12th Quarterly Progress Report
July 1, 2005 to September 30, 2005

Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation: Interactions Between Implant Channels in Forward Masking

Submitted by:

John C. Middlebrooks, Ph.D.[2]
Russell Snyder, Ph.D. [1]
Alex Hetherington, M.S. [1]
Steve Rebscher, M.A.[1]
Ben Bonham, Ph.D.[1]

[1]University of California, San Francisco
Department of Otolaryngology – Head and Neck Surgery
Epstein Hearing Research Laboratory
533 Parnassus Avenue, Room U490E
San Francisco, CA 94143-0526

[2]Kresge Hearing Research Institute
University of Michigan
1301 East Ann St
Ann Arbor, Michigan

This report describes our progress during the 12th quarter of contract NIH-NIDCD-DC-02-1006 (July 1, 2005 - September 30, 2005). During this quarter, we conducted six experiments that continued and extended our investigations of interactions between cochlear implant channels. In addition, we completed two short procedures to examine equipment related issues. The results of these experiments and procedures, as well as other work completed during the quarter, are described in the next section. The bulk of this progress report, Appendix I, documents the results of experiments completed during previous quarters that examine interactions of pulse trains presented on two cochlear implant channels in a "Forward Masking" paradigm. The final section of this report briefly describes the work we plan for the next quarter.

Summary description of work over the last quarter

During the previous quarter we completed six neurophysiology experiments investigating channel interaction in the inferior colliculus (IC) resulting from electrical stimulation using a cochlear implant. These experiments include:

- Investigation of effects of electrode placement within the cochlea on spatial specificity of activation of IC neurons. These studies compare the spatial specificity of activation resulting from stimulation with three types of cochlear electrodes in the same animals: 1) Ball-and-wire electrodes visually placed within the scala tympani. Various placements of these electrodes were investigated, including the following: positioned against the modiolus, surrounded by fluid in the middle of the scala tympani, where we expected response thresholds to be higher and tuning to be broader, and positioned partly within Rosenthal's canal, where we expected thresholds to be lower and tuning to be sharper. 2) A UCSF-type electrode designed for the guinea pig (i.e., the electrode we use for most of our studies). 3) A Nucleus-type animal electrode available commercially from Cochlear Corporation.

  Results of these studies were reported publicly at the Neural Interfaces Workshop in Bethesda in September 2005, and will also be incorporated in a manuscript included with the next progress report. Briefly, bipolar stimulation of broadly spaced electrode pairs within the cochlea, using any of the three electrode types and using symmetric biphasic current pulses, elicited responses over a broad frequency (i.e., characteristic frequency) range within the IC. The distribution of this activity had two distinct foci, one corresponding to the location of each electrode in the bipolar pair. As the electrode spacing narrowed from these broadly separated pairs, the activity foci converged spatially. Using very narrow electrode spacings (not available using the commercial banded electrode), the two foci merged, could no longer be resolved in our measurements and the overall activity pattern became more selective. Further, as expected, proximity of the stimulating electrodes to the modiolus had a strong effect on response threshold, however placement of the electrodes *partly within* Rosenthal's canal did not produce lower thresholds than placements on the osseous spiral lamina (osl). The UCSF-type electrode, designed to be space-filling within the scala tympani and to position stimulating contacts as close as possible to the osl and the excitable structures contained within it, elicited responses with the lowest stimulation currents.
- Continued studies comparing responses to pseudomonophasic stimulus waveforms to responses to symmetric biphasic current waveforms. As described above, bipolar stimulation using symmetric biphasic waveform appears to produce activation of neuronal populations corresponding to the positions of both stimulating electrodes (the active electrode and the return electrode) in the bipolar pair. Use of pseudomonophasic stimulus waveforms can be used to decrease neuronal activation at the return electrode of the

bipolar electrode pair. This has two advantages: 1) it produces more focal stimulation and 2) it creates distinguishably different patterns of activation that are tonotopically appropriate for each of the constituent electrode of the bipolar pair. If reversing the roles of the active and return electrode produces distinct patterns of activation that are perceptually different, use of pseudomonophasic pulse waveforms could increase the number of potential stimulation channels in current prostheses without requiring addition of wires or contacts to the intracochlear portion of the implant. A part of this work was reported at the CIAP meeting in August, 2005.

- Continued studies of current steering. Monopolar current steering, or dividing a fixed stimulus current between adjacent intracochlear electrodes, has been demonstrated in human implant users to provide a perception of "virtual channels" that lie between physical channels (Dowling et al., ARO Midwinter meeting, 2005, abstract #916). We have demonstrated that it is possible to create distinguishable, and narrowly distributed, patterns of activation in the IC by dividing stimulus current between two bipolar electrode pairs. Further, gradually shifting the stimulus current from one bipolar pair to the other results in a gradual shift of the narrow region of activation in the IC. Part of this work was reported at the CIAP meeting in August, 2005.
- Continued studies of responses to broadband acoustical stimulation. Initial analysis of these measurements indicates that acoustical stimulation using bandpass filtered white noise can create a pattern of response within the IC that has two regions of high activation, near the band-edges, that are separated by a region of little or no activation. We are continuing these studies, which may help to identify the validity of cochlear implant simulations that rely on bandpassed white noise to emulate stimulation by intracochlear electrodes. Initial results of this study were reported at the CIAP meeting in August, 2005.
- Study using multi-channel modulated and unmodulated pulse trains. In these initial experiments, pulse trains of 250 and 500 pulses per second were amplitude modulated using 30 Hz sinusoidal envelopes. This envelope modulation frequency was chosen because it lies within the range of phonemic modulation and because previous experiments have demonstrated that nearly all single neurons within the central nucleus of the IC are able to follow at this rate. Our initial studies using these stimuli focus on effects of changing stimulus level, modulation depth, and time delay between the pulse trains and between their envelopes. Results of this ongoing study are not reported here, but will be included in a future progress report.
- Initial experiment using a 32-channel recording probe from NeuroNexus Technologies (completed during the previous reporting quarter and reported here). Figure 1 shows frequency response areas (FRAs) generated from neuronal activity recorded at 32 sites spaced in 100 μm intervals along the tonotopic axis in the inferior colliculus of a cat.

In addition to the physiology experiments described above, we also carried out brief procedures during one physiology experiment to evaluate two equipment related issues that may be of interest to other contract holders. Our report of these issues is of an anecdotal nature rather than a rigorous quantitative one.

The first of these equipment related issues is the evaluation of two configurations of our stimulation hardware. For single-channel bipolar stimulation, two of the eight current sources in our eight-channel stimulator must be connected to the cochlear implant – one to the active electrode, and one to the return electrode (a third extracochlear connection from the stimulator to the animal is also present, but no current flows through this connection during bipolar stimulation). Either of two methods can be used to apply stimulus current to any two of eight implant electrodes. In one method,

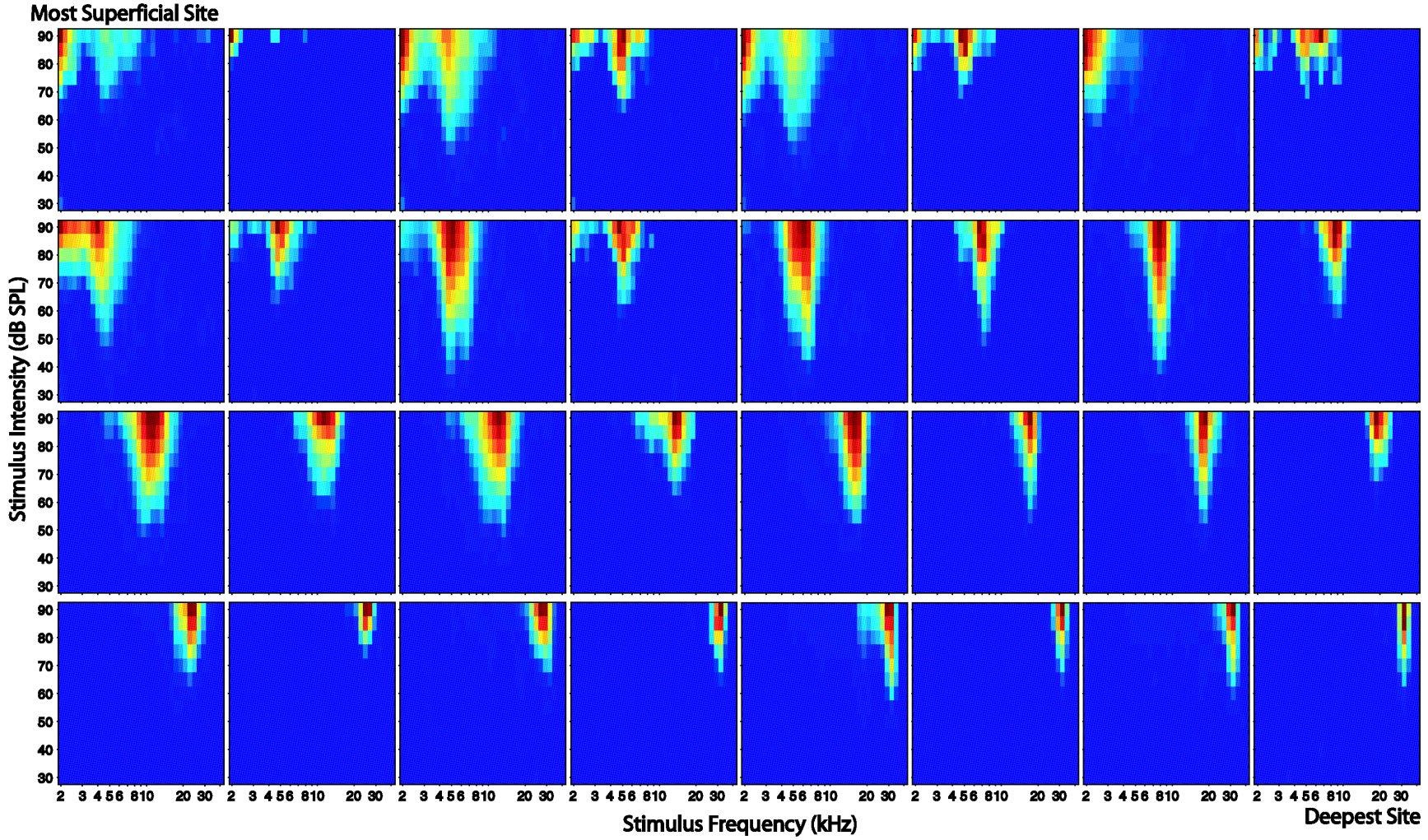

Figure 1. Frequency response areas derived from data recorded using a 32-channel NeuroNexus recording probe. The recording probe had 32 sites arranged at 100 µm intervals along a single shank. Each panel shows an FRA derived from one recording site. In each panel, the abscissa corresponds to stimulus frequency and the ordinate to stimulus intensity. Strength of response is encoded by color – red indicates strong response, blue indicates little or no response. The FRA corresponding to the most superficial site is at the top left, and the FRA for the deepest site at the bottom right. Characteristic frequencies (CFs) of these recording sites ranged from < 2 kHz to approximately 30 kHz.

two current sources are used and connected through the electronic demultiplexor switch (described in detail in QPR #5) to any two of the eight implant electrodes (the active and return electrodes). In the second method, all eight stimulator channels are connected to implant electrodes, and the control voltages on the eight stimulator channels are used to select which two implant electrodes are the active and return electrodes. For the second method, the control voltages of the six inactive channels are set to 0 V, which ensures that no current is applied to those channels. A potential disadvantage of the first method is complexity -- an additional piece of hardware, and programming of that hardware, must be included in setting up each experiment. A potential disadvantage of the second method is that a more wires are connected to the animal -- each wire may act as an antenna, and increase the non-biological background noise measured on the recording electrodes. In our laboratory, the stimulator's control box is located in an equipment rack outside the sound booth and the stimulator's voltage-to-current converters (i.e., the current sources) are located in a box within the sound booth. The cable connecting these two units is approximately 5 m long, and so provides an opportunity for noise pickup.

