The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #2

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Abstract

The principle activities of the team during this reporting period have concentrated on assessing long-term acute recording stability and obtaining frequency maps of auditory cortex resulting from ipsilateral and contralateral acoustic stimulation. During this period as well, the team has made a number of important contacts for potential collaborations that could greatly assist the analysis of the potential for functional restoration of auditory sensation. In addition, we continue to make progress in preparing for the chronic implantation studies with respect to the effects of electrical stimulation and structural/material biocompatibility.

1. INTRODUCTION

1.1. PROJECT GOALS

This contract has three specific aims: 1) develop an array of microelectrodes that is suitable for implantation into the auditory nerve, 2) determine the functional potential for this technology to provide a useful sense of hearing, 3) evaluate the risks and benefits of this technology prior to human experimentation. Activities in the first year of this contract concentrate on validating our proposed technique for accessing the auditory nerve, the dimensions of the array that will be implanted, and the spatial independence of the implanted electrodes. The second year will concentrate on other measures of the functional independence of the electrodes as well as the long-term biocompatibility of the array. The final year of the contract will finish the functional independence studies and center around the chronic electrical stimulation experiments.

1.2. PROGRESS REVIEW TO DATE

To date, we have established a surgical approach to the auditory nerve that is appropriate for both experiments in cats and humans; this approach has been tested in both acute and chronic cat experiments. This particular access to the nerve permits placement of an array of electrodes approximately 1.8mm x 2.2mm and containing 20 microelectrodes. We have shown in acute experiments that rapid pneumatic insertion of the array into the nerve does

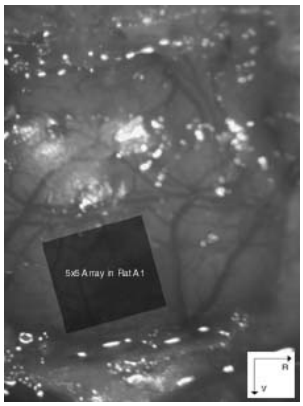
not prevent electrical microstimulation of the nerve from reaching higher auditory centers as measured by eABRs. Current thresholds for stimulation have been found to lie in 10μA-50μA range.

2. WORK DURING REPORTING PERIOD

2.1. ANIMAL ACUTE EXPERIMENTS

2.1.1. UNIT RECORDINGS FROM CAT AUDITORY CORTEX WITH UEA

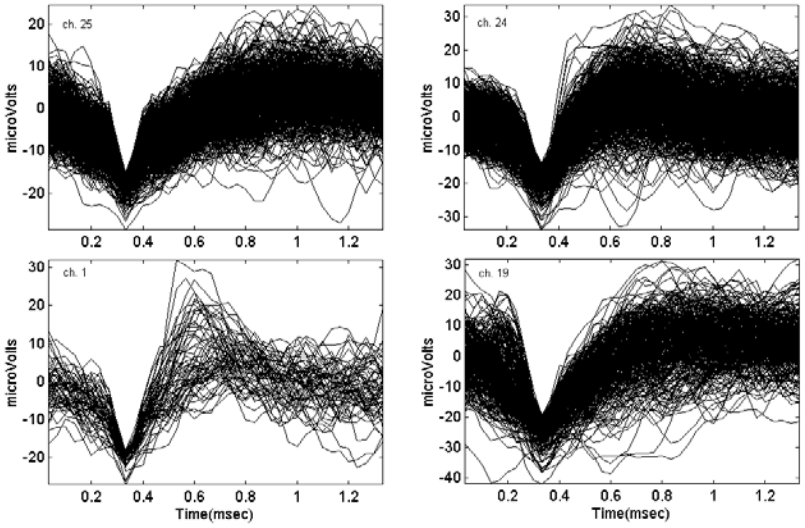
The purpose of these experiments are to demonstrate the feasibility of reliably recording from a large area of cortex using electrode arrays and to determine the consistency between cortical maps of ipsilateral and contralateral stimuli in AI. These data will form the basis for experiments intended to assay the functional selectivity of stimulating electrodes in the VIII nerve by examining the relationship between responses to electrical stimulation in contralateral A1 and the responses to acoustic stimuli in ipsilateral AI. Initial experiments were conducted in urethane anesthetized rats with 5x5 arrays. The stimulus consisted of pure tones (50 ms long) with ascending and descending linear ramps (5 ms duration). 256 such tones of varying amplitude and frequency with a 1 sec inter-stimulus interval were randomly interleaved.



