1st Quarterly Progress Report

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Protective and Plastic Effects of Patterned Electrical Stimulation on the Deafened Auditory System

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INTRODUCTION

This is the first Quarterly Progress Report for the initial three month of funding of a new Contract. The primary objectives of this research, as stated in the Technical Specifications of the original Request For Proposals, are to evaluate *"how certain forms of chronic electrical stimulation of selected portions of the auditory system, and neurotrophic agents, maintain and possibly enhance the anatomical and physiological viability of the remaining auditory system after loss of hair cells, in a manner compatible with preserving and possibly extending the function of an implanted auditory prosthesis."* The specification required that studies be conducted in appropriate animal models of human acquired deafness, using both single and multiple channel stimulation for periods sufficient to evaluate their protective effects on neural structures. Possible protective effects are then to be evaluated by histopathological examination of the cochlea, auditory nerve and cochlear nuclei. In addition, changes in auditory function and underlying mechanisms are to be studied using neurophysiological, and, if appropriate, behavioral measures of auditory system activity. In order to achieve this latter objective, i.e., to better assess and understand changes in the deafened central auditory system function seen after chronic electrical stimulation, an initial goal of our research for this new Contract is the development of *multichannel recording methods and data analysis*. This report reviews the rationale for this approach, presents initial data obtained with the multichannel probe and discusses the complexities of comparing multichannel and conventional tungsten recording.

BACKGROUND

All of the electrophysiological studies reported by our group from previous Contracts have been conducted using standard tungsten microelectrode recording methods. In several previous publications we have examined the selectivity of neuronal responses evoked by cochlear electrical stimulation relative to the topographic (frequency) organization within the auditory midbrain (IC) (Snyder et al., 1990,1991,1995; Leake et al., 2000a,b; Rebscher et al., 2001). Specifically, thresholds to electrical stimulation were determined by conventional audio-visual criteria and plotted as a function of IC depth, generating what we have termed "spatial tuning curves" (STC) providing an estimate of the spread across frequencies, or selectivity of stimulation, in deaf animals (Fig. 1). These studies have compared STC data from: a) animals that were deafened, implanted as adults and studied acutely as controls; b) neonatally deafened, chronically stimulated cats -- including initial experimental groups that were stimulated on a single bipolar channel of the cochlear implant and later experimental groups in which subjects were stimulated on 2 channels; and c) neonatally deafened but unstimulated control animals examined at the same age and duration of deafness as stimulated groups. Data from this latter unstimulated/deafened group suggested that the precise cochleotopic (frequency) organization of the central nucleus of the IC developed normally and was unaltered despite the complete lack of normal auditory input during development in these animals. The spatial selectivity elicited with a standard bipolar intracochlear electrodes, at 6dB intensity relative to threshold was not significantly different from normal in this group (Fig. 2).

However, when neonatally deafened animals were chronically stimulated at a young age using a single bipolar channel of a cochlear implant, IC spatial selectivity was markedly altered, and a significant expansion of the central representation of the stimulated cochlear sector was observed (Snyder et al., 1990, Leake et al., 2000a,b). The area within the central nucleus of the IC (ICC) excited by the chronically activated electrodes at 6 dB above threshold was, on average, almost double that of identical electrodes in either unstimulated control deaf littermates, or in acutely-deafened adults (compare Fig. 1b,c; Fig. 2). This expansion represents a significant distortion and degradation of the frequency selectivity of the central auditory system.

