The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

Quarterly Progress Report #6
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ABSTRACT

The principle activities of the team during this reporting period were focused on: 1) Simultaneous measurement in both hemispheres of frequency maps of auditory cortex resulting from binaural acoustic stimulation. 2) Development of MATLAB based tools for analysis of results on quantifying the selectivity of stimulation of the auditory nerve using electrically evoked, auditory brain stem response (eABR) overlap as the index of selectivity. 3) Radiological and histological analysis of chronically implanted cat auditory nerves. 4) Continued development and *in vivo* evaluations of 'backpack' stimulators to be used in long-term stimulation of chronically implanted auditory nerve via 'Utah Electrode Arrays'.

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, estimating the dimensions of the arrays that can be implanted, and determining 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

Surgical Access: We have demonstrated a viable surgical access that allows placement of the Utah Electrode Array (UEA) into the feline auditory nerve. This allows us to use cats in our acute and chronic experimentation. 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.

eABR Electrophysiological Experiments: We have demonstrated that high velocity implantation of the UEA into the auditory nerve can be accomplished without significant injury to the nerve. This was demonstrated by recording electrically evoked auditory brainstem responses (eABR's) that were evoked by currents injected via a UEA that had been implanted into auditory nerve. Stimulation current thresholds for evoked eABR's have been found to lie in 10μA-50μA range. We were able to record stable eABR's for up to 52 hours in one acutely implanted cat before the experiment was terminated.

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 multi-unit responses to acoustic stimulation. In our six most recent experiments, we recorded acoustically evoked single- and multi-unit responses from an average of 69 of the 100 electrodes of the implanted array.

Measurements of auditory nerve dimensions in human cadaveric heads: We have measured the diameter of the auditory nerve using MRI measurements and compared these estimates with physical measurements of the same nerves. MRI estimates typically underestimate auditory nerve diameter by 32%.

Stimulation selectivity: We have developed a technique by which we can estimate the extent of stimulation overlap in pairs of electrodes in arrays implanted into the auditory nerve. The technique uses paired sequential stimulation via two electrodes and monitoring of the eABR recorded with needle electrodes. With short interstimulus intervals (the second stimulus delivered within the refractory period of the first stimulus), stimulus selectively is reflected in the amplitude of the second eABR. We have seen some electrode pairs with virtually no stimulated fiber overlap, and others with considerable overlap.

Consequences of Chronic Stimulation: We have developed small, portable backpack stimulators that provide 'quasi' constant current stimulation of up to 16 electrodes. The stimulators are worn on a fabric backpack that the cats well tolerate. The stimulators are battery powered, lightweight, and provide 16 channels of stimulation per day. Interconnections (cables and connectors) between the stimulators and the animal, however, have proved to be problematic.

2. WORK PERFORMED DURING REPORTING PERIOD

2.1. ANIMAL EXPERIMENTS

2.1.1 Bilateral recording of acoustic activation of auditory cortex.

One of the goals of this contract is to demonstrate independence of the activation of fibers implanted in the auditory nerve. We are accomplishing this goal using two approaches. We are evaluating the degree of overlap in sets of fibers stimulated by pairs of electrodes implanted in auditory nerve (this will be expanded upon subsequently). We are also planning on examining the spatio-temporal firing patterns of neurons in auditory cortex that are activated by electrical stimulation of electrode arrays implanted in the auditory nerve. These latter experiments will also provide us with estimates of the perceptual frequency space accessed by implanted Utah Electrode Arrays. Specifically, we propose to use UEA's, implanted in primary auditory cortex (AI), to map auditory cortex via ipsilateral acoustic stimulation of a cat. We will then perform electrical stimulation of the contralateral auditory nerve via a UEA implanted in the contralateral auditory nerve. Comparing these acoustic and electrical activation maps will allow us to ascribe presumed frequency percepts to specific electrodes implanted in the auditory nerve. As a prelude to these experiments, we must demonstrate that we can implant UEA's in auditory nerve and that these electrodes can activate higher auditory centers (achieved), and that we can implant UEA's in AI and that we can record spatio-temporal activation patterns evoked acoustically (partially accomplished). We also wanted to quantify the extent of bilateral AI activation produced by electrical stimulation of a single auditory nerve. The results described below provide a prelude to these experiments.

In previous progress reports we showed preliminary results of comparisons of Ipsi- and Contra-lateral spectral response maps to acoustic stimulation. In previous experiments recordings were obtained from the right hemisphere in most experiments. Spectral response maps were obtained sequentially for ipsi- and contra-lateral response maps. To maximize the yield of recorded

neurons, and to compare differences in activation maps across both hemispheres we conducted experiments in which we recorded from left and right hemispheres in a cat simultaneously.

