The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #3

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Abstract

The principle activities of the team during this reporting period were focused on 1) assessment of 48 hour eABR (electrically evoked auditory brain stem responses) recording stability, 2) obtaining frequency maps of auditory cortex resulting from ipsilateral and contralateral acoustic stimulation, and 3) validating MRI estimates of auditory nerve dimensions with cadaveric physical measurements. We are also continuing our chronic cat implantations to study structural/material biocompatibility. Finally, we have designed and built custom stimulators and eABR amplifiers and signal averagers that will be used in subsequent feline experiments.

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

1) Surgical Access: We have demonstrated a viable surgical access that allows placement of the Utah Electrode Array into the auditory nerve of cats. We have also demonstrated a viable surgical access that allows insertion of the UEA into auditory nerve in cadaveric human temporal bones. These accesses should permit

insertion of 20 electrodes in a 1.8mm x 2.2 mm array configuration (for 400 micron spaced electrodes), or 80 electrodes in a 200 micron spaced array.

2) eABR Electrophysiological Experiments: We have demonstrated that high velocity implantation of the UEA into the auditory can be accomplished without significant harm to the nerve. This was demonstrated by recording electrically evoked auditory brainstem responses (eABR's) that were evoked by currents injected via the implanted UEA. Current thresholds for stimulation have been found to lie in 10μA-50μA range. We were able to record eABR's for up to 31 hours in one acutely implanted cat before the experiment was terminated.

3) Cortical Mapping Experiments: We have demonstrated that we are able to implant UEA's into cat auditory cortex, and that we are able to record single and multiunit responses to auditory stimulation. In our previous work, we have been able to record from up to 18 of the 25 electrodes in the implanted array. We have also implanted 10 x 10 UEA's but were only able to record auditory responses from 15 electrodes.

2. WORK PERFORMED DURING REPORTING PERIOD

2.1. ANIMAL EXPERIMENTS

2.1.1 Surgical techniques.

We have conducted a series of acute and chronic implantations in the cat auditory nerve. Twelve cats with normal hearing were used in the acute experiments and nine cats with normal hearing were used for the chronic experiments. In the coursed of these experiments, we have refined our surgical techniques. Details of our anatomical access and surgical procedures in cats have been previously described in progress report 1. Our refined procedures are described here for completeness.

All procedures were done in accordance with guidelines of the Institutional Animal Care and Use Committee of the University of Utah, Salt Lake City, UT. Anesthesia was induced using a 1:1 combination of tiletamine HCl and zolazapam HCl (9 to 12 mg/kg, intramuscularly) and the animals were intubated, cannulated and catheterized. Anesthesia

was maintained by inhalation of 0.8% - 1.5% halothane administered using a closed circuit anesthetic machine. Hydration was maintained using drip of ringer's lactate (8-12 mL/kg/hr), body temperature was maintained by using a water blanket, and vital signs were monitored. The forehead, dorsum of the head and ventrolateral part of the neck were shaved and preparation of the sites was done using povidone iodine.

The animal was turned on its back and a longitudinal ventral incision 4 inches long was done to expose the platysma and the external jugular vein. A piece of fascia was harvested from the neck and preserved in wet gauze for use as a graft to cover the site of UEA implantation. Periosteal elevation and division of the digastric, sternomastiod and the cleidomastoid exposed the bulla. The bulla was opened and the round window exposed. Holes were drilled into the edge of the bulla to provide for self-tapping titanium bone screws that would anchor the bone cement and prevent explantation of the UEA. The round window was drilled under magnification using a diamond burr and the bone over the cochlear nerve thinned. The bone fragments were picked up using a Rosen needle and the cochlear nerve exposed.

The cat was turned to its normal anatomic position and incision made on the forehead to expose the frontal bones. Holes were drilled into the frontal bone and the percutaneous connector screwed to it using self-tapping titanium bone screws. A subcutaneous tunnel was made behind the ear to bring the lead wires to the ventral part of the neck. The lead wire was coiled in the tunnel to provide for mobility in the neck region.