SPATIAL (FREQUENCY) SELECTIVITY OF ELECTRICAL STIMULATION

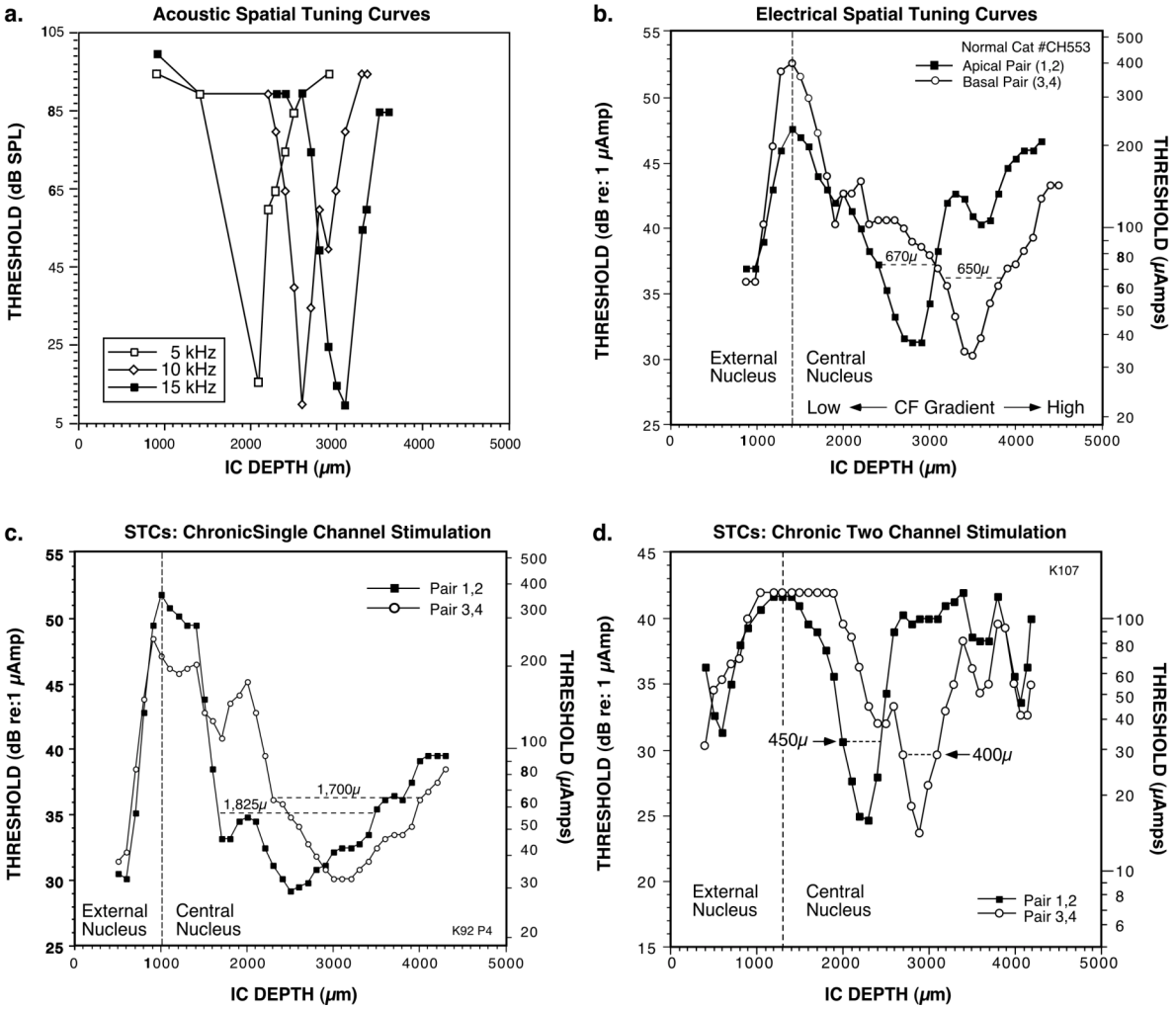

Figure 1. a. Spatial tuning curves (STC) or plots of thresholds recorded in a standardized trajectory through the central nucleus of the inferior colliculus [ICC], show the precise frequency organization in normal cats, which is the basis for 'mapping' the selectivity of electrical stimulation in deaf cats. Thresholds as a function of IC depth are shown in a normal cat in response to three tonal frequencies (5, 10, and 15 kHz). These acoustic spatial tuning curves (STC) show spread of excitation across the IC as a function of stimulus intensity for frequencies corresponding to the cochlear locations of our cat cochlear implant electrodes (apical channel ≈5 kHz; basal channel ≈15 kHz)**. b.** Electrical spatial tuning curves in a control cat acutely deafened and implanted as an adult. Thresholds (intermingled single units and multi-unit clusters) for the apical and basal bipolar channels of the implant are shown as a function of depth for one penetration through the IC. The apical channel (1,2) has its threshold minimum at a more superficial location due to its lower frequency location in the cochlea. The 2 channels excite completely independent, non-overlapping areas at 6 dB above threshold and have spatial tuning curve bandwidths of <700 μm. This corresponds to an STC bandwidth evoked by an acoustic tone delivered at roughly 50-60 dB SPL. **c.** Altered STC from a cat deafened at birth and chronically stimulated on a single bipolar channel (apical electrodes 1,2). The area in the midbrain excited by the chronically activated channel is greatly expanded (STC width=1.5mm), and at 6 dB above threshold it substantially overlaps the area activated by the basal channel. **d.** STC data from a subject that received stimulation on 2 channels using higher frequency, modulated pulse trains and stimulating 1 channel at a time, *alternating* between channels. Both channels maintained highly selective STC widths (450 and 400 μm), and the mean for all penetrations was 700 μm, actually more selective than the mean STC width recorded in normal cats. This is a striking contrast to the STC expansion observed with single channel stimulation, (See Leake et al., 2000b).

In contrast to the expansion observed after single channel stimulation, carefully controlled stimulation on two channels of the cochlear implant (delivered either concurrently or alternating between adjacent channels) may act to maintain more normal frequency selectivity. Figure 1d shows exemplary data from a subject that received chronic stimulation on 2 adjacent bipolar channels of the cochlear implant. In this case ***alternating*** stimulation of 2 channels using amplitude modulated, higher frequency electrical pulse trains, with the intensity set at 2 dB above EABR threshold for each channel, was effective in maintaining (or perhaps even sharpening) selectivity of central representations of stimulated cochlear sectors. As summarized in Figure 2, the data suggest that competing inputs from electrical signals delivered on 2 competing channels, can ***maintain*** the selective representations of each activated cochlear sector within the central auditory system and prevent the expansion and degradation of frequency selectivity seen after single channel stimulation (Leake et al., 2000a,b). We believe these results indicate that the developing central auditory system is capable of substantial plasticity and functional remodeling. The area excited by the stimulated cochlear neurons may become altered over time as the central auditory system adapts to the only available afferent input.