To quantify the "background noise", we recorded raw waveforms from each recording site over several seconds in which no suprathreshold stimulation was provided and then computed the standard deviation of these recorded waveforms. The background noise therefore was of mixed origin – partly biological (e.g., low amplitude neuronal activity with no clearly distinguishable spikes) and partly non-biological. We performed this measurement first with two channels of the current stimulator connected to the cochlear implant through the electronic switch. Following this measurement, we removed the switch and connected all eight of the current stimulator channels to the cochlear implant, and again recorded raw waveforms and computed their standard deviation. The measured values are summarized in Figure 2. Across the sixteen recording electrodes, the mean increase in noise going from two to eight channels was 65 A/D units, which was an increase of 34%.

The second equipment related issue is the change in the quality of signals recorded using the multi-channel probes through the course of the experiment. We often observe that the signal quality on one or more of the Iridium recording sites on the multi-channel probes changes over several hours. Sometimes the change includes a large increase in the magnitude of the background noise, and sometimes this increase is large enough that is no longer possible to identify neuronal spikes using that recording site. A key feature of our recording paradigm is the ability to identify spatial patterns of activity, and to do this it is critical to have the ability to record cleanly from every recording site. Kevin Otto and his colleagues have recently reported a technique to "rejuvenate" electrode sites that "drop out" during multi-day or multi-week chronic experiments (c.f., Johnson et al., IEEE Trans Neural Syst. Rehabil. Eng. 2005 Jun;13(2):160-5). We conducted a brief procedure to determine whether this technique might be able to "rejuvenate" electrode sites that drop out during a relatively short acute experiment.

During one experiment, we observed that the recording quality on two electrodes (#3 and #16) was poor. That is, background noise was high and spike activity on these channels was not clearly distinguishable from the background. To examine the efficacy of the rejuvenation procedure, we first recorded waveforms during several seconds of no suprathreshold stimulation and during periods of when large suprathreshold stimuli were presented. According to the published protocol for rejuvenation, we then applied 1.5 V to each electrode site with respect to a ground electrode located in the neck muscle for 4 seconds. We again recorded waveforms during several seconds of no suprathreshold stimulation and during periods of large suprathreshold stimulation. We quantified the "background noise" level as described earlier, and compared the levels before and after rejuvenation. These values are indicated in Figure 3. Comparison of background noise levels before and after rejuvenation indicated that the procedure effected an average drop of 12% in the background noise level. We noted that one electrode, #3, was a far outlier compared with the rest of the electrodes.

After eliminating this electrode from the pool, we recomputed the average drop in background noise to be 9.5%. We also compared the size of the recorded action potentials before and after rejuvenation. We quantified the action potential

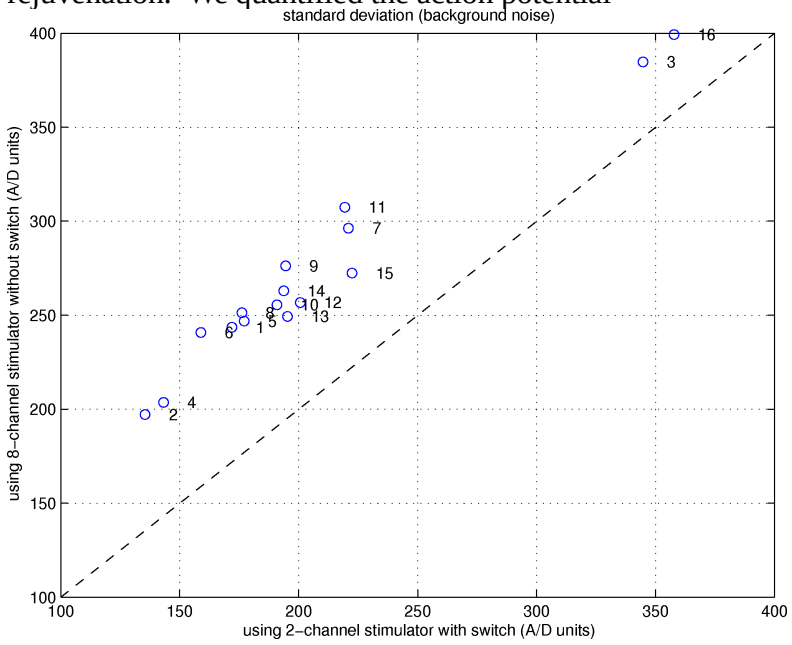

Figure 2: Background noise measured using two different configurations of the eight-channel common-return stimulator. Background noise measured using the first configuration, with two channels of the eight-channel stimulator connected to the cochlear implant, is indicated along the abscissa. Background noise using the second configuration, with all eight channels of the stimulator connected to the cochlear implant, is indicated along the ordinate. Background noise was higher on all recording channels using the second configuration. See text for description of configurations.

magnitude by the amplitude of recorded action potentials in the 90th percentile of action potentials ranked according to size. These values are indicated in Figure 4. This comparison indicated that measured spike size decreased on average by 8.1% after the rejuvenation procedure. Consequently, the signal to noise ratio (i.e., amplitude of action potentials to amplitude of background noise) did not change as a result of the rejuvenation procedure on fifteen of the sixteen electrodes, including fourteen of fourteen electrodes which already exhibited clearly discernible spike activity. However, the signal to noise ratio improved considerably on one of the two electrodes (electrode #3) with poor quality signals, and this improvement was enough that action potentials could be clearly identified above the background noise after rejuvenation when none could be identified before (Figure 5). We would therefore suggest that this procedure might be used selectively on electrodes that exhibit poor recording quality that changes during the course of an acute experiment..

In addition to the physiology experiments described above, we have also made progress in other areas:

- Electrode fabrication: A new guinea pig electrode mold was polished and four new guinea pig cochlear implants were fabricated.

- We have begun analysis of data from the experiments described above, as well as continued analysis of data obtained during previous experiments.

Other

- Our postdoctoral researcher, Steven Bierer, has graduated from our group at UCSF and accepted a research position at the University of Washington in Seattle. He will continue his studies of central neurophysiological responses to electrical stimulation by cochlear implants using the skills and techniques he developed while in our laboratory.
- Data from the study above describing the effects of electrode placement and separation on the spread of activation in the IC were sent to J. Frijns to be used to confirm and tune his computer model of neuronal activation using electrical stimulation in the cochlea.

Travel

- B. Bonham, R. Snyder, S. Rebscher, S. Bierer, and A. Hetherington attended the 2005 International Conference on Implantable Auditory Prostheses at Asilomar in Pacific Grove, CA.
- B. Bonham attended the Neural Interfaces Workshop in Bethesda, MD.

Presentations

- Bierer, S., Bonham, B., and Snyder, R., "Temporal Interactions in the Inferior Colliculus: Responses to Interleaved Electrical Pulse Trains", poster at the 2005 Conference on Implantable Auditory Prostheses, Asilomar, CA.
- B. Bonham, "Cochlear Implant Technology", invited seminar presented to the Department of Biology at San Jose State University.
- Bonham, B., Snyder, R., Middlebrooks, J., Rebscher, S., Bierer, S., and Hetherington, A., "Physiological Measures of CI Channel Interaction", invited presentation at the 2005 Conference on Implantable Auditory Prostheses, Asilomar, CA.
- Rebscher, S., Wardrop, P., Karkanevatos, A., Lustig, L., Ali, J., Bonham, B., Snyder, R., and Leake, P., "Future Development of Cochlear Implant Electrodes", invited presentation at the 2005 Conference on Implantable Auditory Prostheses, Asilomar, CA.
- Bonham, B., Snyder, R., Middlebrooks, J., Rebscher, S., Bierer, S., and Hetherington, A., "Physiological Measures of Cochlear Prosthesis Channel Interaction", poster at the Neural Interfaces Workshop, Bethesda, MD.
- Vollmer, M., Tillein, J., and Bonham, B. "Neuronal Interactions of Combined Electric/Acoustic Stimulation in the Cochlea in Cat Inferior Colliculus", invited presentation at the 2005 Conference on Implantable Auditory Prostheses, Asilomar, CA.
- Tillein, J., Bonham, B., and Vollmer, M., "Responses to Combined Electric and Acoustic Stimulation (EAS) in Cat Inferior Colliculus", poster at the 2005 Conference on Implantable Auditory Prostheses, Asilomar, CA.

Work planned for next quarter

During the next quarter, we plan to focus our experiments predominantly on measurements of responses to electrical stimulation using sinusoidal amplitude modulated (SAM) pulse trains. We also plan to begin a series of experiments that will examine responses to SAM acoustic stimuli to provide a basis for comparison with responses to SAM electrical pulse trains.
We plan to begin a series of experiments designed to examine responses to specific aspects of electrical stimulation by signals corresponding to speech processed by a cochlear implant processor.

