The Feasibility of an Intraneural Auditory Prosthesis Stimulating Electrode Array

A. Final Progress Report

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This final progress report itemizes the findings from the research we have conducted throughout the entire period of contract support. We list below publications that have resulted from the contract research, and the specific aims that we proposed to achieve over this period, a brief summary of the results achieved for each specific aim, and conclusions drawn from each of the specific aims (where appropriate).

Most of our effort over this past three months were focused on examining the selective activation of neurons in AI due to acoustic stimulation and electrical stimulation via UEA's implanted in the auditory nerve. As a result, we will start this final report with a description of the AI maps we have made over this quarter.

Selective Activation Of AI Using Acoustic Stimulation And Electrical Stimulation Via UEA's Implanted In The Auditory Nerve.

Over this quarter, we have conducted eight experiments on acoustic and electrical mapping of AI and have been able to make acoustic maps in 2 animals, and electrical stimulation maps in 4 animals. In one of these animals, we were able to make both acoustic and electrical maps in the same animals. We describe below the results of our best acoustic and electrical maps made in the same animal. We are pleased with the maps we have been able to make, and our ability to make both acoustic and electrical stimulation maps is improving with each experiment. However, we intend to continue of efforts to make more complete maps than we have been able to make to date.

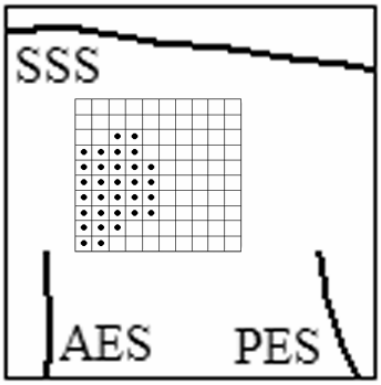


Figure 1. Location of 10 x 10 UEA implanted in AI of cat F04-0219.

The mapping protocol consists of implanting a 3 x 4 electrode UEA in the auditory nerve, turning the animal, and implanting a 10 x 10 UEA in the contralateral AI. We then measure eABR's to ensure the functionality of the auditory nerve, and then do acoustic and electrical mapping of AI. Figure 1 shows a drawing of the placement of the 10 x 10 UEA that was implanted in the AI of cat F04-0219. In this figure, the dots indicate electrodes in which useful multi-unit responses were recorded in response to acoustic stimuli.

Figure 2A shows the PSTH's recorded from these 31 sites that were evoked by acoustic stimulation, and Figure 2B shows the tuning curves generated from the histograms of Figure 2A for each of the 31 electrodes with multi-unit responses. The tuning curves do not include labels on the abscissa nor the ordinate for figure clarity, but the frequency of stimulation is represented on the abscissa with values ranging linearly from 1 through 40 KHz, and the ordinate represents the intensity of the stimulation in dB SPL with a range from 30 through 90 dB. The color represents the number of spikes in the interval of 5 to 30 msec after stimulus onset.

As is seen in the tuning curves, most of the electrodes recorded data that produced multiple peaked curves. The left-most peaks were not frequency dependent in these recordings, but the right-most peaks showed a tonotopic organization similar to that reported elsewhere. We used the right-most curves to produce the characteristic frequency map of Figure 3.