A 25- electrode array was pneumatically inserted in to the primary auditory cortex A1 (about 500 microns from the surface of the cortex). The figure at left is a picture of the auditory cortex of a rat with the approximate location and size of the 5x5 UEA overlaid. Immediately on implantation responses were seen from very few channels. After 1-3 hrs we found that responses tended to be found on an increasing number of channels. A threshold was individually set for all channels. Events crossing the threshold were recorded.

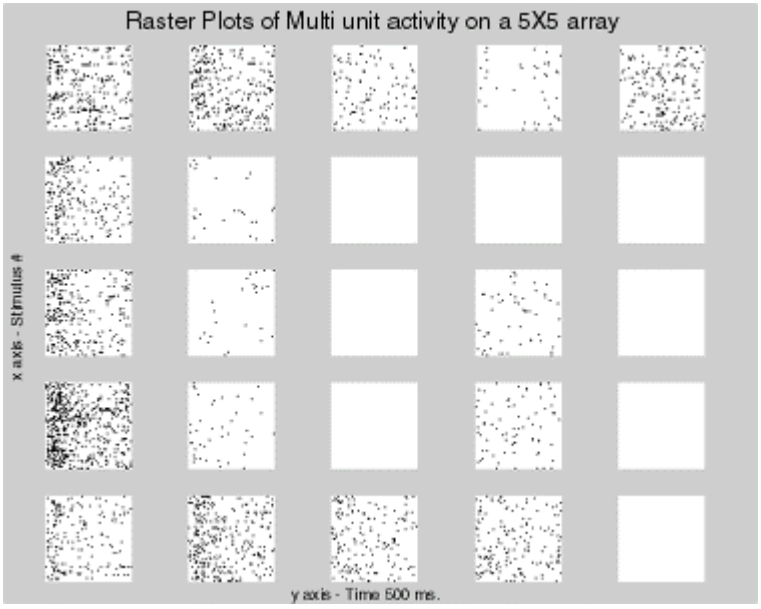
Multi-unit activity was recorded using a multichannel data acquisition system. Subsequently, off-line spike sorting algorithms were used for single-unit analysis. Only multi-unit responses are reported here. Multi-unit responses to pure tones and noise bursts were assessed to determine the location and geometry of primary

auditory cortex. This data was used to determine the optimal site and orientation for array implantation.



On the left the figure shows spikes from 4 channels that were sorted.

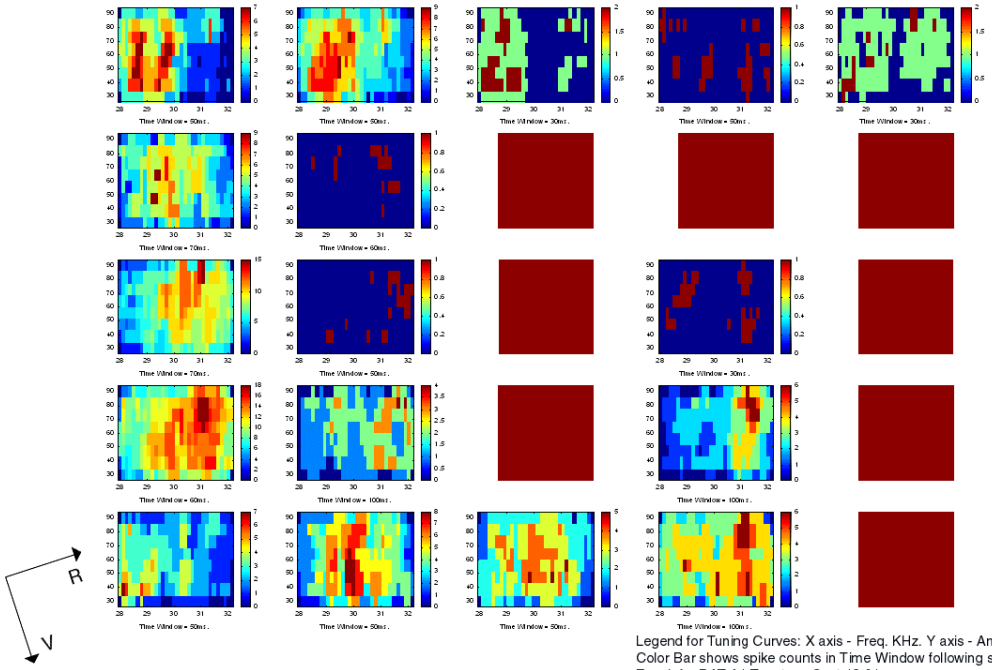
The spikes in a 500 ms. time window after the stimulus are plotted for each channel. Some channels did not yield activity. The raster plots were used to assess the time window to compute the tuning curves. The raster plot below is an example of evoked activity on 17 of the 25 channels in the array. Each line in the raster plot corresponds to the responses to one tone presentation; 256 such lines are shown for each channel, one for each tone presentation.



