Eighteenth Quarterly Progress Report

November 1, 2010 to January 31, 2011
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Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

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Reporting Period: November 1, 2010 to January 31, 2011

Challenges:

1. Our current real time multichannel stimulation strategy has several limitations. We have implemented a strategy for real time stimulation of multiple canals using sine wave carriers of different frequencies to transmit head velocity information to the speech processor of the implanted device. This is a significant step forward and is described in the successes below. However, we have several challenges before us as we move forward with implementation of this strategy. First, it is not possible to entirely disable the microphone input in software when using the auxiliary input of the speech processor. This results in weak but unacceptable contamination of the processed head velocity signal with artifacts due to environmental noise. Our strategy is to encase the processor in sound deadening material, but ultimately we will require a hardware modification the device to eliminate this input. Such a modification will require the participation of Cochlear Corp. Second, our technique of using carriers of different frequencies suffers from the drawback that the speech processor processes each frequency channel somewhat differently. This limitation is due in part to the wider spectral bandwidth for higher channels, which cannot be specified in the clinical software without widening the bandwidth on the other channels. Finally, another challenge to the carrier-based strategy is that the voltage-current relationship must be carefully and separately calibrated for each channel. This hardware related issue is due to internal front-end filtering in the processor.

Our response to these challenges in Quarter 19 will be to initiate a discussion with Cochlear Corporation about implementation of the hardware modifications that we require to clean up the signals delivered through the speech processor. In addition, we will evaluate more completely the limitations of the current implementation, including real time multichannel testing in rhesus monkeys to evaluate the tradeoffs between the chosen carrier frequencies and the intrinsic hardware limitations and processing characteristics of the speech processor. One potential strategy is to assigns multiple "active" channels that are not stimulated, to compress the spectral bandwidth of the channels that are actually producing stimulation trains. The calibration issue will be addressed by a careful mapping of the stimulation outputs produced by comparable inputs in the different channels. Since the devices are identical, a thorough calibration of a single device will provide the data required to produce calibrated inputs for all devices using the same map.

2. A challenge of the current implementation of our stimulation strategy is that there is a bias in the direction of eye movements elicited by stimulation with a unilateral implant. The hope, which has been explored preliminarily in our lab and others, is that the central nervous system will adapt to long term stimulation and reduce this bias, producing symmetric eye movements from stimulation of a single canal, or combined stimulation of several canals unilaterally. Although it is reasonable to believe that this might be the case, there is very little evidence to suggest that such adaptation

actually results from electrical stimulation. The current evidence is that the resting bias and nystagmus from constant frequency stimulation changes over time with long-term stimulation, but the data also suggests that there is still a bias in the modulated eye velocity produced by stimulation.

Our response to this challenge is to propose an alternative stimulation strategy that manipulates the stimulation parameters to provide bidirectional modulation of resting nerve activity; i.e., a stimulation strategy which would drive the afferents of a single ear above and below their resting rate, potentially reducing the bias during modulated stimulation. It has previously been demonstrated in both computational models as well as physiological experiments (e.g., Rubinstein et al, 1999) that high rates of stimulation (e.g., 5000 Hz) presented at appropriate levels, can result in a stochastic pattern of unit discharge. These same models and experiments demonstrate that higher current levels, or higher rates (e.g., 10000 Hz) can result in progressive depolarization block. Based on these results, we expect that a vestibular nerve's spontaneous firing rate, or the bias of modulated firing, can be reduced through the application of such stimuli. Due to the potential importance of having bidirectional control of vestibular nerve firing rate for the treatment of a variety of conditions, we plan to test such stimuli in our monkey model in Quarter 19. Biphasic pulsatile stimuli presented at 5000 pps will be applied at slowly increasing currents. We expect that at low currents, vestibular nerve activity will increase as the electrical stimulation facilitates the spontaneous activity resulting in slow-phase velocities away from the implanted ear. At higher current levels, the firing rate will decrease resulting in slow-phase velocities toward the implanted ear. Stimuli applied at rates around 10 k pps would be expected to have a very narrow, or nonexistent, window for facilitation and would be primarily inhibitory.