The cat was again turned on its back and a UEA of 4x4 or 4x3 dimensions was implanted into the exposed nerve using a process of rapid pneumatic insertion. Figure 1 shows a 3 x 4 array of electrodes implanted into the auditory nerve (three rows of electrodes had been broken off at their bases in this implant so the back of the array looks like a 5 x 5 array of electrodes).

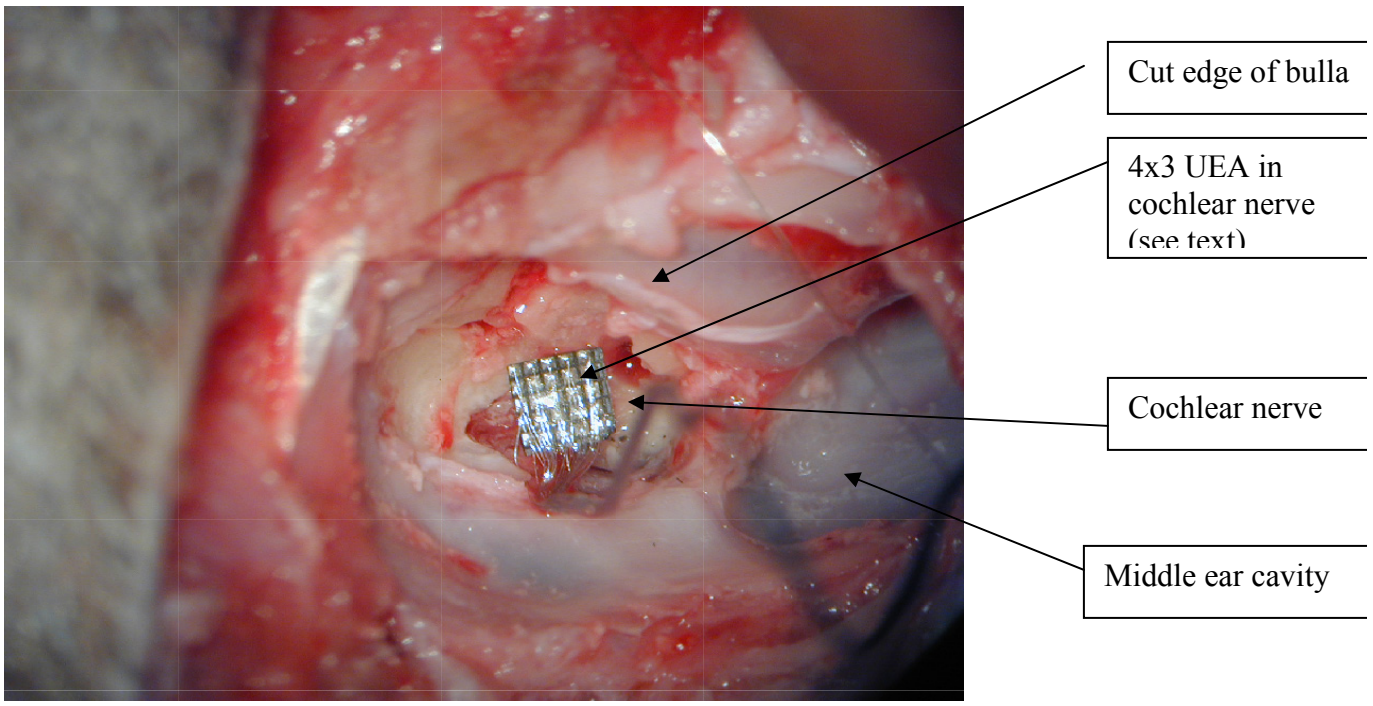

Figure 1. Photograph of a 4x3 UEA implanted into the right cochlear nerve of cat prior to the cochleostomy being covered with harvested fascia and bone cement. Note that 3 rows of the original 5 x 5 electrode array have been removed prior to insertion.