Methods: Surgical techniques used were comparable to those methods discussed in previous reports. An incision was made on the rostral ventral plane, the skin was retracted, and the left and right temporalis muscles were removed. Craniotomies were performed roughly over the areas over the auditory cortex in both hemispheres. The dura was reflected in both hemispheres. The cortex was frequently bathed in saline. A single microelectrode was used to make a coarse map of the auditory cortex. Two 10x10 Utah Electrode Arrays (UEA) were then inserted normal to the surface of the cortex (one array in each hemisphere). Two data acquisition systems (100 channel Neural Signal Acquisition System, Bionic Tech.) were used to simultaneously record from both hemispheres.

After a period of up to 1 hour, we were able to record responses in both hemispheres. We recorded response to pure tones, clicks and tone trains. The animal preparation, and hence, the recordings, were stable for up to 15 hours (entire length of recording).

Results: To determine whether units were responsive to auditory stimuli, we constructed peri-stimulus time histograms (PSTH's figure 1a) by summing responses to similar frequencies and intensities. The trace in figure 1a shows a typical PSTH created from recordings from one of the implanted electrodes. It consists of a sharp onset response followed by a slower, smaller amplitude response, both of which are characteristic of neurons in primary auditory cortex. Spike counts in a 50 ms time window immediately following the stimulus captured the initial transient response, and were used to construct a frequency-intensity response map (a 'tuning curve'). An example of such a tuning curve is shown in figure 1b.

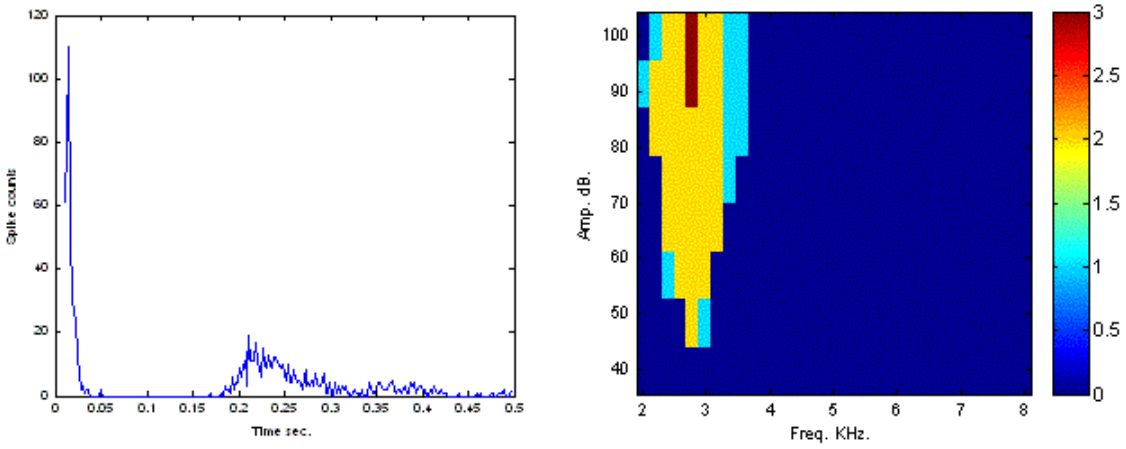

Figure 1: a) An example of a peri-stimulus time histogram (PSTH) of responses seen in one electrode in the UEA. b) Frequency-intensity response map of a neuron in primary auditory cortex. The color bar shows spike counts in a 50 ms time window.

Figure 2 illustrates PSTH's obtained from simultaneous responses to presentation of pure tones recorded with different electrodes across the two hemispheres (note that these have been created from the multiunit responses which typically have been recorded in these dual hemispheric

recordings). The initial transient short latency response (30 – 50 ms) shown in figure 1a can be seen in many units across both hemispheres.

