The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #11

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Abstract:

Over this quarter we have accomplished the following tasks:

Histological Studies

1. We continued using the ultrahigh resolution small animal computed tomography (EVS-RS9 CT scanner) scanner for imaging of the UEA in the cat temporal bone.
2. We have continued processing our chronically implanted cats for histological analysis of cochlear nerves.

Electrophysiological Studies

3. We have conducted three more chronic electrical stimulation experiments of cat auditory cortex using our portable stimulator.
4. We have continued our experiment on the mapping of the activity in the auditory cortex, evoked by electrical stimulation of the auditory nerve.

Studies Directed at Future Work in Inferior Colliculus

5. We visited Dr. Russell Snyder at USCF to initiate collaboration in the IC mapping of cochlear nerve UEA stimulation. There we participated in an IC mapping with CI stimulation experiment.
6. We are developing and validating Michigan probe IC recording systems at Utah in anticipation of IC mapping of cochlear nerve stimulation.

1. **WORK PERFORMED DURING REPORTING PERIOD**

Histological Studies

1. *We continued using the ultrahigh resolution small animal computed tomography (EVS-RS9 CT scanner) scanner for imaging of the UEA in the cat temporal bone.*

At the end of each of 10 chronic implantation experiments, the animal underwent transcardiac perfusion with formalaldehyde fixative in preparation for radiographic and histologic evaluation.

Before harvesting auditory nerves for histologic processing, the animals were scanned with high resolution CT scan in order to localize the electrode tips with respect to the auditory nerve. Volumetric imaging with resolution of 21x21x21 microns was performed with a GE EVS-RS9 computed tomography scanner at the University of Utah Small Animal Imaging Facility, producing a 16-bit volume of 425x420x385 samples (Kindlmann et al. 2003). The resolution of the scan allowed definition of the shanks and tips of the implanted electrode array. There were distinct CT values for air, soft tissue, bone, and the electrode array, enabling the use of a combination of ray-tracing and volume rendering to visualize the array in the context of the surrounding structures, specifically the bone surface. Summation projections of CT values and gradients rendered in different colors permitted us to differentiate between the bone and the electrode array (Figure 1). Volume rendering permits direct inspection of internal structures, without a pre-computed segmentation or surface extraction step, through the use of multi-dimensional transfer functions (Figure 2).

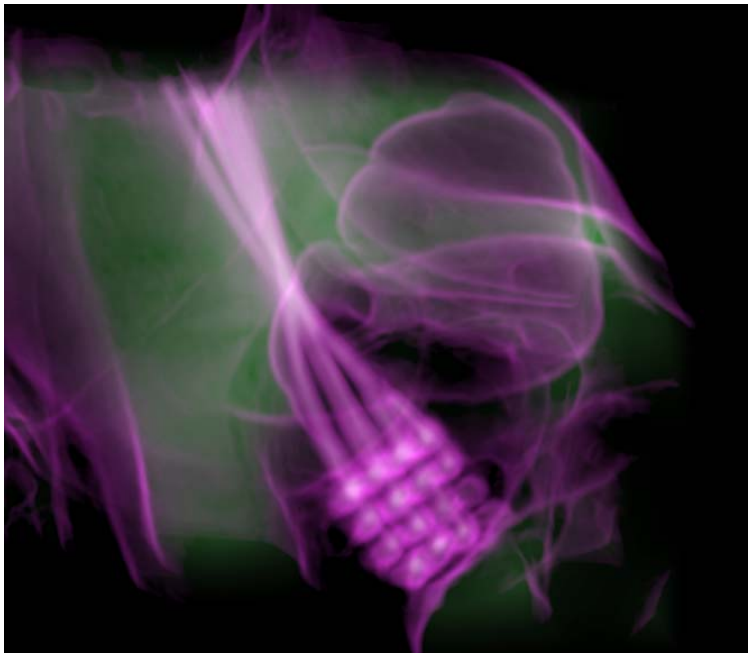


Figure 1. Example of 3D CT reconstruction using a combination of ray-tracing and volume rendering. High X-ray absorption of the electrode array and the wires allowed it to be differentially highlighted. The lead wires are shown leading to the cochleostomy site where the array was implanted in the cochlear nerve.