In each channel spike counts in a time window following the stimulus for each frequency and amplitude are plotted as a tuning curve. Tuning curves from a Rat

A1 are shown in Fig.1 in the appendix. Each pixel of the tuning curve plot shows spike counts elicited by a tone. It can be seen from the tuning curve of each channel that responses were not similar for all tones. Based on the region of maximal response the characteristic frequency of the neuron is determined. The responses of the neuron were stable for up to the termination of the animal (approx. 8 hrs. later). Tuning curves were estimated from tones played ipsilateral to the implanted side of cortex. The characteristic frequency was similar for both kinds of stimulation. The figure below is the set of tuning curves obtained from simultaneously recorded neurons in rat A1. Although the tunings of these multiunit responses are broader than what is obtained with single microelectrodes, it is still possible to see a shift from low to higher frequencies as one moves rostrally.

Fig 1. 5x5 array in rat A1 : The figure shows tuning curves obtained from multiple units across 25 electrodes simultaneously.

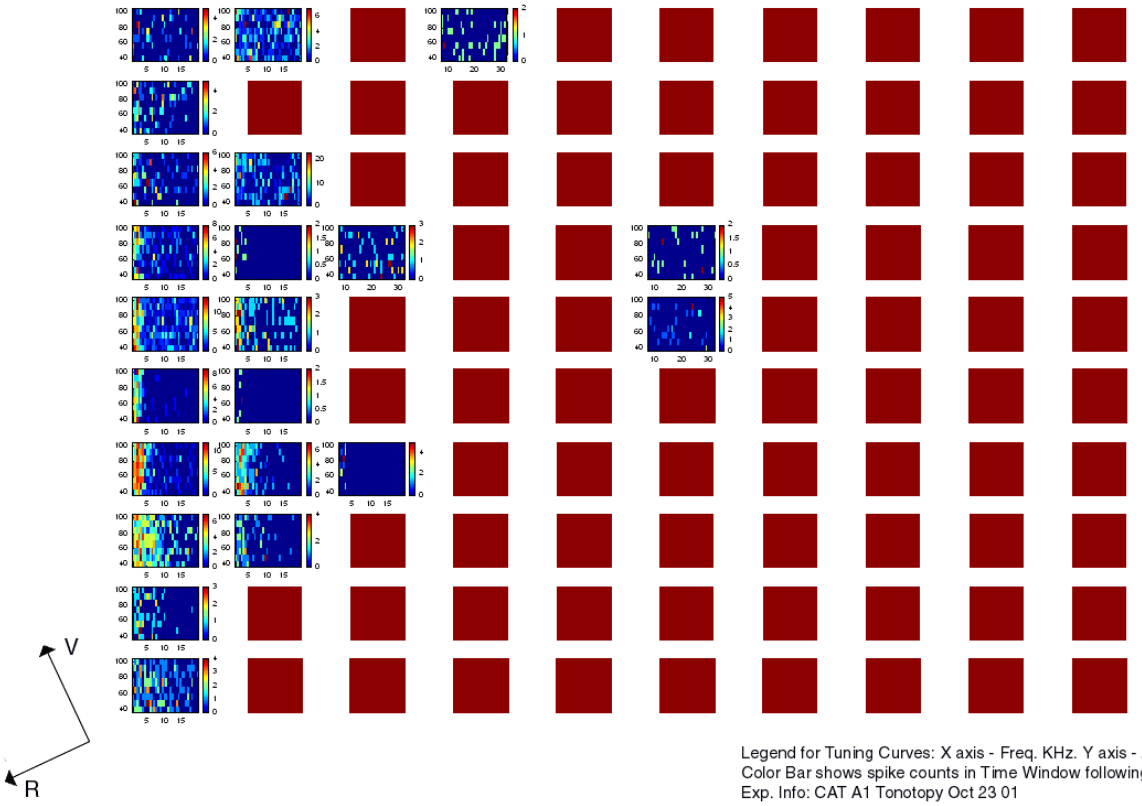


Legend for Tuning Curves: X axis - Freq. KHz. Y axis - Amp. dB. SPL.