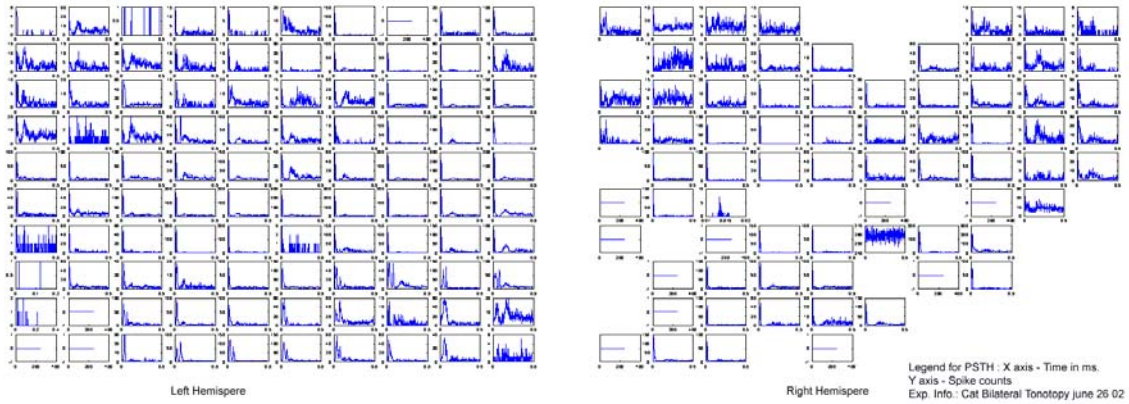

Figure 2: Peri-stimulus time histograms (PSTH's) across two hemispheres. The ordinate of each plot shows spike counts and the abscissa shows a 500 ms time window following the stimulus. Note: the geometry of electrodes has been preserved. An absence of a figure panel indicates that no detectable responses were obtained from those electrodes.

Tuning curves created from responses recorded from each electrode (similar to that of figure 1b) were calculated from presentation of 256 different tones. The sets of tuning curves for both hemispheres are shown in figure 3. Approximately 70 and 40 distinguishable tuning curves were obtained in the left and right hemispheres, respectively.

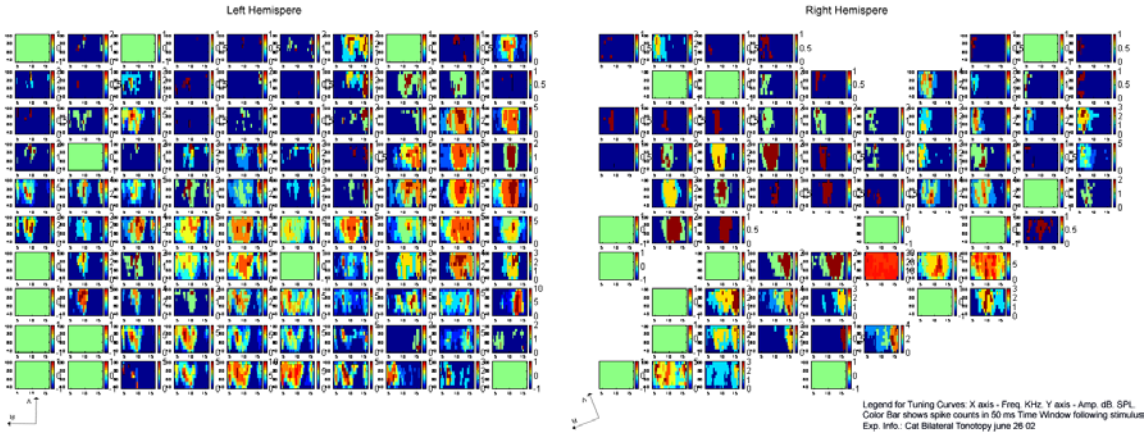

Figure 3: Tuning curve map of responses obtained from simultaneous recordings made across two hemispheres. In each panel, the amplitude of the tones is plotted on the ordinate and the abscissa shows frequency in KHz. The color bar indicates the number of spikes in a 50 ms. time window. An absence of a figure panel indicates that no detectable responses were obtained in those electrodes. Panels filled in light green indicated absence of responses in the time window used to obtain this figure.

Discussion: Apart from the basic information we have obtained regarding the bihemispheric mapping of tones in AI, we have presented these findings to illustrate that we can successfully

map the acoustic responses in AI using implanted 10x10 UEA's. These bilateral recording techniques increased the yield in each experiment and dramatically reduced experimental time (in the time normally required to measure the tuning curve in one unit, we have been able to record data that has allowed us to make tuning curves from 110 sets of multiunits distributed across both hemispheres). Further analysis is required to better understand differences in spectral and temporal processing across the two hemispheres, and a variety of analysis techniques are currently being considered.

We feel that these results demonstrate our potential ability to compare acoustic maps and electrically evoked spatio-temporal activity patterns in AI. We are eager to use the UEA to study the issues of the bilateral representation of a stimulus, and to explore electrical stimulation selectivity and frequency representations in AI. Further, these experiments illustrate that the UEA provides a very useful tool to study spectral and temporal information processing across both hemispheres in anesthetized animals.

