The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

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By:

Richard Normann, Ph.D., Principal Investigator

Clough Shelton, M.D., Co-Investigator

Srikantan Najaragan, Ph.D., Co-Investigator

Arun N. Badi, M.D., Ph.D., Co-Investigator

Center for Neural Interfaces

Department of Bioengineering

University of Utah

Salt Lake City, UT 84112

ABSTRACT:

Over this quarter we have accomplished the following tasks:

1. We have conducted our first experiment on the mapping of the activity in the auditory cortex, evoked by electrical stimulation of the auditory nerve.

2. We continued analysis of data from all our cat experiments on the overlap of auditory nerve fiber excitation evoked by stimuli with pairs of UEA electrodes.

3. We have submitted a manuscript for peer review and publication that describes the auditory nerve overlap experiments.

4. We have relocated the acoustically isolated double walled environmental chamber into the Center for Neural Interfaces.

5. We have conducted two chronic electrical stimulation experiments of cat auditory cortex using our portable stimulator, and performed a histological analysis on the first cat.

6. We have optimized the procedures for activation of the iridium tips on the UEA to be used in the chronic implantation/stimulation experiments.

7. We have begun to model the effects of current injection on the recruitment of auditory nerve fibers.

1. WORK PERFORMED DURING THIS REPORTING PERIOD.

1.1. We have conducted our first experiment on the mapping of the activity in the auditory cortex, evoked by electrical stimulation of the auditory nerve.

One motivation for implanting an array of penetrating electrodes into auditory nerve is that these electrodes should provide much more focal stimulation of auditory nerve fibers than can be achieved with scalar electrodes. We have proposed to test this hypothesis by recording the spatio-temporal activity map in auditory cortex, evoked by stimulation via individual electrodes implanted in the auditory nerve. We have conducted our first experiment directly aimed at this hypothesis. The experiment was not successful in its primary motive, however, but we did achieve a number of minor successes that are described below.

We developed a surgical protocol that allowed us functional access to both the auditory nerve and auditory cortex, a complex problem as access to these regions is on opposite sides of the head. We first reflected the scalp and performed a craniotomy over the auditory cortex. The dura was left intact at this time. The animal was turned over and our typical auditory nerve access was achieved via the bulla [Badi et al] and a 3 x 4 electrode array was implanted in the auditory nerve using our pneumatic, high velocity insertion technique [Rousche and Normann]. The array was immobilized with a small piece of fascia harvested from the area of the implantation, and the array and fascia further immobilized with two part silicone poured into the bulla. The lead wires from the

electrode were looped in the surgical opening to provide strain relief, the opening was closed, and the percutaneous connector sutured to the skin near the region of the opening. The animal was once again turned over to its original position, and the surgery on the cortex continued. The acute connector system for the UEA was positioned and the 10 x 10 UEA lead wires manipulated such that the UEA was located over the auditory cortex and the electrodes were normal to the cortical surface. The array was moved out of the opening and the dura overlying the auditory cortex was reflected. The UEA was relocated over its desired position and inserted using our pneumatic insertion technique [ref]. The dura was closed over the array, and a piece of saline soaked gauze was used to close the opening. A small piece of polyethylene film was placed over the gauze to minimize dehydration of the opening.

The quality of the cortical implantation was next assessed by recording responses to various acoustic stimuli, produced by mechanical percussion of small pieces of metal. These results were most encouraging. Large single units were observed on a number of the cortical electrodes with activity that was clearly acoustically modulated. The animal was next prepared for rigorous auditory nerve stimulation via the implanted auditory nerve UEA and mapping from the cortical array. All eleven electrodes in the implanted stimulating UEA were sequentially stimulated at various levels (20 through 140 microamps), and recordings of cortical activity were made from all 100 electrodes implanted in the cortex. This part of the experiment took approximately 6 hours to complete. The cat was then prepared for acoustic stimulation and mapping. A commercial acoustic stimulator sound tube was positioned in the animals ear contralateral to the implanted auditory nerve, and the animal was stimulated with a random pattern of tone bursts of varying amplitudes and frequencies. All acoustically evoked and electrically evoked responses were recorded using a 100 channel amplifier and data acquisition system (NSAS, Bionic Technologies, Inc. Salt Lake City, Utah). All data was subsequentially analyzed off-line, we failed to obtain acoustically or electrically evoked coherent cortical activation maps.

