Third Quarterly Progress Report

February 1, 2007 to April 30, 2007

Contract No. HHS-N-260-2006-00005-C

Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

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Stimulation Device Development

We have now received finalized designs from at least one cochlear implant manufacturer, Cochlear Corporation, for a prototype vestibular stimulation device. A prototype of this device should ship in the first month of the fourth quarter, for practice implantation by Drs. Rubinstein and Santos in rhesus monkey temporal bone necropsy material. After confirming that the design has produced an electrode with the required shape, stiffness, and lead configurations, the final production specifications will be given to the manufacturer for implementation of a working prototype. We also continue to communicate with a separate team from another manufacturer, Advanced Bionics, who have overcome production difficulties and also plan to fabricate a device in the fourth quarter.

Software Interface Development

We have continued development of the software interfaces for both stimulation and recording. Indeed, the implementation of the recording interface and analysis tools has progressed to the point where Mr. Cent can shift his effort to other projects. He will be leaving the software development team in the fourth quarter, and we appreciate his contributions to date. As a reflection of his efforts, the contract web page now lists 10 programs developed for, or upgraded for, recording and analyzing neural and behavioral data generated in this project during electrical and natural stimulation. These tools will have utility beyond the research project, and will benefit the vestibular and oculomotor research community in general.

On-line Control of Stimulation

In this quarter we have continued to develop software to control the implant stimulation hardware. In preliminary experiments, we will use a rather restricted set of electrical stimuli, as we explore the primary behavioral and physiological response characteristics of the vestibular system to artificial stimulation. Thus, our immediate requirements will be to produce patterned electrical stimuli that do not require a head-related input signal. These include single pulses, unmodulated pulse trains, and amplitude- and frequency-modulated pulse trains. At present we are designing the software around Cochlear Corporation's NIC 2 (Nuclear Interface Communicator) research platform, but we plan to expand its capabilities to interface with the Advanced Bionics BEDCS (Bionic Ear Data Collection System) platform at a later date.

The central component of the implant control software is a graphical user interface (GUI) written in the MATLAB programming environment (version R2006b). An image of the interface is shown in Figure 1. By filling in text fields or selecting from pull-down menus, the user has control over numerous stimulus parameters, such as pulse width (phase) and amplitude. Active and return electrodes can be configured for the monopolar or bipolar modes of stimulation. By manipulating the duration parameter, a single pulse or train of pulses can be chosen. In addition, a pulse train can be sinusoidally amplitude-modulated or frequency-modulated based on specified modulation limits and oscillation rate. Finally, most of the stimulus parameters can be "vectorized" by specifying the first and last elements and a step size (which can be linear or logarithmic). During an experiment, all permutations of the vectorized stimulus parameters will be delivered (optionally in a randomized order), separated in time by a user-selected inter-stimulus interval. The specified parameters are stored for future data analysis.

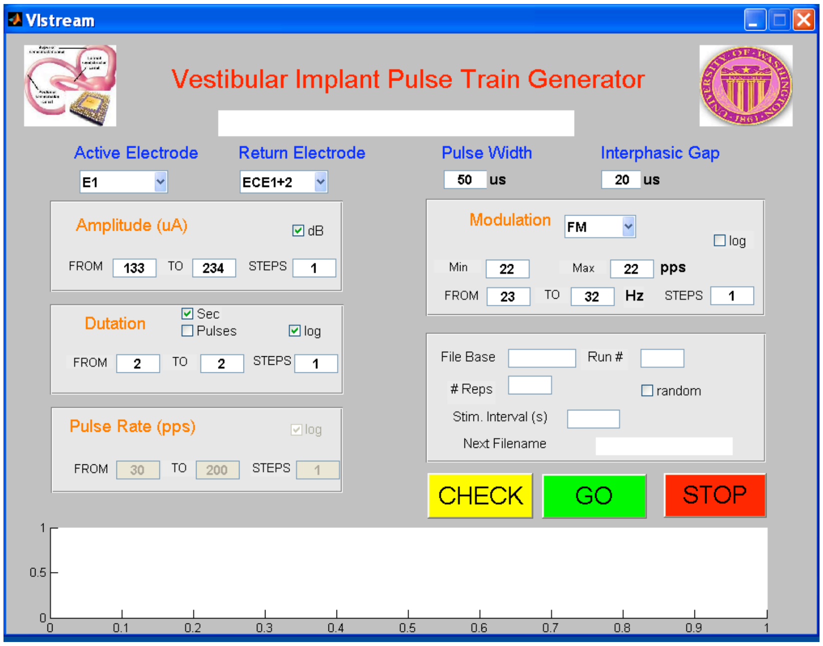

Figure 1, GUI interface for the research pulse train generator.