2.1.2 Stimulation selectivity.

In previous progress reports we described an encouraging approach we are using to demonstrate the extent of stimulation selectivity that can be achieved with direct electrical stimulation via an UEA implanted in the auditory nerve. The technique uses the fact that a subset of auditory nerve fibers that have been electrically excited by a 'masking' stimulus become refractory to further electrical stimulation (test stimuli) if the test stimulus is delivered within 300-350 microseconds of the initial masking stimulus. Thus, if two stimuli are delivered sequentially through two separate electrodes, and if each stimulus excites an independent subset of auditory nerve fibers, then the amplitude and kinetics of the eABR response to the test stimulus (delivered within 300 microseconds of the masking stimulus) will not be affected by the masking stimulus. The effects of the masking stimulus are monitored by comparing two eABR responses to the test stimulus, one delivered within 300 microseconds of the masker, and one delivered 5 milliseconds of the masker. This 5 millisecond eABR response would not be affected by the masker stimulus even if there was substantial overlap in the fibers excited by both masking and test stimuli.

In our previous reports we have shown that some pairs of electrodes show no fiber overlap, while other pairs of electrodes show substantial overlap. Over this present reporting period, we have conducted two experiments to extend these findings to each pair of electrodes in a 3 x 4 UEA implanted in the auditory nerve. Clearly, this is a very time consuming experiment and, when successful, will generate a massive amount of data (66 pairs of electrodes, with 10 stimulus levels per electrode pair at four latencies). Unfortunately, the condition of the cats in these experiments and instrumentation problems resulted in only limited degrees of data acquisition. However, we have developed MATLAB routines that allow us to analyze this massive amount of data in reasonable times when this experiment is fully successful. Our goal is to make a two dimensional matrix of our estimates of fiber overlap between each pair of electrodes implanted in the auditory nerve. We hope to be able to achieve this map in the next reporting period.

2.1.3 Radiological and Histological studies of chronically implanted cat auditory nerve.

(Note: the implantation procedure of 13 chronic cats has been previously reported in progress report 3 and 5. No histology or radiology was reported, but we indicated the probable methods of doing them.)

We have conducted chronic studies of cats implanted with passive unstimulated arrays to assess the biocompatibility of the materials used in the array, the high velocity implant procedure, and the array location post implant. Movement and vibrations of the skull can potentially displace the bone cement used to immobilize the array and this could result in explantation the UEA. Neck muscles could potentially move the lead wires, displace the array, and damage the nerve. There is a significant risk of spread of infection to the central nervous system due to the close proximity of the implant to the fibers of the auditory nerve and to the brainstem. This study was designed to explore these potential problems and to investigate ways to overcome them.

Methods: Recovery and euthanasia: The animals were allowed to recover in an incubator in the Moran Laboratories under constant supervision of the surgeon. Once the animal had demonstrated that it was capable of standing, it was transferred to the cat holding area in the basement of the Biomedical Polymers Research Building. It was isolated from the other cats and given soft (canned) food and water. Pain management was approached aggressively. Adequate post-surgical analgesia was provided by a fentanyl patch placed on the nape of the neck. Additional analgesia was considered in consultation with the vet. In addition, antibiotics (1/2 tablet of Baytril at 22.7 mg per tablet administered orally twice a day) were given over this period and the cat was monitored by the the surgeon. After three days, the cat was reintroduced into the group housing. After 8-10 days, the sutures were removed. Telazol (9 – 12 mg/kg, IM) was used if necessary to immobilize the animal to remove the sutures or to clean the tissues around the percutaneous connector.

Post-operative complications include but were not limited to the vestibular, seventh nerve deficit and Horner's syndrome. But these were usually transient (Bright and Birchard 1985). The treatment meanwhile was symptomatic and consisted of antibiotic ophthalmic ointment (bacitracin-neomycin-polymyxin veterinary ophthalmic ointment applied as a thin film over the cornea 3 to 4 times a day) for 2 –4 weeks to allow the eyelid function to return to normal.

The implanted arrays were not stimulated and the animals were allowed to roam freely. Chronically implanted animals were euthanized up to 180 days after implantation. A large dose of Ketamine was administered IM (20 - 30 mg/kg) to permit introduction of an IV access and deep anesthesia initiated by IV administration of a lethal dose (0.2 mL/kg) of a mixture of Ketamine (100 mg/kg) and Xylazine (Rompin, 10 mg/kg) or sodium pentabarbitol (50 mg/kg). To prevent clotting during the perfusion, heparin was administered (10,000 units, IV). The animal was then perfused through the heart with either a gluteraldehyde-based fixative (1.0% paraformaldehyde, 1.25% gluteraldehyde, in phosphate buffer) or formaldehyde-based fixative (4% paraformaldehyde, in phosphate buffer). Earlier euthanasia was to be considered on the advice of the Clinical Veterinarian if it was determined that there were significant problems associated with the implant. These problems would have included, but not be limited to, erosion of the skin around the percutaneous connector, a chronic and unresponsive infection around the percutaneous connector, or the presence of neurological signs relating to the implant.