Titanium bone screws were inserted into the previously drilled holes in the bulla edge in order to provide anchoring points for the bone cements that would be poured into the cochleostomy. The site of UEA implantation was covered by the previously harvested fascia cut to size. The cochleostomy was closed using a variety of bone cements; we used a synthetic bone analog (Synthes Maxillofacial® bone cement), polymethyl methacrylate low viscosity bone cement and glass ionomer cement (Ketac Cem™, 3M ESPE, Germany). These cements have large coefficients of adhesion, low solubility, and cure in about 15 minutes. The return lead of the UEA was placed in the digastric and sutured. A penrose drain was provided in the bullostomy and the incision closed in layers. The site of percutaneous connector and the subcutaneous tunnel was also closed using 3-0 non-absorbable prolene sutures.

Chronic animals were recovered at this point and returned to the cat pen after recovery from anesthesia. In case of acute experiments the animal was turned into normal anatomical position ready for the electrophysiological experiments.

2.1.2 Long-term acute stimulation of cat auditory nerve.

There are numerous failure modes which would make untenable the concept of direct stimulation of auditory nerve via an array of penetrating electrodes. Two modes we have focused on in this period are the mechanical consequences of insertion of the Utah Electrode Array into the auditory nerve, and acute consequences of the materials used to fabricate the UEA. Both aspects of the biocompatibility of the array and insertion procedure were tested with acute implantation of the UEA into the auditory nerve, and the recording of eABR's for 48 hours post implant. If the surgical implantation of the UEA damaged the auditory nerve (due to some form of nerve crush), eABR's would not be recordable immediately upon implantation. If the materials from which the UEA were fabricated were toxic, eABR threshold would increase over this extended period. Low initial thresholds that remained constant over time would indicate that the implantation procedure and the materials of the UEA were well tolerated by the auditory nerve.

Cats were implanted using the techniques described above. Electrical stimulation was either monopolar with respect to a distant return, or bipolar, using one of the 12 electrodes as a current return for the other 11 stimulus sites. The nerve was stimulated cathodically using a charge balanced biphasic waveform of amplitudes ranging from 2μA to 350μA with 75μs per phase. The waveform was generated using a Grass S88K Stimulator and delivered using a pair of optically isolated constant current stimulators Grass PSIU6 photoelectric stimulus isolation units. The neural response to the monopolar electrical stimulation was recorded differentially with intradermal electrode placements on the vertex and base of the pinna, an electrode placed in the nape of the neck serving as the distant ground. The placements of EABR electrodes follow the Achor standard [1]. The neural response was signal averaged over 1024 trails to improve the signal to noise ratio and obtain eABRs. An example of eABR's evoked with the UEA are shown in Figure 2.

