Ninth Quarterly Progress Report

August 1, 2008 to October 31, 2008
Contract No. HHS-N-260-2006-00005-C
Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

Submitted by:
James O. Phillips, Ph.D.[1,3,4]
Steven Bierer, Ph.D. [1,3,4]
Albert F. Fuchs, Ph.D. [2,3,4]
Chris R.S. Kaneko, Ph.D. [2,3]
Leo Ling, Ph.D. [2,3]
Kaibao Nie, Ph.D. [1,4]
Jay T. Rubinstein, M.D., Ph.D. [1,4,5]

[1] Department of Otolaryngology-HNS, University of Washington, Seattle, Washington
[2] Department of Physiology and Biophysics, University of Washington, Seattle, Washington
[3] Washington National Primate Research Center, University of Washington, Seattle, Washington
[4] Virginia Merrill Bloedel Hearing Research Center, University of Washington, Seattle, Washington
[5] Department of Bioengineering, University of Washington, Seattle, Washington

Reporting Period: August 1, 2008 to October 31, 2008

Challenges:

In Quarter 9 we faced difficult challenges and made substantial scientific progress. Our two primary challenges are listed below.

1. Our multi-axis rotator failed during the quarter. Since the design of the rotator control system was proprietary and based on hardware that is currently unavailable, we were forced to redesign the control system. Our solution was to produce an externally controlled analog linear servo-system that interfaces with the CED data collection and stimulation control software in the laboratory. This activity took two months, but has been completed, restoring full control of the rotator and optimal integration for our continued experiments. During the time that the rotator was down, we shifted our experiments to another booth with a single axis rotator within an earth fixed phase angle coil system. This allowed us to continue our experiments, train our animals on head unrestrained gaze shifts, duplicate our stimulation hardware so that we can now run experiments in parallel in two booths, and create a platform for head unrestrained stimulation experiments. Essentially, we advanced our timeline for the development of these technical capabilities and addressed our immediate short-term need for a replacement testing environment at the same time.

2. We entered the quarter with an open question about the implantation strategy. We had implanted several animals and had two animals that showed NRT-ECAP (neural response telemetry – electrically evoked compound action potential) and one animal that showed robust behavioral responses to stimulation. We were uncertain why some of our implants could be nominally functional but behaviorally ineffective. Our strategy to address this was to record in the vestibular nucleus of both animals with vestibular ECAP and see if we could drive vestibular evoked responses in the vestibular nucleus of both animals. This led to the observation of vestibular evoked potential responses and driven units in the vestibular nucleus of the animal with robust behavioral responses and failure to drive evoked potential responses in the vestibular nucleus of animals that lacked behavioral responses (see below). Subsequently, we have learned that small movement of the electrode during implantation produces a change in the vestibular ECAP consistent with the responses in the animal without behaviorally effective electrical stimulation. This result encouraged Dr. Rubinstein to modify his procedure to provide better fixation of the electrode array, resulting in our second fully successful implantation (see below). We have also modified the design of the electrode arrays that have yet to undergo fabrication.

Current Successes:

1. We have successfully implanted a second animal with a cochlear implant based stimulation device that produces behavioral responses in the plane of the implanted

canal and robust vestibular ECAP. This animal shows better ECAP responses than previous animals (Figure 1), and higher velocity slow phase of nystagmus in response to low current electrical stimulation than our previous best animal (Figure 2), suggesting that the implant fixation and placement is improved with the new technique. Electrical stimulation produces eye movements that are similar in direction to the previously implanted animal; e.g., the slow phase eye movements elicited by stimulation of the right lateral canal are consistently left and up.

