Twentieth Quarterly Progress Report

May 1, 2011 to July 31, 2011
Contract No. HHS-N-260-2006-00005-C
Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve
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Challenges:

1. During Quarter 20 we received notification from Cochlear Corporation that updated Laura 34 research interfaces with new firmware were available. This interface, which was used in most of our recording and stimulation experiments, was modified in response to an issue with the signal level of the radio frequency (RF) link. We received a new interface and immediately evaluated it in several previously implanted rhesus monkeys. The new interface consistently produced a loss or drop out of commanded biphasic stimulus pulses, as determined by the recorded artifact in our animals. Specifically, we observed that the new firmware did not directly support long pulse period well. For example, we saw dropped pulses when the pulse periods were longer than 1ms (1000 pps). In contrast, the older firmware worked quite well for periods up to 7500 μs (133 pps) directly. A second related issue was that the new firmware seemed to be very sensitive to the gap distance between the coils. If we put 20 pages of A4 paper between the processor's coil and the coil in the implant-in-a-box, it provided more reliable, but still imperfect, low rate stimulation. This latter issue was not unexpected given that the modification to the firmware increased the power of the RF link, and in our animal preparation there is a relatively thin tissue layer overlying the implanted coil.

Our response to this challenge was to send our recording data to Cochlear Corporation and to retain two of the original Laura 34 interfaces, as well as one newly revised device. The original interfaces continued to function well for our 4 remaining animals. We have requested several sets of the infant cochlear prosthesis spacer sets, consisting of spacer and magnet pairs. In addition, we are addressing the long pulse period issue by adding shorter null-stimuli periods for low-rate pulse trains. This will create a much larger streaming vector. We hope that this will allow us to move forward with replacement of our devices to the newest version of the Laura 34 firmware. However, we will not replace our existing devices unless we demonstrate consistent driving of the vestibular prosthesis in all of our monkeys with the modified firmware, revised software, and spacer set.

2. We have not obtained long term data in several of our animals. This extended safety and efficacy data would allow us to more fully define the long-term stability of effective electrical stimulation with the prosthesis in healthy control animals and in gentamicin lesioned animals. In response to this issue, and in recognition of the additional benefits derived from continued recording in animals in parallel with an ongoing human trial of the device for the treatment of Meniere's disease, we requested a modification of our contract to continue long-term recording in our monkeys. We have received a preliminary indication that this may be possible, although the process is administratively complex. We do not know, for certain, that this will be possible. However, in anticipation of a modification, we have retained funds in the contract to allow us to continue recording experiments for an additional year in our four remaining

animals. In addition, we have postponed scheduled necropsy and histologic processing of tissue in these four animals, and have instead continued regular measurement of stimulation efficacy with electrical stimulation using frequency and current series, measurement of vestibular electrically-evoked compound action potentials (vECAPs), measurement of auditory brainstem evoked responses (ABRs), measurement of rotational VOR with and without electrical stimulation, and measurement of electrode impedances. All of this data is collected in parallel with neural recording experiments.

Successes: We have made important progress in several areas as noted below.

1. We have continued our brainstem recording experiments. We have recorded activity comparable to the activity reported previously in many additional neurons. We have not yet identified the intermediate stage in neural processing that produces rate-modulated activity from amplitude modulated electrical stimulation. We have, however, identified neurons that show combined frequency following and drop out during current amplitude modulated stimulation which begins to approximate frequency modulation from current modulated electrical stimulation. This stage of processing shows several interesting features, as seen in Figure 1.