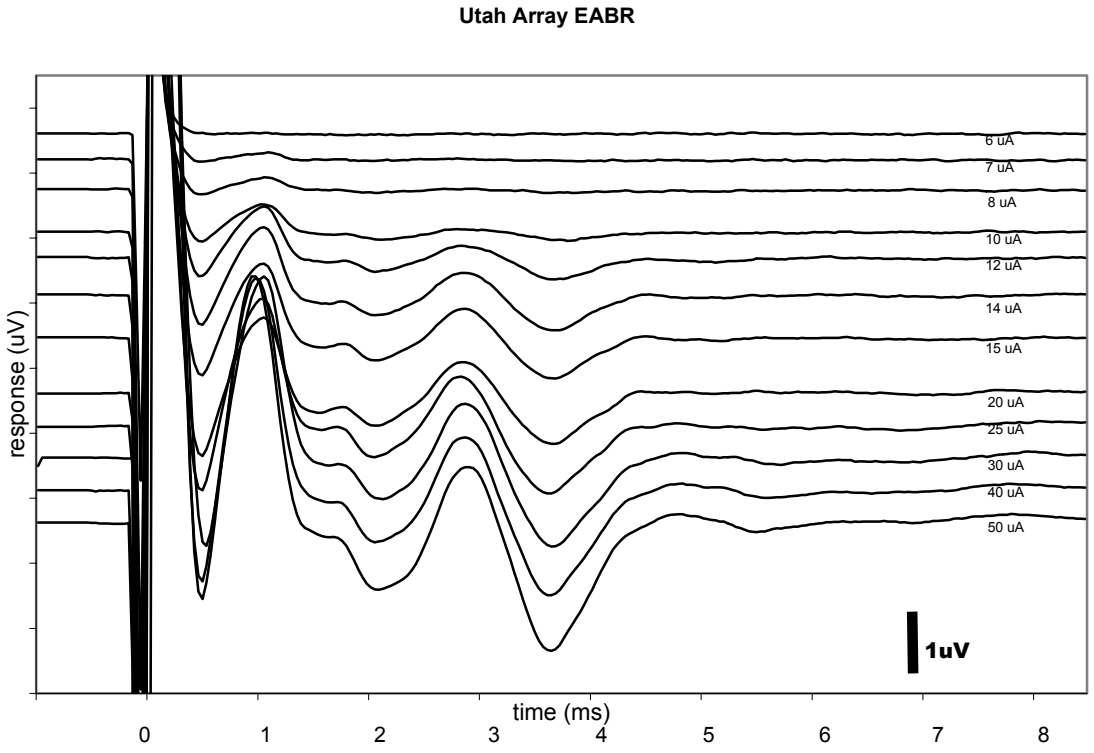

Figure 2. The EABRs in response to varying stimulus intensities. Currents that evoked consistent and reliable peak I and II waves were taken as the threshold. In the above case 8μA was the threshold.

Presence of reliable peaks, comparison with literature [1] [2] and independent confirmation by two experts indicated that the EABRs were genuine. Current delivered to the electrode was varied to obtain the threshold for nerve stimulation and after that systematically varied to obtain the dynamic range of stimulation. Stimulation was done for all the implanted electrodes and continued for a maximum of 31 hours postimplant.

The stability of the thresholds is indicated in Figure 3 where we have plotted threshold on each electrode as a function of time (this example shows a 31 hour implant). As is shown, there was a range of thresholds initially upon implantation, and these thresholds all increased with time. However, the mean threshold at implant (exclusive of the highest threshold electrode) was 5 μA in this particular experiment, a number consistent with excitation of fibers closely apposed to the tips of the electrodes. Over the 31 hours of the

experiment, threshold increased by about a factor of two, which suggests either micromotion of the array with respect to the nerve, or the presence of edema. This issue will be studied in future histological experiments.