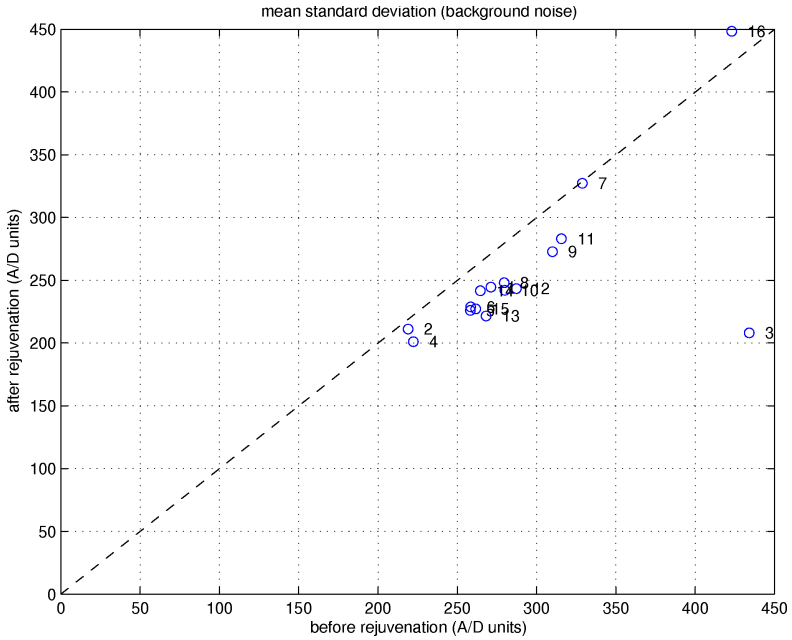

Figure 3: Results of preliminary test of recording electrode rejuvenation. Axes indicate standard deviation of recorded waveforms from each of 16 recording electrodes in the absence of either acoustic or electrical stimulation, which we interpret as biological or non-biological "background noise". Values before rejuvenation of all 16 electrodes are indicated along the abscissa, and values after rejuvenation are indicated along the ordinate. Prior to applying the rejuvenation procedure, two electrodes, #3 and #16, exhibited noise levels substantially higher than the remaining electrodes. After the procedure was applied, background noise decreased on all electrodes except for #16, and background noise on electrode #3 fell within the range of the other 14 electrodes. Values along the dashed diagonal indicate no difference before and after the rejuvenation procedure.

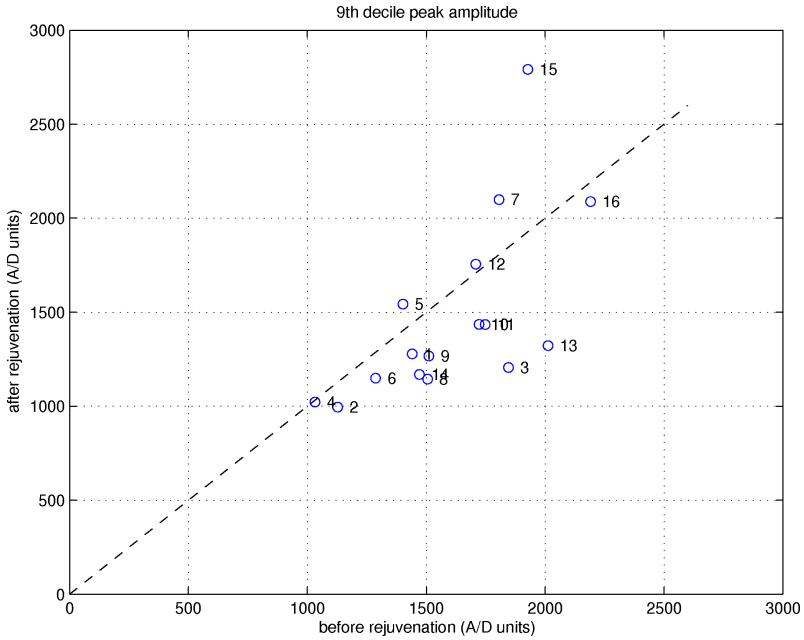

Figure 4: Effect of rejuvenation procedure on measured spike amplitude. Peak response amplitudes recorded on each electrode following presentation of a strong electrical stimulus were sorted, from smallest to largest, before and after application of the rejuvenation procedure. Values along axes indicate spike amplitudes at the 90th percentile (abscissa – before rejuvenation, ordinate – after rejuvenation). Values along the dashed diagonal indicate no difference before and after the rejuvenation procedure. (See text for further description of the utility of electrode rejuvenation.)

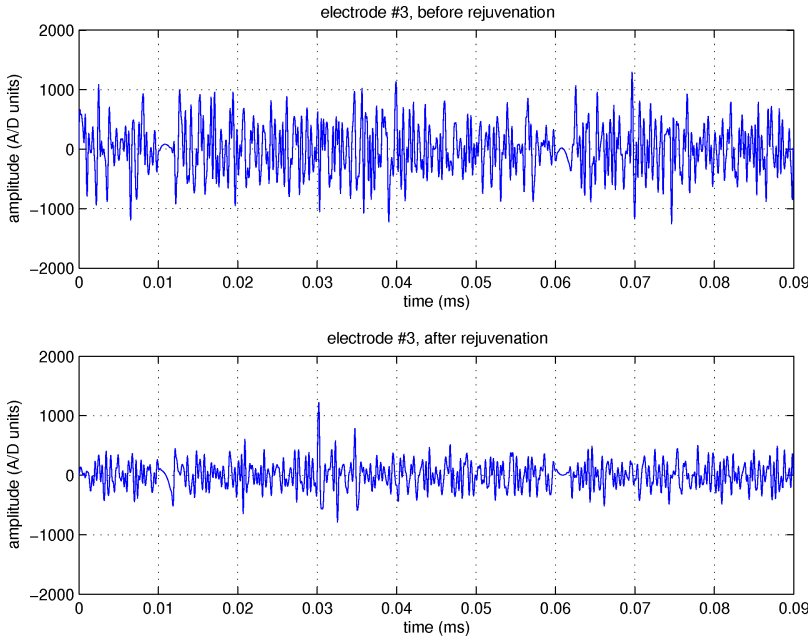

Figure 5: Effect of rejuvenation on electrode #3. Waveforms recorded from electrode #3 before (top) and after (bottom) applying the rejuvenation procedure. Prior to rejuvenation, background noise on electrode #3 was substantially higher than 14 of the other 15 electrodes. After rejuvenation, the background noise level on #3 fell within the range of those 14 electrodes. While action potentials do appear to be present in the top panel, the high level of background noise would prevent reliable identification of those events. In the bottom panel, three relatively clear action potentials appear between 0.03-0.035 s. In these panels, recorded waveforms are blanked (near 0.01 s and 0.06s) before filtering to remove electrical current pulse stimulus artifacts.

12th Quarterly Progress Report
July 1, 2005 to September 30, 2005

Neural Prosthesis Program Contract N01-DC-02-1006

The Neurophysiological Effects of Simulated Auditory Prosthesis Stimulation: Interactions Between Implant Channels in Forward Masking – Appendix I

Submitted by:

John C. Middlebrooks, Ph.D.[2]
Russell Snyder, Ph.D. [1]
Alex Hetherington, M.S. [1]
Steve Rebscher, M.A.[1]
Ben Bonham, Ph.D.[1]

[1]University of California, San Francisco
Department of Otolaryngology – Head and Neck Surgery
Epstein Hearing Research Laboratory
533 Parnassus Avenue, Room U490E
San Francisco, CA 94143-0526

[2]Kresge Hearing Research Institute
University of Michigan
1301 East Ann St
Ann Arbor, Michigan

Multi-channel cochlear implants provide users with substantially better speech recognition than do single-channel implants (e.g., Gantz et al., 1988; Cohen et al., 1993; Fishman et al., 1997). Nevertheless, the number of functionally independent channels of information delivered to the brain by a multi-channel implant typically falls short of the number of physical electrodes present in the device. For instance, users show little or no improvement in speech recognition when the number of activated implant channels is increased beyond about 4 to 7 channels in quiet (Fishman et al., 1997; Friesen et al., 2001) or beyond 7 to 10 in noise (Friesen et al., 2001). In contrast, normal-hearing listeners continue to show improving speech recognition in quiet or in noise as the number of channels is increased to 20 channels in an acoustic vocoder simulation of a cochlear-implant speech processor (Friesen et al., 2001). One of the principal goals of this contract is to increase the number of functionally independent channels available to cochlear implant patients.

The difference between normal listeners and implant users in functional channel number almost certainly is due in part to partial loss of auditory nerve fibers in the implant users. Another likely factor, however, is the overlap in the neuronal populations activated by nearby cochlear electrodes, leading to channel interaction. Hypothetically, that overlap in activation might arise from: (1) summation of simultaneous currents on nearby electrodes; (2) summation of depolarization of auditory neurons by nearby channels activated in quick succession (as in interleaved pulse trains delivered at high rate) (discussed in Middlebrooks, 2004); (3) adaptation of overlapping populations of peripheral and central auditory neurons; and (4) synaptic interactions within the central auditory system. In the present study, we are employing a forward masking paradigm as a means of examining neural adaptation and synaptic interactions in the absence of contributions from summation of stimulating currents and depolarization. We presented masking stimuli consisting of 100-ms electrical pulse trains. Probe stimuli, typically 20 ms in duration were presented 2 or more ms after the offset of the masker. Masker and probe were presented through the same or different intra-scalar electrodes. The influence of the masker on probe responses was quantified in terms of probe mean spike rates and probe thresholds evaluated using a signal-detection procedure. The results demonstrate the importance of restricted tonotopic spread of activation in reducing forward masking and suggest that the forward masking that is observed at the level of the inferior colliculus reflects a cascade of suppression at lower levels of the auditory pathway and neuronal adaptation within the inferior colliculus.

Methods

Experiments were conducted in ketamine/xylazine-anesthetized pigmented guinea pigs. We stimulated with tone and noise bursts in normal-hearing conditions, then deafened the animals, inserted intra-scalar electrode arrays, and stimulated with electrical pulse trains. We recorded single- and multi-unit activity from the central nucleus of the inferior colliculus (ICC). The basic experimental procedures have been detailed previously (previous quarterly progress reports and Snyder et al., 2004), and will be summarized here.

Data useful to the present report were obtained in 14 animals. After induction of anesthesia, the skull was opened and the right inferior colliculus was exposed by subpial aspiration of overlying occipital cortex. Recordings were made with multi-site silicon-substrate probes (Najafi et al., 1985) that comprised 16 recording sites at 100μm intervals along a single shank. The multi-site probes permitted simultaneous recordings of spike activity from single neurons or from small clusters of neurons. The probe was inserted into the ICC, oriented in the coronal plane and from dorso-lateral to ventro-medial at a 45° angle to the sagittal plane. That orientation was approximately parallel to the tonotopic axis of increasing characteristic frequency in the ICC. Each animal was first tested with acoustic tones to establish the position of the recording sites relative to the tonotopic axis,

then the recording probe was fixed in place, the animal was deafened with an intra-scalar injection of neomycin sulfate, and an array of stimulating electrodes was inserted in the scala-tympani. The remainder of this report will focus on responses to electrical stimulation in the deafened condition.