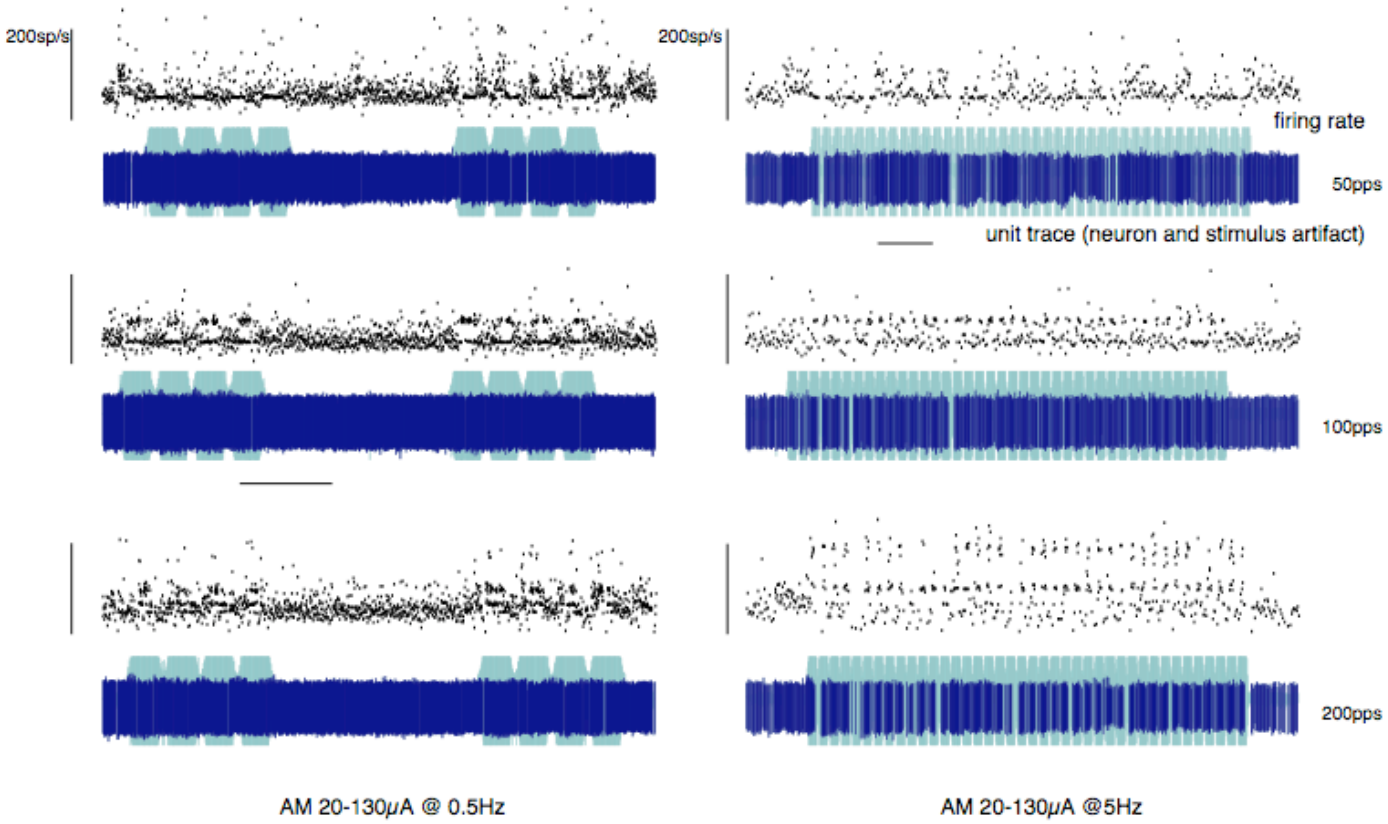

Figure 1. Discharge of a secondary vestibular neuron to sine wave current amplitude modulated electrical stimulation of the right lateral semicircular canal at 0.5 Hz modulation frequency (left column) and 5.0 Hz (right column), 20 – 130 μA, at 50, 100 and 200 pps. The traces on each row are instantaneous discharge frequency (spikes/s, above) and the recorded spike trace with superimposed stimulus artifact (below).

Figure 1 displays a neuron recorded at the location of the medial vestibular nucleus. This neuron paused for saccades, and responded to constant frequency and constant current electrical stimulation of the lateral canal with frequency following up to 50 Hz at 100 uA. At higher currents, the neuron displayed dropouts, following every other or every third electrical stimulus pulse. As can be seen in Figure 1, at 50 pps stimulation rate this neuron is alternately entrained to the stimulus pulses at high current, and discharging at its normal high coefficient of variation spontaneous rate at lower currents during current amplitude modulated electrical stimulation. The net effect is a reverse modulation of the instantaneous discharge frequency of the neuron, since the 50 Hz rate is lower than the average spontaneous rate of the neuron. At a higher stimulation rate of 100 pps, the neuron is now following the higher rate at high currents, and discharging spontaneously at lower currents. At intermediate current levels in the sine wave modulation, the discharge frequency of the neuron shows some drop out, producing an intermediate rate. The neurons discharge rate now approximates the sinusoidally modulated input, which is indicated by the stimulus artifact (although the stimulus artifact saturates the amplifier at higher current levels). At the highest higher stimulation rate of 200 pps, the neuron is still partially following the higher rate at high currents, and discharging spontaneously at lower currents. At intermediate current levels, the discharge frequency of the neuron shows additional drop out, producing an intermediate rate. The neurons discharge rate still approximates the sinusoidally modulated input. A comparison of the 5 Hz modulation frequency traces and the 0.5 Hz modulation rate traces shows that at 5 Hz modulation rate the neuron is capable of following the 200 pps frequency of stimulation with fewer dropouts, whereas at 0.5 Hz the sustained higher levels of discharge are not maintained, and the neuron is modulated only slightly above the 100 Hz peak discharge rate. In both cases, the neuron displays something approximating frequency modulation in response to the amplitude modulated stimulus, but the depth of modulation is greater for the 5 Hz modulation frequency.

In summary, the data of Figure 1 suggest a mechanism for quasi-frequency modulation of secondary vestibular neurons early in the central neural process that converts stimulus amplitude to neural discharge frequency. Basically, the neuron passes through intermediate regions where the frequency following grows with increasing current producing imperfect modulation of the frequency of the neural discharge. Also, this data suggests a mechanism for the increase in the efficacy of higher modulation frequency stimulation, which was discussed in previous quarterly reports. In this case, the higher modulation frequency stimulus produces a deeper frequency modulation in the vestibular neuron because the frequency following is better at higher modulation frequencies. This observation represents a significant step toward understanding the complex mechanisms that underlie the behavioral response to amplitude-modulated stimulation.