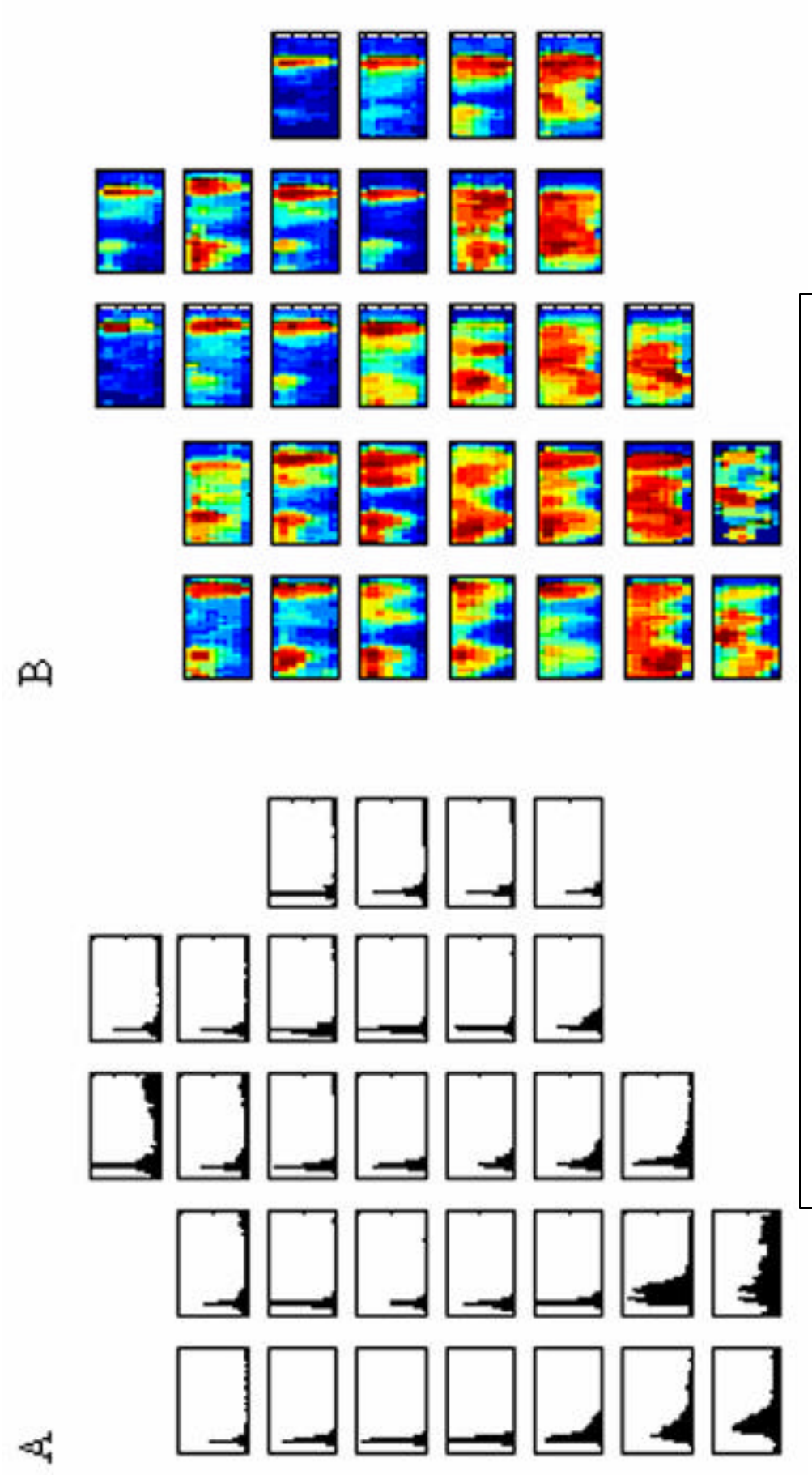


Figure 2. Maps of AI activity evoked by acoustic stimulation in animal F04-0219. A) PSTH's of activity evoked by acoustic stimulation. Ordinate plots spike rates (relative scale), Abscissa plots 0 to 100 msec post stimulus time, in 1 msec bins. B) Tuning curves evoked in AI and recorded with 100 electrode UEA. Abscissa is stimulus frequency from 1-40 kHz, and ordinate is stimulus intensity in dB SPL (30-90 dB).

The color bar in Figure 3 indicates the best frequency for activation each 400 x 400 micron region of auditory cortex from which multi-unit recordings were made. By reference to Figure 1, one can see a moderately well organized tonotopic arrangement of this region of auditory cortex. (Note: the tonotopic organization of AI determined in a recent experiment is illustrated in Appendix 2).

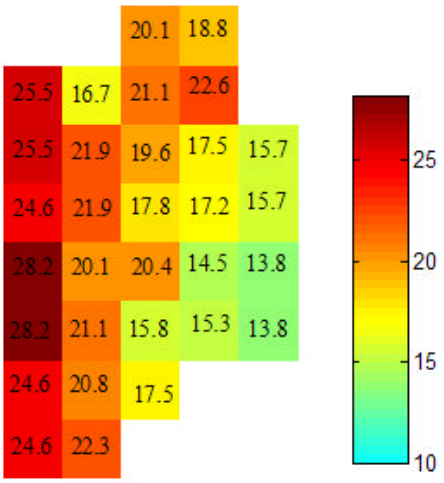


Figure 3: Best frequency map created from data of figure 2.

After this acoustic map was made, we recorded the activity patterns evoked by electrical stimulation of the auditory nerve via a 3 x 4 array of electrodes. In this experiment, only four of the implanted auditory nerve electrodes were able to evoke cortical activity, and the thresholds for activation were between 20 and 50 microamps (depending on the electrode being stimulated).

In figure 4 we present twelve electrical stimulation maps. The four columns represent maps evoked by stimuli delivered through each of the four stimulating electrodes, and the three rows (from the bottom to the top) represent maps evoked by currents of 30, 50 and 80 microamps. As is evident from this set of maps, the thresholds for each stimulating electrode varied between electrodes. What is also clear from a comparison of the activation patterns with the best frequencies from Figure 3 is that the activation patterns evoked by current injections through each electrode differed: auditory nerve electrode 1 activated mainly AI neurons with best frequencies in the 14-18 kHz region, while currents passed through auditory nerve electrode 3 activated AI neurons with best frequencies in the 20-28 kHz region. The selectivity illustrated in this figure was also seen in the other experiments, however, the maps we obtained in these other experiments were made only for electrical stimulation, so the AI activation patterns could not be correlated with best frequency maps. The activation maps for electrical stimulation in animals F04-0226 and F04-0621 are shown in Figures 5 and 6, respectively.