3. We have noted the long-term unilateral loss of vestibular function in one of our rhesus monkeys following implantation with the device. This animal also lost hearing as a result of the implantation. This is concerning primarily because we have noted a short-term reduction in vestibular function in several animals which subsequently recovered. We concluded that these animals had an inflammatory process that quickly recovered without significant impairment of function. It is possible, however, that in this animal we initiated a process that resulted in the long-term deterioration of function due perhaps to the introduction of a foreign body into the vestibular labyrinth. Although we did not observe a change in the efficacy of electrical stimulation in the animal over the same period, suggesting that the afferent innervation was maintained, the change in vestibular function is an important finding. It is particularly relevant in light of the human implantation findings discussed below.

Our response to this challenge is to continue to regularly monitor vestibular function in the four animals that remain on our protocol. In addition, we will request a no cost extension to our project, which would extend ABR, vestibular, and electrical stimulation testing, including single unit recording, in these animals for an additional year. If this request is approved, the resulting long-term data will allow us to evaluate the safety and functional stability of the device over an extended period of time in our remaining animals. Considering our existing investment in the unique resource of these implanted

animals, we feel that this is a prudent measure and a reasonable request consistent with the stated objectives of the contract.

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

1. We have activated, and evaluated the function of, our vestibular prosthesis in a single human subject. The device was implanted as part of a 10 patient human feasibility and safety trial of the device as a treatment for Meniere's disease. Roughly two weeks following the initial implantation procedure, the subject returned for activation of the implanted device. The subject was seated on an exam table, with a safety lap belt, wearing a light occluding mask for 3 dimensional eye tracking at 100 Hz (NKI). Stimulation began at low current using monopolar stimulation with the active electrode being the most distal electrode on the lateral canal array, and the return being the ball ground plus case ground. Stimulation trials consisted of constant frequency trains at 300 pps lasting 2 s. The stimuli were biphasic pulses of 100 µs duration per phase and an 8 µs interphase gap. The currents were increased by 10 µA per step starting at 10 µA with two 2 s trains of stimulation at each current. Eye movements and subjective sensations were monitored for each stimulation, and the subject was encouraged to report not only any sensation of motion, but also any indication of discomfort, sound, tactile sensation or muscle contraction. The subject reported a sensation of motion elicited by the lateral canal electrode at 100 µA. Nystagmus was noted at 125 µA. The nystagmus was predominately right beating, in the plane of the implanted canal (figure 1).

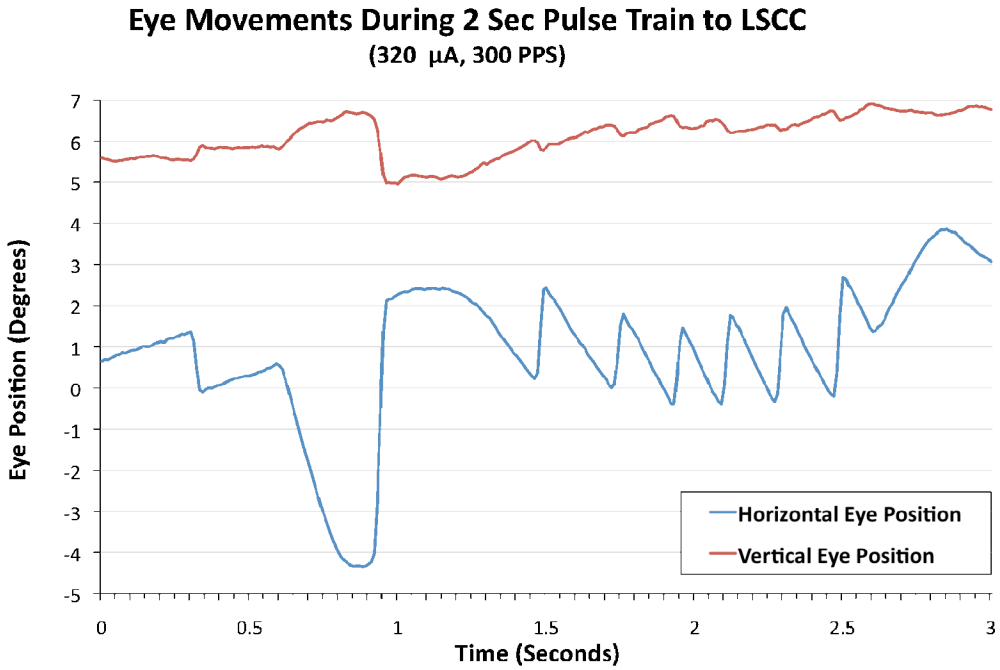

Figure 1. Eye movements resulting from 2 s duration constant frequency electrical stimulation of the lateral semicircular canal in a human subject.