In addition, we have begun studying the characteristic discharge of recorded neurons to rotation at different stimulus velocities across frequency. We hope to characterize the sensitivity of these neurons at each frequency. Our hypothesis is that we are differentially activating neurons with non-linear rotational velocity sensitivity with our electrical stimulation. This might help to further account for the non-linearities in frequency following that we have encountered in previous quarters. Also, we are comparing the eye

velocity sensitivity during electrical stimulation with the eye velocity sensitivity during rotational stimulation, to see whether there is a difference in the velocity sensitivity to the two forms of stimulation. These studies are ongoing in combination with a modeling effort by a new bioengineering graduate student in the laboratory who is using the known physiological characteristics of irregular and regular afferents to construct a model of summation of electrically driven afferent inputs to secondary vestibular neurons.

2. We continue to collect and have begun to summarize our long-term electrical stimulation and ABR data. The ABR analysis resulted in a manuscript that is listed in Section 6, below. An example of the long-term electrical stimulation data for the lateral canal of two animals is summarized in Figure 2.

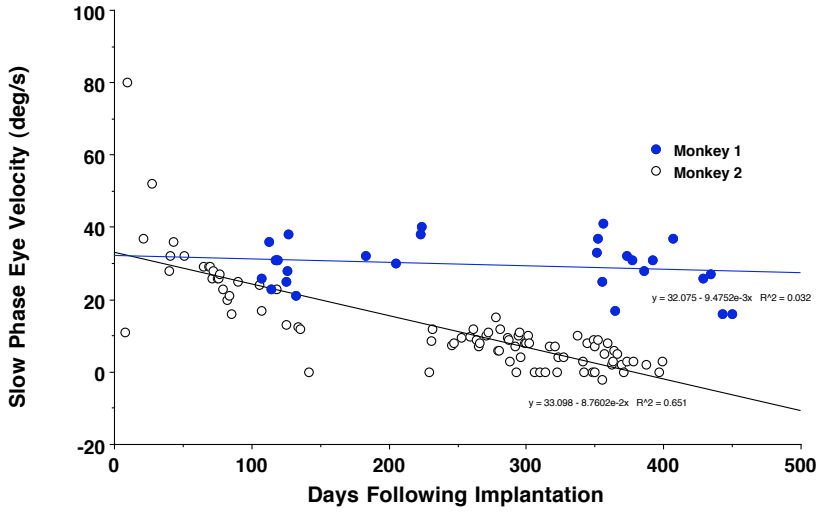

Figure 2. Slow phase velocities produced by lateral canal stimulation over a period of more than a year in two monkeys. The monopolar stimulation parameters were held constant with 2s trains of constant frequency and current biphasic pulses, 100 µs duration, 8 µs gap, 300 pps, at 125 (Monkey 1) or 100 (Monkey 2) µA. All velocities are directed away from the stimulated ear (leftward slow phase velocity for right lateral canal stimulation).

In both animals, a stimulation current and frequency producing moderate slow phase velocities was selected for longitudinal measurements. Monkey 1 showed almost no loss of stimulation efficacy with time. Monkey 2 showed a significant loss of stimulation efficacy, resulting in decreased slow phase velocities over the course of 400 days post implantation. The two animals were implanted and treated similarly. By increasing the phase duration of the biphasic pulses used over time, we were able to maintain robust responses to electrical stimulation in Monkey 2. However, as this data suggests, the current required to drive those responses increased significantly between 150 and 200 days post implantation. We do not know the process that produced reduction of the slow phase velocity in Monkey 2. We are continuing the analysis of all of the velocity data at multiple frequencies to determine whether this represents a change in the gain of the

response or an offset in the resulting slow phase velocities that were generated. We are also analyzing the electrode impedance data to determine if these changes are due to changes at the site of stimulation or to central adaptation to repeated stimulation. Furthermore, we plan to perform histological reconstruction of the temporal bones of these monkeys to see if there are correlations between electrode location or tissue morphology and the efficacy of stimulation.

3. We now have one monkey with three working electrode arrays, each placed in separate semicircular canals. Although we had previously implanted a single animal with three electrodes in all three semicircular canals, this surgery was not performed using the "hybrid" technique pioneered by Dr. Rubinstein. In that first animal, Dr. Newlands performed a more invasive revision surgery using fine wire electrodes and a percutaneous head plug. While the results of that surgery were promising, effective stimulation with the electrodes from the more invasive surgery lasted only a few weeks. More recently, Dr Rubinstein was able to implant all three semicircular canals using a modification of the “hybrid” technique. We now have an animal that is fully implanted and has comparable responses from each of the semicircular canals. Figure 3 shows the slow phase velocity that results from stimulation of each canal with a series of 2s trains of varying frequency and current. The resulting slow phase eye velocity versus frequency curves show very similar characteristics. With increasing frequency of stimulation, there is increasing slow phase velocity largely in the plane of the implanted semicircular canal. With increasing current, there is also an increase in slow phase velocity. This is our first demonstration of the efficacy of stimulation of all semicircular canals using the "hybrid" approach in a single animal. This animal is currently undergoing longitudinal behavioral recording and electrical stimulation studies.