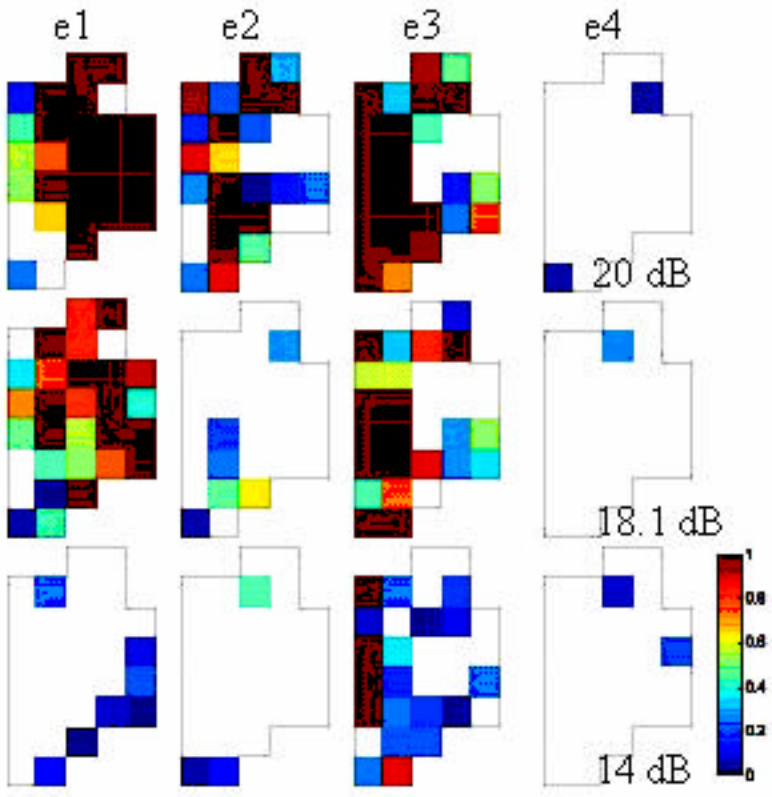


Figure 4. AI activation patterns evoked by currents passed through 4 electrodes implanted in auditory nerve (columns). Current level is increased from the bottom row to the top row.

These experiments provide good evidence that currents injected into the auditory nerve via an array of penetrating electrodes differentially excite groups of neurons in AI.

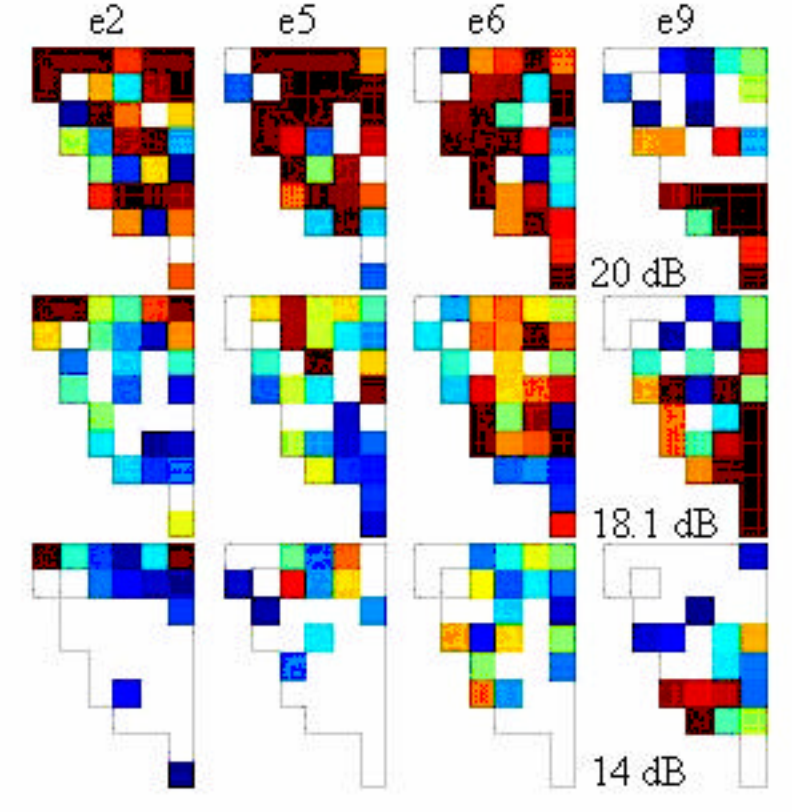


Figure 5. AI neuronal activation patterns in animal F04-0226, evoked by currents injected into auditory nerve via electrodes implanted therein. Current amplitude is indicated in the rightmost column (referenced to 10 uamps). Magnitude of responses is indicated by colors, with warm and cold colors reflecting large and small responses, respectively.