While this first experiment was unsuccessful, the surgical protocol appeared to be verry effective and it will be followed in subsequent experiments. This should result in eventual successful mapping of both acoustically evoked activity patterns as well as UEA evoked activity patterns from the same region of auditory cortex.

1.2. We continued analysis of data from all our cat experiments on the overlap of auditory nerve fiber excitation evoked by stimuli with pairs of UEA electrodes.

Our analysis of the excitation of independent sets of auditory nerve fibers is continuing. We have fully analyzed the functional independence of excitation in a total of five successful cat experiments. The analysis uses electrically evoked auditory brainstem responses (eABR's) as the index of nerve fiber excitation and the amplitude of the eABR as an index of auditory nerve fiber recruitment. Thus, the analysis depends upon identification and measurements of eABR waveform components.

In previous progress reports we have submitted, we have described the kinetics of the electrically evoked auditory brainstem response (eABR) recorded with a pair of electrodes implanted in the scalp of the cat, with respect to a ground electrode located in the cat's neck.

Because of the stimulation site (intraneural stimulation), the kinetics of these responses differed from those in published reports using scalar stimulation [1-3]. To better understand the nature of the intraneurally recorded eABR's, we have performed an experiment wherein we specifically examined the kinetics of the eABR's evoked by intraneural and surface stimulation of the auditory nerve. Electrode arrays were implanted and experiments were performed on the anesthetized cat as described in previous progress reports and in published reports [4-6]. The eABR recordings were made with a pair of scalp electrodes located over the vertex and over the rear of the skull (at the midline of the skull). A needle was inserted in the back of the neck and served as a distant ground. Amplification was achieved with a commercial amplifier (25,000 gain, 300 and 3000 Hz corner frequencies, 6 dB/octave roll off) and data was stored on a Pentium class computer with a custom data acquisition program. Stimuli were delivered via a programmable stimulator and electrode switching was controlled by the custom data acquisition program.

Plotted in Figure 1a is an intensity-response series evoked by electrical stimulation of the auditory nerve with a 0.5 mm diameter platinum ball electrode (Medtronic Xomed Surgical Products, Inc. Jacksonville, Fla), placed in the scala, via the round window (400 to 1500 microamps). The current return electrode was placed in the clavotrapezius muscle. The scalar stimuli ranged from 400 to 1500 uamps and were biphasic, 100 usec/phase. The major peaks in the eABR waveform can be readily appreciated in this figure, and the latencies of these peaks closely agree with those in the published literature. To appreciate the differences in the kinetics of responses evoked by the UEA from those of responses evoked by the scalar stimuli, we have plotted in Figure 1b responses evoked by the UEA. We have also noted that the response kinetics observed with UEA stimulation differ somewhat from experiment to experiment, possibly due to differences in the depth of implantation and in the fiber populations that are being excited by various electrodes. However, the latencies of the peaks of the UEA evoked responses are similar to those evoked by scalar stimulation, and allow definitive identification of the peaks. Unfortunately, the large stimulus artifact often obscures wave I (or makes quantification of its amplitude very difficult). For this reason, and because the amplitude of wave II is generally very robust and more easily quantified, we have used wave II as our index of the degree of auditory nerve activation.