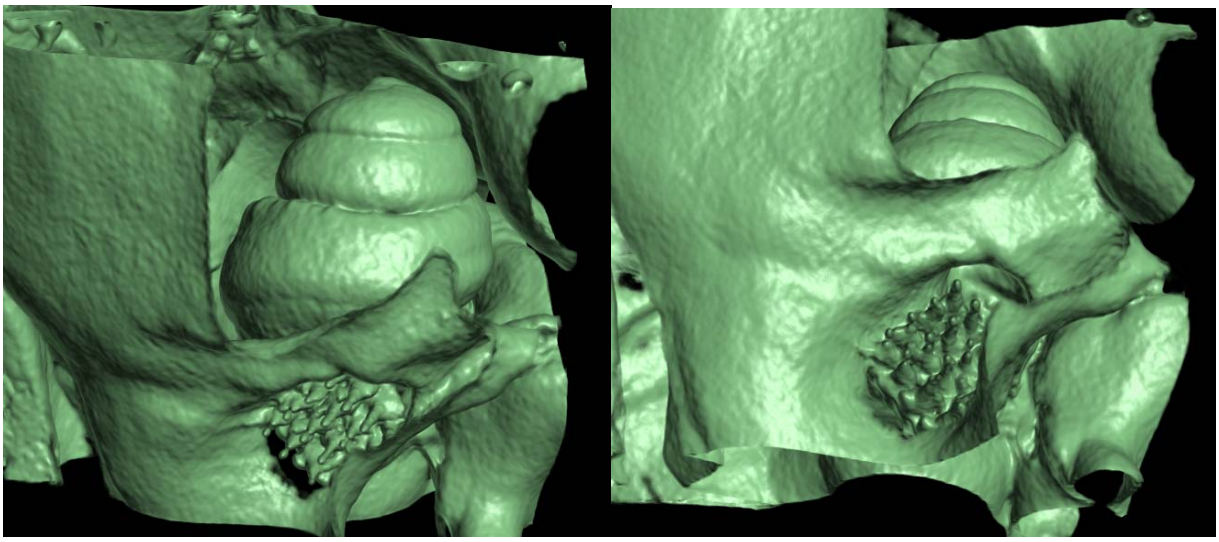


Figure. 2. Reconstructions at 21 micron resolution from 3D CT images of cat temporal bone implanted with UEA.

These studies indicated that the tips of the UEA were difficult to resolve as the 4,000 angstroms of platinum deposited on the electrodes thick were barely absorbed by the X-rays.

To investigate the possibility of enhanced imaging of UEAs, we deposited 8,000 angstroms of platinum on the electrodes, and implanted them into more anatomically accessible test structures like the rat olfactory bulb. A plain film CT of such UEAs, implanted into a rat olfactory bulb is shown in Figure 3. We could resolve the entire structure of the electrodes and upon 3D reconstruction of the data we were able to show that the tips of the electrodes could be visualized. We propose to use 8,000 angstroms platinum deposited on UEAs implanted into the cochlear nerve to better determine the exact location of the electrode tips in the nerve.

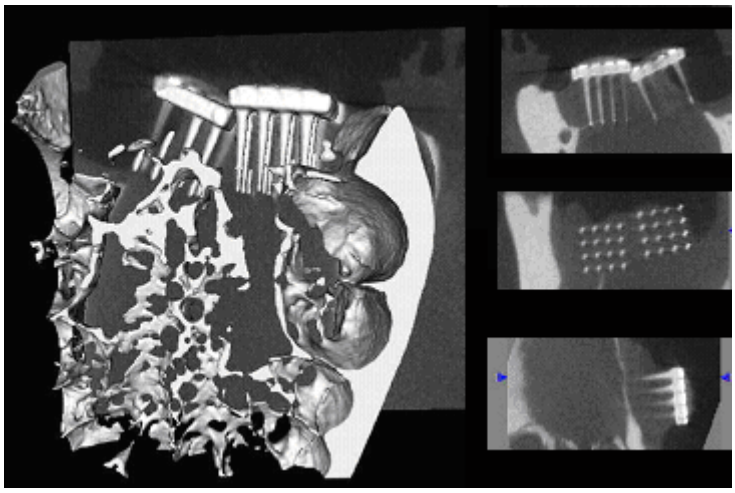


Figure 3. High resolution scanning (27 micron) of UEAs with 8,000 angstroms of platinum deposited on the tips. The large figure on the left of panel is 3D reconstruction of 2 UEAs implanted into each olfactory bulb of rat. The three small panels on the left are 3 orthogonal x-rays of the rat rostral cranial fossa with UEAs implanted on each bulb.

2. *Histopathology of cat temporal bone.*

After the high resolution CT scanning, the array was carefully explanted and the auditory nerve harvested. The unimplanted contralateral nerve was also explanted as a control. Figure 4 shows dissection of the chronically implanted unwired UEA in situ and the adjacent figure shows the nerve after the array was explanted. A significant fibrosis overlying the implant site can be seen in this figure. Two of the implanted electrodes were broken upon explantation and can be seen in the Figure 4. The unimplanted contalateral nerve was also harvested for comparison to the implanted side.