Typically, the nystagmus began with a high velocity initial slow phase, followed by a sustained nystagmus of lower velocity. As the current was increased, the velocity of the

slow phase eye movement increased (Figure 2). The patient subjectively reported a sensation of en-bloc yaw rotation toward the implanted ear, which increased with increasing stimulation current. In addition the subject reported a consistent roll rotation to a static tilt toward the implanted ear, consistent with some current spread to the utricle of the right ear. The sensation of yaw rotation predominated at moderate to higher currents, which also elicited slow phase eye movements. The subject did not report any discomfort, nor did the subject experience any sound or tactile sensation. Facial twitches were not elicited by the electrical stimulation.

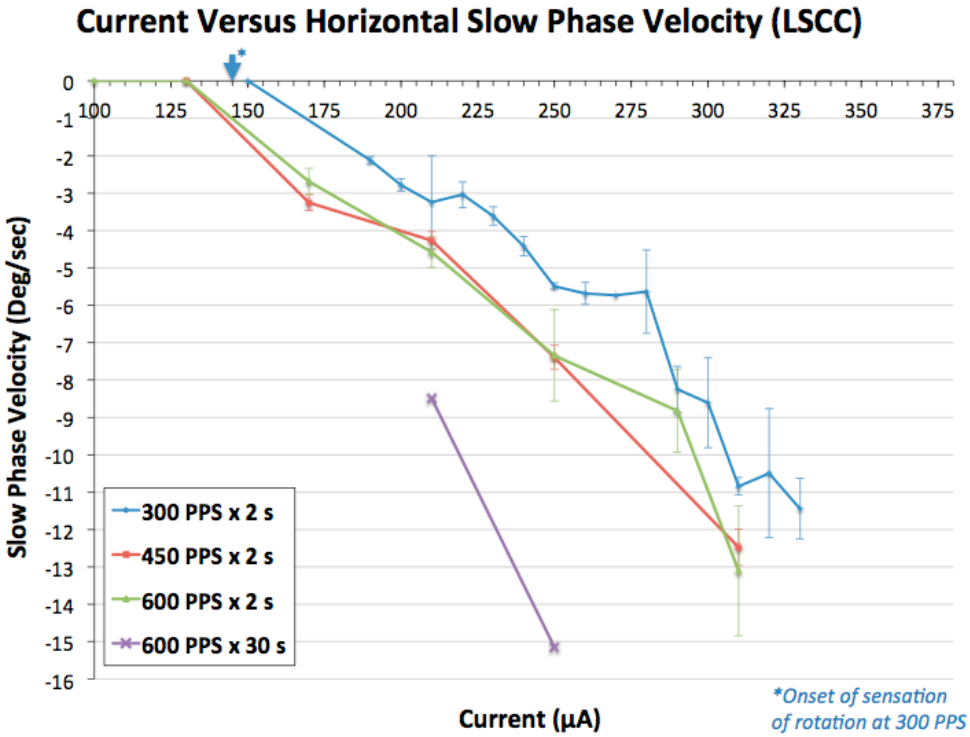

Figure 2. Average slow phase velocity versus stimulation current for 2s or 30s constant frequency electrical stimulation of the lateral canal at various stimulation frequencies. The arrow indicates the onset of a subjective sensation of movement in the subject during 300 pps stimulation.

After obtaining a complete series of 2-second stimulation trials at 300 pps, a 600 pps current series was obtained. The higher frequency stimulation elicited a more compelling sensation of yaw rotation and higher velocity nystagmus that scaled with stimulation current (figure 2). In addition, two 30-second stimulation trials were obtained. Each stimulation produced a very compelling sensation of en-block yaw rotation (actually rotation of the seated subject and chair) that was sustained for the full duration of the stimulation and then slowly decreased following stimulation. The slow phase eye movements during the stimulation were right beating and there was an afternystagmus following stimulation that was well correlated with the subjective sensation (figure 3). The eye velocities obtained during 30 second stimulation were greater than those obtained during 2 second stimulation. The time course of the velocity increase is seen in figure 4. Peak velocities obtained with stimulation, excluding the velocity transient at

stimulation onset, were approximately 23 deg/s. Such velocities were far lower than the velocities obtained by comparable stimulation in the rhesus monkey.