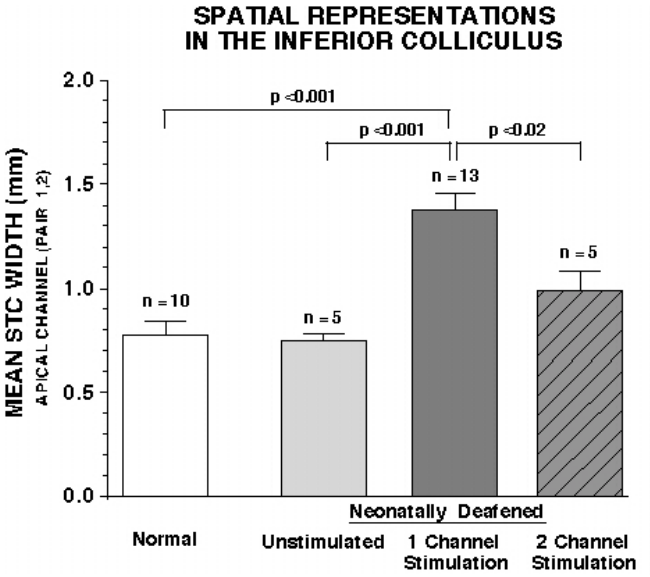

Figure 2. Summary graph of average electrical STC widths in 4 experimental groups (6 dB width, apical channel, averaged for all recording sites in each cat; error bars = SD). STC width in 10 prior-normal controls was 0.78 mm; the mean in 5 neonatally deafened, unstimulated cats was virtually identical at 0.74 mm. The single-channel intracochlear stimulation group had a mean STC width of 1.39 mm; and the 2-channel stimulation group had a mean of 1.00 mm. *Thus, the mean STC width for single-channel stimulated animals was expanded to almost double that of controls and deafened, unstimulated subjects,* ***but chronic 2-channel stimulation maintained more selective STC widths that were not significantly different from normal*** **(Figure taken from Leake et al., 2000b).**

Again it should be emphasized that Figure 2 shows data from highly controlled 2-channel stimulation experiments in which the thresholds on the 2 channels were well matched. In contrast, in other subjects when *simultaneous* stimulation was delivered on 2 channels of a model analogue cochlear implant processor or in subjects in which thresholds on the 2 channels differed greatly, stimulation *failed to maintain* channel selectivity and elicited marked expansion and fusion of the central representations of the activated channels. These potentially important findings (Leake et al., 2000b) suggest that under suboptimal conditions the central auditory system may not discriminate simultaneous inputs from 2 adjacent implant channels as distinct, resulting in pronounced degradation or distortion in central representations. As we have emphasized in our published reports, we believe that central representations in these animals can be highly variable and idiosyncratic, because they are *markedly influenced* by intersubject variables like threshold, neural degeneration, individual stimulation history, and especially the selectivity of initial stimulation elicited by individual channels of the cochlear implant.

Research in other sensory systems (particularly the visual system), has demonstrated that the initial sensory input during early development initiates a *critical period*, after which organizational changes driven by aberrant or distorted initial inputs are largely irreversible (see Cynader and Mitchell, 1980 for review). If the changes in the auditory midbrain seen in our single-channel experiments and in the 2-channel analog processor subject above were *irreversible*, they would likely limit the efficacy of subsequent selective multichannel stimulation. Unfortunately, this clearly can be a problem in very young children using a cochlear implant, because fitting a processor and setting channel loudness levels is so difficult. If one channel initially is set at too loud an intensity, it may dominate the input, perhaps producing the type of distortions seen in our single-channel experiments (Leake et al., 2000a,b). Given the potential importance of these findings, an important goal for our future studies is to determine if expansion of central auditory representations driven by *initial* single-channel stimulation after neonatal deafening is *reversible* if competing inputs from multiple channels of an implant are introduced subsequently. However, we believe that in order to adequately address this goal and also to improve efficiency of electrophysiological studies of multichannel interactions, we will need more efficient new methods for recording from the IC. Specifically, we will utilize multiple-channel silicon recording probes obtained from the Center for Neural Communication Technology at the University of Michigan, Ann Arbor, MI (Fig. 3).

1. Examination of Neuronal Responses Recorded *Simultaneously* at Multiple Sites Across the IC Using Multichannel Recording Probes.

An example of a single-tine 16-channel silicon probe is shown in Figure 3. Experiments to date have utilized primarily this probe, which has 16 recording sites separated by intervals of 100 µm, thus spanning a length of 1.5 mm. The multichannel probes are inserted along a standardized trajectory, parallel to the IC frequency gradient, as in our previous studies with conventional tungsten recording electrodes (Snyder et al. 1990,1991; Leake et al., 2000b, Vollmer et al., 1999).