Two types of intra-scalar array were tested. The first, referred to here as the UCSF guinea-pig implant, has been developed under the present contract. It consists of a space-filling silicone-elastomere carrier molded to the guinea-pig cochlea. It supports 6-10 ball electrodes in close proximity to the osseous spiral lamina. The second, referred to here as the Nucleus6 implant, is a 6-electrode banded array identical to the distal 6 electrodes of the Nucleus 22 clinical device from Cochlear Corp. The Nucleus6 array lacks the close apposition of electrodes to the spiral lamina and permits considerable shunting of current through the lateral aspects of the banded electrodes. Nevertheless, our use of that array provided some insight into the stimulus conditions present in clinical devices that are in use by many patients. The present report draws on data from 11 animals implanted with the UCSF guinea-pig implant and 3 implanted with the Nucleus6.

Stimulus presentation and data acquisition were accomplished with System-3 hardware from Tucker-Davis Technologies (TDT) controlled by an Intel-based personal computer. Custom software was written in MATLAB script. Intra-cochlear electrical stimuli were generated by a custom optically isolated multi-channel current source controlled by a TDT RA8 digital-analog converter. Electrical pulses were biphasic, initially cathodic, lasting 40 μs per phase. Trains of such pulses were presented at various rates, as stated in the following text. Electrical artifact was rejected using a sample-and-hold procedure for pulse rates up to ~500 pulses per second (pps) and using comb filters for faster rates (Middlebrooks, 2004). Neural spikes were detected on-line for on-line monitoring of experiments. Digitized neural waveforms were stored on computer disk for off-line spike sorting using custom software. Analysis presented in this report is based on spikes sorted off line.

Neural responses were evaluated by distributions of mean spike rates and by a signal-detection procedure based on trial-by-trial neural spike rates. In the signal-detection procedure, thresholds were determined by comparing spike counts on trials in which a stimulus either was present or absence. Level discrimination was tested by comparing spike counts on trials in which a higher- or lower-level stimulus was present. In either case, a receiver-operating-characteristic (ROC) curve was derived from the distributions of spikes elicited by higher and lower (or absent) levels. The area under the ROC curve gave the percent correct detection or discrimination. The percent correct was converted to a standard deviate (*z-score*), which then was expressed as a discrimination index (*d'*). A criterion of $d' = 1$ is used for threshold.

Results and Discussion

In this ongoing research, we are evaluating the degree to which a leading masker suppresses the response to a trailing probe stimulus. In particular, we are interested in the influence of overlap of activated neural populations, which is determined largely by stimulating-electrode configuration, and by the influence of phasic versus tonic responses at the recording site in the ICC, which is sensitive to electrical pulse rate among other factors.

Spatial Spread of Masking

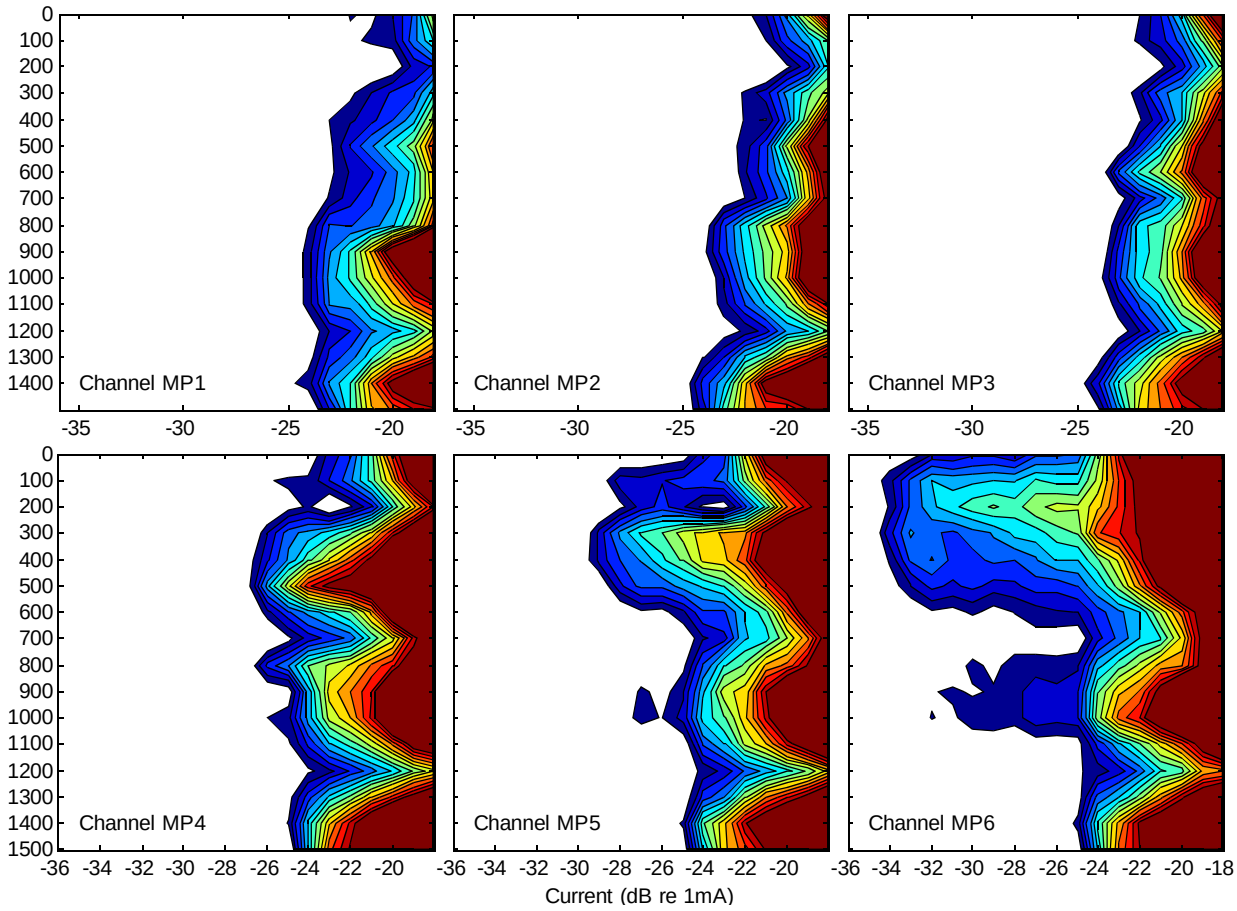

Figure 1. Spatial tuning curves elicited by monopolar stimulation at 6 intra-scalar sites.

We evaluated the degree to which spread of activation by various intra-scalar electrode configurations might influence the magnitude of forward masking. Figure 1 represents the responses to stimulation through a UCSF guinea-pig array using a monopolar electrode configuration in which the active electrode was a single intra-scalar electrode and the return electrode was a wire in a neck muscle. Note that Figures 1 through 7 all show data are from the same animal (GP0320) so that they can be compared directly. Each panel shows the response to one channel ranging from basal (MP1) to apical (MP6). In each of these spatial tuning curves (STCs) the vertical axis represents depth in the ICC, with the top representing the superficial ICC, sensitive to low frequencies and the bottom representing deep ICC, sensitive to high frequencies. The horizontal axis represents stimulus current, expressed as dB relative to 1 mA. The contours represent cumulative d' in steps of ½ d' unit. The left-most, lowest, contour in each panel represents d'=1, which we take as threshold. That is, the envelope of colored contours can be interpreted as the range of stimuli eliciting statistically detectable spike activity on single trials. In the monopolar configuration illustrated here, spread of excitation from each electrode is broad, and one can detect only a faint cochleotopic trend, with more apical electrodes producing more superficial ICC activation.

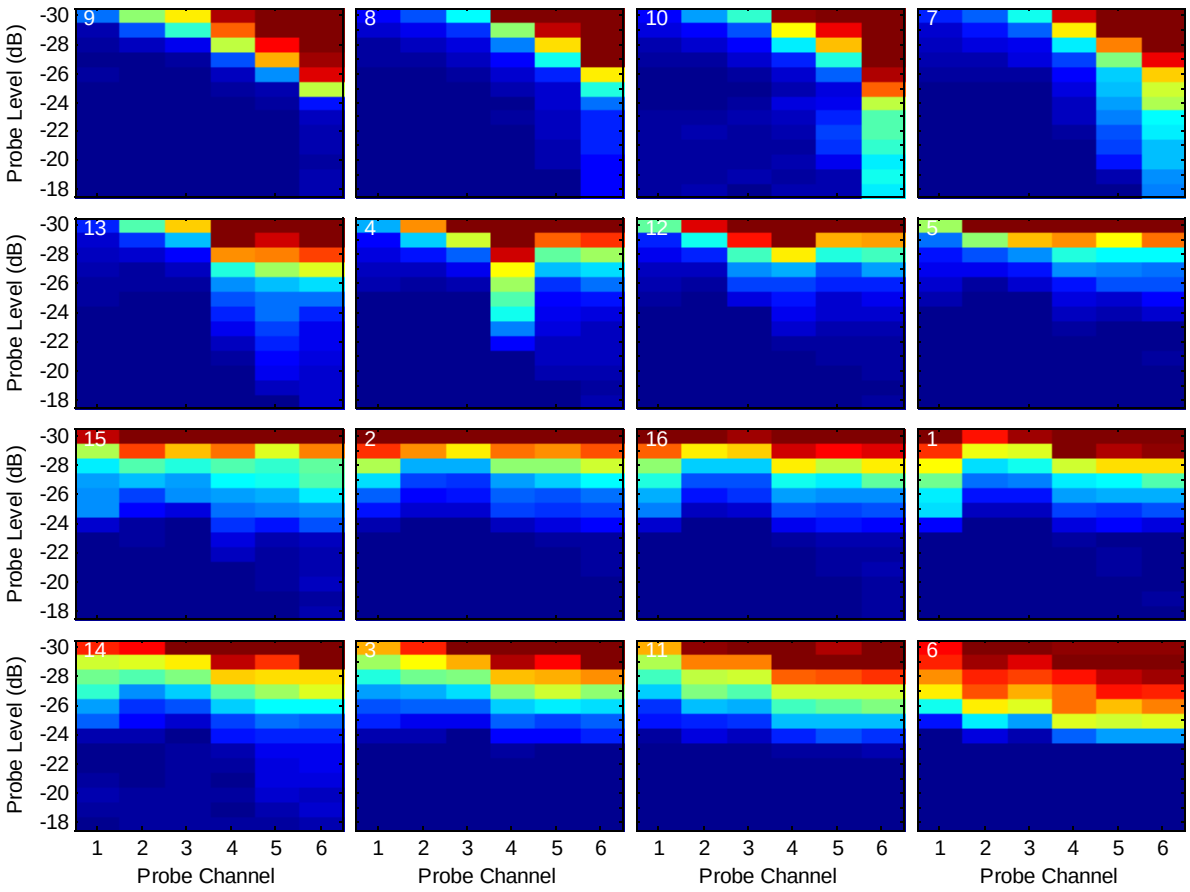

Figure 2: Probe Channel Response Areas (CRAs) for monopolar stimulation.