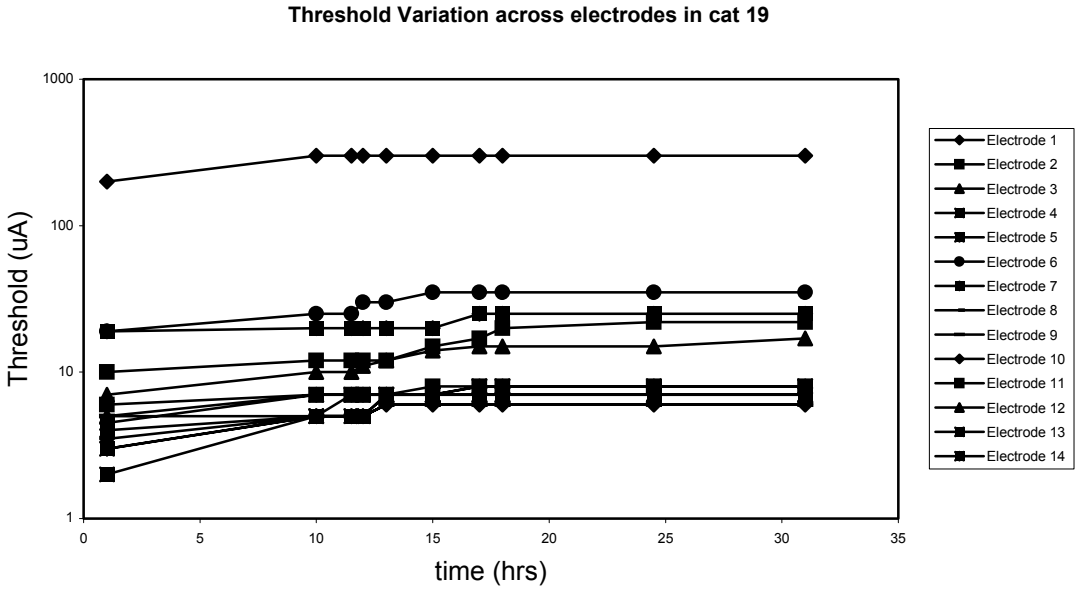

Figure 3. Semichronic stability of thresholds of all electrodes in cat 19 implanted with a 4 x 4 UEA with 14 functioning electrodes. There is minimal rise of the mean threshold and minimal change in the standard error indicating that all the electrodes were stable for up to the 31 hours shown in this figure. This validates the surgical closure and use of bone cement in the semichronic preparation. We correlated the position of the electrode in the nerve with the threshold and concluded that the high threshold electrode (diamonds) was on the periphery of the nerve and hence was probably not implanted in the nerve.

2.1.3 Unit recordings from cat auditory cortex with UEA.

The purpose of these experiments is 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 acoustic stimulation. 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.

Since the previous progress report, we have conducted five successful experiments in cats anesthetized with halothane. We are currently in the process of extensive analysis of this large body of data. We are extremely encouraged at the large yield of recordings (~70-80 active electrodes with acoustically evoked responses) obtained from cat AI using the UEA.

Our stimulus consists 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 interstimulus interval were randomly interleaved. In addition to tone pips, other stimuli consisted of trains of tone pips and noise-bursts (25 ms long, 75 dB SPL) that were repeated at varying intervals. Responses to these stimuli were used to obtain modulation-transfer functions. 10x10 UEAs were pneumatically inserted to a depth of 1000 microns in AI. Figure 4 shows an example of the geometry of an array implanted in cat AI.

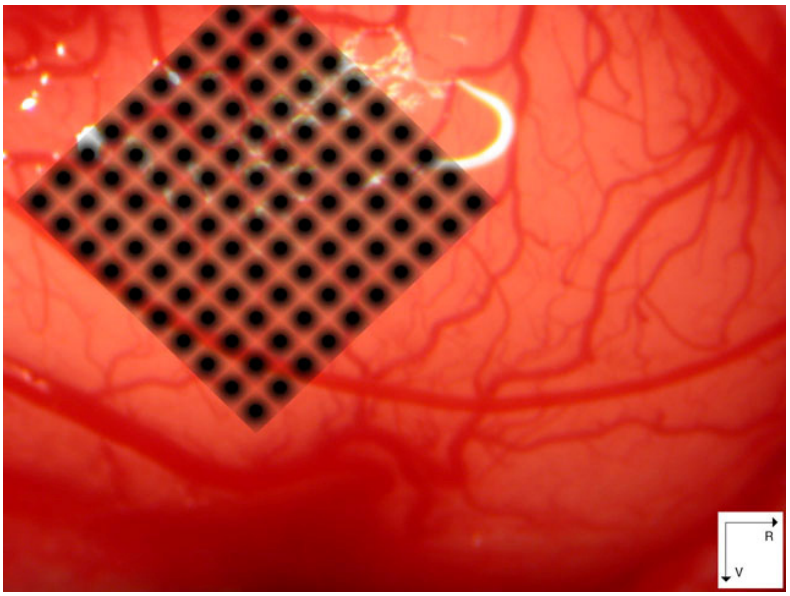

Figure 4. The geometry of the array in cortex. The spacing between two electrodes in the array is 400 microns.