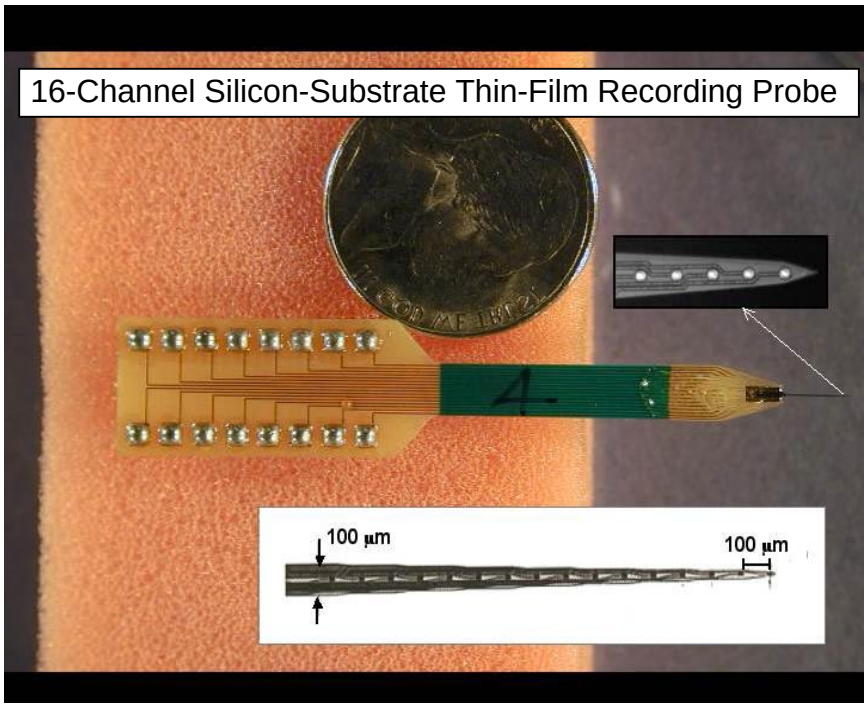

Figure 3. An example of a multichannel recording probe provided by the Center for Neural Communication Technology at the University of Michigan, Ann Arbor for these studies. Initial probes had 16 recording sites at 100 µm intervals and thus allowed simultaneous recording of neural activity over a 1.5 mm depth in the IC. These probes have been used for the initial studies in cats reported here. Recently, *longer* 16-channel probes have been manufactured with a 200 µm separation between recording sites, which allow recording over a 3000 µm distance, to better cover the frequency range of ≈2-20kHz in the cat ICC.

Initial studies to develop the multichannel recording system were conducted in guinea pigs (under a separate project) because they are inexpensive, easier to work with and have a smaller IC. The portion of the guinea pig ICC that is tuned to frequencies between about 2 and 20 kHz is about 1.5 mm, exactly the length of the 16-channel probes that were initially available (Fig. 3). However, to encompass a similar range of frequencies in the cat ICC and also to define the border with the external nucleus requires a probe at least twice that length. More recently 5-mm 16-channel probes with recording site separation of 200 µm - spanning 3000 µm - have become available. Figure 4 illustrates initial data recorded with this new probe in a normal-hearing cat. Neural frequency response areas to acoustic tonal stimuli (tuning curves) are shown as recorded from the ICC. Recordings obtained *simultaneously* on eight of the 16 channels have been selected to illustrate the range of frequencies in the IC encompassed by these probes, i.e., in this case about 5 kHz to about 30 kHz. This range is sufficient to bracket the range of frequencies accessed by our current cat cochlear implants (on average, about 5 to 15 kHz). Thus, in normal (control) subjects, the silicon probe can be inserted to an appropriate depth as determined by responses to acoustic tones and the characteristic frequency (CF) at the location of each recording site documented. This acoustic "calibration" is then utilized to assign CFs to subsequent recordings of neural activity elicited by intracochlear electrical stimulation after the animal is deafened.

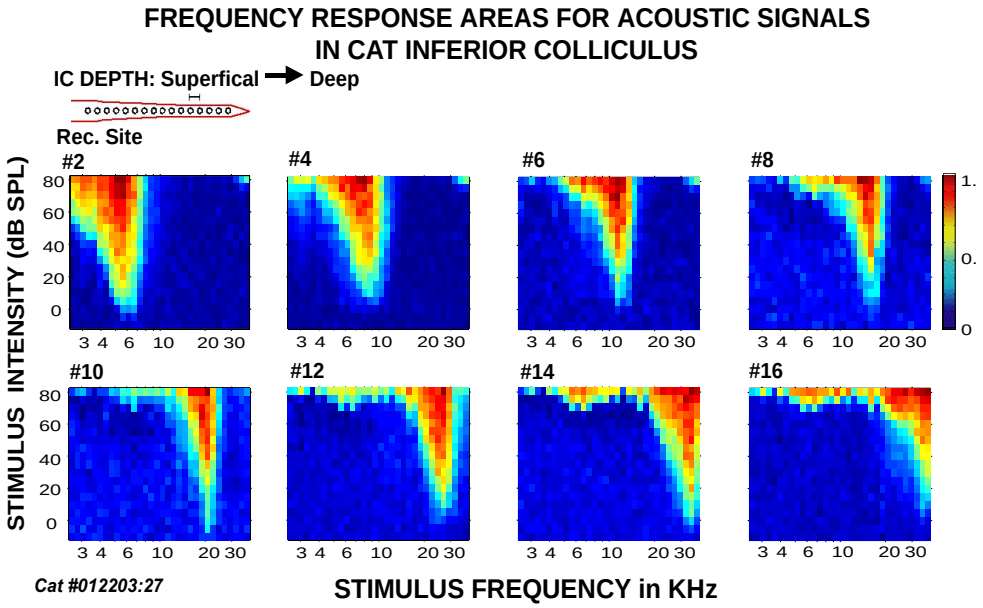

Figure 4. Data from cat IC, recorded with a 16-channel Michigan probe. This method allows us to record neural activity *simultaneously* from sites distributed across a large portion of the IC tonotopic gradient. The colors represent normalized spike rates (percent of maximum) as shown in the color scale at right. The data shown are responses to acoustic tones recorded on 8 of the 16 sites on a 5.0 mm probe. The sites are separated by 200 µm and are numbered from most superficial to deepest. Site 2 is tuned to about 5 kHz and site #14 is about 30 kHz. This is sufficient to bracket the frequency range stimulated with our cat implants.

