) or psychophysical tuning curves (e.g., Houtgast, 1972; Moore, 1978; Shannon, 1977). These studies map the reduction in response magnitude (or threshold) to a fixed-frequency-and-level probe as a function of frequency and level of a preceding masker tone. The temporal interactions have been measured by inserting a variable silent interval (Δt) between the masker and probe and recording the amplitude (or threshold) of the probe response (e.g., Harris and Dallos, 1980; Delgutte, 1990; Calford and Semple, 1995; Brosch and Schreiner, 1997).

Forward masking has also been useful for examining the psychophysical interactions between AP channels in cochlear implant subjects (Lim et al, ’89; Chatterjee and Shannon, ’98; Tong and Clark, ’86), although none of these studies has provided a completely satisfactory measure of intracochlear excitation spread and channel interaction (see Hanekom and Shannon, ’98; Chatterjee and Shannon, ’98). This has led some investigators to emphasize that the inferred activation patterns could be highly selective, or at least as selective as those evoked by some acoustic stimuli (see Fig. 12, Chatterjee and Shannon, ‘98). However, even these results must be interpreted with caution, since the acoustic stimuli (i.e., a 1 kHz tone at 70 dB SPL), which were used as a basis for comparison, produce broad (300 Hz – 10 kHz) activation patterns in the auditory nerve array (see Fig. 5, Kim and Molnar, ‘79). Thus, there is little consensus among psychophysical (behavioral) studies regarding either the magnitude of intracochlear spread of activation from AP channels, the factors that govern it or the nature of the interactions between channels.

In the current experiments, we examined the location and spread of evoked neural activity when the cochlear was stimulated by a single tone (or electrical pulse trains from a single electrode channel), when it (the probe) was presented by itself and when it was preceded by a masking tones of the same or different frequencies (or electrical pulses on the same or a

second electrode channels). We recorded the neural responses across the tonotopic organization of the central nucleus of the inferior colliculus (ICC) using 16-channel silicon probes inserted into the ICC of pentobarbital-anesthetized cats or ketamine anesthetized guinea pigs. Variations in the responses to the probes indicated that there exists frequency-specific post-stimulus reduction in (or masking of) the probe response that was present for all masker intensities above a minimum masking-threshold. The range of frequencies that induced suppression could be entirely below, entirely above, or encompass the characteristic frequency of the neurons at a given recording site depending upon the CF (location) of the ICC neurons being recorded. In some cases, the frequency range for reduction was larger for higher intensity maskers; while in others, the frequency range for suppression did not increase (producing V-type or I-type masked FRAs). The minimum intensity that induced suppression at a given frequency was often lower than the minimum intensity for single tone excitation at that frequency. Responses to the probe-tones were more strongly suppressed when the probe-tone was immediately followed by the masking-tone. Suppression diminished as the interval between the masker offset and probe onset increased. It was largely absent when this interval was greater than 30 ms. In the examination of isolated single unit response the reduction of the probe response occurred whether probe responses or masker responses were sustained or transient. Thus the reduction in the probe responses were independent of the overall discharge rate evoked by the masking stimulus and are thus independent of adaptation at least at the level of the ICC.

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Work Planned for the Next Quarter

1) We will continue experiments looking at channel interaction using electrical stimulation. We will attempt to increase the number of channels, whose interactions we can study by using stimulation paradigms that activate more selective regions of the auditory nerve array. These paradigms will include more closely spaced longitudinal bipolar contacts and radial and off-radial bipolar contacts on on our existing intracochlear electrode.

2) Work will finish our work on the acoustic model of channel interaction and prepare a manuscript for publication. We will define the development of the interaction by varying the duration of the masking tone. Finally, we will estimate the relative magnitude of the interaction by varying the intensity of the probe tone.

3) We will explore the possibility of using printed circuits on very thin polyimid films to generate the current carrying elements of our intracochlear electrodes. We are exploring the possibility, which should greatly reduce the fabrication time required to produce an electrode, in order to me our own needs and the demands of our collaborators.

4) Experiments will be continued to look at the effects of implant contact configuration and stimulus waveform on single channel and multi-channel stimulation. We will examine the spread of excitation using pseudomonophasic waveforms, tripolar and bipolar configurations as well as morphing between monopolar and tripolar/bipoar configuratioins.