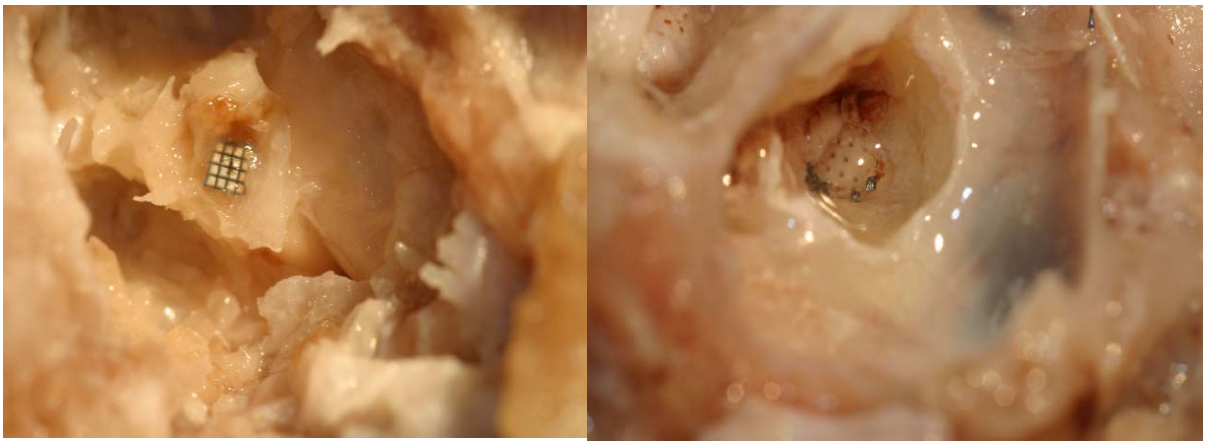


Figure 4. Example of dissection of implanted cochlear nerve. The left panel is an example of cochlear nerve *in situ* with the UEA implanted into it. Right panel shows example of temporal bone with cochlear nerve *in situ* and array explanted.

After harvesting of unimplanted and implanted auditory nerves, the specimen was dehydrated in an alcohol based fixative, osmium stained, and hard plastic embedded. 1µm, 5µm, or 20µm thickness sections of the nerve was examined to determine the area of the nerve represented by the implantation and to determine fibrosis and nerve injury. An example of sections of the unimplanted auditory nerve is shown in Figure 5.

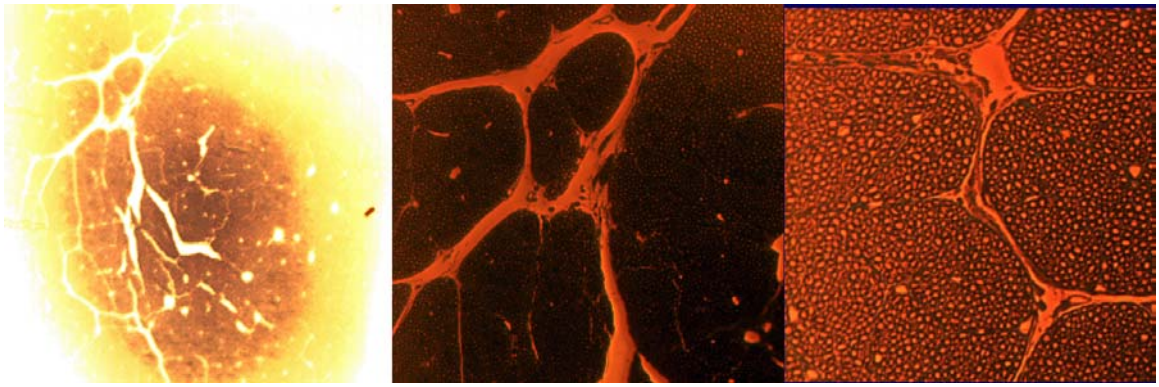


Figure 5. Sections of unimplanted auditory nerve, at 4x, 10x, and 20x magnifications.

In the five nerves we have processed to date, we found significant fibrosis around the base of the implant and around the electrodes themselves. However, the array was seen to remain implanted in the nerve. We also found viable nerve fibers around the UEA electrodes, but at a greatly decreased density compared to the unimplanted nerves. We have not shown sections of the implanted nerves as the quality of these sections was poor. We plan to continue harvesting and analyzing the rest of the chronic cat cochlear nerves. We expect that our embedding / staining / sectioning techniques will improve.

Electrophysiological Studies

3. *We have conducted two more chronic electrical stimulation experiments of cat auditory cortex using our portable stimulator.*

The past quarter we have implanted 3 cats with modified chronic assemblies that were developed in previous quarters. Each assembly is comprised of two 10x10 UEA's attached to one percutaneous connector (Microtek). Only one of the arrays was electronically wired to the connector, while the wires of the other array were fixed into the titanium base attached to the connector. The "dummy" array was implanted into the left primary auditory cortex and the "active" array was implanted into the right auditory cortex (Figure 6). By comparing the immunohistochemical response (method described in the previous quarterly report) of the control array to a stimulated array (using the portable-constant current stimulator described previously) we hope to quantify the histological consequences of chronic intracortical microstimulation.