Figure 5 presents representative multichannel recording data for electrical stimulation, showing patterns of activation in the ICC of a deaf cat for a 30 ms 100 Hz electrical sinusoid. In this display, the ordinate represents IC depth and the abscissa represents post-stimulus time. The upper row of panels shows responses at 4 different intensities to a bipolar pair of electrodes, pair <1,2>, stimulating neurons located at about the 5 kHz region of the cochlea. At low intensity the excitation is relatively restricted and centered at about 3 mm in the IC. As intensity is increased, excitation spreads across all depths of the IC (i.e., most of the represented frequency range). Clear responses to all 3 cycles of the electrical sinusoid also emerge at higher stimulus current levels. The lower row shows responses to an implant channel centered at ≈ 15 kHz cochlear place, electrode pair <3,4>. Its focus of activity is centered deeper at about 3.5 mm, in a higher frequency region of the IC.

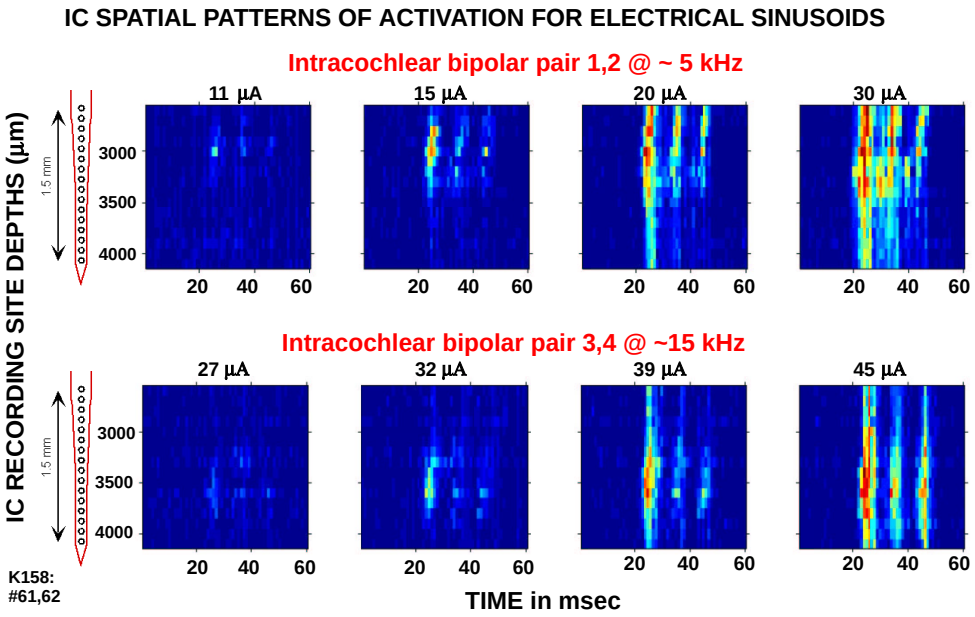

Figure 5. Patterns of neural activity elicited in cat ICC by electrical sinusoidal stimulation of the cochlea. The upper row shows responses to activation of a bipolar pair of electrodes (pair 1,2) located at about 5 kHz in the cochlea. At low stimulus intensities (left) we see restricted excitation centered at about 3 mm IC depth. At higher stimulus levels excitation spreads across all depths (frequencies), and responses to the 3 cycles of the 30 ms 100 Hz sinusoid emerge. The lower row shows responses to a second intracochlear bipolar pair located at about 15 kHz. Its focus of activity is centered at about 3500 µm, in a higher frequency region of the IC. Simultaneous recording from multiple sites in the IC is more efficient than traditional tungsten microelectrode recording.

Multichannel recording obviously provides a much more efficient approach to characterizing responses and mapping spread of excitation as compared to standard recording with tungsten microelectrodes. We can essentially record an entire STC function *in about half an hour*, in comparison to 7-8 hours of recording time to complete a penetration with conventional microelectrodes. Multichannel recording and the 3-dimensional data matrices (i.e., recording site, stimulus intensity, post-stimulus time) generated also will greatly facilitate examination of complex stimuli and phenomena such as channel interactions.

One ultimate goal for these experiments will be to develop *chronic recording with multichannel probes*. This would provide the most direct approach to determining whether deleterious effects of initial stimulation such as spatial expansion of representations are reversible, (i.e., "*whether animals deafened and stimulated when young with stimuli that induce plastic alterations are reversible when the animals mature"* as required by the specifications for this new Contract). Recording chronically in implanted animals would provide compelling evidence, by directly demonstrating alterations induced by initial suboptimal (e.g., single-channel) stimulation and documenting in real-time the course of any reversal of these effects that might (or might not) occur with subsequent introduction of optimized stimulation strategies. However, there are myriad difficult technical challenges that must be addressed before we can realistically propose to undertake such *chronic* multichannel recording experiments. The studies we are currently conducting, as presented below, are providing valuable experience with the Michigan probes and will lead to further development of our multichannel recording set up, spike discrimination/sorting techniques, data analysis software, etc., all of which are prerequisite to attempting chronic experiments. Appropriate connectors and other hardware necessary for chronic recording with these probes are currently under development at Center for Neural Communication Technology at the University of Michigan. If work proceeds on schedule, we hope to be in a position to consider chronic experiments in the final year of this new Contract period, or at least in a subsequent renewal period.

2. Comparison of Spatial Tuning Curves Recorded with Tungsten Microelectrodes and Response Images Recorded with Silicon Multichannel Recording Probes.