Immediately after implantation, responses were seen in a few channels (10-20). After 1-3 hours, responses tended to be found a large number of channels. After 4 hours, responses were found to stabilize. We have successfully obtained recordings in cortex for more than 36 hours. Thresholds were individually set for each channel and 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. The average shape of action potentials recorded in an array is shown in figure 5. About 1-3 single units could be recorded from each electrode in the array. Blank panels indicate channels where no action potentials were recorded.

Figure 5: Average shape of the extracellular action potential in each of 83 active channels in the array.

To obtain frequency-response areas, the number of spikes in a 50-millisecond time window after the stimulus was calculated for each channel. An example of such data is shown in figure 6. Each sub-panel represents an FRA for each channel of the array. The x-axis represents different frequencies of the tone and the y-axis indicates different

intensities. The color scale indicates the spike-count in a 50 millisecond window following the onset of the tone. From this data it is clear that seventy-nine of the 83 active electrodes have clear acoustically evoked responses. Some channels did not yield auditory evoked activity. The characteristic frequency of each multi-unit cluster increases from the rostral to the ventral direction, consistent with the tonotopic map of cat AI. The most ventral electrodes are presumed to be located outside AI based on reversal in the tonotopic gradient and response latencies. Interestingly, some electrodes show multi-peaked tuning curves that have previously been observed in cat AI.

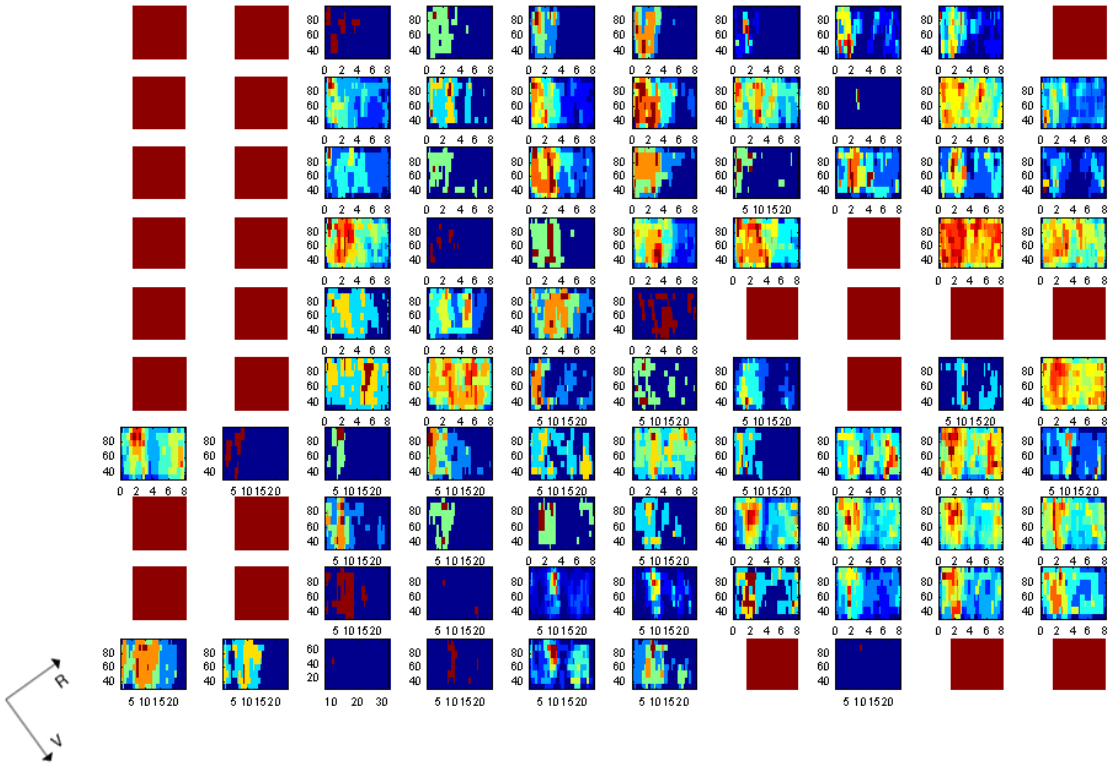

Figure 6: Tuning curves in each active channel of the array. Each sub-panel panel indicates the number of spikes that occur within 100 milliseconds of the onset of a tone presented at different frequencies and intensities.