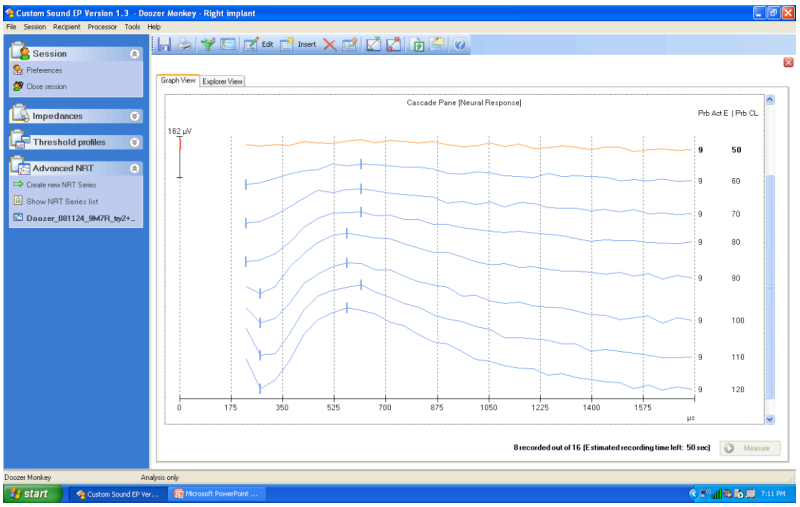

Figure 1. ECAP recorded one week post surgically using Nucleus Custom Sound clinical programming software following a successful revision surgery yielding robust nystagmus from electrical stimulation.

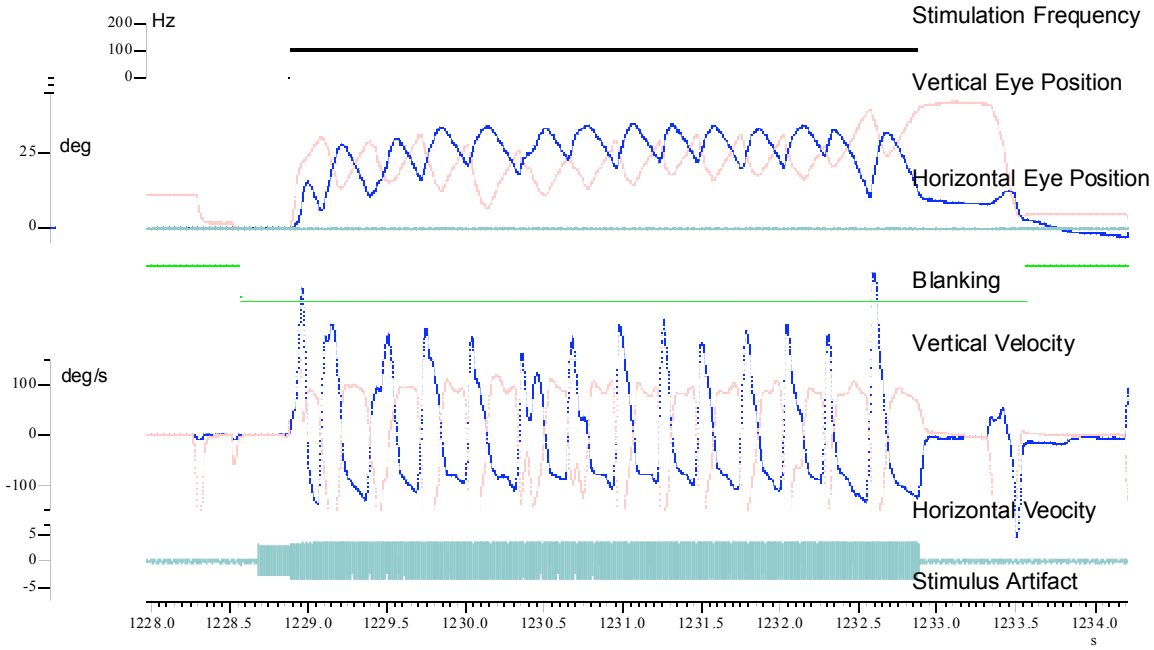

Figure 2. Nystagmus resulting from stimulation of a second animal with robust ECAP. The stimulation parameters are monopolar from electrode 9, 100 pps at 100 µA, 4 s duration, 400us pulse width, and 8us gap. The dark blue traces are horizontal eye position and velocity, and light red traces indicate vertical eye position and velocity. The interrupted green line indicates target blanking, and the stimulation artifact is displayed as the bottom grey trace. The highest amplitude artifact indicates active stimulation.

2. We have driven evoked vestibular field potentials in a rhesus monkey with ECAP and behavioral responses. In a second monkey with weak ECAP and no behavioral responses we have failed to evoke vestibular field potentials. Figure 3 shows vestibular evoked field potentials recorded through a tungsten microelectrode with stimulation at two different current intensities during a track through the cerebellum and brainstem. As can be seen in the figure, as the microelectrode is advanced from well above the vestibular nucleus, to immediately dorsal to the nucleus, and then into the medial vestibular nucleus, the field potential becomes apparent and then grows in amplitude. Larger stimulation currents are associated with larger field potentials. This result suggests that the stimulation of the lateral canal activates numerous fibers in the vestibular nerve that project to the appropriate secondary neurons in the vestibular nucleus.