The GUI software controls an L34 speech processor via the NIC 2 research interface. Since the MATLAB toolbox for NIC 2 does not support the bipolar stimulation mode and is limited in the number of pulse repeats that it can make, we found it necessary to incorporate the Python programming language to interface with the L34 processor. The additional data exchange between MATLAB and Python was implemented using the Python 'io' module which has the capability of loading and saving MATLAB variables. As currently implemented, the MATLAB GUI calls the customized Python code to generate a pulse sequence and stream it to the speech processor.

For practical purposes, the MATLAB, Python, and NIC 2 software will run on a separate computer than the one used to acquire eye movement and neural signals. For this reason, we have programmed the NIC hardware interface to produce a TTL output pulse. The TTL pulse is sequenced in a similar manner as pulses delivered to the speech processor, but it is output via a separate connector rather than to the implant. During an experiment, the TTL pulse will be detected by the Spike2 data acquisition system, allowing the stimulus and signal recording to be synchronized.

Recording Technology Development

We have been in communication with Dr. Jamille Hetke of NeuroNexus about the construction and testing of our multiple single unit recording electrodes (deep-penetrating NeuroNexus/FHC electrodes). The Neuronexus team has overcome fabrication issues to produce a working prototype electrode that has been evaluated in vivo. The device is now available for final fabrication at FHC. We will be the first group to receive these electrodes.

On-line Recording

We have also been progressing on multiple unit recording alternatives. During Quarter 3, Ms. Ibaretta has been fabricating new tungsten core microelectrodes for our use and we are beginning the fabrication of new twisted strand tetrodes. In addition, we have ordered a different type of electrode from Thomas Recording (Giessen, Germany). This device is a four-channel "tetrode", fashioned from multiple cores of quartz-platinum alloy and tungsten around a single shaft. The four channels are grouped at the end of the electrode: one electrode site consists of the sharpened tip and the three others are embedded around the diameter of the shaft just above the tip. The four metal cores are insulated from each other by quartz glass. Unlike the NeuroNexus / FHC electrode, the geometry of the tetrode is not suitable for recording along its shaft – which, for example, would allow simultaneous recordings from a population of neurons situated several hundred microns across the vestibular nuclei. On the other hand, Thomas Recording electrodes are already used by a large number of researchers, so we expect to obtain multi-channel neural data with them in a timely fashion. These electrodes will provide a reference standard as we begin our work with the NeuroNexus/FHC electrodes.

To facilitate the acquisition of neural signals, we have initiated construction of a combined 16-channel post-amplifier and switch box. The hardware will route signals from the Plexon pre-amplifier to provide additional gain and filtering, conditioning steps that will help eliminate magnetic coil artifacts and other sources of noise. Also, a rotary switch on the box will allow a user to select one channel at a time for audio monitoring. This feature will be useful for quickly identifying neurons of interest during an experiment, such as those producing spikes correlated with eye movements or synchronized to electrical stimulation. Our current plan is to choose one channel having well-isolated spikes for on-line spike detection and analysis. However, every channel will be recorded to computer for more extensive off-line analysis.

Off-line analysis of neural data

Drs. Leo Ling and Steven Bierer have continued to develop software tools for off-line analysis of multi-channel spike trains, including spike sorting. One development this quarter was the creation of MATLAB functions to load and write Spike2 files, the format of the Cambridge Electronics (CED) data acquisition system. These programs make extensive use of CED's "SON library" for the C programming language. With this set of interface functions, sophisticated spike detection and spike sorting algorithms can be implemented in MATLAB to handle the multiple channels of neural data. Once the spike data is processed, the results can be written back into Spike2 format to take advantage of analysis programs already in use by the lab.

Behavioral Testing

We have begun behavioral testing of the rhesus monkeys to confirm that their behavior falls in the range of normal performance established in the laboratory for the project test paradigms. This testing includes saccades, vestibulo-ocular reflex, smooth pursuit, and gaze shifts. By the date of the implantation of the stimulating array, we will have fully documented the pre-implantation behavior of the monkeys.

Preliminary Pre-Implantation Behavioral Results

Two rhesus macaques had previously been implanted with scleral eye coils to track their eye movements during training and experimental sessions. In the present quarter, it became necessary to remove the eye coil from one of the animals (Animal 1) because the coil had shifted. The coil was removed and a new coil implanted into the other eye during the same surgery. Both animals are now being behaviorally tested, in preparation for VOR and electrical stimulation experiments. In the early stages of training, the monkey must fixate on a spot of light and follow the spot as it is stepped to various positions. The ability to maintain gaze on a target is necessary for calibrating the direction and amplitude of eye movements. The training also facilitates the acquisition and analysis of eye movements produced by rotational and electrical stimulation.