We are currently in the process of analyzing FRAs and modulation-transfer functions for ipsi vs contralateral stimulation.

2.1.4 Chronic animal experiments.

A total of 11 animals have been implanted with passive devices during this period (two of these died during surgery due to anesthesia complications). The remaining 9 have

recovered remarkably well given the invasiveness of the surgical access. These animals will remain implanted for varying periods for up to 6 months before being perfused for histology.

2.2. HUMAN TEMPORAL BONE AND IMAGING STUDIES

The insertion of a UEA in a human clinical application requires detailed knowledge of the integrity and size of the cochlear nerve. T2 Fast spin echo magnetic resonance imaging using a FIESTA imaging sequence gives an enhanced view of the nerves of the internal auditory canal by using cerebrospinal fluid as a contrast medium. In order to correlate these findings with direct measurements of the nerve in-situ, we conducted a double-blinded study to detect any significant differences. This component of the project is summarized below, and a paper on this subject will be presented by Dr. Tony Owa at the 37th annual meeting of the American Neurotology Society in Florida.

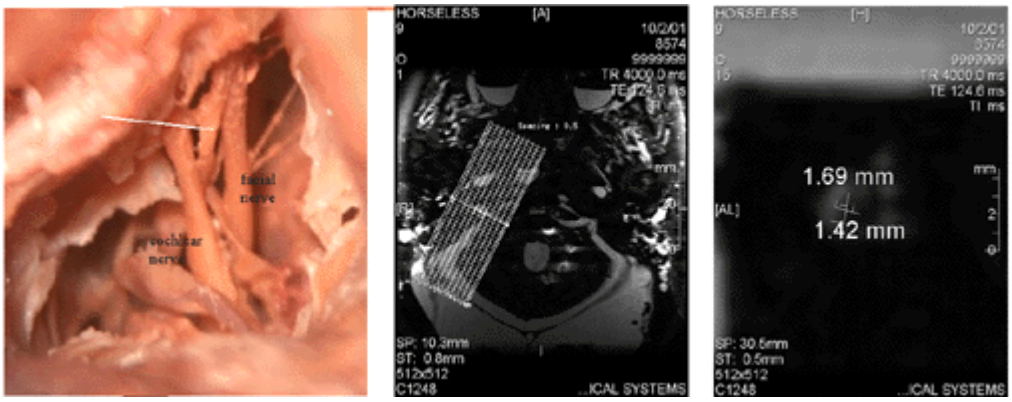

Figure 7. left: dissected human cochlear aperture. Center: low resolution MRI image of temporal bone. Right: High resolution image of cochlear nerve

The ventricular system of cadaveric heads were filled with saline and scanned using a T2 weighted fast spin echo protocol focused on the vestibulocochlear nerves. The vestibulocochlear nerves were then exposed and measured in-situ using an x-y-z stereotactic micrometer. Measurements of the nerve width were made at cochlear aperture and these were compared with the MRI measurements (see figure 7). Both the radiologist and the dissector were unaware of each other's measurements at the time of the study. Four specimens were obtained, but one was discarded, as we were unable to

keep fluid within the ventricular system. A total of six cochlear nerves were dissected. Direct measurements ranged from 1.16-1.33mm compared to 0.65-1.1mm with MRI measurements. The average nerve diameters 1.27mm (direct measurements) compared to 0.83mm (MRI).

We conclude that MRI scanning tends to underestimate the size of the auditory nerve at the cochlear aperture by 32%, but this factor varied between specimens. This finding has a major impact on pre-operative decisions regarding the insertion of the intraneural implant.