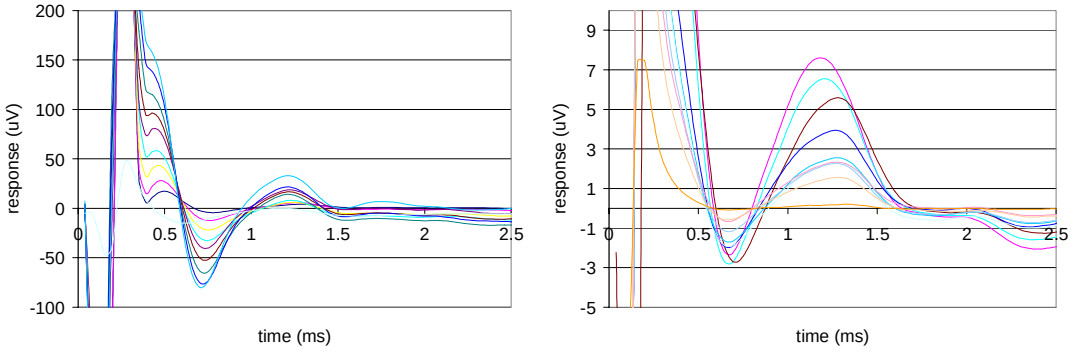

Figure 1 – a) eABR's evoked by scalar stimulation with a ball electrode. b) eABR's evoked by stimulation via a UEA implanted in the auditory nerve.

In our stimulation independence experiments, we are using a dual stimulus masker/probe paradigm, delivering the second stimulus at times 5000 usec and 300 usec after the masker

stimulus. The short masker/probe interval was chosen to be within the refractory period of the fibers stimulated by the masker stimulus. A comparison of the responses evoked at these two masker/probe intervals reveals the degree of functional overlap between the populations of fibers excited by the two stimuli. Because of the very focal stimulation associated with intraneural stimulation, one would expect little overlap for low amplitude stimuli, and we have found virtually no overlap between sets of nerve fibers excited by pairs of electrodes, provided that the stimulation is within a parathreshold region of currents (within 30% of threshold). For stronger stimuli, we begin to see overlap in excitation evoked by some pairs of electrodes, and for very strong stimuli (approximately 2 times threshold), we see significant overlap in some pairs of electrodes.

1.3. We have prepared a manuscript that describes the auditory nerve overlap experiments.

A manuscript that describes the stimulation of independent populations of auditory nerve fibers with the UEA has been submitted for peer reviewed publication.

1.4. Relocation of the acoustically isolated double walled environmental chamber into the Center for Neural Interfaces.

The relocation of Dr. Sri Nagarajan from the University of Utah to the University of California, San Francisco has required the relocation of the sound-proof environmental chamber used in our acoustic electrophysiological experiments from Dr. Nagarajan's original assigned space into the Center for Neural Interfaces. The relocation of the chamber was mandated by a space reassignment to a new faculty member in the Bioengineering Department. The relocation has required the renovation of one room in the Center for Neural Interfaces (removal of two non-load bearing walls and refinishing the space). Because of the size and weight of the environmental chamber, this relocation has proven to be a very complex task. The renovations of the Center for Neural Interfaces laboratory space, the disassembly, moving, and reassembly of the chamber has taken a little over three weeks to accomplish, and during this time we were unable to perform any electrophysiological experiments.

1.5. We have conducted two chronic electrical stimulation experiments of cat auditory cortex using our portable stimulator, and performed a histological analysis on the first cat.

An important component of this contract is to learn the consequences of electrical stimulation on both the neural tissues being stimulated and the electrode tips that are doing the stimulation. We have reported previously on our efforts to develop a portable, wearable electrical stimulator for our implanted cats, and our efforts to achieve a long term percutaneous signal interconnect. The stimulator we are using stimulates all 11 interconnected electrodes simultaneously at 103 Hz, with a biphasic stimulus waveform (cathodic first, 193 microsecond pulse width per phase, no interphase interval). Stimulation was performed on an 16 hour on / 8 hour off duty cycle. Quasi constant-current stimulation is achieved with the use of a high resistance resistor in series with each electrode. The signal interconnect is achieved with a skull mounted 12 pin

microtech connector screwed into a titanium pedestal mounted on the animals skull.