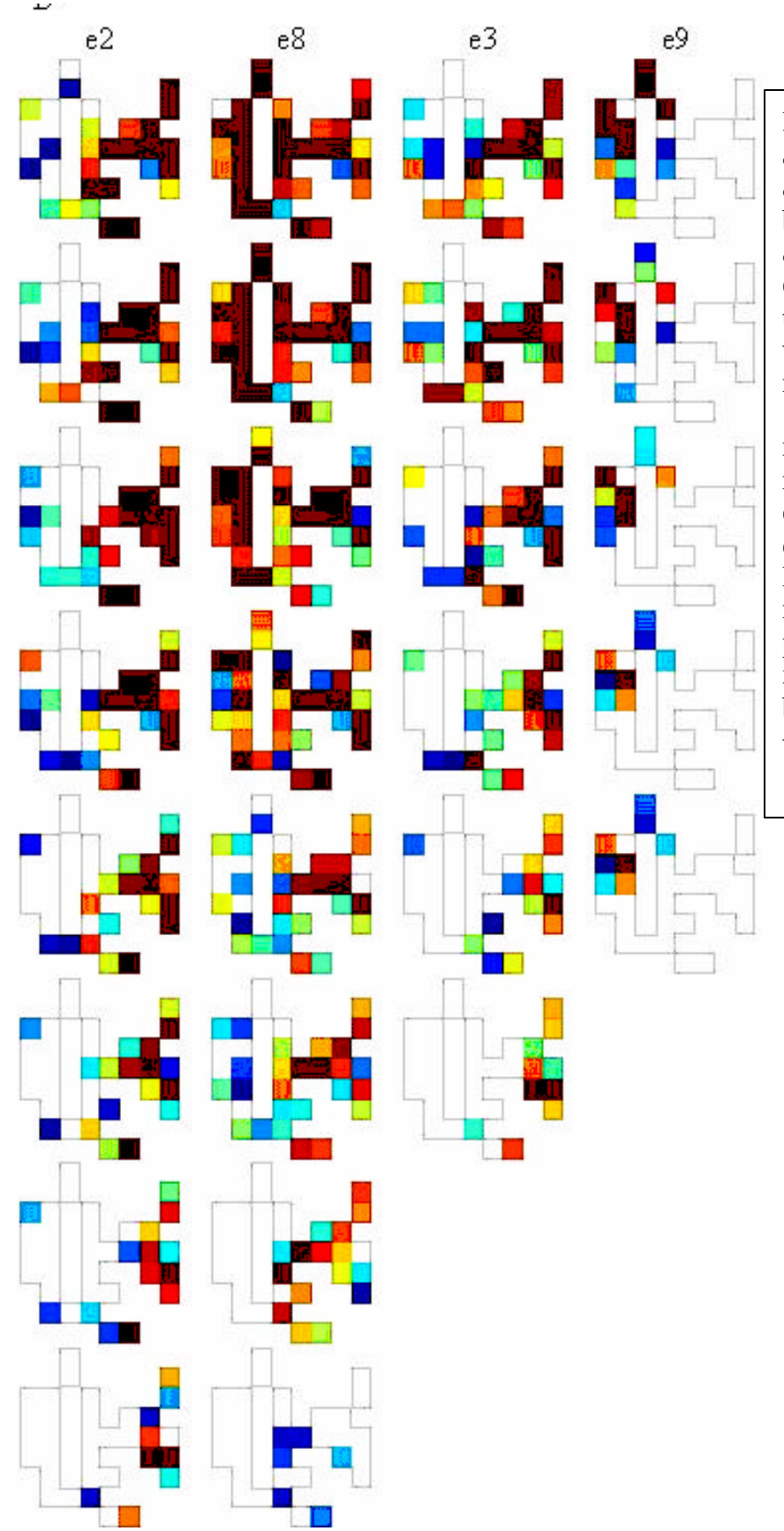


Figure 6. AI neuronal activation patterns in animal F04-0621, evoked by currents injected into auditory nerve via four electrodes implanted therein. Currents injected were (from top to bottom rows): 240, 220, 200, 180, 160, 150, 130, 110, and 90 microamps. Magnitude of responses is indicated by colors, with warm and cold colors reflecting large and small responses, respectively. Activation patterns for low currents in electrodes 3 and 9 have been omitted because they were below threshold.

Publications and presentations resulting from contract support.

Badi A.N., "Towards a Novel Auditory Prostheses" Master of Engineering Thesis, University of Utah. 2001

Badi A.N., Hillman T., Shelton C., Normann R.A., "A Technique for Implantation of a 3-Dimensional Penetrating Electrode Array into Modiolar Nerve of Cats and Humans", Arch Otolaryngol Head Neck Surg. 2002 Sep;128(9):1019-25.

Badi A.N., Kertesz T., Shelton C., Gurgel R., Normann R.A., "Development of a Novel VIII Nerve Intraneural Auditory Neuroprosthesis", Laryngoscope 2003 May;113(5):833-42.

Badi A.N., "Towards an VIII Nerve Auditory Neuroprostheses" Doctor of Philosophy Thesis, University of Utah. 2003

Hillman T., Badi A.N., Shelton C., Normann R.A., "Anatomical and Clinical Considerations for a Novel VIII Nerve Auditory Prostheses", accepted for publication, Otology Neurotology.

Owa A. O., Badi A.N., Gull J., Wiggins R., Shelton C., "Evaluation of the Accuracy of T2 Fast Spin Echo Magnetic Resonance Imaging of the Cochlear Nerve", accepted for publication, Otology Neurotology.