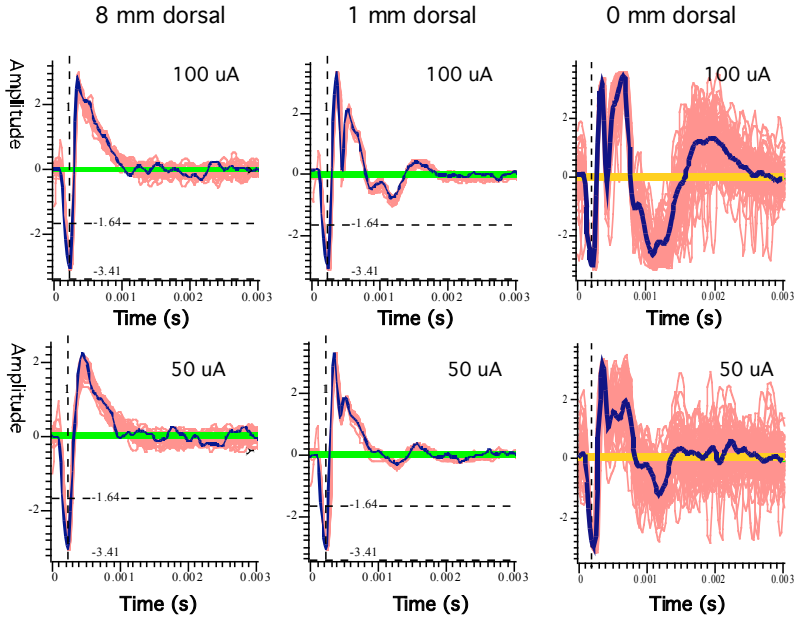

Figure 3. Stimulus artifact and field potentials recorded through a tungsten microelectrode during 10 Hz monopolar stimulation of the right lateral canal. Panels represent recordings during a single track with the tip of the recording electrode located 8mm, 1mm and 0mm dorsal to the right medial vestibular nucleus. Stimulation intensities were 50 or 100 μA. Thick blue lines represent the average of 40 consecutive stimulus trials. Although the stimulation artifact did not change, a field potential emerged as the tip of the electrode approached the medial vestibular nucleus.

3. In the animal in which we recorded evoked vestibular field potentials, we have successfully driven single units in the vestibular nucleus. We isolated single units in the ipsilateral medial vestibular nucleus and then applied a low frequency (10 Hz) stimulation train at 100 μA through the most distal site in the lateral canal array. This stimulation consistently drove the recorded unit displayed in figure 4.

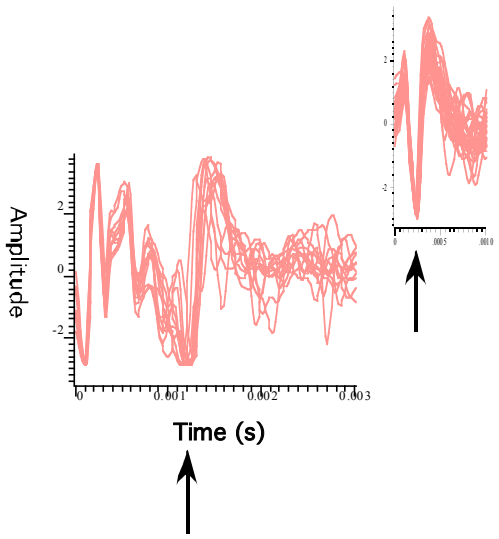

Figure 4. 20 consecutive responses of a single neuron (vertical arrow) in the right medial vestibular nucleus to 10 Hz stimulation of the right lateral canal at 100 μA. Inset illustrates the activity of the same unit without stimulation. Traces are aligned on stimulus onset or the onset of unit discharge. All traces (main panel and inset) are shown at the same scale.

4. We have parametrically driven nystagmus in a variety of combinations of natural and electrical vestibular stimulation. We have examined the time course of nystagmus elicited by FM modulated electrical stimulation (figure 5) and continuous frequency electrical stimulation (figure 6) at the same frequencies and current levels. Increasing the depth of modulation (difference between maximum and minimum stimulation frequency in pps) increases the depth of the velocity modulation during frequency modulation. However, unlike constant frequency stimulation, there is no decrement in slow phase velocity over time, either across trials or within a single stimulation trial. This suggests that modulated stimuli are more resistant to behavioral habituation than are constant frequency stimuli.