Before we attempt to stimulate auditory nerve on a chronic basis, we are validating our techniques by stimulating cat auditory cortex. We report herein our first successful experiment at stimulation of cat auditory cortex using this chronic system.

Cat subject F02-096 was successfully implanted on February 20, 2003. The animal was initially stimulated with all 11 channels simultaneously approximately 10 days after surgery. Current levels ranged from 26 uA to107 uA (see table 1).

When stimulation of this cat was initiated, the summated current used at that point was 810 ua, and this summated current induced a seizure. Stimulation was immediately terminated. Three of the channels with the largest current injections were disabled, and stimulation recommenced. No additional seizures or behavioral indications of the stimulation were observed. Two of the three disabled channels were eventually enabled, but at reduced current levels.

The tissue was fixed, removed, and sent to Dr. Eduardo Fernandez in Alicante, Spain for sectioning and staining. GFAP has yet to be performed on these samples, but the results of H&E staining is shown in Figure 2. There are clear clusters of lymphocytes and astrocytes near the tips of some of the implanted electrodes.

We have estimated the extent of the glial proliferation with a damage index (judged subjectively, 0 = no response, 2 = maximal response) in the sample shown in Figure 2, and plotted our subjective estimate of damage versus the total coulombs injected at each electrode. As shown in the Figure 3, there is a poor correlation between these two parameters. Some electrodes in which large currents were injected showed no response, while other electrodes that had much smaller amounts of injected currents showed a large response. Clearly, more work needs to be conducted before we can make any definitive statements about the consequences of current injections.

Our second chronic cat was successfully implanted on May 2, 2003. We have had problems keeping the titanium pedestal successfully mounted on the animal's cranium. The pedestal has broken loose of the skull on two separate occasions before the animal could be attached to the stimulator backpack. We think this may be partly due to the young animal's relatively small size and thin skull. Our third attempt at attachment seems to be holding and the animal is recovering from surgery.