2.3 INSTRUMENTATION

2.3.1 Portable Stimulator.

Our need for a portable stimulator to be used in the 60 hour electrical stimulation requirement of the contract has motivated us to develop a hybrid digital/analog system with colleagues in Spain. Unfortunately, progress in the development has proceeded slowly due to poor availability of VLSI components. This has caused us to begin the design of a simple analog based stimulator that we will be building and testing this next quarter.

2.3.2 eABR data acquisition system.

In our experiments to date, we have relied upon the use of an ABR data acquisition system that was loaned to us by colleagues in the Otolaryngology Department on an 'as needed' basis. This has proven to be awkward so we have acquired all the components needed to assemble our own system. The system is built in a Labview environment, and consists of an STG 1002 constant current stimulator (Multi Channel Systems), a CP511Grass bioamplifier, and a PCI-MIO-16E-4 data acquisition card (National Instruments) and a Cyber 24 relay board (Cyber Research) to achieve computer controlled switching between electrodes. The system has recently been assembled and tested and appears to provide all the functionality we require.

3. PLANS FOR NEXT REPORTING PERIOD

3.1. ACUTE EXPERIMENTS

3.1.1 Acute AI mapping.

Our acute mapping experiments will continue. We expect to be able to acutely implant a 12 electrode UEA in the auditory nerve, and by electrical stimulation of the fibers, evoke single unit responses in AI which will be recorded with 10 x 10 UEAs. We will compare ipsilateral acoustically stimulated maps with contralateral electrical stimulation via the UEA implanted in the auditory nerve. We will determine the acoustic characteristic frequencies associated with neurons in AI that are excited by electrical stimulation via the auditory nerve implant.

3.2. CHRONIC IMPLANTS

3.2.1. Passive implants.

We expect to complete our passive chronic cat implants over this next quarter, and we will begin conducting histological evaluation of the implanted auditory nerves. Histology will be conducted in the pathology department at the University of Utah, and/or by Dr Fred Linthicum, Jr. at House Ear Institute who has agreed to participate in the experiments.

3.2.2. Active implants.

We will complete the development of our portable stimulators, and begin implantation of cats who will undergo the 60 hour stimulation required in this contract. The stimulated auditory nerves will be studied histologically and compared with the results from passively implanted cats.

4. PUBLICATIONS AND PRESENTATIONS

The following presentation has been made over this quarter.

A.O.Owa, A.N.Badi, J. Gull, R. Wiggins, T. Hillman, and C. Shelton. Evaluation of the Accuracy of T2 Fast Spin Echo Magnetic Resonance Imaging of the Cochlear Nerve. Will be presented at the 37th Annual meeting of the American Neurotology Society, to be held in may 2002 in Boca Raton, Fl

5. DISCUSSION

It appears that the UEA can be safely implanted in the auditory nerve, but we feel more work will be required in developing an implant technique that will permit long term eABR's in freely moving and behaving animals. The problem of mechanical immobilization of the array in the bulla and the nerve has motivated our investigations into array immobilization using various cements and fixation strategies. It also appears that the surgical access in the cat is much more complex than in the human cadavers we have worked with. Thus, the problem of chronic immobilization of the implanted array should be less severe in the human than in the cat.

We also look forward to our histological studies where we can begin to better understand the long and short-term consequences of array implantation into the auditory nerve. The small and gradual increase in eABR thresholds over the period of acute implantation is likely due to edema which should be revealed in our histological studies of acutely implanted tissues.

6. LITERATURE CITED

1. Achor, L.J. and A. Starr, *Auditory brain stem responses in the cat. II. Effects of lesions.* Electroencephalogr Clin Neurophysiol, 1980. **48**(2): p. 174-90.

2. Beitel, R.E., et al., *Electrical cochlear stimulation in the deaf cat: comparisons between psychophysical and central auditory neuronal thresholds.* J Neurophysiol, 2000. **83**(4): p. 2145-62.