One of the three cats was sacrificed one month after implantation to inspect the healing and effectiveness of the bi-lateral surgery. The second cat has been stimulated for 56 hours over two weeks in 8-hour blocks (following 6 weeks of recovery from the surgical implantation, a time sufficient to ensure that the acute inflammatory responses should be stabilized). The animal was observed during all periods of stimulation. No obvious effects of the stimulation could be seen in the cat's behavior. At the end of the stimulation period, we also attempted to record spontaneous single and/or multi-unit activity from the active array without success. However, the average impedance was moderately stable throughout the course of the stimulation paradigm (Figure 7). The animal will be sacrificed soon and tissue will be harvested for immunohistological processing. The third cat is still recovering from surgery. Surgery dates for two more cats have been scheduled during the next two weeks. We plan to include histological data for at least two of the four cats in the next quarterly report.

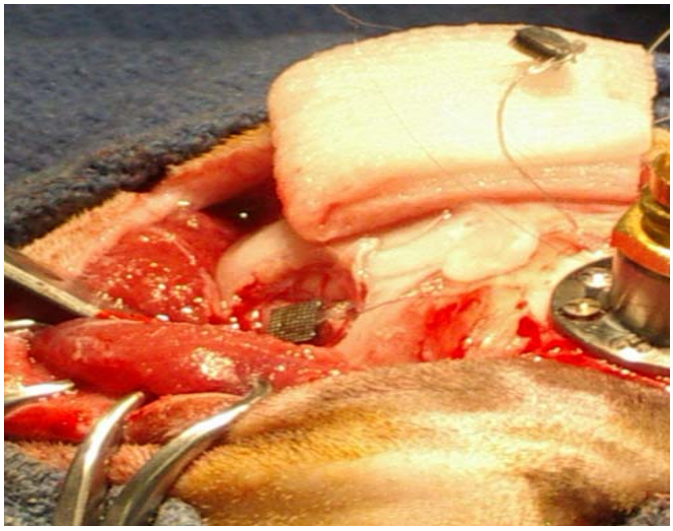


Figure 6. An example of the implantation in AI done in chronic animals.

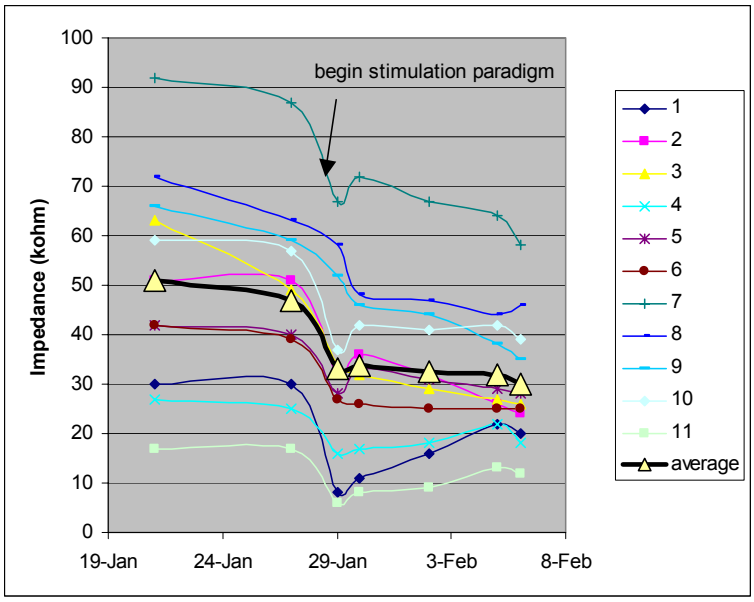
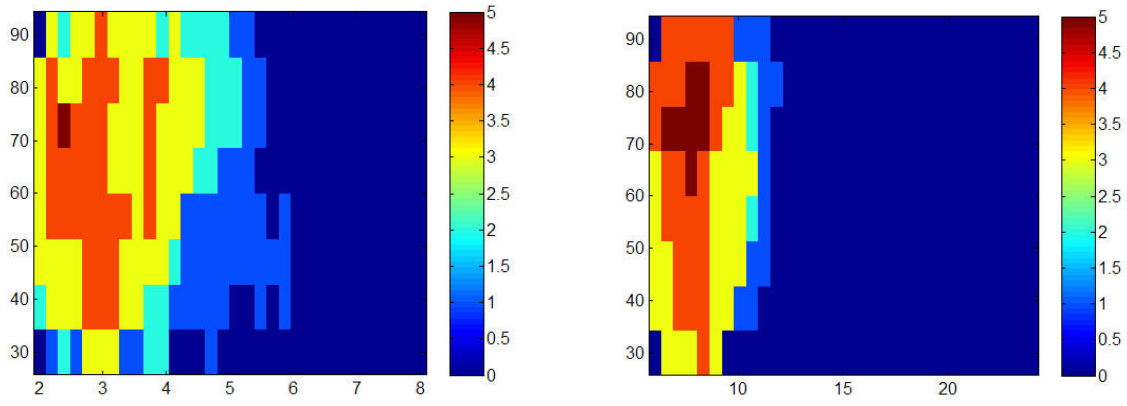


Figure 7. Impedances of the implanted electrodes in one chronic animal vs. time.