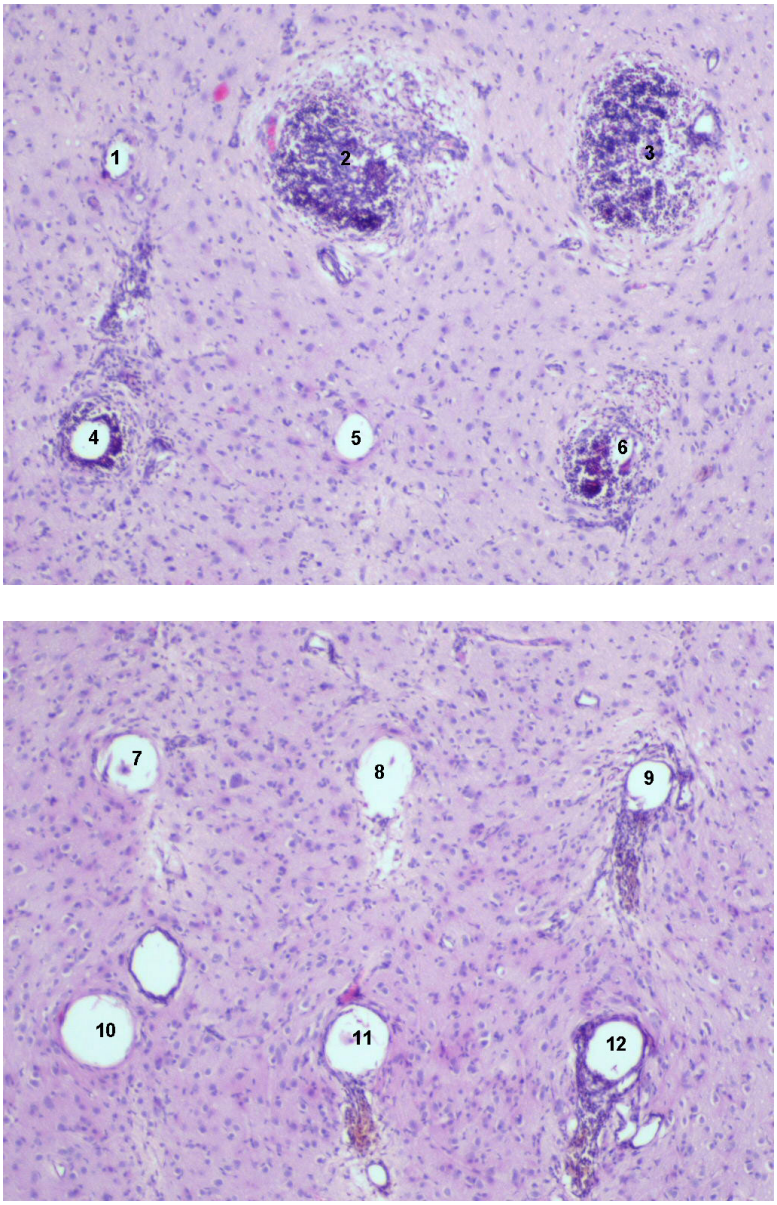

Figure 2 - Example of the extent of the glial proliferation with a damage index (judged subjectively, 0 = no response, 2 = maximal response) resulting from current stimulation via a 3 x 4 UEA implanted into auditory cortex.

Electrode Number	Current (uA)	StimulationDuration (hrs)	Coulombs injected	Damage Index
1	100	0.001	0.0	0
2	94	64	21.7	2
3	94	64	21.7	1.7
4	43	64	9.9	1
5	29	64	6.7	0
6	26	64	6.0	1.5
7	80	46	13.2	0
8	107	46	17.7	0
9	0	n/a	0	n/a
10	107	64	24.7	0
11	43	64	9.9	1
12	0	n/a	0.0	0.8

Table 1 gives a breakdown of the current levels and stimulation times for all the electrodes in an experiment.

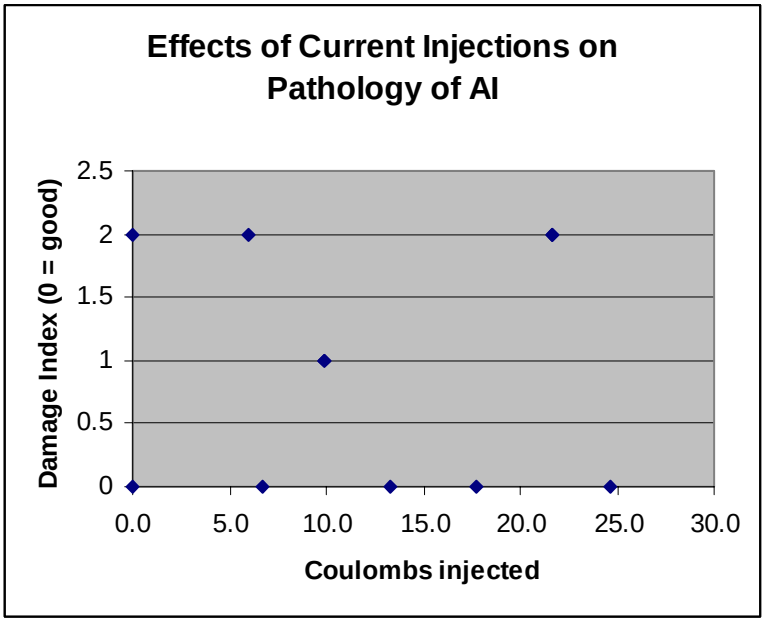

Figure 3 - A plot of our subjective estimate of neuronal damage in AI versus the total coulombs injected at each electrode.