Badi A.N., Owa A. O., Shelton C., Normann R.A., "Channel Independence in an Intraneural VIII Nerve Auditory Neuroprosthesis", submitted to Otology Neurotology.

Manuscripts in preparation

Seung-Jae Kim, Manyam, S., and Normann, R.A. "Selective Activation Of Auditory Cortex By Electrical Stimulation Of The Auditory Nerve With An Array Of Penetrating Electrodes".

Seung-Jae Kim, Manyam, S., and Normann, R.A.,"High Resolution Mapping Of Auditory Cortex Activation Evoked By Acoustic Stimulation".

Badi A.N., Shelton C., Normann R.A., "Biocompatibility and Radiological Studies in Cats Chronically Implanted with a Novel Auditory Neuroprostheses"

McDermott, R., Tresco, P., and Normann, R.A., "Histopathological Consequences of current injections on feline auditory cortex".

Intellectual Property:

Invention Disclosure, University of Utah. On the surgical procedure for implantation of Utah Array in VIII nerve of cats and humans. Co-inventors are Arun Badi of Bioengineering, Clough Shelton and Todd Hillman of Div of Otolaryngology, Head and Neck Surgery, University Hospital, University of Utah.

Invention Disclosure, University of Utah. On the development of a novel auditory prostheses using Utah Array. Co-inventors are Richard Normann, Arun Badi of Dept of Bioeng and Clough Shelton of Div of Otolaryngology, Head and Neck Surgery, University Hospital, University of Utah.

Invention Disclosure, University of Utah on the development of a novel optic nerve visual prostheses using Utah Array. Co-inventors are Richard Normann, Arun Badi, and Eric Nielsen, all of Dept of Bioeng, University ofUtah.

Conference Publications:

Badi A.N., Hillman T., Shelton C., Normann R.A., "Anatomical Considerations for an VIII Nerve Auditory Prostheses", Society for Neuroscience, New Orleans, 2000.

Badi A.N., Owa A. O., Shelton C., Normann R.A., Maynard E., "Novel Auditory Prostheses Using an Intraneural Stimulating Electrode Array", 32nd Neural Prosthesis Workshop, 2001, NIH, Bethesda, MD.

Badi A.N., Kertesz T., Hillman T., Shelton C., Normann R.A., "Feasibility Studies for a Novel VIII Nerve Auditory Prostheses", XXXIV International Conference of Physiological Science, Christchurch, New Zealand, 2001.

Badi A.N., Kertesz T., Hillman T., Shelton C., Normann R.A., "Studies For A Novel VIII Nerve Auditory Prostheses", Conference on Implantable Auditory Prostheses, Asilomar, California, 2001.

Badi A.N., Kertesz T., Hillman T., Shelton C., Normann R.A., "Electrophysiological Studies Towards Development Of A Novel VIII Nerve Auditory Prostheses", Society for Neuroscience, San Diego, 2001.

Hillman T., Badi A.N., Shelton C., Normann R.A., "Cochlear Nerve Stimulation with Novel Penetrating Electrode Array", Combined Otolarynogological Spring Meeting Triological Section, Palm Desert, California 2001.

Badi A.N., Owa A. O., Sincic R., Shelton C., Normann R.A., "Channel Selectivity and Chronic Studies of a Novel VIII Nerve Auditory Prostheses", Society for Neuroscience, Orlando, 2002

Manyam, S., Zoar, Badi A.N., Nagarajan, S., "Studies Using Multichannel Array in Auditory Cortex of Cats", Society for Neuroscience, Orlando, 2002

Owa, A. O., Gull, J., Wiggins, R., Badi, A.N., Shelton, C., "Evaluation of the Accuracy of T2 Fast Spin Echo Magnetic Resonance Imaging of the Cochlear Nerve", One Hundred Thirty-Fifth Annual Meeting of the American Otological Society, Boca Raton, Florida, 2002.

Badi A.N., Hillman T., Shelton C., Normann R.A., "Towards a VIII Nerve Auditory Neuroprosthesis" American Academy of Otolaryngology Head & Neck Surgery Annual Meeting, Orlando, 2003

Shelton C., Normann R.A., Badi A.N., Kennedy R., "Intraneural Cochlear Nerve Electrode Array: An Alternative Approach to Hearing Restoration" 4th International Symposium on Electronic Implants in Otology & Conventional Hearing Aids, Toulouse, France, 2003

Gurgel R., Badi A.N., Shelton C., Normann R.A., "Radiological and Histological Effects of Intraneural Implantation on the Cochlear Nerve", American Academy of Otolaryngology Head & Neck Surgery Annual Meeting, Orlando, 2003

Hadley K., Smith M. E., Badi A.N., Normann R.A., "Differential stimulation of the recurrent laryngeal nerve in the cat model using an intra-neural electrode array", American Academy of Otolaryngology Head & Neck Surgery Annual Meeting, Orlando, 2003

Badi A.N., Kim S. J., Shelton C., Normann R.A., "Electrode Independence in a Novel VIII Nerve Auditory Prostheses".