Radiological Studies –Plain Film X-ray: We used plain film X-ray analysis in three euthanised animals to determine the post-implant position of the UEA. The intact head of each specimen was placed on a Kodak Corporation X-Omatic® (Eastman Kodak Company, Rochester, NY)

film cassette, which contained a single sheet of AFGA SCOPIX CRSB® (Agfa Corporation, Ridgefield Park, NJ) electronic imaging non-screen, direct exposure film. The orientation of the specimen on the cassette varied depending on the desired image of the specimen. The major orientations were for dorsal-ventral, lateral, antero-posterior, and oblique images of the specimen. After proper orientation, the specimen and cassette were placed in a Faxitron Cabinet® X-ray system (Faxitron Corporation, Wheeling, IL). In the Cabinet X-ray, the specimens were approximately 20 cm from the X-ray source. Multiple kV settings ranging from 47-70 kV were tested, and all exposures lasted for three seconds, the optimal exposure duration. The x-ray films were then processed in an AFGA CP 1000® (Agfa Corporation, Ridgefield Park, NJ) automated film processor following standard operating procedures for the developer, which are simply to load the film and allow automated processing.

Fluoroscopic imaging of an implanted cat skull was also attempted with an OEC C-arm fluoroscopy unit® (GE OEC Medical Systems, Salt Lake City, UT). As fluoroscopy takes virtual images, we used all available kV settings to optimize the picture resolution and contrast. The cat's head was approximately 20 cm from the x-ray source.

Radiological Studies –CT Scan: Three cat heads were scanned post-implantation by a Marconi Mx 8000® CT scanner (Marconi Medical Systems [now owned by Philips corporation], Highland Heights, OH) using the following protocols: axial, non-helical protocol, 1 mm and 0.5 mm increments at 1.75 mm/s table speed, 200 and 250 mA, 120 kV and Z of 1.00. The gantry tilt of the scanner was adjusted so that the scanning line through the cat's heads produced both coronal and transverse sections. The images were reconstructed with an ultra-high-resolution kernel, 512 matrix. The images were reconstructed with both 1 mm and 0.5 mm slice intervals through the entire scan.

Histological Analysis: Histological analysis of the implanted cochlear nerve was performed in three animals to confirm the position of the electrodes and to examine the tissue for adverse response to the surgery and the implantation procedure. After varying periods of implantation, the animals were deeply anesthetized and perfused via a cardiac puncture with the array in place using formaldehyde as a fixative. The array was left in place while the head was stored in formaldehyde. This preserved the electrode implant site in the nerve. The temporal bone on either side was harvested and the soft tissues attached to the bone were cleaned. Gross examination of the temporal bone was carried out and the position of the array visualized though the internal auditory meatus.

We decalcified two temporal bones with the array in place to document electrode placement in the cochlear nerve. The specimens were immersed in a decalcifying reagent, 1 L of a 5% formic acid solution. The solution was changed approximately every 48 hours. Endpoint decalcification was determined by manually estimating the flexibility of the sample. The specimens were decalcified for 2 weeks**.** The gross images of the decalcified temporal bone with the array in place documented the location of implantation. The unimplanted temporal bone served as the control.

Tissues were placed in cassettes and transferred to 70% ethyl alcohol until time of processing. Cassettes were placed in the processing pot of a standard tissue processor and dehydrated using an increasing gradient of ethyl alcohol, then Xylene, and finally paraffin. After embedding with paraffin, the tissues were placed overnight on a cold plate. These paraffin embedded tissues were

cut into 15 μM sections by a Leica RM 2155© microtome (E Licht Co., Denver, CO). Tissue sections were stained with a standard Hematoxylin and Eosin staining protocol.

Results:

Animal surgery and recovery issues: All the chronic surgeries and recovery were uneventful and vestibular dysfunction was transient. After complete recovery, the animals were feeding normally and did not lose weight.

Radiological Studies –Plain Film X-ray: The radiological results revealed the *in situ* position of the UEA in the temporal bone of three animals. We tested a variety of kV settings from 40 to 70 kV and found that a relatively high kV (67 kV) at a three second duration provided the best results for identifying the UEA within the structures of the temporal bone. This high kV decreased the contrast of the bony structures and was ideal for viewing areas of high bone density, such as the temporal bone. We examined the dorsal-ventral, lateral, antero-posterior, and orthogonal images and were able to identify the array and lead wires in spatial relation to the cochlea, the internal auditory canal and the jugular bulb, as seen in figure 4. When analyzing structures on the implanted side, the unimplanted contralateral side served as a control. The cochlea, modiolus, and jugluar bulb on the implanted side appeared intact, suggesting that they were not damaged during the surgical procedures of drilling and high-speed implantation.