Channel Response Areas (CRA) plot the sensitivity of each recording site to cochlear channel of stimulation, analogous to frequency response area plots in normal-hearing conditions. In the CRAs in Fig. 2, each panel represents the response at one recording site, with the superficial-to-deep ICC dimension represented by panels progressing from left to right, then top to bottom. The vertical axis represents stimulus current (in dB re 1 mA), the horizontal axis represents the channel number (from 1, basal, to 6, apical), and colors from blue to red represent increasing mean spike rate. Again, the monopolar stimuli produced little cochlear specificity, with deep recording sites showing nearly uniform sensitivity to all stimulus channels and superficial sites showing a preference for apical stimulus channels.

Robust forward masking was observed when the masker and probe pulse trains were presented on the same stimulating electrode. Figure 3 shows responses recorded from one ICC recording site. This figure represents a series of post-stimulus-time (PST) histograms in which each horizontal row of symbols represents mean spike rates (colors) as a function of time. The interrupted red bar across the bottom indicates the duration of the leading masker and the trailing probe, both of which consisted of 254-pps pulse trains. The probe level was held constant at -21 dB (re 1 mA). The lowest row of data (labeled 'Ctrl') shows the unmasked control condition, and subsequent higher rows show increasing masker levels as indicated on the vertical axis. Increasing masker levels resulted in increasing response to the masker, initially phasic then changing to tonic phase locking to the pulse rate. As the response to the masker increased, the response to the probe gradually was suppressed, with the tonic response to the probe disappearing at the level at which the masker level began to exceed the probe level.

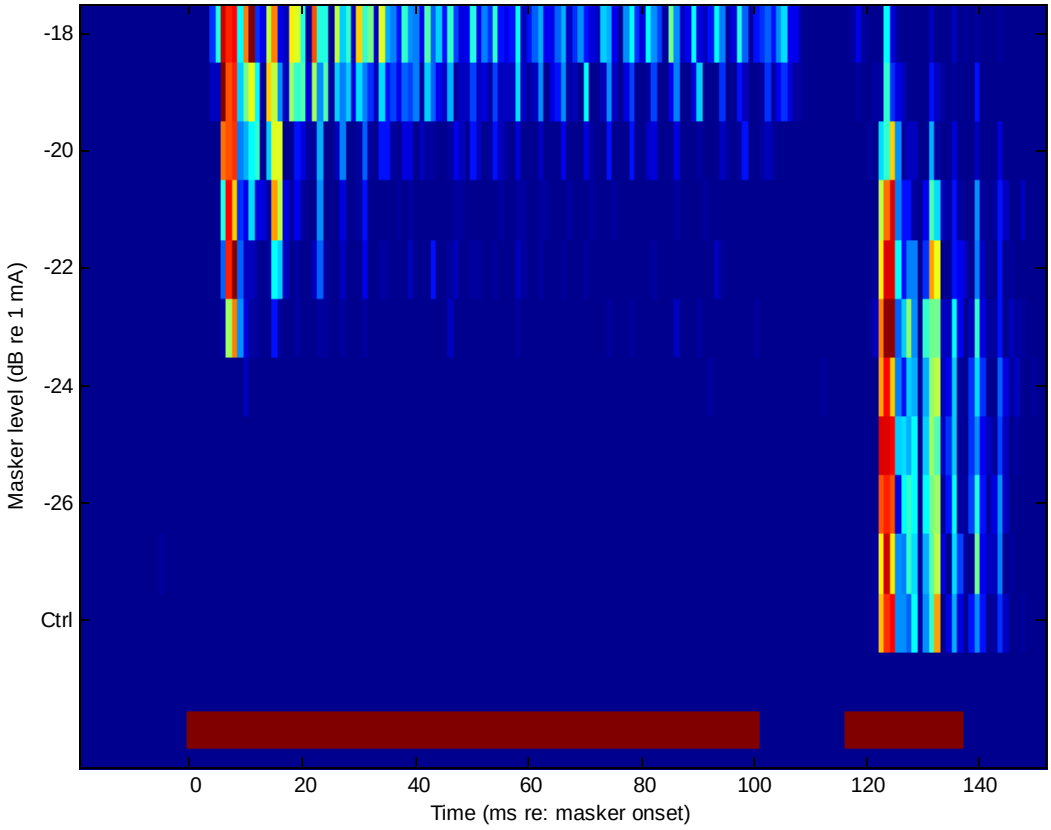

Figure 3: Post-stimulus-time histogram demonstrating forward masking.

Stimulation with the monopolar electrode configuration showed little sensitivity to the relative cochlear locations of masker and probe electrodes. The masked CRAs in Fig. 4 show the response to a probe on channel MP3 held at a constant stimulus level of -22 dB re 1 mA. The varying channel numbers and levels refer to the masker, which was a 100-ms pulse train, 254 pps, with a 16-ms gap between masker offset and probe onset. In these plots, hot (orange and red) colors indicate strong probe responses (i.e., absence of masking), and cool (blue and green) colors indicate weak probe responses due to masking. The superficial 8 recording sites, which showed the highest thresholds for unmasked probe stimulation, show fairly irregular masking patterns. The deepest 8 sites show fairly uniform masking across masker channels, with somewhat greater sensitivity to masking by the more apical cochlear electrodes, MP3 to MP6. Apparently, the great spread of cochlear excitation resulting from monopolar stimulation results in great spatial spread of masking

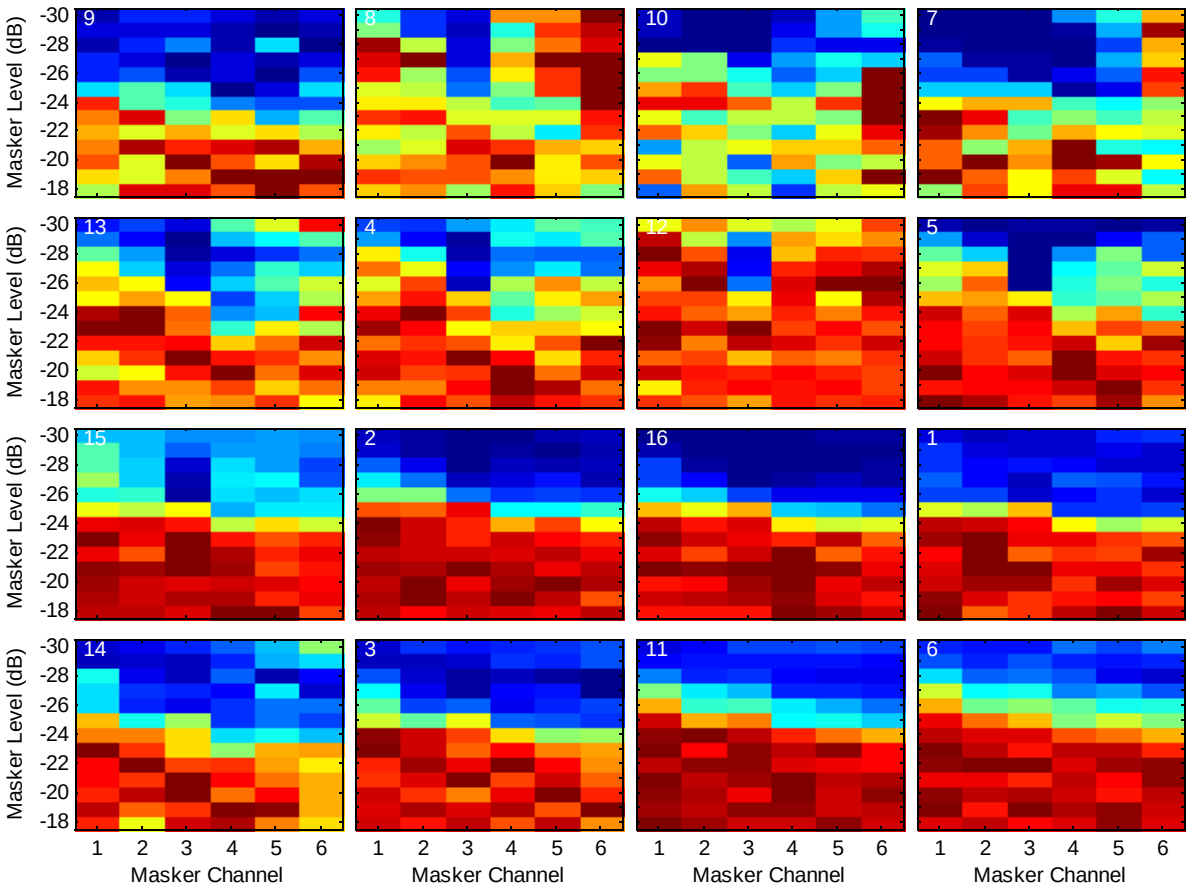

Figure 4: Masked channel response areas for monopolar stimulation.

A narrow bipolar cochlear electrode configuration produced substantially more focal stimulation; in that configuration, the active electrode was a single intra-scalar electrode and the return was the adjacent, more-apical, intra-scalar electrode. Figure 5 shows STCs for bipolar stimulation. In this example, the overall spread of above-threshold activation was not much narrower than that observed for the monopolar configuration, but the regions of maximal activation were considerably narrower. Also, a cochleotopic progression of deep-to-superficial ICC activity corresponding to basal-to-apical cochlear stimulation was more evident for the bipolar configuration.