5. We have developed software to produce rate modulated (FM) behavioral responses with a PDA based stimulation system. We have successfully demonstrated that the PDA speech processor provided by Dr. Philipos Loizou of University of Texas, Dallas (N01-DC-6-0002) can be a useful replacement stimulator to our current NIC 2 research platform.

A significant effort in Quarter 9 was focused on modifying the PDA stimulator codes to generate a desired pulse train on a specific electrode. To generate nystagmus from electrical stimulation of the vestibular end organ in our implanted monkeys, a constant-rate and constant-amplitude pulse train was used. As a proof of concept, we chose a stimulation rate of 200 pps or 600 pps and a pulse width of 400 μs per phase on a single electrode (monopolar stimulation). Dr. Arthur Lobo helped us create a specific FPGA file for the PDA's SDIO card. We modified the PDA C codes to produce the desired pulse train. Some unnecessary parts of the PDA stimulator program were removed or changed to bypass the audio processing path in the original program. We also created a new timer to control the package communication between the PDA and the SDIO card. A

slider bar was added to the PDA control panel for varying the amplitude of the pulse train from 0 to 255 clinical levels.

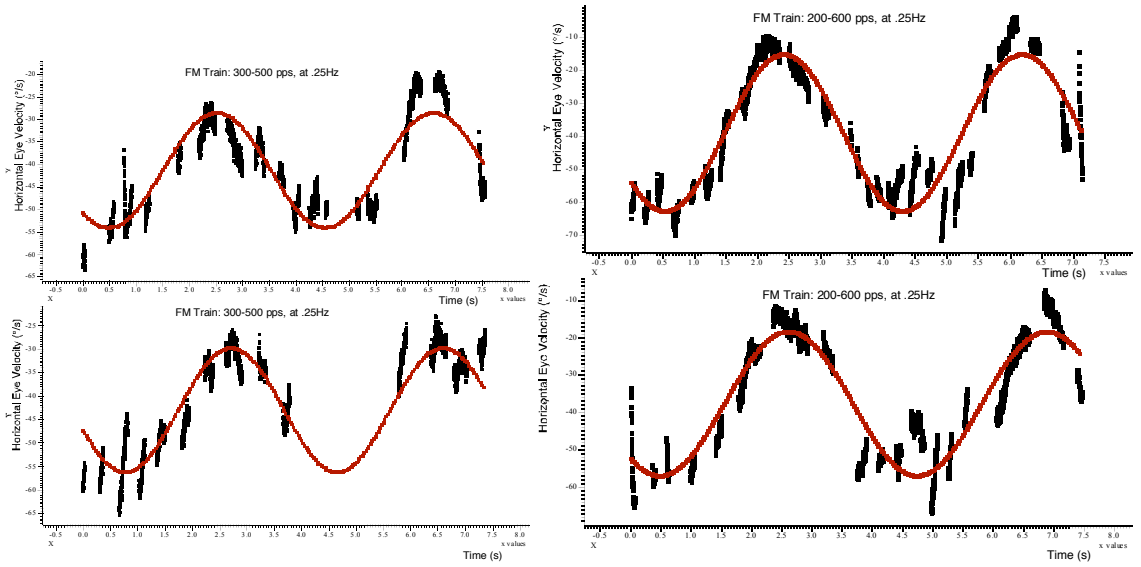

Figure 5. Modulation of two cycles of slow phase eye velocity with frequency modulated stimuli on successive trials. For both panels, the stimulation was monopolar, 70 µA, 400 µs per phase with an 8 µs gap. A. Slow phase eye velocity resulting from two 8 second stimulation trials with stimuli modulated between 300 and 500 pps at a modulation frequency of .25 Hz. B. Slow phase eye velocity resulting from two 8 second stimulation trials with stimuli modulated between 200 and 600 pps at a modulation frequency of .25 Hz.