Color Bar shows spike counts in Time Window following stimulus.
Exp. Info: RAT A1 Tonotopy Sept 13 01

After initial success with 5x5 arrays in rats, which consistently yielded responses in 72% of electrodes that were implanted, we moved to using 10x10 arrays in cats. In cats, our initial experiments are to establish feasibility of use of recording arrays for cortical mapping of AI. The relationship between responses in AI to ipsilateral and contralateral monoaural acoustic stimuli (single-unit analysis) will

be documented. Cat auditory mapping experiments are being carried out in similar procedures to the above described rat experiments. Tuning curves obtained from one such experiment are shown below. The plot shows responses to contralateral acoustic stimulus. About 15 clearly tuned units can be seen from this plot. In the other channels stable recordings could not be obtained.

Fig 2. 10x10 array in cat A1 : The figure shows tuning curves obtained from multiple units across 100 electrodes simultaneously.

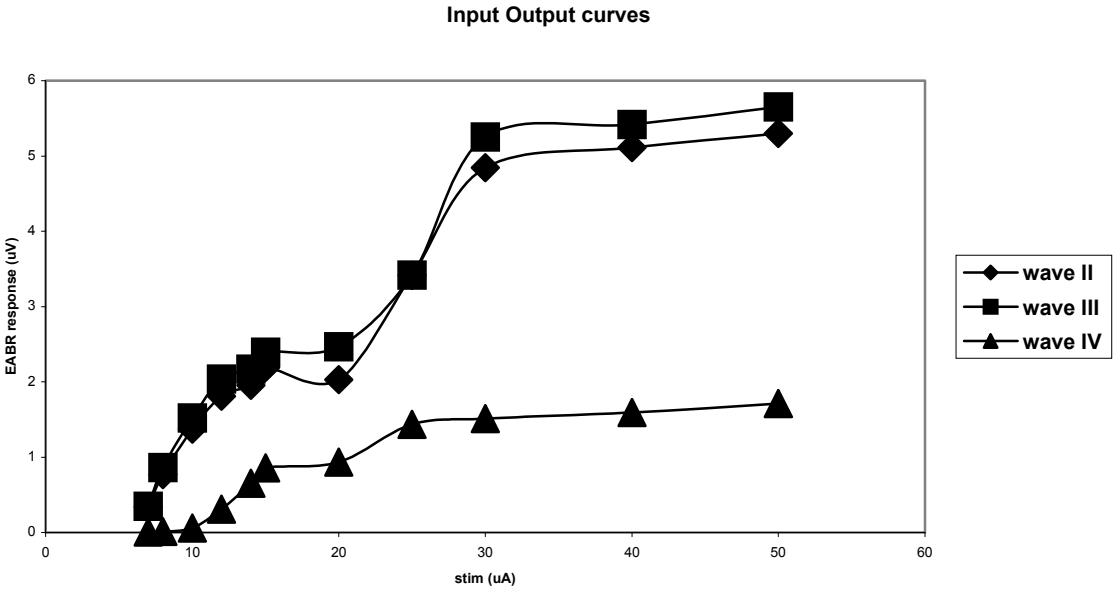


Legend for Tuning Curves: X axis - Freq. KHz. Y axis - Amp. dB. SPL.
Color Bar shows spike counts in Time Window following stimulus.
Exp. Info: CAT A1 Tonotopy Oct 23 01