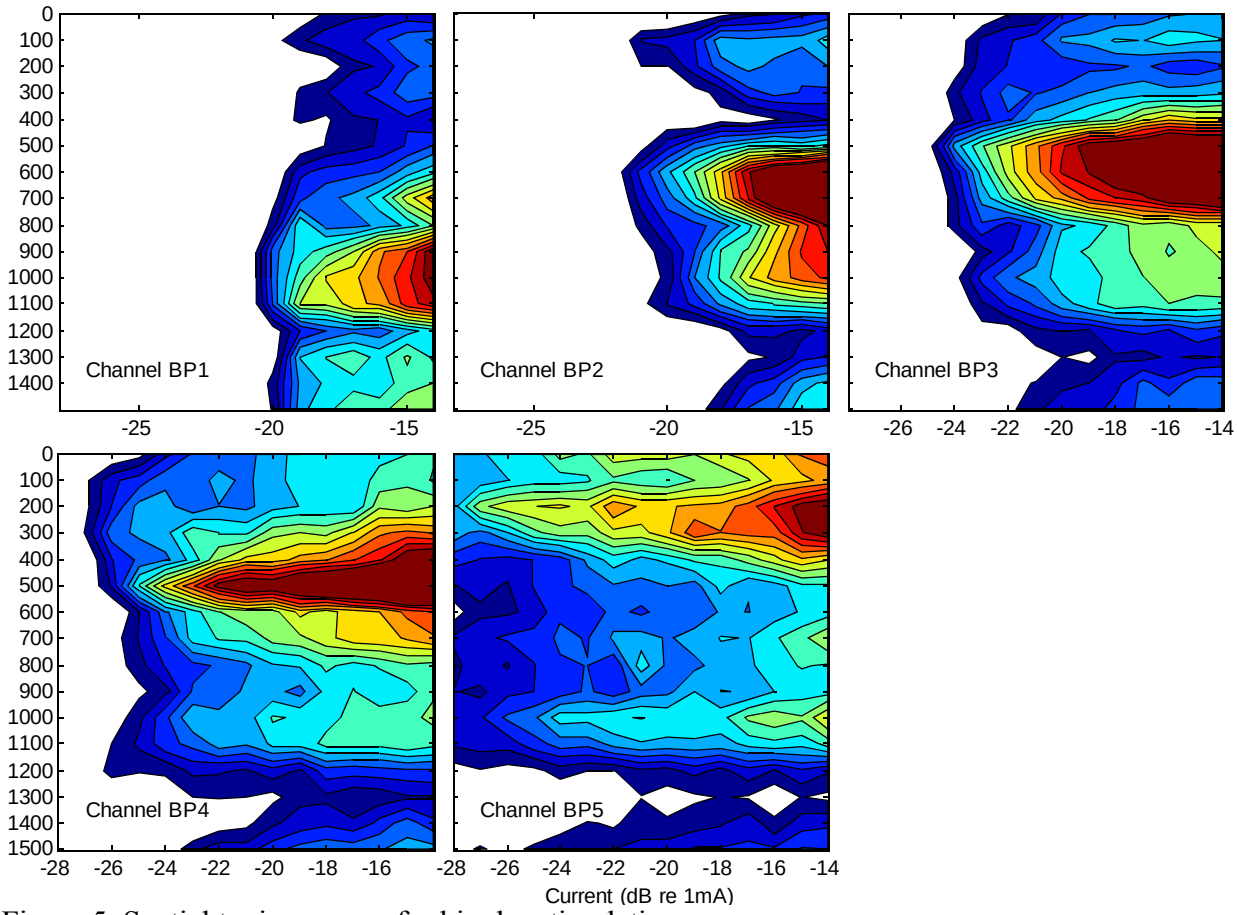

Figure 5: Spatial tuning curves for bipolar stimulation

The enhanced cochleotopic specificity resulting from bipolar stimulation also was evident in the form of probe CRAs. In the CRAs show in Fig. 6, one can see selectivity for the most apical cochlear channel (BP5) in the superficial-most 4 recording sites, selectivity for more basal cochlear channels (sites BP2, 3, and 4) in the next deeper 4 sites, and selectivity for the most basal channel (BP1) in the deepest 8 recording sites.

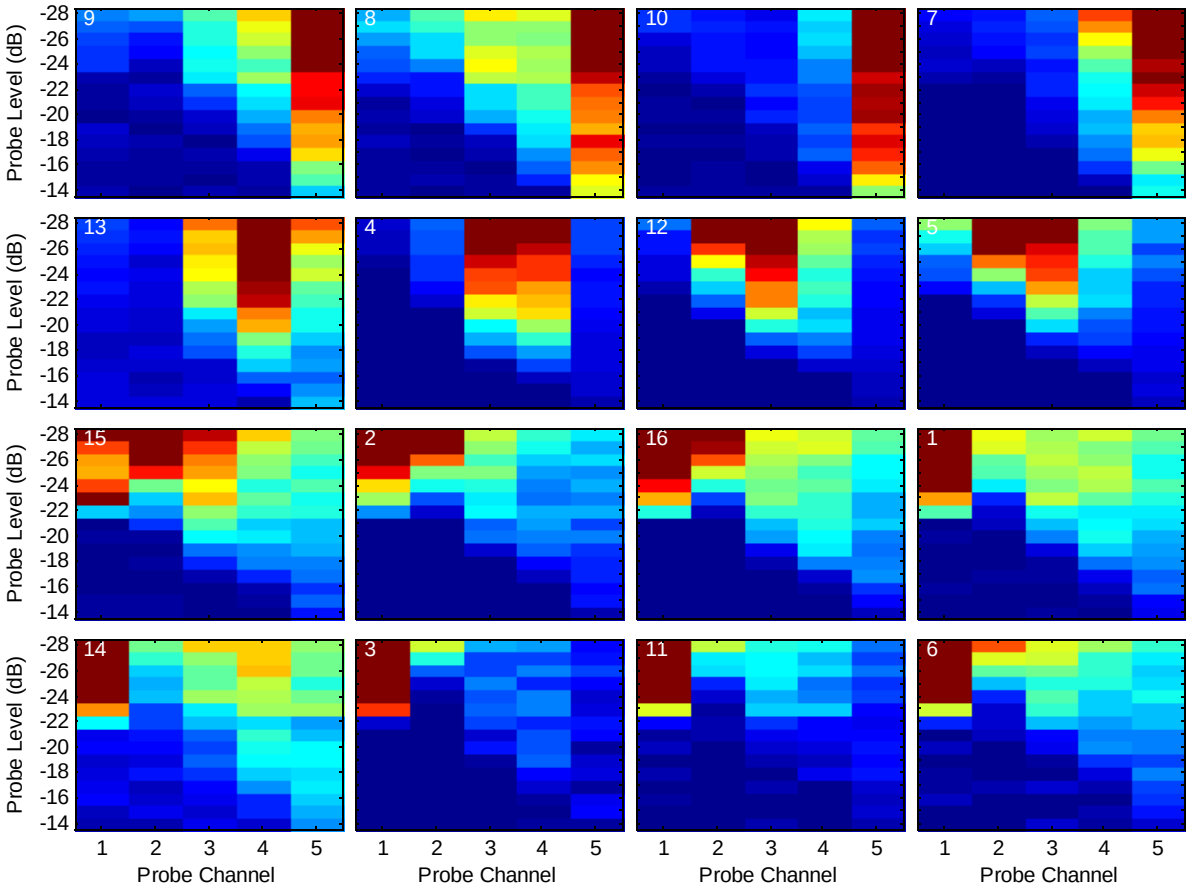

Figure 6: Channel response areas for bipolar stimulation.

The more restricted spread of excitation produced by bipolar stimulation resulted in more restricted spatial spread of forward masking. In the example shown in Fig. 7, the probe channel was BP3, held at a constant level of -21 dB re 1 mA. The CRA shows the effects of varying masker channel and level. At all but the deepest recording sites, masking channel BP3 produced the strongest masking, with considerable masking from adjacent channels BP2 and 4, and negligible masking from more-distant channels BP1 and 5. We note that for nearly all recording sites, the strength of masking was greatest when the masker channel corresponded to the probe channel (i.e., when masker and probe were BP3). This is irrespective of the difference across recording sites in preferred cochlear channel. That suggests that strong forward masking observed in the ICC was determined more by spatial overlap of active neural populations in the auditory nerve or lower brainstem than by the strength of the response to the masker at the level of the ICC. At the deepest 3 recording sites in the example in Fig. 7, somewhat stronger masking was produced by more apical channels BP4 and 5 than by BP3. This is somewhat paradoxical, since those sites showed much stronger excitatory responses to stimuli on the most basal channel, BP1 (as shown in Fig. 6).

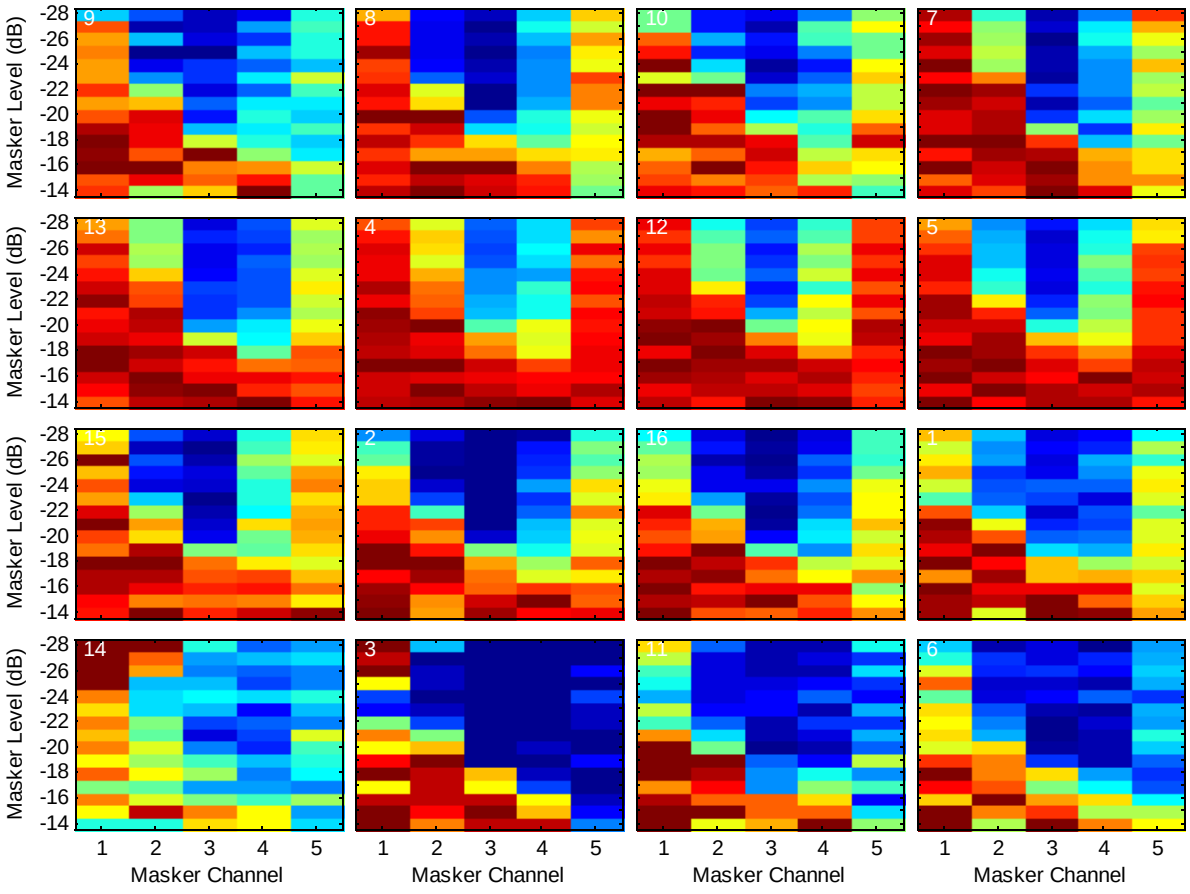

Figure 7: Masked channel response areas for bipolar stimulation.

Figures 8 and 9 explore in another animal (GP0509) the effects of spatial overlap of cochlear excitation on forward masking. These data were obtained in an animal implanted with a Nucleus6 cochlear electrode array, which provided a looser fit to the guinea-pig scala tympani than did the USCF guinea-pig array. Figure 8 shows in the form of STCs the spread of excitation along the tonotopic axis of the ICC resulting from bipolar stimulation. In this example, the tonotopic progression of activation was less pronounced than in the case represented in Fig. 5, and there was more overlap among channels.