The availability of multiple sites of stimulation in each of three semicircular canals gives us a broad range of capabilities in terms of combined stimulation of multiple canals either alone or in combination with rotation in multiple canal planes. An illustration of this capability is shown in Figure 4, which shows the result of sinusoidal current modulated electrical stimulation in each semicircular canal alone, and in combination with other canals. Sinusoidal current modulated electrical stimulation of the anterior canal produces largely vertically modulated eye velocity, as does sinusoidal current modulated electrical stimulation of the posterior canal. Sinusoidal current modulated electrical stimulation of the lateral canal produces largely horizontally modulated eye velocity. Combinations of in phase current modulated electrical stimulation of the lateral and anterior canals produces oblique eye movements that are up and to the left (down and to the right), whereas in phase current modulated electrical stimulation of the lateral and posterior canals produces oblique eye movements that are down and to the left (up and to the right). Therefore, in the same animal we see vector summation of the effects of electrical stimulation of each individual canal when the stimulations are combined. This is a demonstration of the directional summation that we inferred from two canal combined stimulation previously. We now have a working model of rotations in all canal planes to produce directional summation.

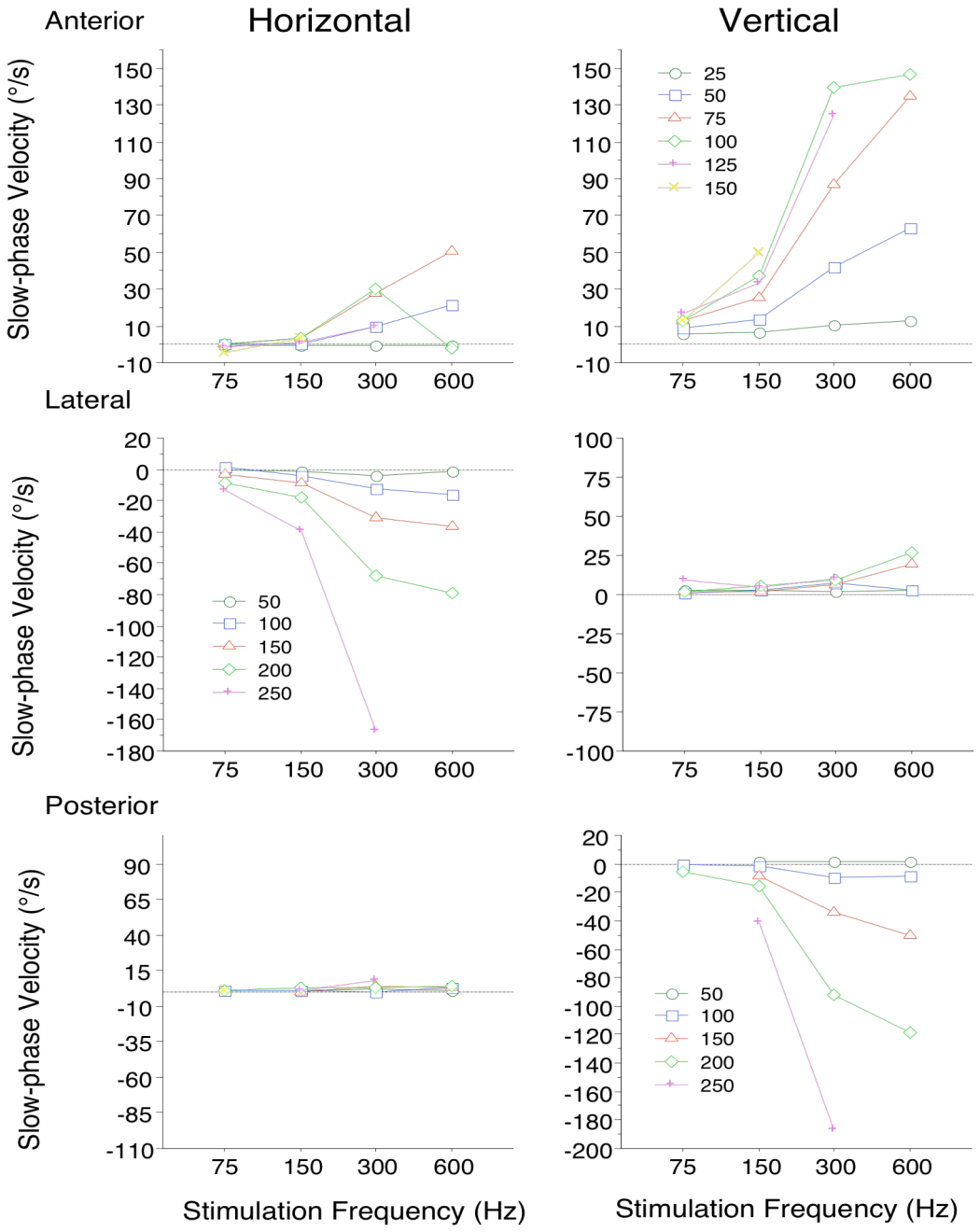

Figure 3. Slow phase velocity versus frequency at different currents for multiple canal stimulation in the right ear of a single animal. The canal that is stimulated is listed on the upper left of each row. Horizontal and vertical slow phase velocities are displayed. Negative horizontal velocities are leftward, and positive horizontal velocities are rightward. Negative vertical velocities are downward, and positive vertical velocities are upward. Stimulation trains were 2s of monopolar biphasic pulses of 100 µs per phase and 8 µs interphase gap.