2.1.2. 31-HOUR STIMULATION OF CAT AUDITORY NERVE

We were able to stimulate 150 of 164 implanted electrodes in the 12 cats to obtain EABRs. As all the electrodes were intact on explantation, this discrepancy cannot be explained as electrodes breaking on implantation. More likely is that variations in the manufacturing of the arrays resulted in microelectrodes that could not pass current. To establish the threshold stimulation current, the amplitude of stimulation was systematically varied till peak I and peak III appeared reliably and consistently. The thresholds of the EABR varied from 2μA to 140μA in 12 cats; the mean stimulation threshold was 10 ± 6.78μA (n = 150 electrodes in 12 cats). As a preliminary step to measuring the strength-duration curves for

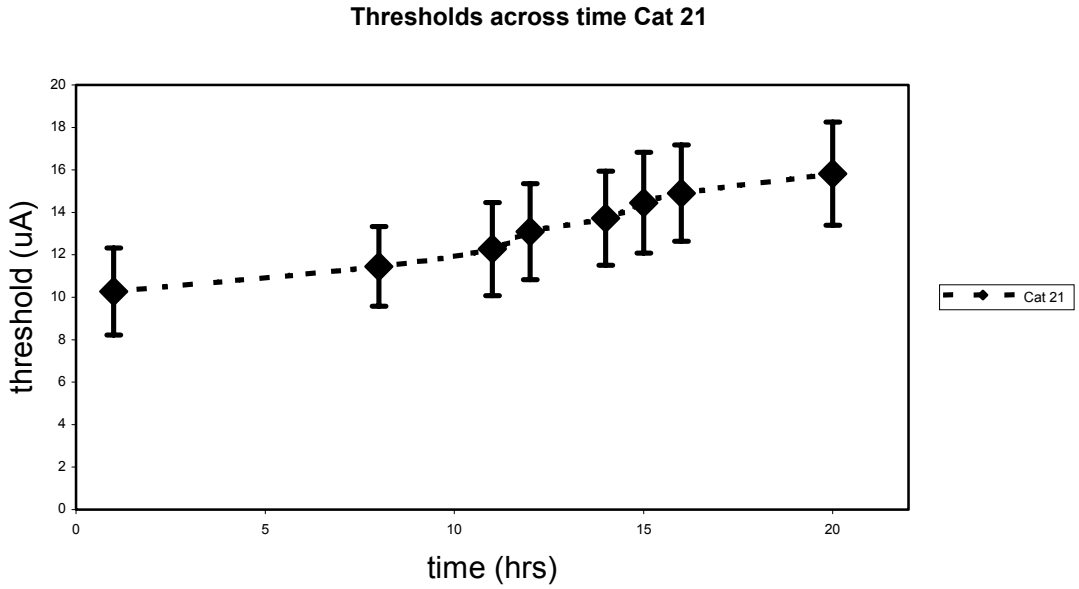
microstimulation, we have created input/output plots of the height of each peak in the EABR response for different stimulus levels. The dynamic range for one of the stimulated electrodes is shown below.



We obtained EABRs for 31 hours in one cat and for more than 20 hours in two cats to characterize the stability of threshold and quality of EABRs in a semichronic time frame. An example of the stimulation stability in one of the 20-hour preparations is shown below. The curve is the mean and standard deviation of the functioning electrodes plotted as a function of the time post-implant. Electrodes with an initially high threshold tended to have increasing thresholds over the duration of the implant. A *post facto* analysis of the position of these electrodes revealed that these electrodes tended to be on the periphery of the implant site suggesting that these electrodes may not have been in the nerve at all. Aside from this limited number of failures, the thresholds of the remaining electrodes were relatively stable in the experimental time frame.