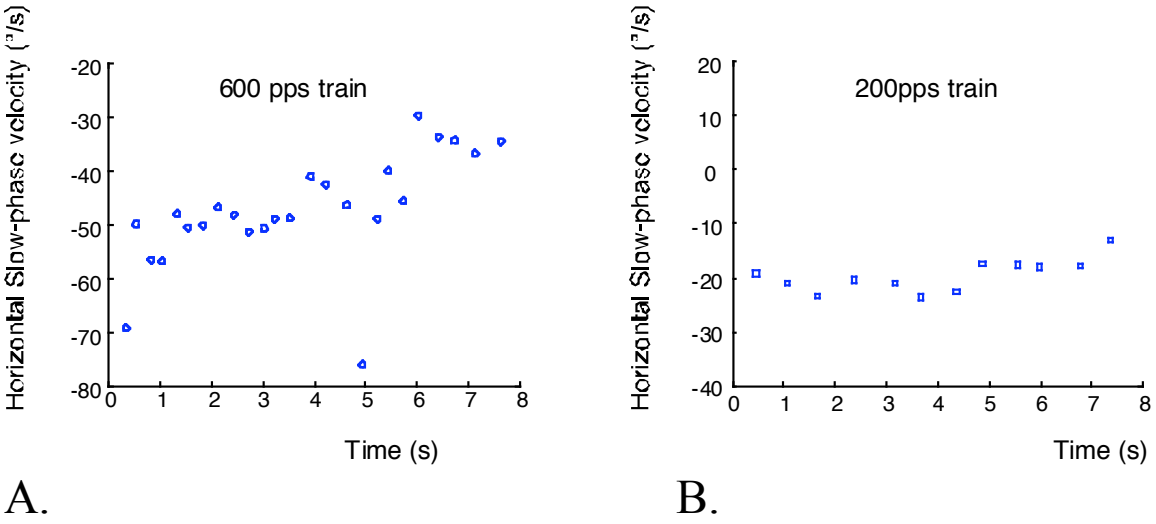

Figure 6. Slow phase eye velocity resulting from 8 seconds of constant frequency stimulation at 200 and 600 pps (the limits of the frequencies used for FM modulation in Figure 5 above). The stimulation was monopolar, 70 µA, 400 µs per phase with an 8 µs gap. There is a decrease (upward trend) in eye velocity over time as the stimulation proceeds.

As illustrated in Figure 7, the PDA uses a SDIO (Secure Digital Input/Output) card to generate the radio frequency (RF) signal carrying stimulation parameters. A PC can

program the PDA and download the pulse train generation codes to the PDA through a USB connection. The SDIO card has a programmable FPGA for receiving control data and generating RF signals required by a specific communication protocol. The FPGA control code is downloaded from the PC by a JTAG link. Once both programs are downloaded, the PDA can be detached from the PC and servers as a stand-alone processor. Unlike the NIC2 platform, it can process any parameter change request immediately and it can be also potentially used to process rotational signals in real time.

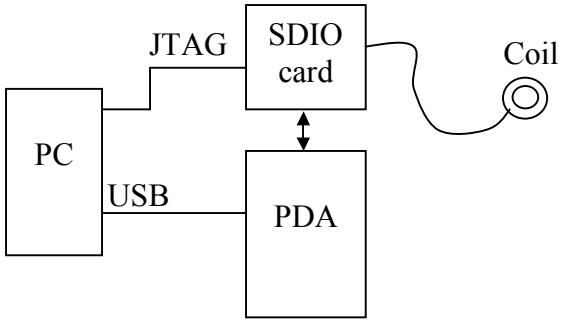

Figure 7: Diagram of the PDA stimulation configuration.