1.6. We have optimized the procedures for activation of the iridium tips on the UEA.

The iridium oxide tipped electrodes we will use for the chronic stimulation paradigm had to be developed and optimized in-house. As reported previously, we have optimized the

metalization of our electrode tips with a low stress iridium film of quantifiable thickness. We have also optimized our protocol for formation of activated iridium oxide films (AIROFs) at the tips utilizing the cyclic voltammetry system previously reported.

The optimal conditions for the anodic growth of iridium oxide films depend upon the system, protocol, and electrolyte being utilized (P.G. Pickup & V.I. Birss, "A Model for Anodic Hydrous Oxide Growth at Iridium," *J. Electroanal. Chem*., 220 (1987), pp. 83-100, Elsevier Sequoia S.A.). Activation is achieved by cycling the voltage across the iridium – electrolyte interface through critical voltages whereat state changes in the iridium oxide occur while staying within the water window of the electrolyte so that current is not shunted into the process of gas evolution. To optimize our protocol, we investigated the biasing and magnitude of our cycling potential.

The water window for our system, though mildly variable from tip to tip by about 20 mV magnitude, tends to be very symmetric about a zero bias. In order to bias our cycling potential and stay within the water window, it was necessary to lower the magnitude of our cycling potential. At zero bias our typical magnitude is around 1.9 V at the edges of the water window. At a bias of +100 mV or – 100 mV the magnitude becomes 1.7 V. As illustrated in Figure 4, a biasing of –100 mV led to a very slight growth of oxide while switching to a positive bias immediately resulted in a more robust growth.

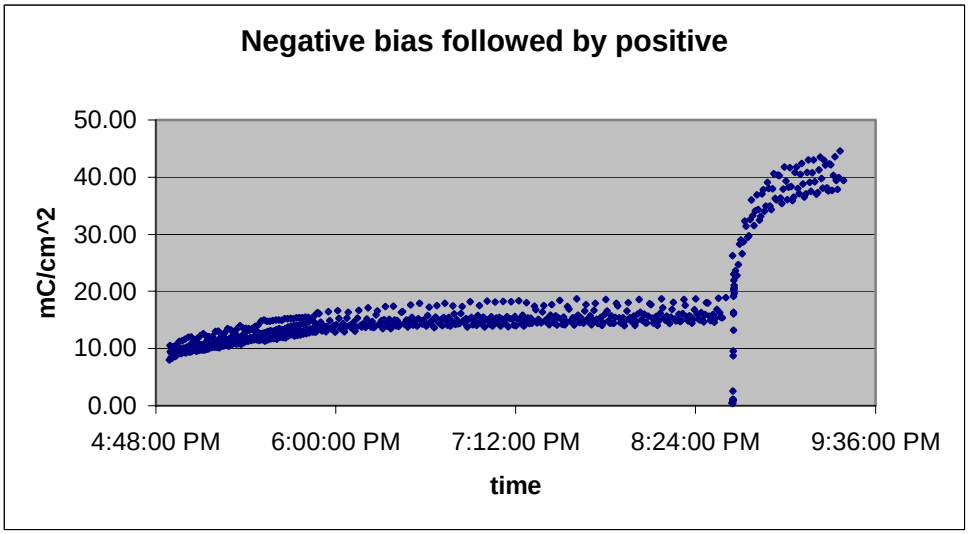

Figure 4 – The effects of the polarity of bias voltage on the activation of iridium on the tips of the electrodes.

Figure 5 compares biases and magnitudes of charge injection capacity. The activation sequence began at a bias of +100 mV with a magnitude of 1.7 V. This resulted in fairly poor oxide growth. The second phase is a bias of 0 mV with the same 1.7 V magnitude. A mild increase in the slope of the growth line can be seen indicating slightly increased growth potential. The third phase is a bias of 0 mV once again, but with the magnitude turned up to the maximum allowed by the water window, 1.9 V. A much more robust activation is observed, not reaching its plateau of maximal activation within the hour observed. This leads us to believe that an activation protocol with a zero bias and a

magnitude just within the water window allows the greatest activation potential for our electrodes in this system.