One initial goal of experiments conducted with the silicon probes is to characterize in detail the central processing of signals that simulate specific features of signals used in CIS and to compare responses recorded from the probes with similar data obtained with our conventional tungsten recording methods.

To demonstrate some of the specific technical issues being addressed in the development of multichannel recording methods in cats, the figures presented in this section of the QPR will compare data from one tungsten electrode penetration and one silicon probe penetration in the same animal. The animal was a deafened, chronically stimulated cat, and responses were elicited by electrical stimulation of the cochlea. In these examples, the electrical stimulus was an a 100 Hz electrical sinusoid 30 ms. in duration (i.e., 3 cycles). During the first (tungsten) penetration, thresholds were identified audiovisually. As the tungsten electrode was advanced through the IC, thresholds to bipolar stimulation of intracochlear electrode pairs <1,2> and <3,4> were determined individually, using our standard audiovisual criteria at 42 locations separated by 100 µm intervals from dorsal to ventral through the IC. The thresholds for the apical intracochlear electrode pair <1,2> (positioned at about 5 kHz cochlear place) plotted as a function of IC depth are shown as a white line in Figures 6a and b. These functions represent our standard spatial tuning curves (STC). For electrical stimulation delivered on electrode pair <1,2> the tungsten-recorded STCs exhibited two minima (Fig. 6). One minimum occurred at approximately 900 µm, which is within the physiological boundaries of the external nucleus, and a second is seen at approximately 2900 µm, within the boundaries of the central nucleus of the IC (ICC).

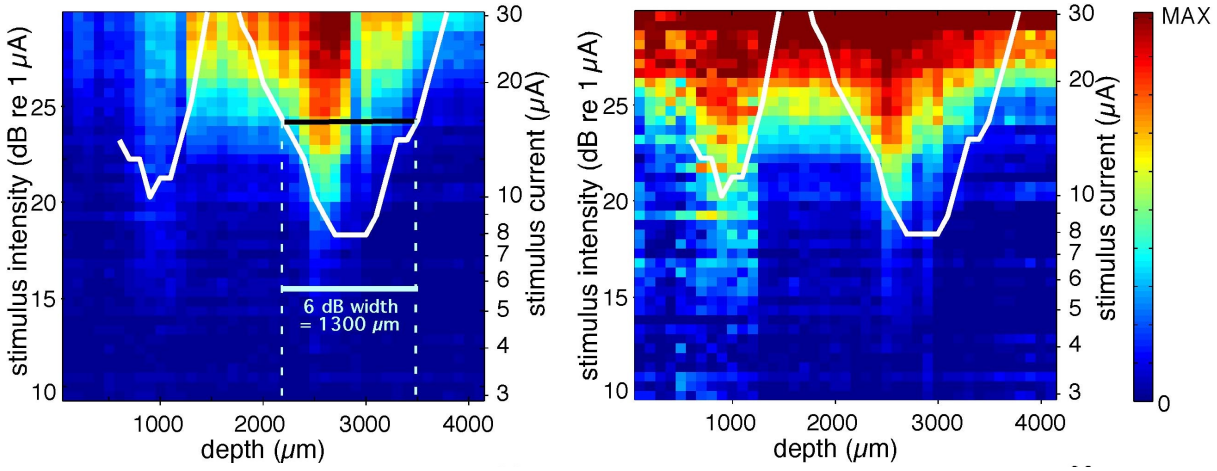

Figure 6. Threshold vs. depth or STC functions for tungsten recording (white lines) penetration compared with patterns of neural activity recorded with the multichannel probe (colored pixel displays) in the IC of the same cat. The responses were elicited by electrical sinusoidal stimulation of the cochlea with activation of a bipolar pair of electrodes, pair <1,2> located at about 5 kHz in the cochlea. At low stimulus intensities restricted excitation is centered at about 2900 µm ICC depth. At higher stimulus intensities excitation spreads across all depths (frequencies) of the IC. STC width is 1300 µm at 6 dB above minimum threshold. In panel **a** the probe data are displayed as the number of spikes recorded above the background rate during 20 stimulus presentations at each location as indicated by pixel color. (See color scale at right.) In panel **b** the probe data from Figure 6a have been normalized by dividing number of spikes recorded at each location and stimulus intensity, by the maximum number of spikes recorded at that location (usually recorded at the highest stimulus intensity).

The STC function for the more basal stimulating electrode pair <3,4> (positioned at about 15 kHz cochlear place) is shown as a white line in Figures 7a and b. This STC function also exhibited two minima -- one at approximately 800 µm and a second at approximately 3000 µm, again corresponding to the external and central nuclei, respectively. Comparing the STC in Figures 6 and 7, we see that in the external nucleus, the threshold minimum for electrode pair <1,2> was deeper or more ***ventral*** than the <3,4> minimum, which is consistent with the tonotopic gradient in that nucleus (i.e., high-to- low frequency gradient, opposite to the ICC frequency gradient). In the central nucleus, the minimum for the <1,2> pair occurred ***dorsal*** to the minimum for pair <3,4>, which is consistent with the well-known low-to-high tonotopic gradient in the ICC. The minimum threshold for the <1,2> pair was about 18 dB (dB re 1 µA), corresponding to 8 µA. The minimum threshold for the <3,4> pair was 29 dB, corresponding to 28 µA. The threshold variation, or the difference between the stimulus intensity at threshold and the intensity at which all recording sites in the IC were activated, comprises a basic measure of neural dynamic range. This difference measured for the <3,4> pair was about 7 dB (36-29 dB), substantially less than the dynamic range seen for pair <1,2> pair (more than 12 dB). Moreover, when measured at 6 dB above threshold the STC width or area of the IC activated by the electrical stimulus for pair <1,2> was 1300 µm. In contrast, 6 dB-STC width was 2000 µm for the pair <3,4>, i.e., considerably broader and less selective activation reflecting its higher threshold and smaller dynamic range.