During a training session, the monkey sits in a custom-fit chair within a darkened sound-attenuating booth. The monkey's head is restrained and centered between a set of magnetic coils, which generate the magnetic fields for sensing movement of the implanted eye coil. A laser and mirror galvanometer, located behind the animal's head, projects a small visual target onto a dark screen in front of the animal. A small tube is placed near the animal's mouth to deliver an applesauce reward. The eye coil signal is demodulated by custom hardware into horizontal and vertical components and recorded by the PC-based data acquisition system (Spike2, Cambridge Electronic Design). The same computer controls the position of the visual target and the delivery of food rewards (via an infusion pump) and acoustic tones (via speakers inside the booth). Whenever the animal's eye position is close to the target, a high pitch tone is played. If the correct gaze is held long enough, a food reward is delivered, accompanied by a brief conditioning tone to let the animal know a reward is being given.

Typical examples of targeted eye movements made during a testing session (Animal 1) are shown in Figure 2, which displays the horizontal and vertical eye signals with the respective target positions. The first two shifts of the visual target away from center (0 degrees) were along the horizontal axis, first in the positive (rightward) and then in the negative (leftward) direction. The horizontal signal indicates that the monkey made saccades of the correct direction and amplitude, maintained fixation in the new position, and then made a new saccade as the target returned to the starting point. The vertical component of eye position changed minimally during these movements. The third target shift was vertical in the positive (upward) direction, and the animal made a proper vertical saccade to fixate on the new target position and a second vertical when the target returned to the center.

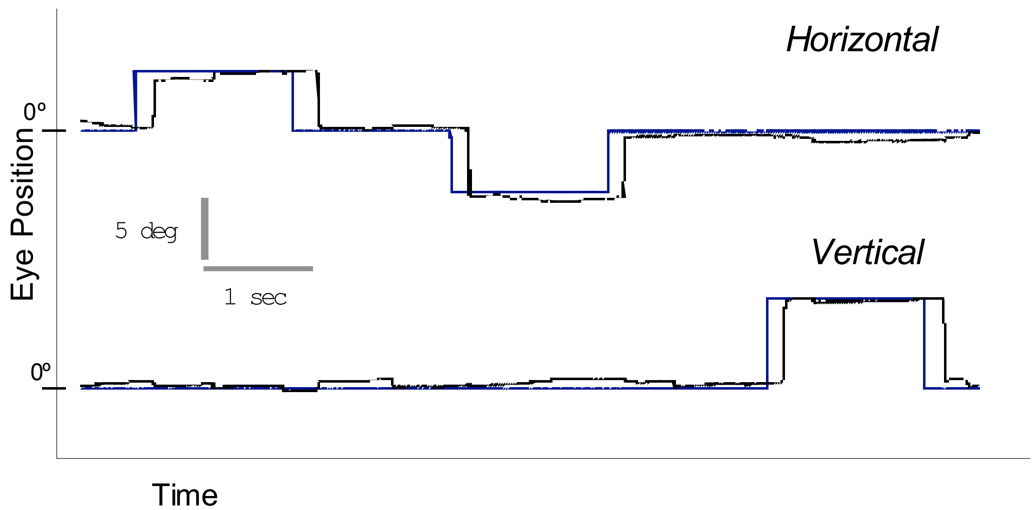

Figure 2: Horizontal and vertical eye movements obtained in the same test session.

Eye movements were also elicited by oscillating the target back and forth along the horizontal axis. The oscillations were sinusoidal at a frequency of 0.5 Hz. Although the animal in Figure 3 made several saccadic intrusions during the task, it was able to track the target closely on other cycles. This example indicates a normal ability to make smooth pursuit eye movements.