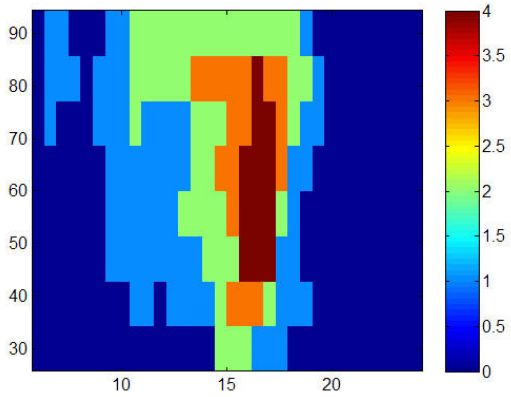
4. *We have continued our experiments on the mapping of the activity in the auditory cortex, evoked by electrical stimulation of the auditory nerve.*

We have conducted 7 acute experiments of mapping of the activity in the auditory cortex, evoked by electrical stimulation of the auditory nerve in normal hearing cat. Examples of acoustic tuning curves are shown in Figure 8. Each panel in the figure represents a tuning curve obtained to randomly presented tones at 50 dB level.



(a)

(b)



(c)

Figure 8. The cortical activity from A1 obtained by counting spikes in response to acoustic stimulation of tones of different frequencies at 50 dB SPL. Stimulus frequency is on the abscissa, and the scales differ for plot (a) and for (b) and (c). Stimulus amplitude is on the ordinate. The number of spikes evoked by each stimulus (normalized) is indicated in the color bar. For Figure 8a the BF can be discerned to be 3 kHZ for the neuron we are recording from. For Figure 8b it is 8 kHz and for Figure 8c it is 16 kHz.

We could not, however, obtain stable AI maps to electrical stimulation. The most common problem was the sparsity of drivable units that could be reliably recorded from the UEA implanted in AI. Our experiences with recordings of acoustically evoked and electrically evoked activity from A1 have been frustrating. The problems of performing two complex surgeries on opposite sides of the animals head require turning the animal by 180 degrees. This contributes to the lack of robustness in this procedure. This continued difficulty has caused us to explore the use of the inferior colliculus as a substitute auditory center from which to record electrically evoked patterns of neural activity.

Studies Directed at Future Work in Inferior Colliculus

5. *We visited Dr. Russell Snyder at USCF to initiate collaboration in the IC mapping of cochlear nerve UEA stimulation. There, we participated in an IC mapping with CI stimulation experiment.*

The difficulties we have experienced in recording reliable acoustic maps from AI has motivated our interest in moving to IC as our index of selectivity of auditory nerve stimulation via implanted USEAs. This decision was also made after a visit to Dr. Russell Snyder's laboratory at the University of California at San Francisco where we had the opportunity to observe this surgical approach to the feline IC, his use of a "Michigan" 16 electrode probe, and the recordings he was able to make using these techniques. The paragraphs below describe the techniques we will use to exploit this approach.

The cat's head will be stabilized with a metal bar fixed to the skull with stainless steel screws in the calvarium and dental acrylic. This system will allow for easy turning of the cat without compromising access to either ear canal. The IC will then be exposed as previously described by Snyder (Snyder et al. 1995). A linear incision will be placed over the right parietal skull and the temporalis muscle reflected. A 1.5 x 1.5 cm craniotomy will be then be performed as shown in Figure 9**.** The dura overlying the occipital lobe will be incised and reflected. The occipital pole of the occipital lobe will be removed by aspiration to expose the bony and dural tentorium. A wedge of the tentorium will be removed as needed to provide full exposure to the dorsal and lateral portion of the IC (Figure 9)**.**

Once the IC is adequately visualized, a silicon-substrate, thin-film, multi-channel recording probe (Center for Neural Communication Technology, Ann Arbor, MI) (Drake et al. 1988) (Najafi and Wise 1986), will be inserted into the center of the IC. The probe will be rigidly connected to a custom-built pre-amplifier that will be held in a micromanipulator. The probe electrode will be inserted at a standardized trajectory of 45 degrees off the sagittal plane in a dorsolateral to ventromedial trajectory in the coronal plane.