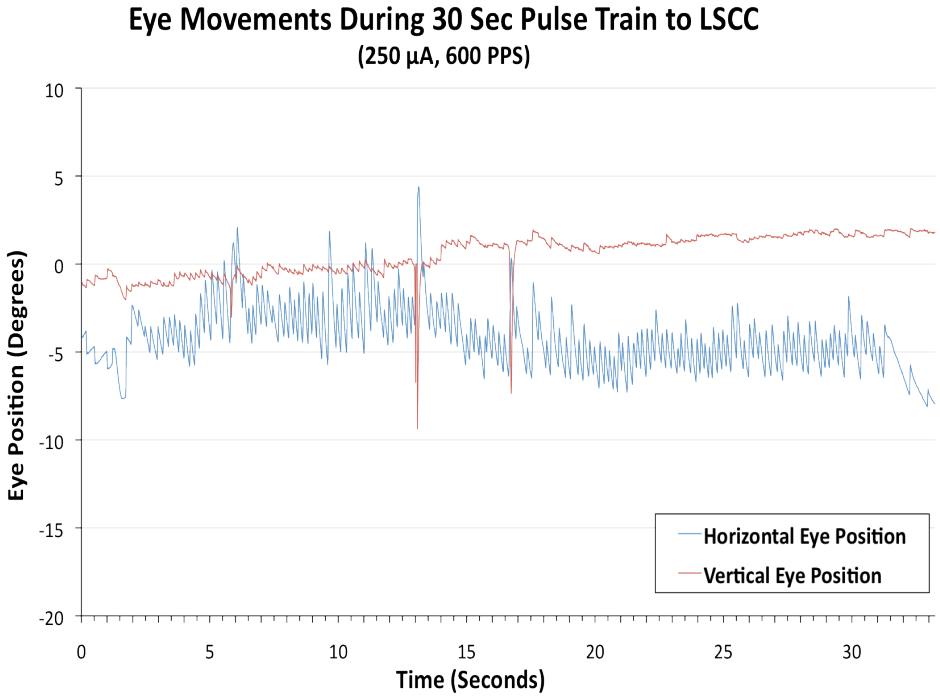

Figure 3. Eye movements resulting from 30 s duration constant frequency electrical stimulation of the lateral semicircular canal in a human subject.

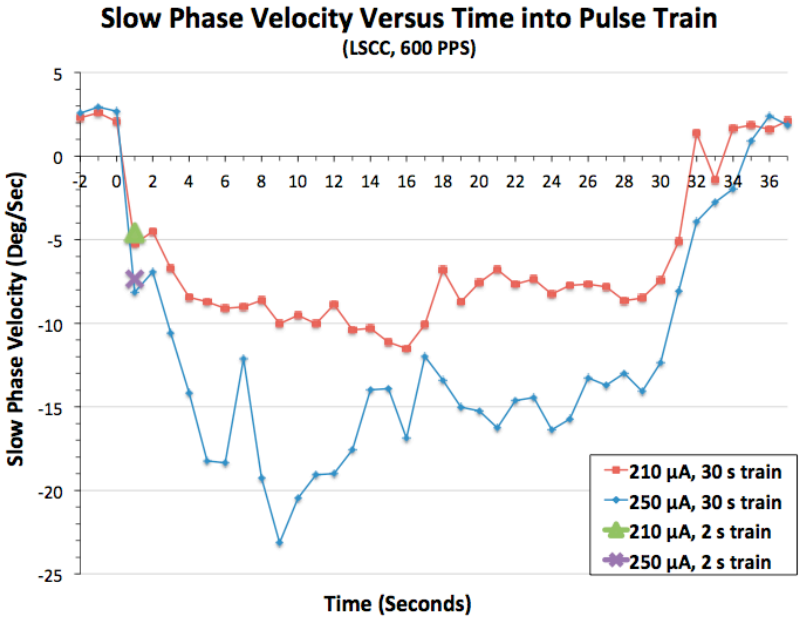

Figure 4. Average slow phase velocity versus time from onset of stimulation for 30s constant frequency electrical stimulation of the lateral canal at various stimulation currents. 2 s stimulation train average slow phase velocities are also plotted for comparison.