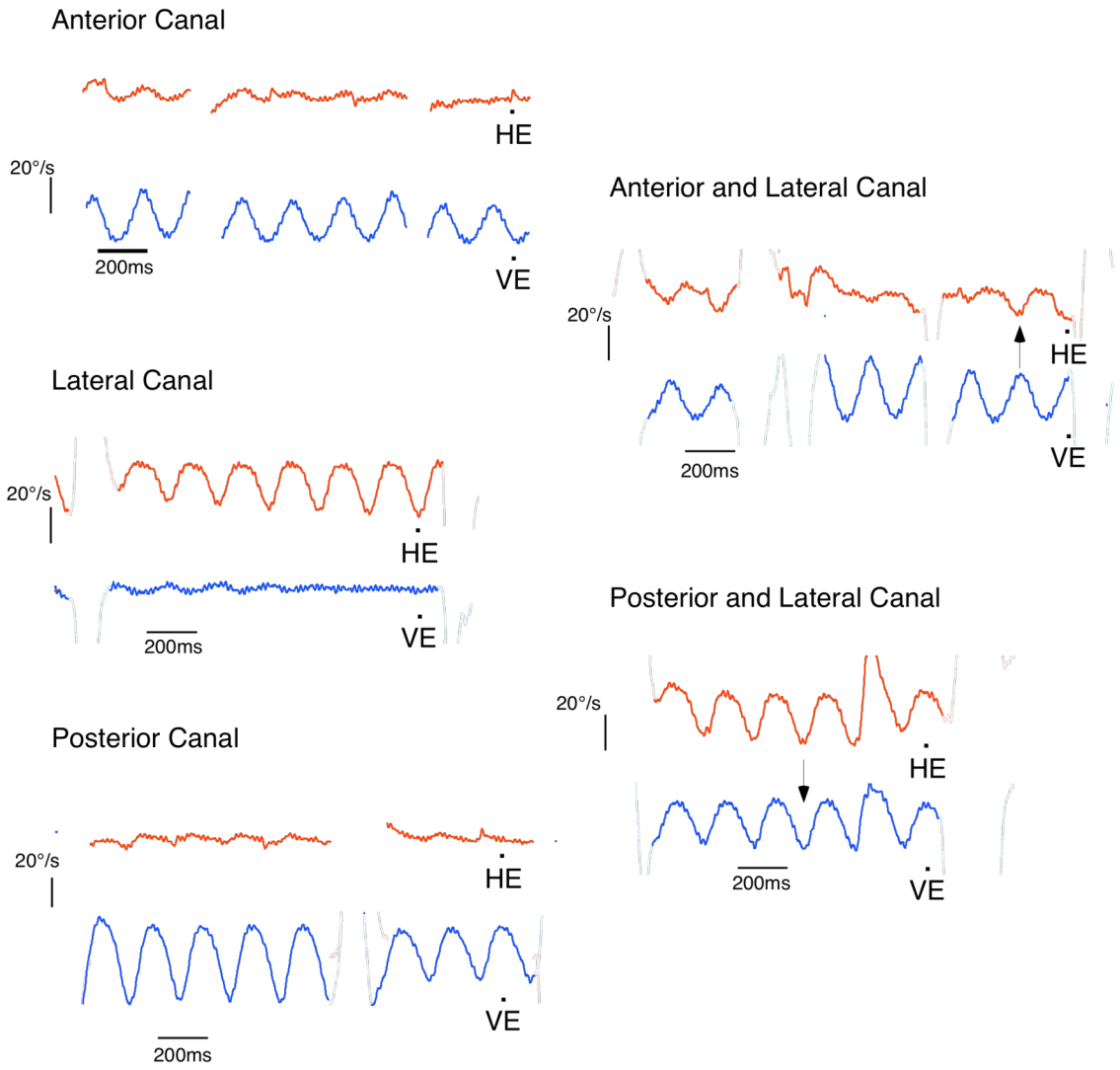

Figure 4. Eye velocity in response to 5 Hz current amplitude modulated electrical stimulation of individual canals in the right ear, and in phase combined current amplitude modulated electrical stimulation of multiple canals in the right ear. Blue traces indicate vertical eye velocity (VEdot) and red traces indicate horizontal eye velocity (HEdot). Note that the oblique eye velocity is up and to the left for combined stimulation of the right anterior and right lateral canals (up vertical arrow), and down and to the left for combined stimulation of the right posterior and right lateral canals (down vertical arrow).

4. We have been performing combined rotational and real time electrical stimulation experiments to control the gain and direction of the rotational vestibulo-ocular reflex (VOR) at different frequencies. In the past, these experiments were limited to gain control, and primarily gain reduction. In these experiments, we varied the phase and depth of modulation of amplitude modulated real time electrical stimulation to produce changes in the VOR. Figure 5 shows the result of a gain increase experiment, where the VOR resulting from yaw rotation in the dark in increased with addition of yaw

modulated electrical stimulation. In Figure 5, increasing current right lateral canal electrical stimulation is in phase with rightward head velocity. The result is an instantaneous increase in the gain of the VOR with the application of the electrical stimulation.