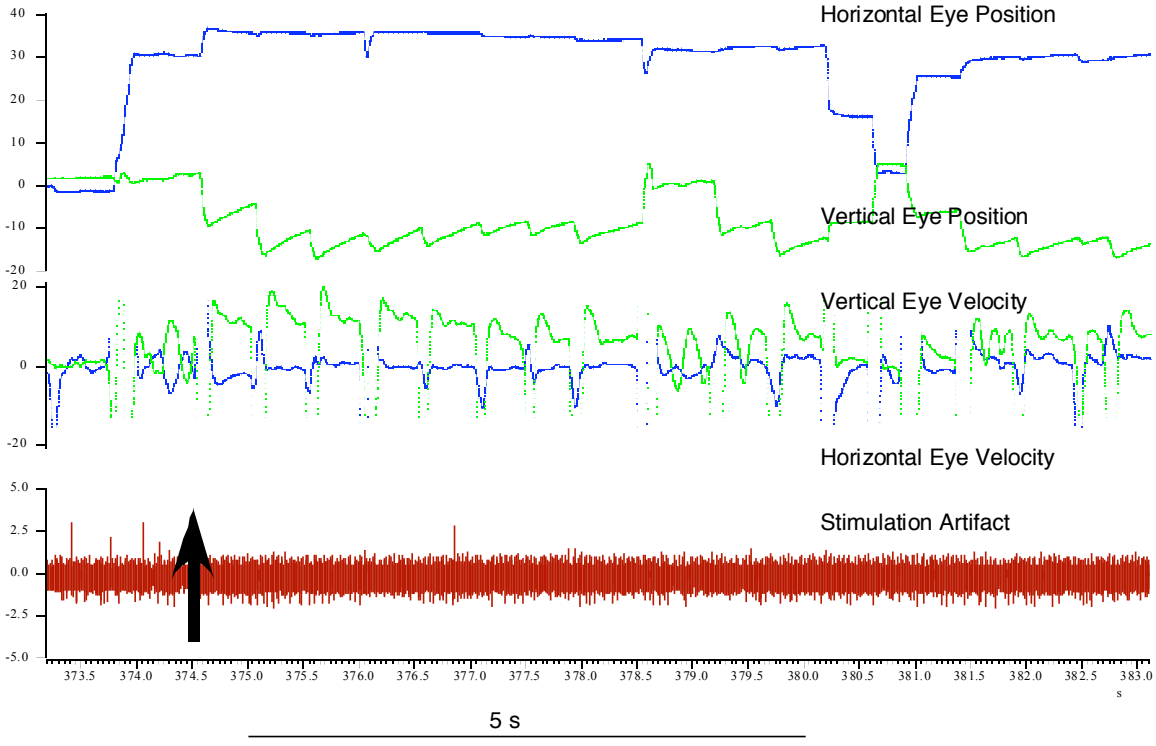

Figure 8. Stimulation of nystagmus using a PDA based stimulation paradigm. The stimulation was rapidly ramped from 0 μA at time 373.5 to 40 μA at time 374.5 (stimulation onset, vertical arrow).

We recently tested the PDA stimulator on an implanted monkey. Nystagmus was recorded during stimulation initiated by activation of the PDA within the recording booth. The PDA was connected to a remote current source similar to that used for bench testing with the NIC II research platform. As can be seen in figure 8, nystagmus was successfully elicited by application of a constant frequency pulse train at 200 pps at approximately 40 μA (40 CL). Despite several limitations to these procedures, which will be addressed in the next quarter, robust nystagmus was elicited by stimulation with the PDA.

6. We have presented our work at several international meetings, and have abstracts accepted for talks at two additional meetings.

Dr. Phillips presented a paper on our work at the Berlin meeting of the Collegium Oto-Rhino-Laryngologicum Amicitiae Sacrum, August 24th – 27th, 2008.

> "A minimally invasive prosthesis for electrical stimulation of individual canal channels in the vestibular nerve."
> *James Phillips, Steven Bierer, Albert Fuchs, Chris Kaneko, Leo Ling, Kaibao Nie, and Jay Rubinstein*.

In addition, Dr. Ling and Dr. Nie each presented posters at the How the Brain Moves the Eyes and Head: Neural Mechanisms of Oculomotor and Vestibular Function meeting, October 5-8, 2008 in Medford, Oregon.

> "The characteristics of nystagmus induced by a vestibular stimulator."
> *Leo Ling, Trey Oxford, Steven Bierer, Albert Fuchs, Kaibao Nie, Jay Rubinstein, Chris Kaneko, and James Phillips*
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> "Implementation of a vestibular stimulator with a cochlear implant research platform." *Kaibao Nie, Steven Bierer, Leo Ling, Albert Fuchs, James Phillips, and Jay Rubinstein*.

Dr. Rubinstein also gave two talks based on our work.

> "A minimally invasive prosthesis for electrical stimulation of individual semicircular canal ampullary nerves" presented at the American Academy of Otolaryngology-HNS Chicago, IL, 9/23/08 as an invited panel member on New Technology in Inner Ear Implants.
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> "A minimally invasive prosthesis for electrical stimulation of individual semicircular canal ampullary nerves" presented at the Fifth International Temporal Bone Dissection Course, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea, 10/4/08.

We have had two additional abstracts accepted for presentation at the Society for Neuroscience.