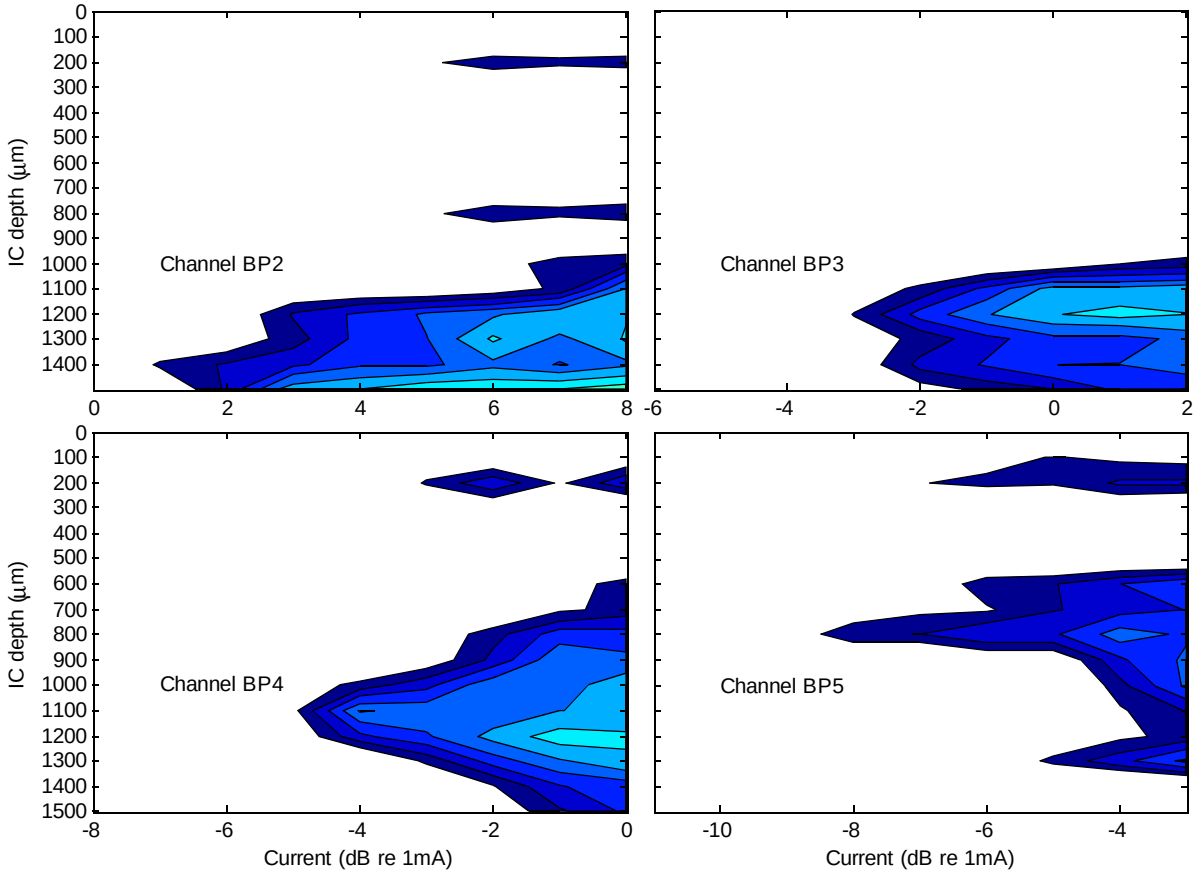

Figure 8: Spatial tuning curves for bipolar stimulation (GP0509).

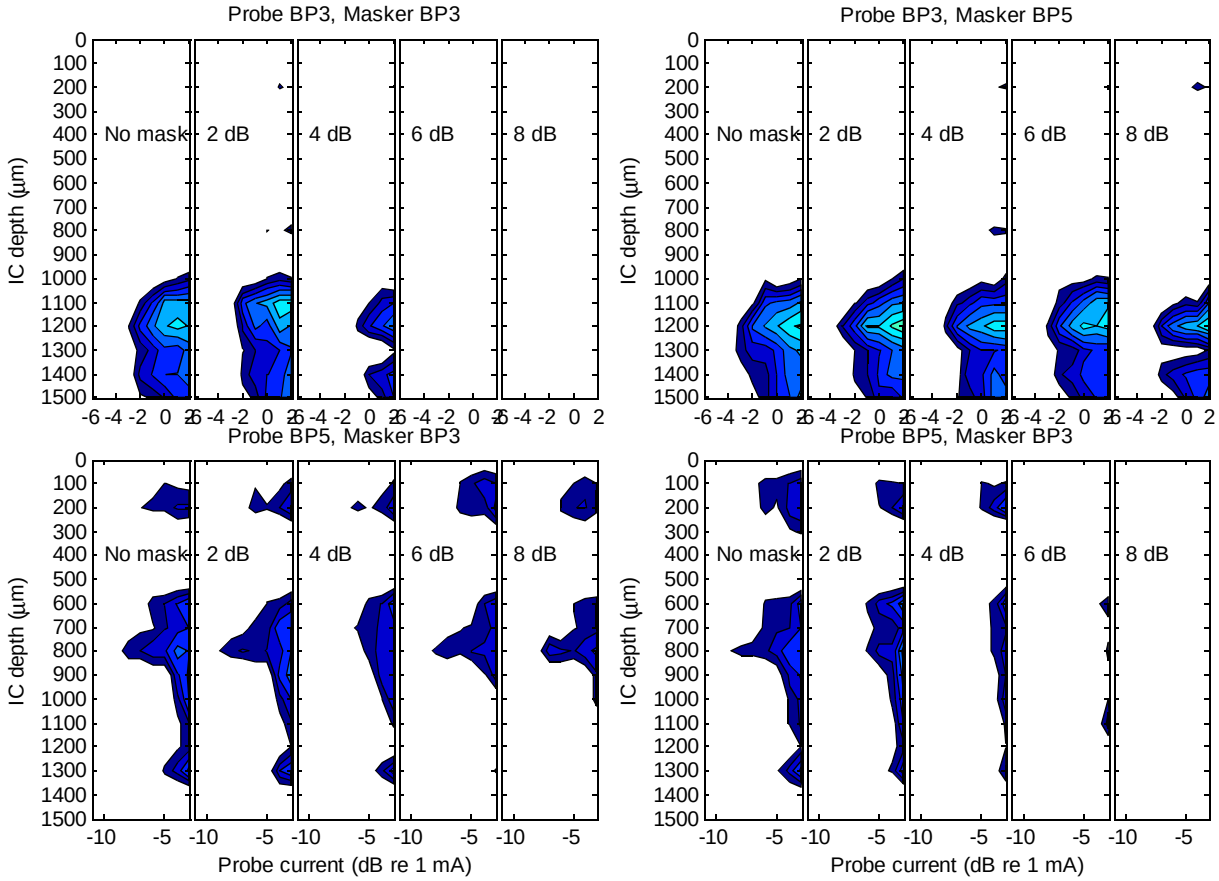

Figure 9: Masked spatial tuning curves for bipolar stimulation (GP0509).

The effect of relative location of cochlear masker and probe electrodes is demonstrated in the masked STCs in Fig. 9. Each block of 5 STCs represents a different combination of masker and probe channels. Within each block of 5, the current on the masker channel increases from left to right, from no masker (the unmasked probe condition) through 2 to 8 dB above the threshold for eliciting an excitatory response to the masker alone. In the upper left block of panels, a probe on channel BP3 was strongly masked by a masker on BP3. A masker 4 dB above the masker threshold elevated the probe threshold by 2 dB or more, depending on the recording site, and masker levels 6 and 8 dB above the masker threshold elevated probe thresholds to levels higher than were tested. In contrast, effects of masking on the BP3-probe threshold were considerably weaker when the masker was presented on channel BP5 (upper right block of panels). A 2-dB elevation of probe threshold was produced only by a masker at 8 dB above the masker threshold. A complementary result was obtained for a probe on channel BP5. Robust threshold elevation was observed when masker and probe both were on BP5 (lower right block of panels), and displacement of the masker to channel BP3 resulted in reduced masking. Note that in this example, the greatest effect of masker BP3 on probe BP5 was on the deep ICC sites that overlapped with the BP3 excitation pattern.

These comparisons of within-channel vs cross-channel forward masking show that forward masking is strongest when there is considerable overlap between the spread of activation by masker and probe electrodes. That overlap can result either from broad patterns of activation (as in

the monopolar configuration) or from presentation of masker and probe through the same electrode. The effect of overlap of masker and probe activation seemingly is stronger than the effects of ICC tonotopy. That is, there is relatively little effect of the magnitude of response of various ICC recording sites to particular maskers. Those observations lead to the "sub-ICC" hypothesis that the forward masking observed in the ICC is dominated by adaptation and/or inhibition occurring in the auditory nerve or in sub-midbrain auditory nuclei. Studies described in previous Quarterly Progress Reports have identified electrode configurations that minimize spread of activation, either by manipulating physical electrode geometry or by manipulating the relative current fractions that flow through multiple active and return electrodes. In continuing forward masking studies, we will explore the effects of those manipulations on spatial spread of forward masking.

Contribution of ICC Adaptation to Forward Masking

An alternative (or supplement) to the ICC-adaptation hypothesis is that the forward masking observed in a particular ICC neuron is due to adaptation of that neuron. That "ICC-adaptation" hypothesis predicts that the response of a given ICC neuron to a probe stimulus would be masked in proportion to the magnitude of that neurons response to the probe. All ICC neurons show robust phasic responses to the onsets of suprathreshold masking stimuli, but the extent of ongoing tonic responses varies among ICC neurons and varies with masker pulse rate. We are exploring the effects of pulse rate on forward masking as a means of manipulating the firing probability of ICC neurons at times near the end of masker pulse trains, close in time to the probe onset.

The responses of one ICC neuron to electrical pulse trains at various rates are shown in Fig. 10. The left panel shows a series of PST histograms. For pulse rates up to about 127 pps, the neuron showed clear phase-locked firing persisting throughout the duration of the 200-ms stimulus. At 180 pps, the response began to fade during the latter half of the pulse train, and the response was predominantly phasic at rates of 254 pps and higher. This transition from tonic to phasic firing at increasing pulse rates is consistent with previous reports (e.g., Snyder et al., 2000). The left panel shows the vector strength, which is a measure of the precision of phase locking. Phase locking was precise at low stimulus pulse rates and declined to around random chance levels at around 254 pps.