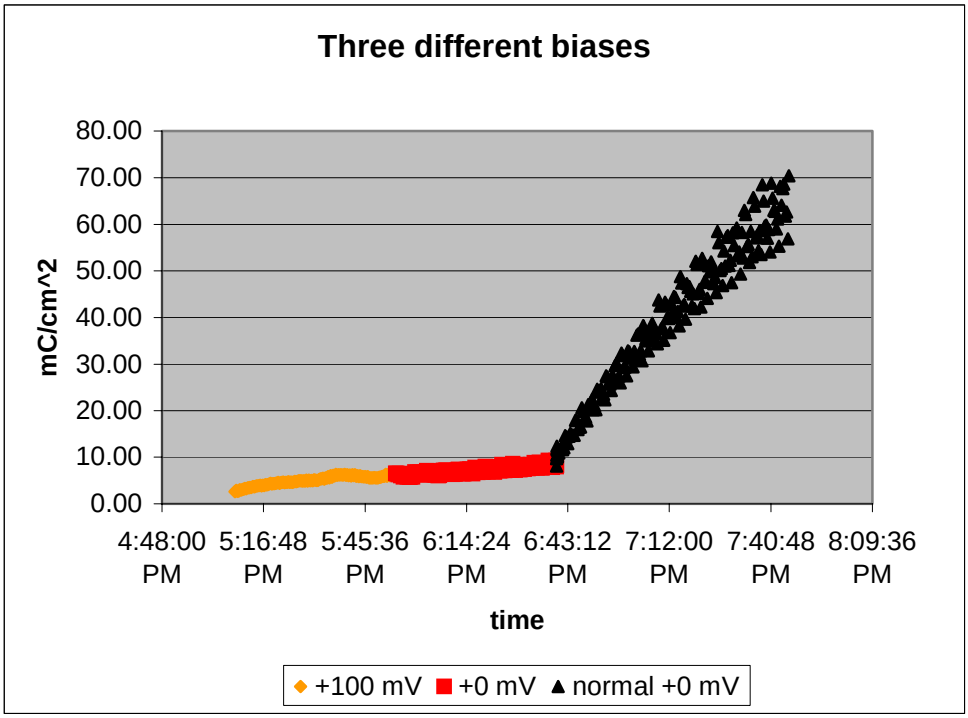

Figure 5 – Activation of iridium tips as a function of bias voltage and amplitude of activation voltage.

An analysis of impedance data for 40 of our tips so far activated using the above optimized procedure indicates an average drop in impedance to 28.9% ± 22.2 % of the original value. Average electrode impedance before activation is 120 kΩ and average impedance following activation is 32 kΩ. Charge injection capability of the electrode tips activated using the above protocol results in a 17.0 ± 11.5 times increase from the initial charge injection capability of pure iridium. Variance in charge injection increase probably results from variable initial surface areas as well as variance in time cycled (between 45 and 75 minutes).

1.7. We have begun to model the effects of current injection on the recruitment of auditory nerve fibers.

We have worked over the past three quarters on quantifying the selectivity of nerve fiber stimulation that can be achieved with the implanted electrode arrays. We have done this using electrical masking experiments with pairs of electrodes implanted in the auditory nerve, and we are also recording the patterns of activation of visual cortex that result from stimulation of the auditory nerve. To put these electrophysiological estimations of excitation selectivity on a more firm analytical foundation, we have recently performed a series of modeling experiments to validate our assumptions regarding recruitment of fibers with extrinsic electrical current injections via intrafascicular electrodes.