At the time of sacrifice, a visual inspection was performed on the site of implantation and of the explanted UEA. In all cases there was no visual hemorrhage into the implanted site as evidenced by both unaided eye examination of implanted site as well as microscopic examination with x40 magnification. None of the explanted UEAs had any broken electrodes and the microelectrode

morphology was undistinguishable from unimplanted UEA under x40 magnification.



2.2. Animal Chronic Experiments

Two more animals have been implanted with passive devices during this period and have recovered remarkably well given the invasiveness of the surgical access.

2.3. Human Temporal Bone and Imaging Studies

This work continues to progress well with three of the five heads imaged and the auditory nerves bilaterally dissected. Based on feedback at the Neuroprosthesis meeting about our results concerning the dimensions of the exposed nerve, we are in the process of validating our measurements. We expect that by the next reporting period, this work will be completed and the importance of pre-operative imaging established for an intraneural auditory prosthesis.

3. Plans for Next Reporting Period

3.1. Acute Experiments

This quarter we will make a significant push in the areas of the spatial and functional selectivity of electrical stimulation through electrodes organized either as a flat or sloped plane. The spatial selectivity experiments will take two distinctly separate tact's: 1) build on our success at obtaining recordings from arrays implanted in cat A1 and map the selectivity cortically and 2) expose the auditory nerve as it enters the

brainstem and record compound action potentials resulting from stimulation of the nerve. In collaboration with Dr. Blake Wilson, we plan to stimulate the cochlea via a cochlear electrode array while obtaining recordings from the axons around the tips of our microelectrode arrays. This procedure should give us rough estimate of the distributions of frequencies of the en passant fibers and allow us to compare planar and sloped electrode array geometries.

3.2. CHRONIC IMPLANTS

3.2.1. PASSIVE IMPLANTS

As the passive chronic implants are progressing, this is the quarter that we will finalize our collaboration with the House Ear Institute to get their assistance in evaluating the implanted auditory nerves.

3.2.2. ACTIVE IMPLANTS

3.2.2.1. STIMULATOR DEVELOPMENT

The development of a multi-channel stimulator for the 60-hour stimulation requirement of this contract remains a challenge. After some modifications of the device designed by our collaborators in Spain, we have begun the process of decreasing the size of the device to fit unobtrusively on the back of a cat and to improve the battery life performance. Based on our testing of the device, it should be capable of independently stimulating 16 of the 20 implanted electrodes at the frequencies specified in the contract proposal. We will also continue to explore the potential of adapting Phil Troyk's (Illinois) or Kensall Wise's (Michigan) multichannel stimulators to our needs.

3.2.2.2. EABR SYSTEM

We have acquired all of the parts for our EABR system and have begun the process of integrating the system components. As the system is designed, we will have maximum flexibility in the types of waveforms we can produce and how those waveforms are routed to the implanted electrodes. This system will allow us to automate the process of obtaining EABR in both chronic and acute preparations as well as allow use to investigate the temporal aspects of multichannel stimulation.

4. PUBLICATIONS AND PRESENTATIONS

During this reporting period, members of the team have made presentations of results relating to this project at the Neuroprosthesis Workshop at the NIH and the Society for Neuroscience meeting in San Diego. Additionally, manuscripts are being prepared describing the long-term acute studies and the results of the human temporal bone dissections and imaging.

5. DISCUSSION

For the three months covered by this report, we have made significant progress in determining the dimensions of the arrays that could be implanted into humans. We have also demonstrated that the process of rapidly inserting a number of microelectrodes into the auditory does not significantly impair the bulk function of the nerve for periods up to 30 hours. It will be interesting to see how our closing of the implant site affects these observations especially as a delayed inflammatory reaction resulting in swelling of the nerve could have a significant impact of the viability of the auditory nerve fibers. Although the transbulla approach we have adopted provides a much smaller access to the nerve than others, the ability to manufacture the Utah Electrode Array in a more dense configuration as well as change the length of the electrodes in a graded fashion should allow a significant number of electrodes to be placed in the nerve. Our upcoming results in the area of spatial independence of the electrodes should provide invaluable information of the upper limits of the density of the electrodes.

6. LITERATURE CITED

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