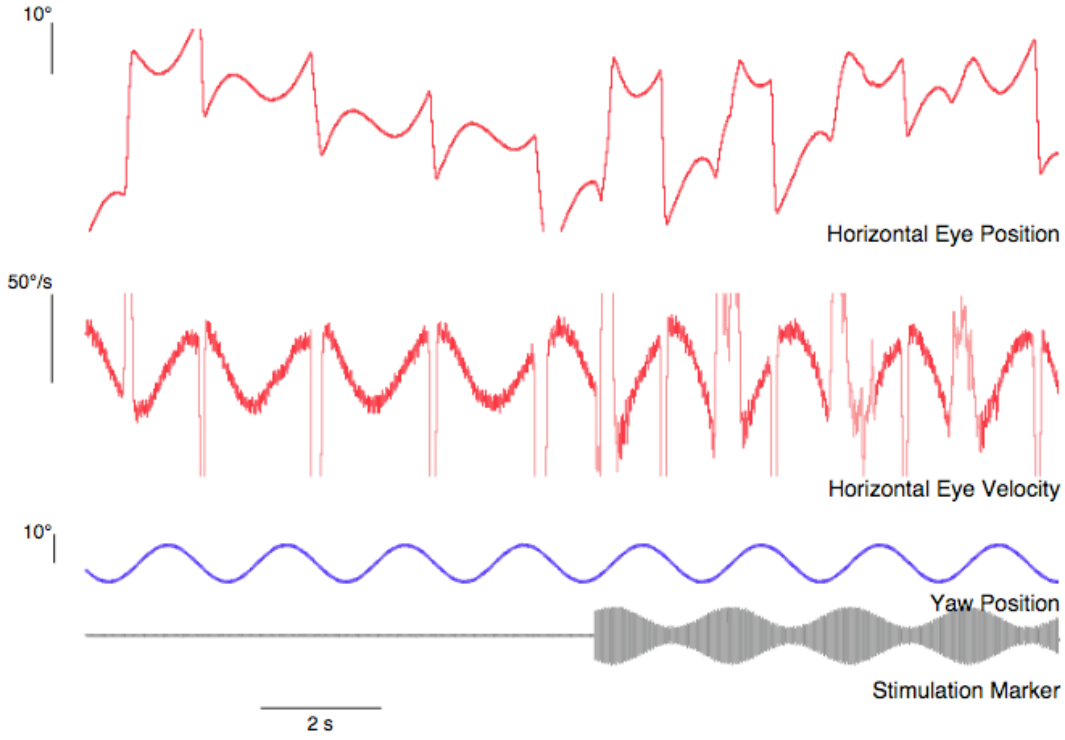

Figure 5. Increasing gain of the horizontal VOR with amplitude modulated electrical stimulation of the right lateral canal. The onset of electrical stimulation is indicated by the onset of an amplitude modulated electrical artifact (stimulation marker) in phase with right yaw velocity (90 deg out of phase with right yaw position).

In figure 6, the same strategy is used to decrease the gain of the vestibulo-ocular reflex. In this figure, the electrical stimulation of the right lateral canal is applied in phase with leftward head velocity (180 deg out of phase with rightward head velocity), which reduces the gain of the VOR. In this experiment, the offset of electrical stimulation is shown, indicating that the change in gain is instantaneous and aligned on the cessation of electrical stimulation. Therefore, in both Figure 5 and Figure 6, the change in VOR gain occurs immediately with the onset or offset of electrical stimulation.

While the empirical demonstration of real time gain modulation onset and offset is important, it raises another question. We had inferred from our stimulation results that summation of natural and electrical stimulation should result in a vector summation of the effects of each alone. This was not empirically demonstrated for multidirectional inputs in previous experiments however. In order to demonstrate this, we drove current modulated electrical stimulation of the anterior or posterior canal in real time with

horizontal head velocity, i.e., increased hozizontal head velocity to the left produced increased stimulation current. This stimulation paradigm produced oblique eye movements as seen in Figure 7. Sinusoidal yaw rotation combined with anterior canal stimulation produced sinusoidally modulated oblique eye movements up and to the right (down and to the left). Sinusoidal yaw rotation combined with posterior canal stimulation produced sinusoidally modulated oblique eye movements down and to the right (up and to the left). Sinusoidal yaw rotation combined with posterior canal electrical stimulation that increased in current with increasing head velocity to the right produced sinusoidally modulated oblique eye movements down and to the left (up and to the right). The result was a vector addition of the individual components produced by the natural and electrical stimulation alone, as predicted in previous quarterly reports. Elimination of the electrical stimulation immediately eliminates the oblique modulation of eye velocity. This data suggests that linear summation of natural and electrical vestibular stimuli exists not simply within a given plane of stimulation, but across stimulation planes as well. Essentially, this fulfills the final criterion for effective reconstruction of any rotational input into an electrical stimulus that can augment or correct for misaligned vestibular responses. We can instantaneously, and in real time, increase or decrease the gain of the natural VOR, or change the direction of the response. This is a powerful tool that allows us to not only replace missing vestibular input, but to modify defective processing of vestibular input, resulting from an uncompensated partial peripheral lesion, or even from a central lesion of the vestibular system. If the brain cannot correct a problem with the output, we can modify the input to match the demands of the current adaptation state.