Kim, S.J., Manyam, S., Badi, A., and Normann, R.A.,"Neural Responses in Feline Auditory Cortex to Direct Auditory Nerve Stimulation", Society for Neuroscience, San Diego, 2004.

Invited Talks:

Invited to present the advances in novel neuroprosthesis development at the Thirty Third Neural Prosthesis Workshop, October 2002, held at the Lister Hill Center (National Library of Medicine).

Invited to deliver a seminar on the advances in cochlear implant technology at the Conference on Implantable Auditory Prostheses, Asilomar, California, 2003.

Invited to present progress on our contract research at the Neural Prosthesis Workshops, 2001-2003, held at the National Institutes of Health.

Proposed Specific Aims and summary of results of contracted research.

Anatomic studies to develop chronic feline and human modiolar implant systems.

SA1. Perform anatomical studies on feline and human cadaveric specimens to refine our current surgical access to the modiolar portion of the cochlear nerve. We have developed a surgical access in both feline and human cadaveric models (described in PR#1). **Conclusions: Surgical access is feasible in both the human and feline. The trans-bulla approach in the feline model allows access to approximately 2-3 mm of the auditory nerve, enough to insert a 3 x 4 (12 electrode) 400 micron spaced electrode array. The approach is the easiest investigated, but is still complex and can result in injury to the nerve during exposure of the nerve and insertion of the electrode array.**

SA2. Determine the value of peri-operative MRI in candidate selection, cochlear nerve implant design, and surgical planning. We have compared MRI images of the auditory nerve with physical measurements of the same nerves in human cadaveric specimens and described our findings in PR#3, in a presentation at the 37th annual meeting of the American Neurotology Society, and in a publication in Otology Neurotology. **Conclusions: MRI imaging of the auditory nerve does not permit accurate determination of the auditory nerve dimensions (as revealed by direct physical measurements of the same nerves). Further, as the differences in MRI estimates of nerve diameter compared to direct measurements did not vary in a systematic fashion, there appears to be little value in peri-operative MRI in candidate selection. However, there can be use of the technique in surgical planning where precise measurements of nerve diameter would be less of a critical issue.**

SA3. Adapt existing manufacturing techniques for graded-length microelectrode arrays (USEA) to requirements for long-term implantation into the cochlear nerve of cats. We made a number of modifications to the basic Utah Electrode Array architecture to make it more suitable for auditory nerve implantation. These were dicing the array to a 3 x 4 (12 electrodes) or 4 x 4 (16 electrodes) or 5 x 5 (25 electrodes) geometries (described in PR#1), metalizing the electrode tips with iridium and activating them with cyclic voltametric currents (described in PR#7 and #8), and insulating the electrode shanks with parylene or increasing the thickness of the shank insulation with 2 microns of silicon nitride. **Conclusions: Relatively straightforward modifications of the UEA can produce implant systems well suited to use in auditory nerve implantation experiments.**

Acute feline electrophysiological studies.

SA4. Provide evidence that implantation of high-count microelectrode arrays into the cochlear nerve by means of rapid pneumatic insertion does not significantly damage the

nerve. The lack of significant injury to the auditory nerve resulting from high velocity implantation of the Utah Electrode Array into the auditory nerve has been demonstrated by our ability to record eABR's evoked by electrical stimulation of the auditory nerve via current injected with the implanted electrode arrays (described in PR#3). UEA stimulation thresholds required to evoke eABR's were as low as 8 uamps (described in PR#3) and only increased moderately over the two day post implant times that experiments were performed (described in PR#3). **Conclusions: Our experiments provide a proof-of-concept that implantation of penetrating electrode arrays into the auditory nerve using high-velocity implantation is feasible. However, not all surgical implants resulted in successful experiments. Specifically, we were not able to successfully evoke low threshold eABR's in all felines acutely or chronically implanted with UEA's. We believe that this is a consequence of the complex surgical implantation procedures, and fact that during array implantation, the electrode insertion tool tends to limit visibility of the array and the nerve. This makes it difficult to achieve direct visually guided implantation of the UEA into the auditory nerve.**

SA5. Demonstrate that electrical stimulation of the cochlear nerve through a USEA evokes both ABRs and correlated activity in primary auditory cortex (A1) of cats. We developed dedicated LABVIEW based instrumentation that was used to automate all eABR stimulation and data acquisition experiments (hardware used in these experiments, and LABVIEW programs used in the instrumentation can be obtained by contacting Richard Normann (normann@utah.edu)). We have demonstrated that UEA stimulation evokes both eABR's (illustrated in PR#3) and neural responses in AI of cats (technique described in PR#8 and responses illustrated in PR#9). Much of our effort over the last two years of the contract was occupied with recording of both acoustic and electrical evoked responses from AI using 10 x 10 UEA's. **Conclusions: The auditory nerve stimulation and measurement of eABR's evoked by stimulation of UEA's implanted in the auditory nerve is easy and reliable using the dedicated instrumentation. However, high-quality single-unit recordings from AI, evoked by current injections into the auditory nerve were more difficult to obtain. This appears to be a consequence of the compounding of two complex surgical procedures: 1) exposure of the auditory nerve, implantation of the UEA into the auditory nerve, securing the lead wires and connector to the animal, turning the animal to allow surgery on the auditory cortex, and 2) the surgical exposure of AI, and implantation of a 10 x 10 UEA at that site. A fully successful experiment requires that all surgical procedures are successful. This has been achieved with only moderate success to date.**