Using this trajectory, the probe will traverse the central nucleus of the IC at a right angle to its 'isofrequency laminae' and will pass through the full range of frequencies represented in the ICC (Snyder, Sinex et al. 2000; Snyder, Vollmer et al. 2000; Snyder and Sinex 2002). Each probe has 16 recording sites along a single shank distributed at 200μm intervals (center to center). The shank is 15 μm thick and 100 μm wide at its most proximal site and tapers to 15μm at the most distal site. The impedances at each site are 1.5-4 MΩ. In the cat, the 1.5mm distance from the most distal to the most proximal recording site allows simultaneous recording of responses from neurons sensitive to frequencies spanning approximately four octaves. The probes will be inserted manually until the most distal site records activity from neurons with best frequencies of approximately 30 kHz. Once this location has been reached, the cortical deficit will be filled with warm 2% agar dissolved in Ringer's solution. When the agar has solidified, the agar and the surrounding parietal and temporal bones will be covered with a thick layer of dental acrylic, sealing the bony defect and fixing the probe into place (Figure 10).

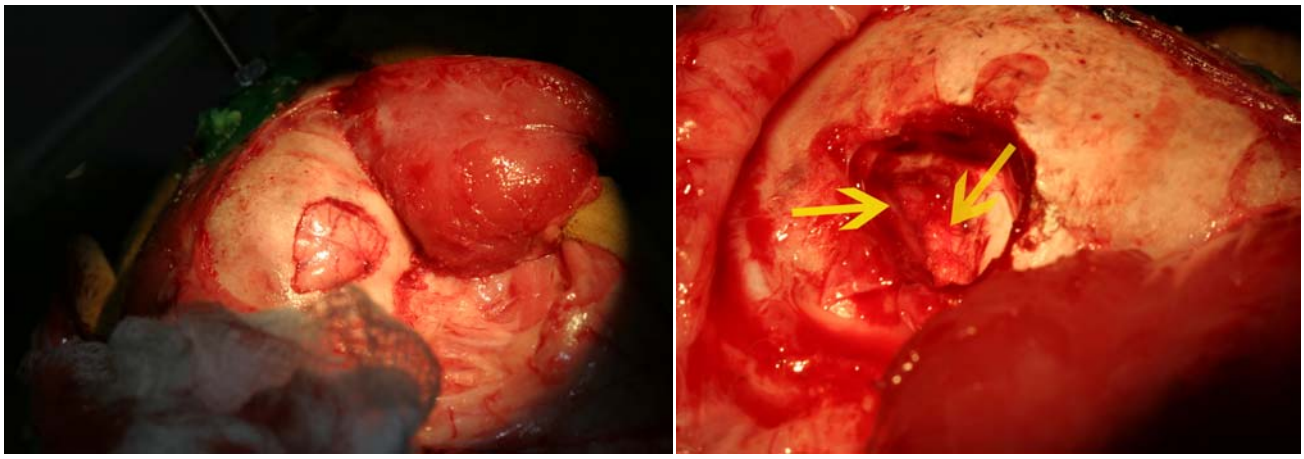


Figure 9. Left shows the craniotomy over the occipital pole. Right shows the exposure of the IC after aspiration of the occipital lobe.

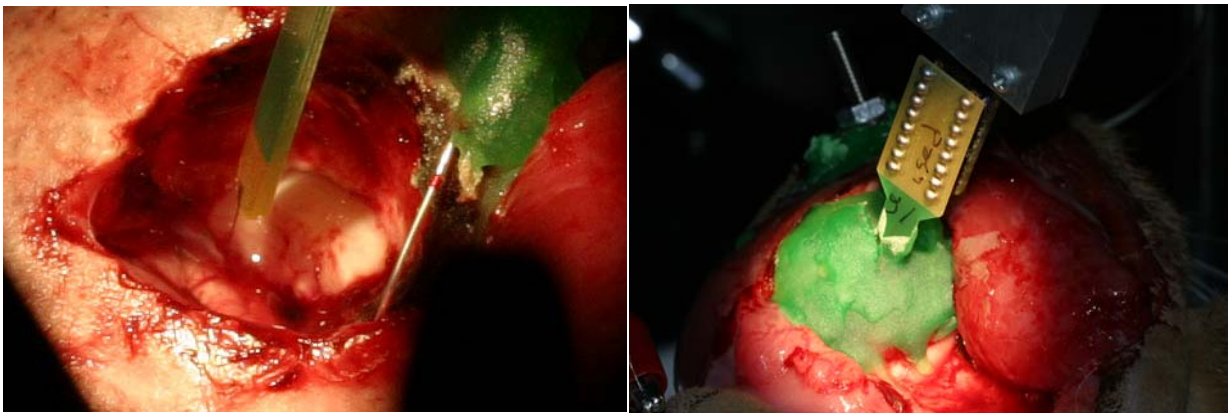


Figure 10. Photographs illustrating the insertion of the Michigan probe and its fixation to the skull with dental acrylic.