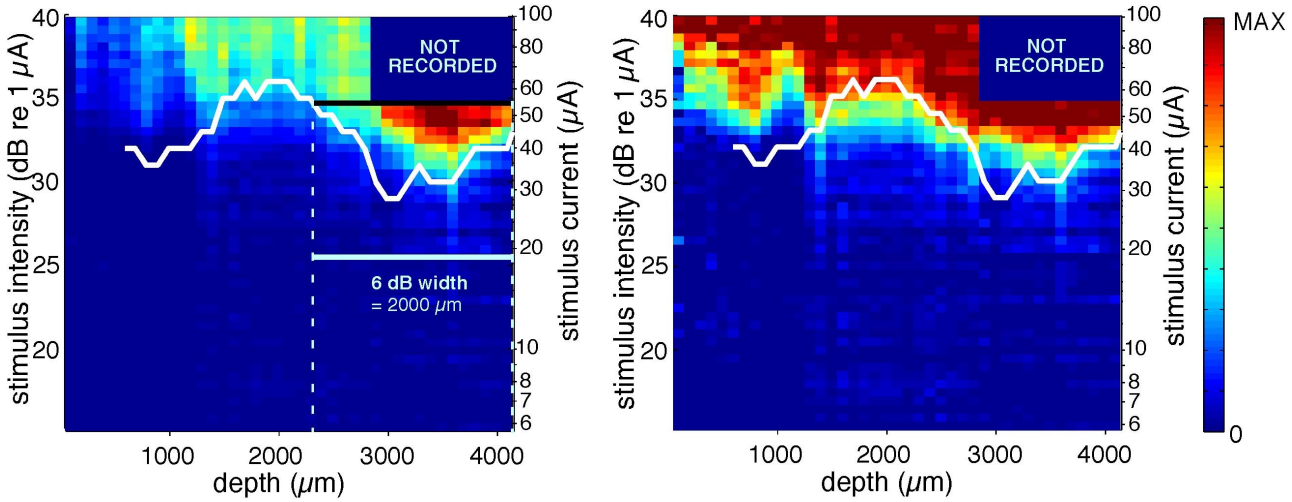

Figure 7. STC functions for tungsten recording (white lines) penetration compared with neural activity recorded with the multichannel probe (colored pixel displays) in the IC of the same cat shown in the previous Figure. The responses were again elicited by electrical sinusoidal stimulation of the cochlea, but in this figure, stimulation was with the bipolar pair of electrodes, pair <3,4> located at about 15 kHz in the basal cochlea. STC width is 2000 µm at 6 dB above minimum threshold. The solid blue rectangle in the upper right of each figure indicates levels/locations at which no recording was done. **a.** The number of spikes recorded above the background rate during 20 stimulus presentations at each location is indicated by pixel color. **b** The data from Figure 7a have been normalized by dividing number of spikes recorded at each location and stimulus intensity, by the maximum number of spikes recorded at that location (usually recorded at the highest stimulus intensity).

Data recorded from a second penetration through the IC using a 1.5 mm 16-channel silicon probe are also shown in each of the figures as colored pixel displays. The second penetration was made along a track parallel to and as close as possible to the first tungsten penetration. As the probe was advanced, data again were recorded from 42 electrode locations spaced 100 um apart. Since the probe was only 1.5 mm long, this sample represents data compiled from three partially overlapping probe depths in order to encompass the IC depths (frequency

range) excited by the intracochlear stimulating electrodes. The sinusoidal stimulus was presented 20 times at each intensity. The number of spikes recorded above the background rate during these presentations at each location is indicated by pixel color in figures 6a and 7a. Note that the increase in number of spikes recorded at a location with a small maximum number of spikes (e.g., at the depths of 1200 and 2900 μm in Fig. 6a) is coded with a color near the (dark blue) background level. Thus, setting a threshold criterion corresponding to an absolute number of spikes above the spontaneous background level likely would miss small but highly significant increases in spiking at such sites. The consequent misidentification of threshold could be problematic for comparisons with thresholds recorded audiovisually during the tungsten electrode penetration.

Alternatively, the threshold criterion can be set based upon the number of spikes recorded relative to the maximum at each location. Data from Figures 6a and 7a can be normalized by dividing number of spikes recorded at each location, for each stimulus intensity, by the maximum number of spikes recorded at that location (generally recorded at the highest stimulus intensity). These normalized data are presented in 6b and 7b, respectively. The normalization enhances the response from electrodes that have low maximum rates. However, in this case responses recorded at locations that saturate above the maximum stimulus intensity presented are artificially increased by this manipulation. Despite the limitations of each of these criteria for threshold, it is noteworthy that a relatively close correspondence is seen between the tungsten and probe data in Figures 6 and 7, even though the data were collected in *different penetrations* through the IC.