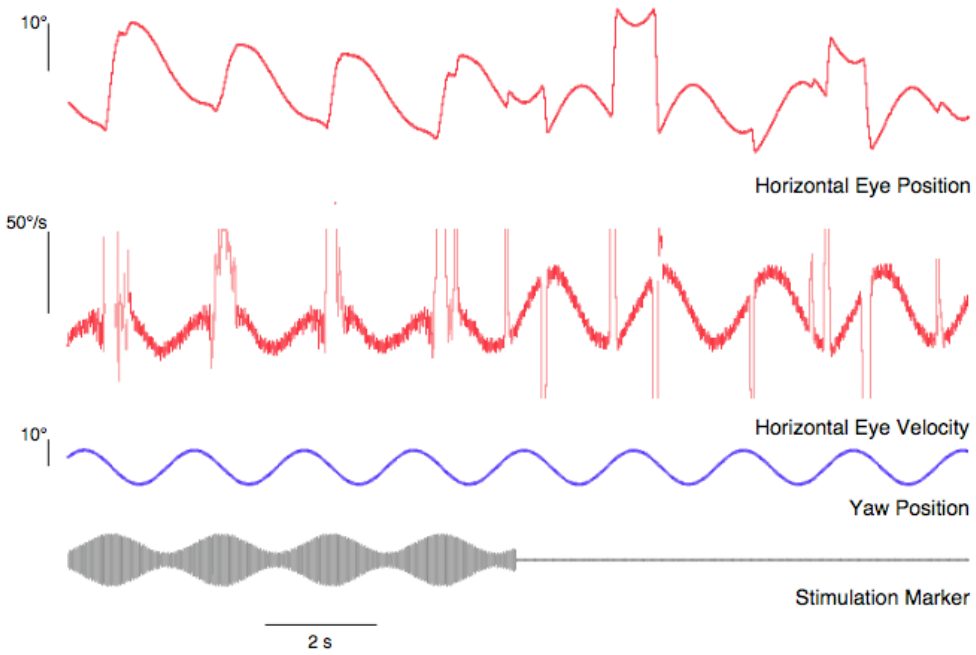

Figure 6. Decreasing gain of the horizontal VOR with amplitude modulated electrical stimulation of the right lateral canal. The offset of electrical stimulation is indicated by the offset of an amplitude modulated electrical artifact (stimulation marker) in phase with left yaw velocity (90 deg out of phase with left yaw position).