An acoustic map of IC will then be performed. Shown in Figure 11 is an example of tuning curves of the acoustic map of IC. The electrodes generally recorded multi-unit activity, and the tuning curves were not generated from spike-extracted data. The tuning curves are typical of those made by Dr. Snyder, and are remarkably robust. The panels from upper right to lower left represent tuning curves generated from responses of electrodes located at progressively deeper locations in the IC. Each curve is highly tuned, and the characteristic frequency of each curve progressively moves to higher frequencies as one moves deeper into the IC. The tuning curves illustrated in Figure 11 were not obtained immediately upon array implantation. Rather, the position of the array in the IC had to be ”fine-tuned” to obtain the optimized curves (and to obtain decent curves on the majority of electrodes). Dr. Snyder pointed out that the fine-tuning of the electrode position, and the excellent tuning curves that eventually result from this tuning are the rule rather than the exception in his experience. Dr. Snyder is confident that our

collaboration will allow us to obtain similar quality tuning curves in experiments that will be conducted at the University of Utah.

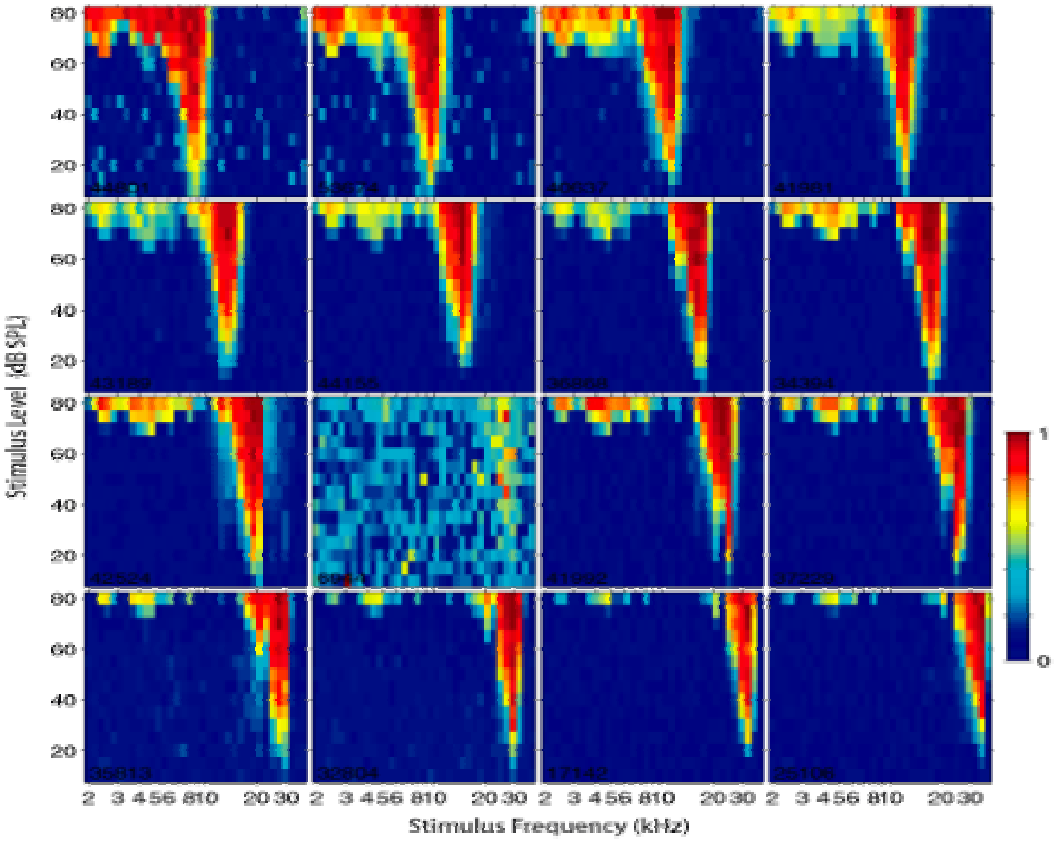


Figure 11. 16 tuning curves generated from single- and multi-unit responses recorded with a Michigan 16 site probe implanted in inferior colliculus. The ordinate plots the loudness of the acoustic stimuli, the abscissa plots the frequency of the stimulus, and the color bar represents the average normalized number of spikes evoked by each stimulus. The plots are organized horizontally from the upper left to the lower right, with each plot reflecting activity recorded on each of the 16 electrodes, with the response recorded with the most distal (tip) electrode shown at the lower right and the responses recorded with the most proximal electrode shown in the upper left.

6. *We are developing and validating Michigan probe IC recording systems at Utah in anticipation of IC mapping of cochlear nerve stimulation.*

After visiting UCSF and participating in the Michigan probe IC recording experiments, we began adapting our existing recording setup to accommodate Michigan probes. To validate the recording setup and the Michigan probe, we implanted the Michigan probe into rat olfactory bulb and recorded spontaneous and odor evoked units from different layers of the olfactory bulb. We are happy to report that we were successful at this (Figure 12). We plan to switch to Michigan probe IC recordings for mapping the acoustic and electrical stimulation selectivity in IC.