> "A multichannel vestibular prosthesis based on cochlear implant technology"
> *J. O. Phillips, S. Bierer, A. F. Fuchs, C. R. S. Kaneko, L. Ling, K. Nie, T. Oxford, J. T. Rubinstein
> Society for Neuroscience, 18.10, 2008
>
> "A template-based spike sorting technique to resolve temporally overlapping spike waveforms."
> *S. M. Bierer, L. Ling, J. O. Phillips
> Society for Neuroscience, 169.19, 2008

7. We have revised the design of our vestibular implant based on observations from re-implantation of the device and our evoked potential recordings. The revised design is shown in Appendix A of this report.

In the next quarter:

1. We will have presented our work at the Society for Neuroscience. Dr. Phillips will have given a slide presentation and Dr. Bierer will have presented a poster.

2. We will reproduce much of the data obtained in our first monkey with a successfully implanted device in a second monkey with a working implant. This work is ongoing currently.

3. We will have explored the utility of intraoperative ECAP during surgical implantation of rhesus monkey with our device. During the first month of quarter 10, we recruited Dr. Paul Abbas to assist us with recording intraoperative and post-operative vestibular ECAPs. This work, which will be detailed in the next quarterly progress report, was highly successful, allowing us to document that small displacements of the electrode array produced significant changes in the vestibular ECAPs. Also, with improved recording techniques, we were able to observe a correlation between the amplitude and timing of the recorded ECAPs and the resulting behavioral responses elicited by stimulation of the same electrode arrays. We are continuing these experiments with the knowledge gained from Dr. Abbas.

4. We will more fully evaluate PDA based stimulation. Our initial stimulation trials with the PDA based device supplied by Dr. Loizou required activation of the PDA manually via an on-screen slide scale GUI (graphical user interface) within the recording booth, and a bench top current source. This configuration compromised the eye movement recording because there was a researcher in an open, and therefore not dark, booth immediately adjacent to the behaving animal. In the next quarter, we intend to activate the PDA remotely from a laptop using USB interface software. This will allow PDA based electrical stimulation of an animal in the standard test environment.

5. We will have revised monopolar electrodes that produce only weak responses in two animals with combined fine wire electrodes and canal plugging. Dr. Shawn Newlands, who has performed canal plugging in our laboratory previously, performed these procedures in the first month of Quarter 10. The animals have not yet been behaviorally evaluated. We anticipate that these experiments will yield valuable short term data on the unilateral canal plugging and stimulation that will be utilized as our experiments move forward.

6. We will have an additional abstract accepted for presentation in a national meeting. Dr. Rubinstein recently received word that his abstract titled "Prosthetic implantation of the semicircular canals with preservation of rotational sensitivity: A hybrid vestibular implant" was accepted for presentation at the AOS/COSM Spring Meeting in May 29-30, 2009.

7. We intend to compare the behavioral responses in canal plugged monopolar stimulation with minimally invasive stimulation with the U.W. Cochlear vestibular implant.

8. We intend to perform two additional implant revisions using NRT/ ECAP to guide the surgery. We have a single unopened sterile implant and two animals to revise. One animal has an implant that fails to drive behavioral responses, but is otherwise functional. This animal will be revised first, with the objective of replacing the electrode arrays and preserving the implant. If this is successful, then a second animal, will receive the unopened sterile implant in a second surgery. We have high expectations for the results of these surgeries based on our recent surgical success.

9. We intend to continue characterizing unit responses in animals with electrically driven behavioral responses, first driving unit responses electrically, and then characterizing the neurons with natural stimulation and during orienting behavior.

Appendix A: Confidential.

Revised design of the UW-Cochlear vestibular prosthesis array.

Our current observations suggest that the reason for the failure of some of our previous surgeries is related to failure to secure the electrode arrays in the canal. Small movement of the electrode array causes the working array to become ineffective in generating nystagmus. This is an especially acute problem in rhesus monkeys that are quite active immediately post surgically. One solution to the problem has already been successfully applied, which is to secure the array with tissue glue. However, the tip of the array is still very short, making the relative movement required to compromise the effectiveness of the electrode array quite small. The new design extends the length of the electrode array tip from 1.7 to 3.4 mm, thus allowing for deeper insertion and, theoretically, a more robust and stable electrode array. Dr. Rubinstein's previous experience with the electrode placement suggests that the array will have sufficient stiffness for this deeper insertion procedure to be successful.