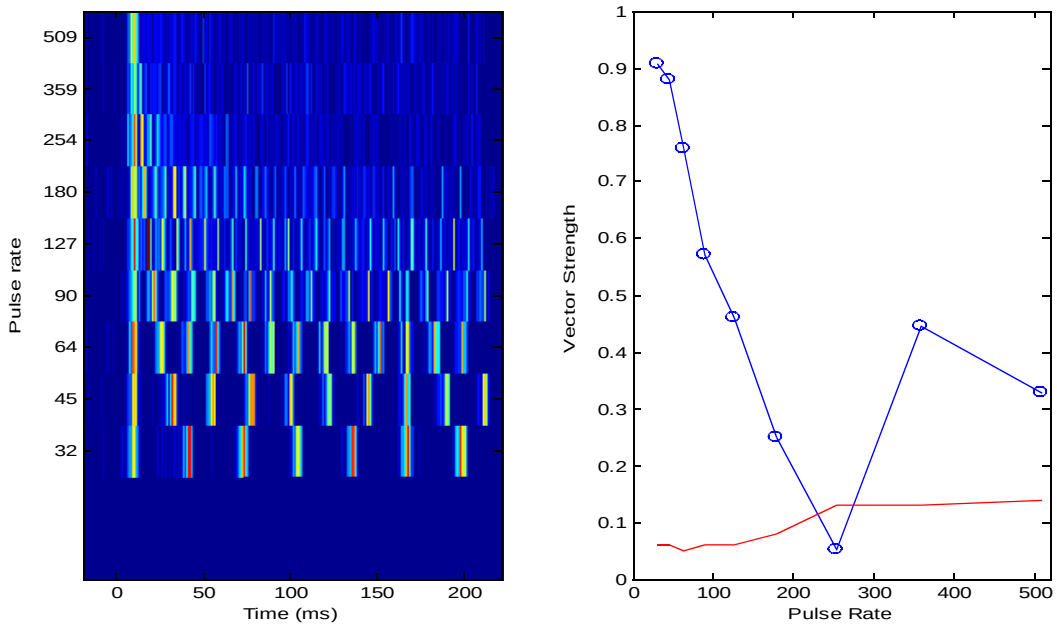

Figure 10: Responses to varying electrical pulse rates. Left panel: Post-stimulus-time histograms at elicited by various rates. Right panel: Vector strength (i.e., precision of phase locking) as a function of pulse rate. The red line indicates the Rayleigh criteria for significant phase locking. Data, shown by the blue line, lying above the red line are statistically significant at the $p<.001$ level.

We tested the effect of masker pulse rates on forward masking. Figure 11 shows data from the same neuron represented in Fig. 10. Each panel shows a PST histogram, with the 94-ms masker pulse train shown by the blue bar and the probe, a single electrical pulse, represented by the red square. Masker and probe were delivered through channel BP3, and the probe level was held constant at 4 dB above its unmasked threshold. Top, middle, and bottom rows show responses to pulse rates of 64, 254, and 4069 pps, respectively. In each row, masker levels increase from no masker to 2, 4, and 6 dB above threshold for a response to the masker. The delay between masker offset and probe pulse was 2 ms. The 64-pps masker produced a tonic phase-locked response. In the masked conditions, the probe response cannot be distinguished from the response to the last pulse of the masker, but a signal-detection analysis demonstrates a substantial threshold shift, even by the 2-dB masker. In contrast, the responses to the 254- and 4069-pps were considerably more phasic. Substantial shifts in the thresholds for detection of the probe were evident only at masker levels of 4 dB and higher. Figure 12 plots threshold shifts as a function of masker level for the three pulse-rate conditions. The 254- and 4069-pps maskers produced comparable thresholds, whereas masking by the 64-pps pulse train began at lower masker levels and produced greater threshold shifts.

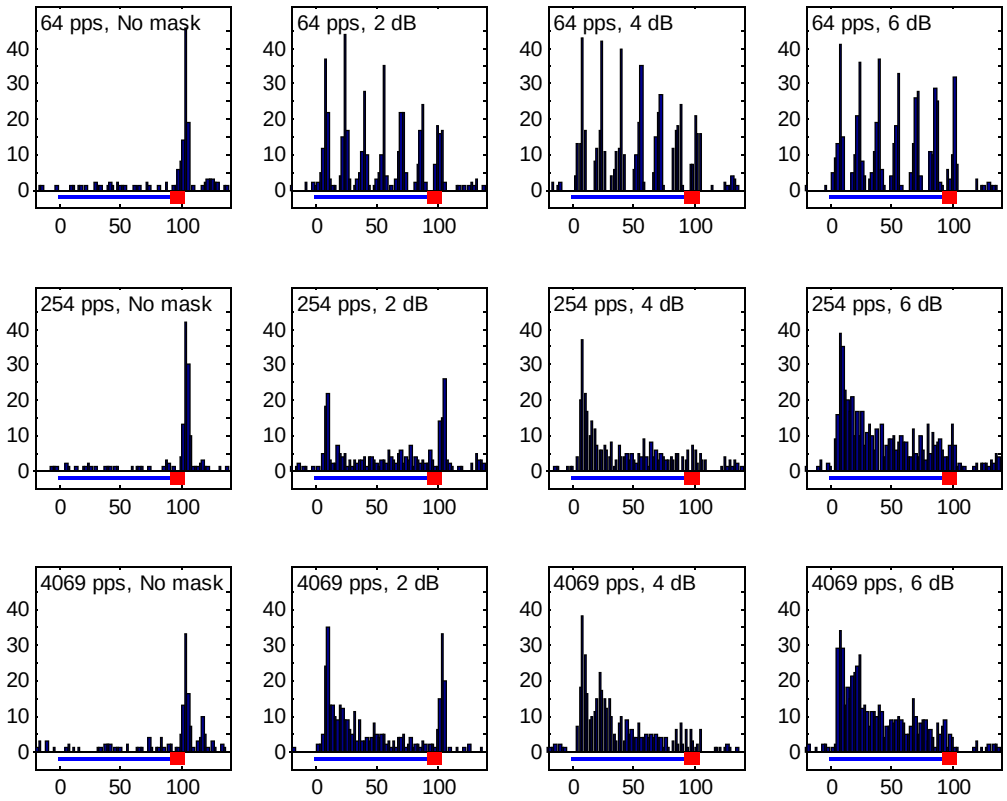

Figure 11: PST histograms showing effect of masker pulse rate on response to a probe.

The results from comparisons of forward masking by various pulse rates are consistent with the ICC-adaptation hypothesis in that pulse rates that produce tonic responses to the masker tend to produce stronger masking than pulse rates that produces predominantly phasic responses. We intend to extend our pulse-rate studies, testing conditions in which the probe response is not occluded by the response the end of the masker and varying the length of the masker, thereby varying the delay from the initial masker onset response to the probe onset. We are further testing the ICC-adaptation hypothesis by computing the probability of a spike elicited by a probe conditioned on the presence or absence of a spike elicited by the masker as a function of time prior to the probe onset. Results of that analysis so far are inconclusive, partly because of what seems to be a clear influence of sub-ICC adaptation and inhibition and partly because of the difficulties in dealing with a large parameter space. Future experiments will be guided by the practical motivation of attempting to minimize channel interaction in realistic stimulation paradigms and by the theoretical motivation of exploring the loci and physiological mechanisms of forward masking.

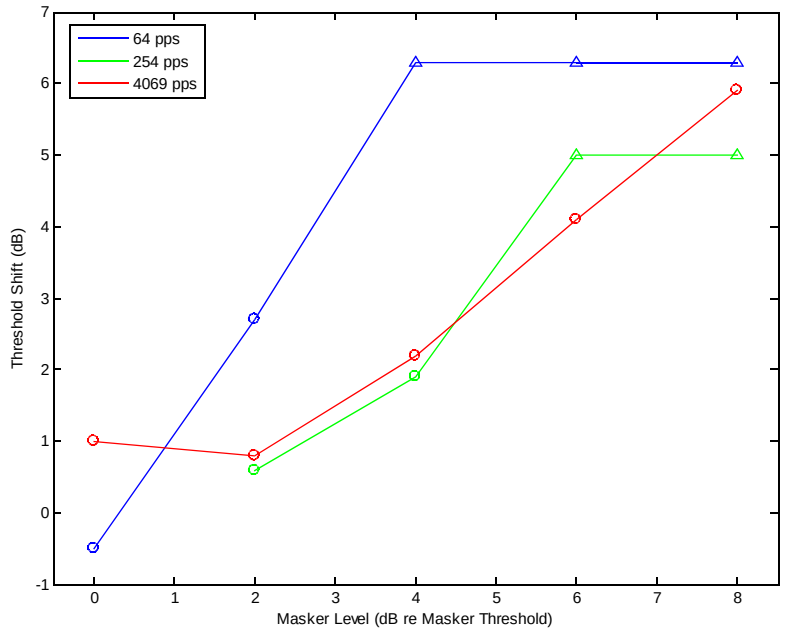

Figure 12: Threshold shifts as a function of masker level. Open triangles indicate masker levels at which probe thresholds were too high to measure.

References

Cohen, N.L., Waltzman, S.B., and Fisher, S.G. (1993). A prospective, randomized study of cochlear implants. *N Engl J Med* **328**, 233-237.

Fishman, K.E., Shannon, R.V. and Slattery, W.H. (1997). Speech recognition as a function of the number of electrodes used in the SPEAK cochlear implant speech processor. *J. Speech Hear. Res* **40**, 1201-15.

Friesen, L.M., Shannon, R.V., Baskent, D. and Wang, X. (2001). Speech recognition in noise as a function of the number of spectral channels: Comparison of acoustic hearing and cochlear implants. *J. Acoust. Soc. Am.* **110**, 1150-1163.

Gantz B.J., Tyler R.S., Knutson J.F., Woodworth G., Abbas P., McCabe B.F., Hinrichs J., Tye-Murray N., Lansing C., Kuk F. and Brown C. (1988). Evaluation of five different cochlear implant designs: audiologic assessment and predictors of performance. *Laryngoscope* **98**, 1100-6.

Middlebrooks, JC: Effects of cochlear-implant pulse rate and inter-channel timing on channel interactions and thresholds. J. Acoust. Soc. Am., 116:452-468, 2004.

Najafi, K., Wise, K.D. and Mochizuki, T. (1985). A high-yield IC-compatible multichannel recording array. *IEEE Trans Electron. Devices* **32**, 1206-1211.

Snyder, RL, Bierer, JA, and Middlebrooks, JC: Topographic spread of inferior colliculus activation in response to acoustic and intracochlear electric stimulation. J. Assoc. Res. Otol. 5:305-322, 2004.

Snyder, RL, Vollmer, M, Moore, CM, Rebscher, SJ, Leake, PA, and Beitel, RE: Responses of inferior colliculus neurons to amplitude-modulated intracochlear electric pulses in deaf cats. J. Neurophysiol. 84: 166-183, 2000.