SA6. Demonstrate that patterned spatial and temporal stimulation through the electrodes of the USEA evoke patterned electrical responses (e.g. single units, local field potentials) in cat A1. As illustrated in the beginning of this report, we have shown that passing electrical currents through different UEA electrodes implanted in the auditory nerve evokes different patterns of electrical activity in AI (measured with 10 x 10 UEA's implanted in AI) (also illustrated in PR#9). **Conclusions: neurons in AI can be selectively activated with direct current injections via UEA's implanted into the auditory nerve. Different patterns of activation were evoked by stimulation via different electrodes implanted in the auditory nerve. This was a primary motivation for the contracted research we have conducted. However, we have not directly compared in the same animal the AI activation patterns evoked by auditory nerve**

stimulation with those evoked by cochlear stimulation. This would be useful in the evaluation of which stimulation mode provides the greater selectivity.

SA7. Determine the number of available independent stimulating channels the USEA provides from recordings of evoked A1 activity during varying stimulation protocols. The goal of this Specific Aim was to demonstrate that electrical stimulation of the auditory nerve via implanted UEA's excited independent sets of auditory nerve fibers. While we had proposed to demonstrate this with electrically evoked AI recordings, we have also demonstrated it using the eABR overlap (or masking) technique (described in PR#4 and PR#7). In these experiments, we demonstrated that some pairs of implanted UEA electrodes stimulated independent sets of auditory nerve fibers, while other pairs of electrodes stimulated overlapping sets of auditory nerve fibers. **Conclusions: The eABR overlap experiments provide additional supporting evidence for the selective activation of AI described in SA6. The overlap experiments conducted to date were more complete than the AI mapping experiments, and provide strong evidence that direct auditory nerve current injections via implanted UEA's can excite independent subpopulations of auditory nerve fibers, a prerequisite for the selective activation of AI neurons.**

Chronic biocompatibility studies.

SA8. Evaluate histopathological effects of 6- and 12-month passive USEA implants in cat cochlear nerve. This specific aim has occupied a great deal of our effort throughout the entire contract period and has focused on auditory nerve tissue harvested at 6-12 months post implant. We have photographed auditory nerves implanted with UEA's during the harvesting of the nerves (described in PR#5). We have used plane-film X-ray and CT imaging to verify chronic electrode placements (described in PR#6). We have used high resolution CT to image the modiolus and the electrode arrays implanted in the auditory nerve to verify that the arrays have remained implanted over the entire post-implant period (described in PR#9, PR#10 and PR#11). We have serial sectioned implanted nerves and seen both fibrotic responses to the implanted electrodes and normal looking auditory nerve fibers in close apposition to the implanted electrodes (illustrated in PR#8 and #12). **Conclusions: UEA's can be implanted in the auditory nerve of cats using the trans-bulla surgical approach, and the implanted electrodes can remain in their original implant site for periods exceeding six months. Although the implanted electrodes can provoke a significant inflammatory response in some cases, in many cases the implanted electrodes have normal appearing fibers surrounding their tips. This indicates that electrodes can be chronically implanted in the feline auditory nerve.**

SA9. Develop chronic USEA implant system with portable programmable multichannel microstimulators. We have designed, built and tested programmable, backpack constant-current microstimulators (the single channel prototype was described in PR#5 and the final 11 channel system used in chronic stimulation was described in PR#9). The performance specifications of the stimulator is described in PR#9. A detailed schematic diagram of the stimulator is appended to this report. The design of the backpack system used to support the stimulators is described in PR#5. **Conclusions: The portable stimulator worked as specified.**

SA10. Histopathologically evaluate consequences of chronic electrical stimulation of cat cochlear nerve through multiple electrodes of chronically implanted USEAs in cochlear nerve. We have not been able to complete this specific aim due to delays in the design of our backpack stimulators, and due to difficulties of connecting our backpack stimulator to the skull mounted connectors. Further, because of the difficulties in achieving high quality histopathological analysis of the auditory nerve, we focused initially on demonstrating the consequences of current injections into auditory cortex. Our goal here was to demonstrate that our histological tools had sufficient sensitivity to reveal the consequences of high current intensity injections on the neuroanatomy around the tips of the current injecting electrodes. Three cats were implanted and AI was stimulated for a minimum of 60 hours. In order to ensure that the cats did not detach the backpack stimulators from their skull mounted connectors, each cat was stimulated under continuous experimenter supervision. Eleven of the implanted 100 electrodes were stimulated at 25, 50, 75 and 100 microamps (biphasic 200 microsecond pulses at 100Hz). At the end of the period of stimulation, the animals were sacrificed and the tissue was prepared for histological analysis. The histological studies are ongoing, and have not been completed at the time of this report. **Conclusions: Long term periods of stimulation will require improved chronic electrical interconnections to the implanted UEA to ensure that the implanted animals cannot disconnect the stimulators during the period of stimulation.**