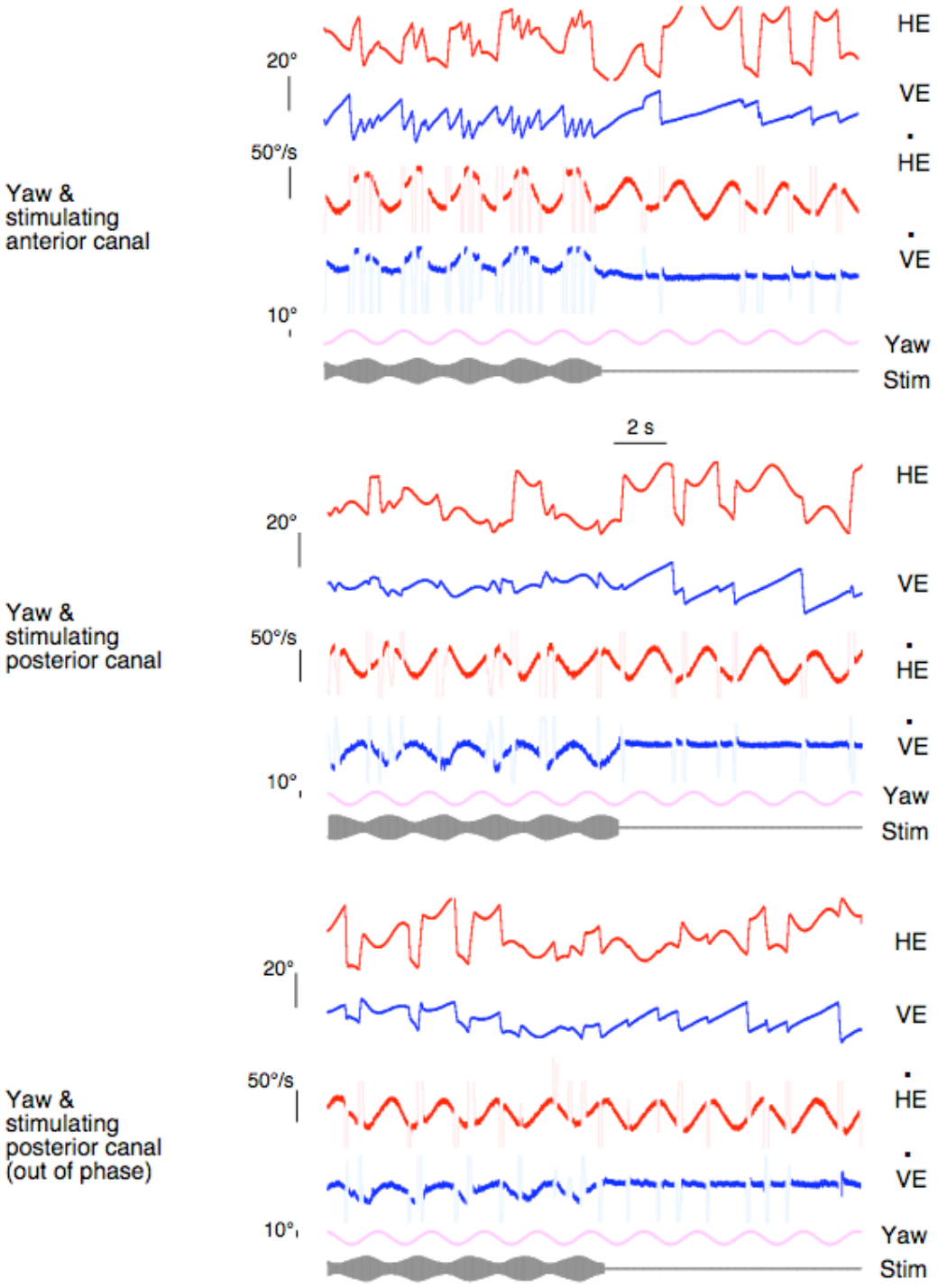

Figure 7. Electrical stimulation of the anterior and posterior semicircular canals during yaw rotation. The electrical stimulation current increases with head velocity to the left (upper and middle panels) or to the right (out of phase, lower panel). HE is horizontal eye position, VE is vertical eye position, HE dot is horizontal eye velocity, VE dot is vertical eye velocity, Yaw is chair position, and Stim is the stimulation artifact.

5. We have begun fabrication of an externally mounted motion sensor and processor that can sense three dimensional head rotational velocity and acceleration in real time. The device is designed to process those inputs based on empirically derived transforms such as those shown in Figure 2. It uses those processed inputs to modulate the gain of several sine wave inputs multiplexed into a single audio signal which is then used to drive a behind the ear (BTE) processor in real time to modulate the current or frequency output of the internally implanted stimulator. The device, which is shown schematically in Addendum 1, is fabricated on a single multilayer circuit board. It is driven by an external battery pack, which will run for 48 hours on two AAA batteries. The device incorporates a capacitive storage that will allow for continued operation during battery changes. The device is designed to have a case total dimension of 7 mm x 15 mm x 30 mm, and will attach to the head via a sintered titanium bone screw and fin attachment, similar to a bone anchored hearing aid (BAHA). The device has inputs for power, a bidirectional programming interface for instruction download and data logging, and a mode selection input to change modes of operation in real time. The device has a single output that is a micro audio connector for output of the amplitude modulated multiple sine wave carrier signal to the audio input of the BTE processor. The software interface for the device is written in C programming language and is currently implemented in a virtual machine running on a PC computer. That interface has been extensively tested and was used in many of the real time experiments described in this report.

6. We have submitted one manuscript this quarter. The title and authors are listed below.

Steven M. Bierer, Leo Ling, Kaibao Nie, Jay T. Rubinstein, Trey Oxford, Amy L. Nowack, Chris R. Kaneko, Albert F. Fuchs, James O. Phillips, Auditory outcomes following implantation and electrical stimulation of the semicircular canals. Hearing Research (submitted)

7. Dr. Rubinstein presented our results at two scientific meetings this quarter.

The first presentation was at the 82nd Annual Meeting of the German Society of ORL, Head & Neck Surgery 2011, 6/1/2011 to 6/5/2011, Freiburg im Breisgau, Germany. The second presentation was the Willard E. Fee, Jr., M.D. Lectureship, 6/10/2011, at Stanford University. The title of both presentations was "Preclinical and first human studies of a vestibular implant."

Objectives for Quarter 21

1. In the next quarter we will continue recording longitudinal eye movement responses to electrical stimulation at different frequencies and current amplitudes. In addition, we will record eye movement responses to natural rotational stimuli, ABR, vECAPs, and electrode impedance. Our objective is to fully characterize the longitudinal efficacy of the electrodes during electrical stimulation, and to correlate that with variables that could effect the behavioral responses. These experiments will be performed in

gentamicin lesioned and non-lesioned animals. Our hypothesis is that there will be no difference in the longitudinal results in the two groups. However, we have no data currently to indicate the reason that some animals show a decrement in efficacy whereas others do not.

2. We will continue recording from the brainstem of our existing monkeys. We are looking specifically for neurons that integrate amplitude modulated stimuli to produce a rate coded response. In addition, we will continue to record from omnipause and burst neurons to see where the vestibular signals are located that affect ongoing gaze shifts during electrical stimulation. Our hypothesis is that these are not direct inputs to the motoneurons via the direct VOR, but rather they are carried through indirect inputs that modulate the activity of the premotor burst generator.

3. We will continue looking for vestibular afferent fibers, although these have proved difficult to find and record in our preparation. Characterization of these afferents will provide a useful link in our analysis of the mechanisms underlying behaviorally effective electrical stimulation.

4. We will continue to characterize the sensitivity of recorded neurons to natural rotational stimuli at different rotational peak velocities to see whether there is a difference between neurons that are driven by electrical stimulation and those that are not.

5. We plan to bring the new Laura 34 interface firmware online. This will allow us to use a comparable interface in the human and monkey experiments.

6. We plan to test the newly developed bone anchored sensor array and processor. This will be done in parallel with other experiments and will not impact these in any way. This device will be mounted to the acrylic cap on the monkey's head so as to eliminate any additional risk associated with the bone anchor system. This technology will allow us to perform long-term stimulation studies in our animals. In addition, it will allow us to use continuous electrical stimulation driven by natural head movement in vestibular deficient animals.

7. We will continue to analyze and publish our data. We have two additional manuscripts currently nearing completion, which we will submit in the next quarter.