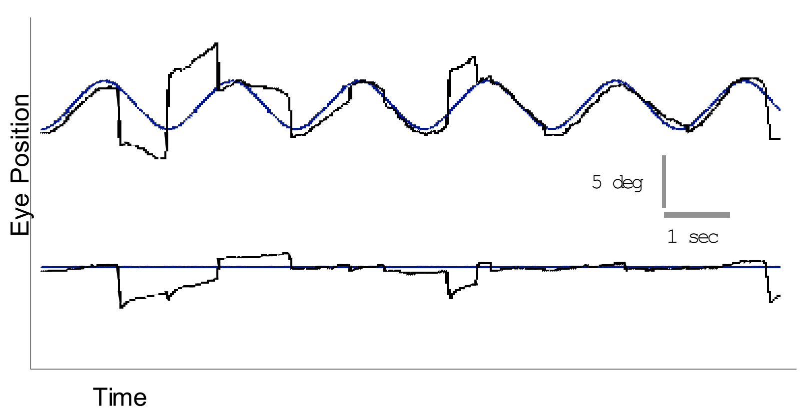

Figure 3. Smooth pursuit eye movements

During a different behavioral session, we tested the vestibular-ocular reflex (VOR). For this task, the animal's chair was rotated sinusoidally about a vertical axis (yaw rotation). Since the magnetic field coils move with the chair, the resulting eye coil signal is related to the relative position of the eye in the monkey's head, not to position in space. The booth was completely dark and the visual target was turned off. Figure 4 depicts the average horizontal eye velocity for one of our monkeys and the corresponding chair velocity during 20 cycles of 0.5 Hz yaw rotation. This animal displayed a gain of 0.75, and a phase of -179°, which is appropriate for rotation in the dark at this frequency in rhesus monkey.

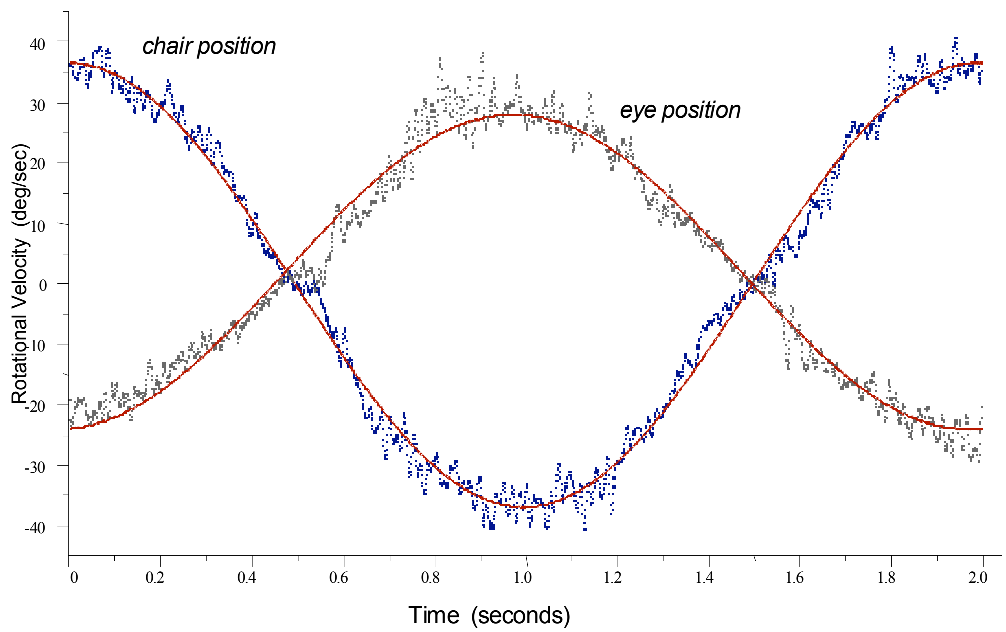

Figure 4 Vestibulo-ocular reflex eye movements: The figure displays the multi-cycle averages of eye (red) and chair (blue) velocity (differentiated eye position) with each point representing a single time bin at the 1 kHz sampling rate.

Meetings and Conference Presentations

One of the objectives of our contract was to disseminate information about the development of the vestibular prosthesis to clinical and research groups both locally and nationally. During the third quarter, we have continued our local presentations with regular updates in the Clinical Vestibular Disorders Group, which meets monthly. In addition, we have had three related presentations to the research meeting for affiliates of the Neuroscience Division of the Washington National Primate Research Center. In preparation for our national virtual conference, we have been working on implementation of a simple videoconferencing scheme using widely available computing solutions. Our current strategy is to use Macintosh and PC computers running I-Visit. In preparation for this, we have configured local conferences using I-Visit, and compared that with the performance of I-Chat, which works flawlessly but has user and platform limitations, and Skype, which is even more limited although a multiplatform solution. In Quarter 4, we will implement a local Web conference and send out invitations for a late summer distributed conference.

Overall Progress

Although we have made good progress on the objectives of this contract, advancing both the design and implementation of software and recording hardware, we are still looking forward to two critical milestones. First, we must receive and implant our stimulating electrodes to begin the critical evaluation of the stimulation strategies that we are developing. Second, we must implement our preferred multiple single unit recording strategy with the NeuroNexus/FHC electrodes. Although we are developing alternatives to this later technology, it still represents our preferred approach.