Appendix Material:

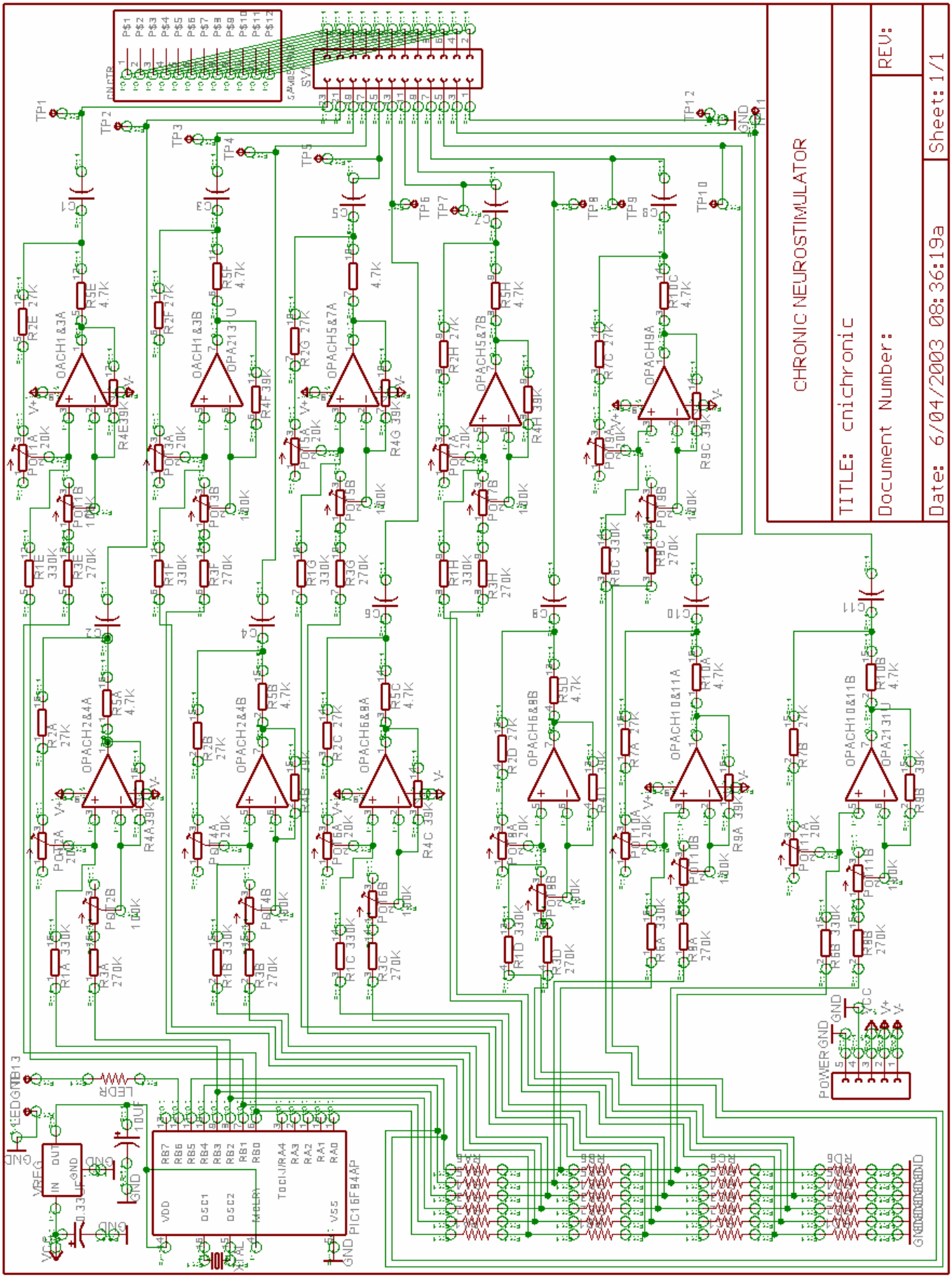
Appendix 1: Schematic diagram of portable 11 channel stimulator.

(Note: for details on the stimulator, please contact Richard A. Normann at the following email site:

normann@utah.edu

Gerber files of the printed circuit layout can also be provided to those interested.

Appendix 2: Acoustic mapping of AI. The top panel shows three tuning curves made from responses recorded with 3 of the 100 UEA electrodes implanted in AI. The middle panel shows tuning curves made from 26 of the 100 UEA electrode where acoustically evoked multiunit responses were recorded (the location of each tuning curve is correlated with the location of the electrode from which the curves were generated). The bottom plot shows the best frequencies of each of the regions of AI from which the tuning curves were generated. The tonotopic organization of AI, although incompletely mapped, is reflected in the pseudo colors (blue is 1 kHz, and dark red is 35 kHz).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Appendix 2: Tonotopic organization of AI determined from recent experiment.