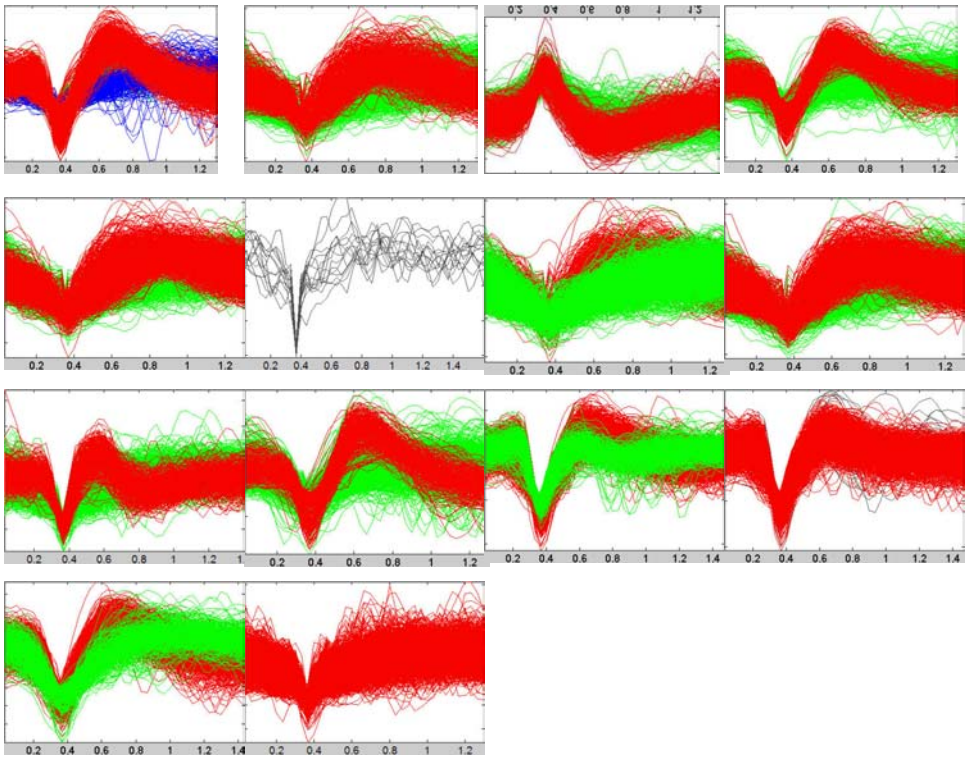


Figure 12. Simultaneous 16 channel recording of multiple units from olfactory bulb of rat. Two channels did not record any action potentials and hence those panels are blank. This experiment was done to validate our Michigan array recording setup.

2. PLANS FOR THE NEXT REPORTING PERIOD.

We will focus on the following components of the proposed work:

1. We will continue to map excitation patterns in AI in response to stimulation of the auditory nerve with implanted UEA's.
2. We will continue our exploratory work of using Michigan probes in IC.
3. We will perform more histology of cochlear nerves chronically implant with UEAs.
4. We will continue development and validation of backpack stimulators.
5. We will write the final report for this contract.

3. PUBLICATIONS AND PRESENTATIONS

We presented our findings of the 21 micron resolution 3D CT reconstruction of the cat temporal bones implanted with the UEA, at the NIH Symposium on Biocomputation & Bioinformation. Kindlmann, G., Normann, R.A., Badi, A. N., Bigler, J., Keller, C., Coffey, R., Jones, G. M., Johnson, C. R., "Imaging of Utah Electrode Array, Implanted in Cochlear Nerve", NIH

Symposium on Biocomputation & Bioinformation, Digital Biology: The Emerging Paradigm, NIH, Bethesda, MD, 2003.

We also presented our findings on the electrode independence study at the Society for Neuroscience conference 2003. Badi A.N., Kim S. J., Shelton C., Normann R.A., "Electrode Independence in a Novel VIII Nerve Auditory Prostheses". Society for Neuroscience, New Orleans, 2003.

We resubmitted our manuscript to Otology Neurotology that detailed our study of electrode independence of UEA implanted in the cochlear nerve.

4. DISCUSSION

We report satisfactory progress in all aspects of the contract goals except for the AI recordings. We have tried AI recordings of electrical stimulation for about 3 quarters and have been able to produce satisfactory electrical maps in only one experiment. We are concurrently investigating possibility of using Michigan electrodes in AI to map the electrical stimulation instead of AI. Our preliminary acoustic mapping experiment at UCSF and use of Michigan probe at Utah has been excellent. We propose to make the transition to IC recordings in the next quarter apart from performing histology in remaining chronic animals.

5. LITERATURE CITED

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