The goal of this work is to develop an anatomically accurate three dimensional model of

the auditory nerve, using values for the biophysical parameters of the auditory nerve fibers and the endoneurium obtained from the literature. After developing an anatomically correct model, we will use the resources of the Scientific Computing and Imaging Institute (a software modeling environment called 'SCI-run') at the University of Utah to estimate the current distribution that flows through the auditor nerve fibers in response to current injections via a point current source. Once the current distributions have been determined, we can determine the spatial distribution of neurons that are depolarized to a threshold level by the injected currents. This will allow us to determine 1) fiber recruitment as a function of current injection, 2) fiber recruitment as a function of the 3-D distribution of nodes of Ranvier, 3) the dependence of fiber excitation on fiber diameter, and 4) the dependence of fiber excitation on distance from the current injection site. The ultimate goal of this model will be to predict mean separation between current injecting electrodes and maximal levels of injected currents that produce minimal (less than 10%) excitation overlap. These estimates will be validated with our ongoing electrophysiological experiments. If the model is demonstrated to be accurate, we can use the model to optimize stimulation parameters (pulse duration and pulse amplitude) to minimize excitation overlap.

The auditory nerve has a complex 3-D fiber geometry where the fibers spiral in a helix with distance. Creating an accurate 3-D model of this complex architecture has been postponed while we work on a nerve with a simpler 3-D geometry, the cat sciatic nerve. We are using this nerve to develop and refine anatomical modeling tools and our current distribution estimation algorithms. This is a system with which we have considerable electrophysiological experience (extensive determinations of thresholds and variance of thresholds between electrodes, and complete force recruitment curves for many implanted electrodes). We have used histological sections of sciatic nerve made by our colleague in Spain (Dr. Eduardo Fernandez) to generate our anatomically based model.

Preliminary results using the sciatic model indicate that larger axons showed higher maximal current density and therefore higher firing probability than smaller diameter axons. Further, current density within the axon decreased roughly with the inverse square law; discrepancies could be accounted for by anisotropies in the realistic volume conductor. Finally, myelination was an effective barrier for axonal activation; thresholds were strongly reduced by decreasing the distance between the stimulating electrode and the closest node of Ranvier. With multi-electrode stimulation, the model estimated independence of activation as a function of electrode separation and stimulus level. These initial results in the cat sciatic nerve encourage its continued use to better understand and develop effective stimulus protocols for functional electrical stimulation of the auditory nerve.

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 extend our fiber excitation independence experiments to stimulation via Utah

Slanted Electrode Arrays.

3. We will chronically implant UEA's in the A1 for 4-8 more cats and evaluate the consequences of 64 hour stimulation using H&E and GFAP staining.

3. PUBLICATIONS AND PRESENTATIONS

Our paper detailing the acute & semichronic electrophysiological experiments, radiological and histological studies in cats was published in Laryngoscope [6]. Dr Badi presented and defended some of the work already done towards his doctoral thesis. An abstract detailing the histological work on chronic cats was accepted at the American Academy of Otolaryngology, AAO-HNS Foundation 2003 Annual Meeting program to be held in Orlando, Fl. An abstract detailing the functional independence protocol was also accepted at the same meeting. Another abstract dealing with spatiotemporal selectivity was submitted to the Society for Neuroscience Meeting to be held at New Orleans.

4. DISCUSSION

We periodically examine our original proposed time line and we are pleased to report that we have accomplished what we had hoped to accomplish at this time. However, we appreciate that there are two major components of the program that must be accomplished over this next year: our chronic stimulation project and our cortical mapping project. Both of these projects are complex and each has components that will be particularly challenging. The stimulation project will require us to histologically examine the auditory nerves that have been chronically stimulated. In order to extract the auditory nerve from its bony surroundings, and to do so without damaging the nerve will require special expertise. Dr. Fred Linthicum from the House Ear Institute will be visiting us this next quarter to facilitate this process.

In order for us to make reliable maps of the acoustically and electrically evoked activity profiles in auditory cortex, we must have a quality implantation of a UEA in the auditory nerve, and a quality implantation of a UEA in the auditory cortex. As we have been successful at each of these procedures, we are confident that we should be able to perform both procedures simultaneously. However, the successful outcome of this experiment may require a number of attempts before both aspects of the experiment are each successfully accomplished.

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