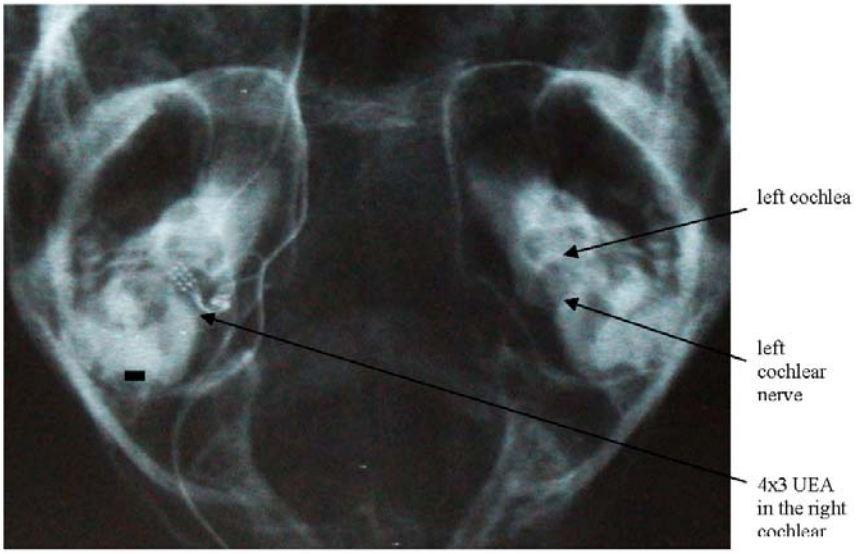

Figure 4. Plain film X-ray. The film demonstrates a dorsoventral x-ray of a cat skull with a 4 x 3 UEA implanted in the right cochlear nerve. The left temporal bone landmarks are labled. Scale: 1 mm.

The radio-opaque platinum covering the microelectrodes and metallic bond pads revealed the location of the UEA. The dorsal-ventral films showed the metallic bond pad directly perpendicular to the x-rays and hence the UEA was clearly identified. The UEA was seen to be in the internal auditory canal where the cochlear nerve emerges from the modiolus. From the x-rays, it was determined that the geometry of the UEA was maintained after implantation indicating that the array remained intact and in its intended site of insertion. The plain x-ray films obtained from the antero-posterior and lateral orientations did not reveal the location of the UEA because the density of the temporal bone and the base of the skull obscured the metallic

bond pads. We attempted to visualize the UEA in the skull using three-dimensional fluoroscopy. We were able to see virtual images of the skull and manipulate the angle of the image in all axes. This approach, however, did not provide any useful information. Despite being able to manipulate the location of the specimen in three dimensions, the resolution and contrast of fluoroscopy could not be adjusted to provide a higher definition image showing the position of the UEA.

Radiological Studies –CT Scan: For the CT images, two different current levels were used, 200 mA and 250 mA. Both yielded approximately the same image results in regard to contrast and resolution. The size of the slice was also varied from 1-mm slices to 0.5 mm slices. The 0.5 mm slices were preferable as the smaller slice size allowed us to view more images in the area surrounding the array and did not decrease the density resolution (Haaga 1994). The CT scans of the implanted heads provided a three-dimensional perspective of the position of the UEA. While the CT images did not resolve the fine structural detail, i.e. the microelectrodes of the UEA, its overall structure could be seen in relation to temporal bone landmarks such as the cochlea and the internal auditory canal. The axial CT images, seen in figure 5, clearly showed the base of the array adjacent to the cochlea in the internal auditory canal, indicating that the electrodes were embedded in the nerve. By using the sequential coronal CT sections, seen in figure 6, the position of the array was revealed to be within the internal auditory canal adjacent to the cochlea, where the cochlear nerve emerges from the modiolus. In both axial and coronal sections the contralateral unimplanted side was used as a control. As with the x-ray imaging, the CT scans suggest that the UEA remained in its original insertion site in the cochlear nerve.