Finally, as another alternative to the two methods depicted above, a threshold criterion can be constructed based upon the likelihood of observing a specific number of spikes given the spontaneous background rate. For example, suppose that observation of the spontaneous background activity at a particular location indicated that on average, one spike is recorded during any 30 ms interval. Three increasing intensities, A, B and C, of the 30 ms sinusoidal stimulus are then presented 20 times each. On average, one spike is recorded during stimulus A, 1.3 spikes are recorded during stimulus B, and 1.8 spikes are recorded during stimulus C. The conclusion that there is no increased response to stimulus A seems relatively straightforward, but what about stimuli B and C? If one models the background spike activity as a Poisson process (traditionally used for neuronal modeling) in which the occurrence of a spike is independent of other spikes, the answer can be determined analytically. The probability of observing 1.3 or more spikes is 0.08, and the probability of observing 1.8 or more spikes is 0.0004. Thus, one could conclude that the increase in response observed during stimulus B is not significant, whereas the increase in response during stimulus C is highly significant, and thus the response threshold lies somewhere between the intensities of B and C. Figures 8a and 8b show this type of probability analysis for the data depicted in Figures 6a and 7a, respectively. Each pixel is colored according to the likelihood of occurrence of the recorded number of spikes if no stimulus had been presented. This criterion provides a quantitative measure of threshold *without requiring measurement of the saturated response* at each location. The latter condition actually can be quite important for electrical stimulation, because in regions of the IC that have higher thresholds for a given stimulating electrode pair, it is often impossible to drive the elicited response to saturation without exceeding the safety (gassing) limits for intensity of stimulation with our platinum/iridium intracochlear electrodes. To date, this method for defining threshold in the multichannel recording is the one that appears best suited to our needs, although we will continue to explore alternatives as we gain more experience with this multichannel recording with the probes.

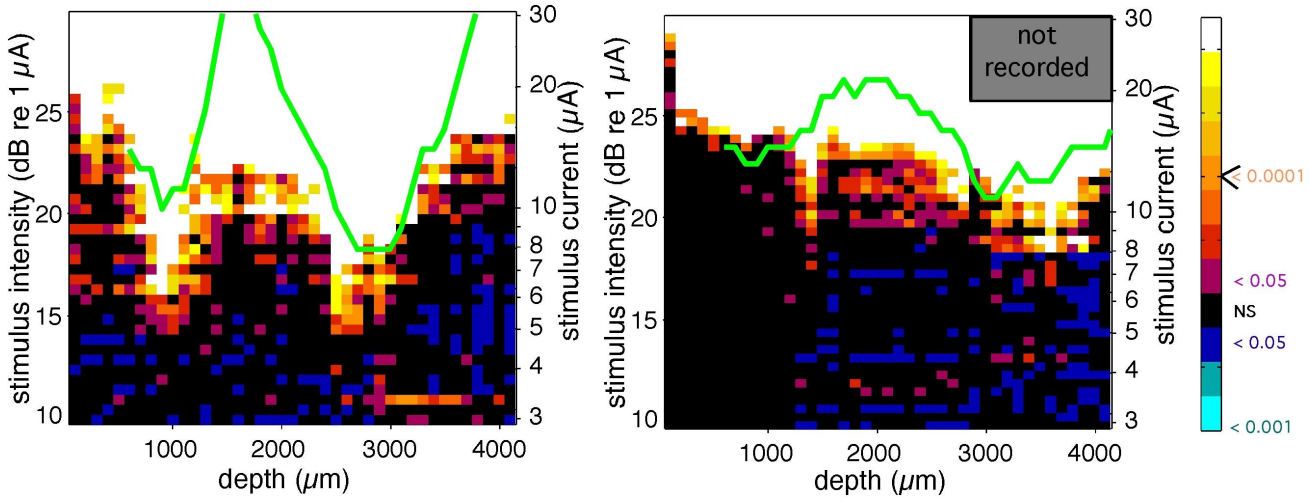

Figure 8. STC functions for a tungsten recording (green lines) penetration compared with neural activity recorded with the multichannel probe (colored pixel displays) in the IC of the same cat shown in the previous two Figures. The gray rectangle in the upper right in **b** indicates levels/locations at which no recording was done. The data from Figures 6a and 7a are shown in **a** and **b**, respectively, with the color scale representing likelihood of observing the number of spikes recorded at each location and stimulus intensity. Black represents background spontaneous activity, and all colors above black are significantly higher spike counts.

It is interesting to note that with all of the three criteria used above to define thresholds with the multichannel probes, some neural activity was recorded on the probe at levels significantly lower than the thresholds recorded with tungsten. This is true in the probability analysis even at a probability of < 0.000l (pixels coded in light orange or above as indicated by the arrowhead in Figure 8). Of course, this may just reflect a difference between the two penetrations in the IC. Additional experience with the probe and direct comparisons with tungsten recording are required to determine whether there is any systematic difference in response thresholds estimated with the two recording methods.

WORK PLANNED FOR THE NEXT QUARTER

1) Histopathological studies of cochlear specimens from chronically stimulated and control experimental animals will be continued for our new series in which the anti-apoptotic drug desmethyldeprenyl (DES) has been administered over the period of several weeks in deafened neonates until the time of cochlear implantation.

2) Daily chronic electrical stimulation will continue for two subjects and both will be studied in a terminal electrophysiological experiments during the next quarter. One of these animals has undergone stimulation using the Advanced Bionics BDCS processor.

3) Two new litters of kittens are expected during the next quarter and 2-3 littermate pairs will be selected for neonatal deafening and DES treatment with or without subsequent chronic stimulation. In these subjects DES treatment will be continued throughout chronic stimulation periods, rather than just in the interim period after deafening and prior to implantation.

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