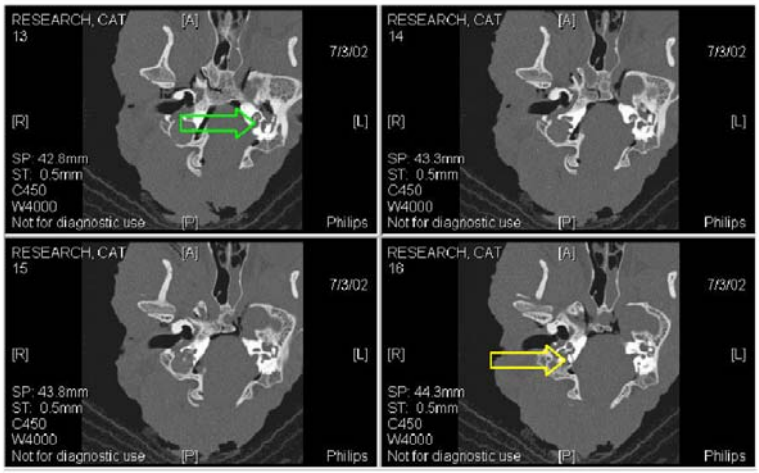

Figure 5. Axial CT scans. The axial san sections are 0.5 mm apart in the vicinity of the implanted 4 x 3 UEA in a cat head. The green arrow points to the unimplanted contralateral left cochlear nerve emerging out of the left cochlea. The yellow arrow points to the UEA implanted into the right cochlear nerve, seen emerging out of the right cochlea.

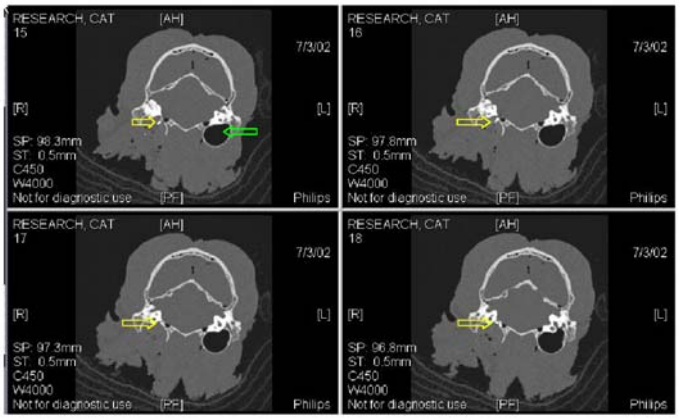

Figure 6. Coronal CT scans. This figure demonstrates coronal CT scans of a cat head that has been implanted with a 4 x 3 UEA. The scan sections are 0.5 mm apart in the vicinity of the implanted UEA. The green arrow points to the pneumatized bulla on the unimplanted contralateral left temporal bone. The yellow arrow on the upper scans points to the lead wires going to the UEA, while the yellow arrows on the lower two scans point to the UEA implanted into the cochlear nerve.

Histological Analysis: Histological analysis was performed in three cats. This provided us further validation of the surgical access, the insertion technique and anatomical effect of the array on the integrity of the nerve over this chronic timeframe. Macroscopic analysis of a decalcified specimen was performed to provide information about the location and orientation of the array along the nerve, while microscopic analysis was performed to collect information about the depth of the electrode tracks, absence of microscopic hemorrhage and absence of damage to the nerve fibers.

We examined the gross anatomy of the temporal bones after the decalcification. The implanted UEA was visualized through the internal acoustic meatus. The array was seen to be intact and within the cochlear nerve.

Histological evaluation of the H&E stained cochlear nerve at the implanted site, shown in figure 7 did not reveal any formation of connective tissue. This was unexpected, we believe this is due to the process of pulling the electrode out of the nerve, and the expectation that there was connective tissue adherent to the array also getting explanted. Electrodes were located inside the nerve as evidenced by the tracks. The mean distance between the tracks was 400 μm, as expected. The minor variation in the track separation distance is presumably artifactual due to tissue fixation, decalcification and processing. The figure also demonstrates minimal damage to the nerve at the site of implantation as indicated by absence of hemorrhage into the implanted site and preservation of normal tissue architecture compared to the proximal control.

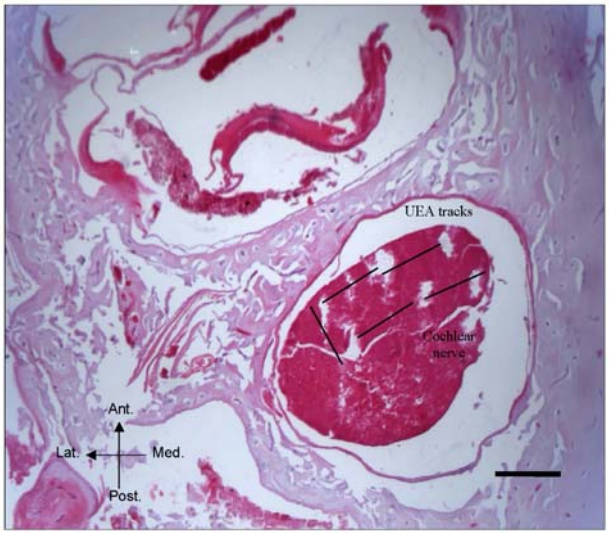

Figure 7. Histology of a chronically implanted cochlear nerve in cat right temporal bone. The figure shows a magnified H & E stained section of a cochlear nerve that was implanted with a 4 x 3 UEA. The tracks of the UEA are evident in the cochlear nerve. The nerve demonstrates normal fibers with absence of hemorrhage into the nerve. Scale 0.4 mm.

The histology distal to the implantation appears normal indicating no nerve damage to the axons going from the implanted site to the brainstem. The histology of the implanted side was compared to the unimplanted side serving as a control. We believe that this demonstrates nerve survival in the chronic timeframe of up to 1 year.

Discussion: The present study was done to demonstrate the long term implications of implantation of passive arrays. We have investigated the radiological proof of electrode location and the histological consequences of the intraneural implantation in the chronic timeframe.

Previous studies (Branner, Stein et al. 2001) have demonstrated that acute and chronic implantation of the UEA and its varying length variant, the USA, does not cause significant damage to the peripheral nerves in an animal model. However, the complex surgery and implantation procedure in our case raises valid questions about the potential safety of the surgical procedure and the biocompatibility of the implant. The uneventful recovery of the animals indicates that there is no inadvertent vestibular or facial nerve damage. It also indicates that there is no significant risk of meningitis and brainstem complications.

Post implant radiological studies in this series of experiments have indicated that the UEA was intact and remained in the initial portion of the cochlear nerve. This further validates the implantation procedure and the stability of the bone cements used.

Histological studies done in this study indicates that the UEA is in the cochlear nerve and it causes minimal damage to the nerve for up to 1 year. Absence of significant unaided eye and microscopically evident hemorrhages in the site of implantation indicates that the vascular supply to the nerve was not compromised by the implantation procedure, a positive indicator of nerve survival.

Questions remain about the chronic stability and biocompatibility of the implant in an actively stimulated array.

2.1.4 Development of Backpack stimulators.

The problems of interconnections between our portable backpack stimulator and the implanted UEA have caused us to revisit this problem. We are now proposing to use a chronic interfacing technology with which we are very familiar: the use of a microtech 12 pin connector/titanium pedestal mounted directly on the animal's skull. This system provides a secure connection of the interconnect cable to the microtech connector, with release being provided by the interconnection with the backpack stimulator. Arrays are being fabricated with this system.

3. PLANS FOR NEXT REPORTING PERIOD

3.1. ACUTE ANIMAL EXPERIMENTS

3.1.1 Auditory nerve stimulation selectivity

Our two electrode overlap technique for examining the selectivity of stimulation will receive considerable effort over the next quarter. Our instrumentation and analysis techniques are refined to the point that effort now needs to be expended only on the animal experimentation. We expect to conduct a sufficient number of animal experiments to ensure the successful outcome of this component of our contract.

3.1.2 Acute AI mapping.

The graduate student originally assigned to this project will continue working on the AI mapping project, under the co-direction of Drs. Nagarajan and Normann.

3.2. CHRONIC ANIMAL IMPLANTS

3.2.1. Passive implants.

We will continue our histological evaluation of the implanted auditory nerves. Histology will be conducted in the pathology department at the University of Utah, at the pathology laboratory at the VA hospital, and/or by Dr Fred Linthicum, Jr. at House Ear Institute, or by DR. Eduardo Fernandez at the Miguel Hernandez University in Alicante, Spain.

3.2.2. Active implants.

We expect to have a successful array/stimulator interconnection scheme in place and to have demonstrated efficacy of our backpack stimulators over the next reporting period.

4. PUBLICATIONS AND PRESENTATIONS

Dr. Arun Badi has described our progress at the 2002 Neuroprosthesis Workshop held at the NIH in October. We have also described our anatomical and electrophysiological findings in two poster presentations at the Society for Neurosciences annual meeting held in Orlando, Florida in November, 2002. A paper describing our acute electrophysiological findings has been submitted for publication.

5. LITERATURE CITED

Badi, A. N., T. Hillman, et al. (2002). "A technique for implantation of a 3-dimensional penetrating electrode array in the modiolar nerve of cats and humans." Arch Otolaryngol Head Neck Surg **128**(9): 1019-25.

Branner, A., R. B. Stein, et al. (2001). "Selective Stimulation of Cat Sciatic Nerve Using an Array of Varying- Length Microelectrodes." J Neurophysiol **85**(4): 1585-94.

Haaga, J. R. (1994). Computed tomography and magnetic resonance imaging of the whole body. St. Louis, Mosby.

Rousche, P. J. and R. A. Normann (1992). "A method for pneumatically inserting an array of penetrating electrodes into cortical tissue." Ann Biomed Eng **20**(4): 413-22.