Electrical stimulation of the superior semicircular canal was performed in a manner analogous to that reported above. The threshold for subjective sensation was 190 μA and the threshold for nystagmus was 225 μA. The subject experienced a subjective rotation down and to the left in the plane of the implanted canal. Figure 5 displays the slow phase velocity of the eye movements elicited by stimulation of the superior canal. As the current was increased, the velocity of the eye movements increased. Increasing stimulation frequency had a limited effect on the velocity of the elicited eye movements. The subject did not report any pain or auditory sensation.

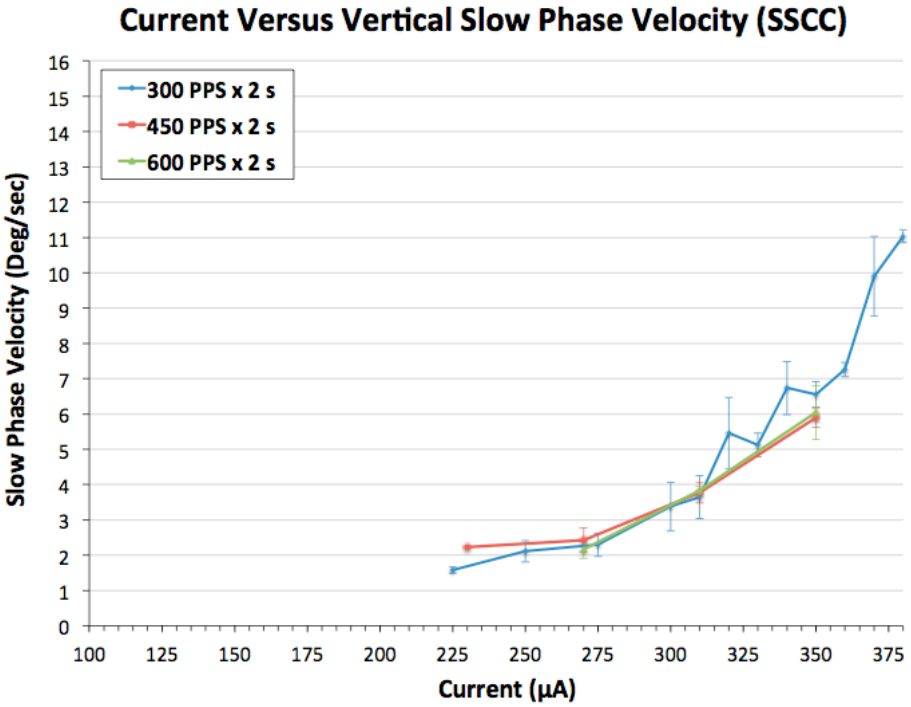

Figure 5. Average slow phase velocity versus stimulation current for 2s constant frequency electrical stimulation of the lateral canal at various stimulation frequencies.

Electrical stimulation of the posterior canal was attempted after stimulation of the other canals. This testing was limited to lower currents due to a dull sensation of pain or pressure coming from the site of surgical incision. No eye movements were elicited at low currents, and no sensation of movement was produced. We hypothesized that the dull pain sensation was related to the recent surgical incision and electrical activation of the facial nerve, and we elected to postpone stimulation of that canal over a range of currents to a later date.

The subject subsequently returned for further testing with the implanted device approximately 3 weeks after the initial testing session. In this session, the device was activated only briefly for mapping. The electrical stimulation with the device continued to drive eye movements in the plane of the stimulated lateral and superior semicircular canals. The subject also underwent rotational and caloric testing for evaluation of natural vestibular responses, and an audiogram. The subject showed a post surgical decrease in hearing function in the implanted ear, an increased asymmetry in velocity step rotational

testing toward the implanted ear, a reduction in rotational vestibulo-ocular reflex gain during sinusoidal rotational testing, and an increased caloric weakness in the implanted ear. All of these measures indicate that the subject had a reduction in hearing and rotational function in the implanted ear following surgery. The subject is scheduled to return for further functional assessment during Quarter 19.

2. We have expanded the real-time signal interface described in the previous quarter to handle up to three stimulation channels. The MATLAB-based interface program directs a National Instruments data acquisition board to read in three band-limited signals (e.g. velocity signals from a rotational sensor), transforms and mixes each with a different sinusoidal carrier waveform, and outputs the summed signal to the Cochlear Freedom implant processor. The processor, which is set up using the standard clinical software, spectrally separates the composite signal back into three channels and delivers pulses to the designated electrodes at current levels modulated by each channel's time-varying signal amplitude.

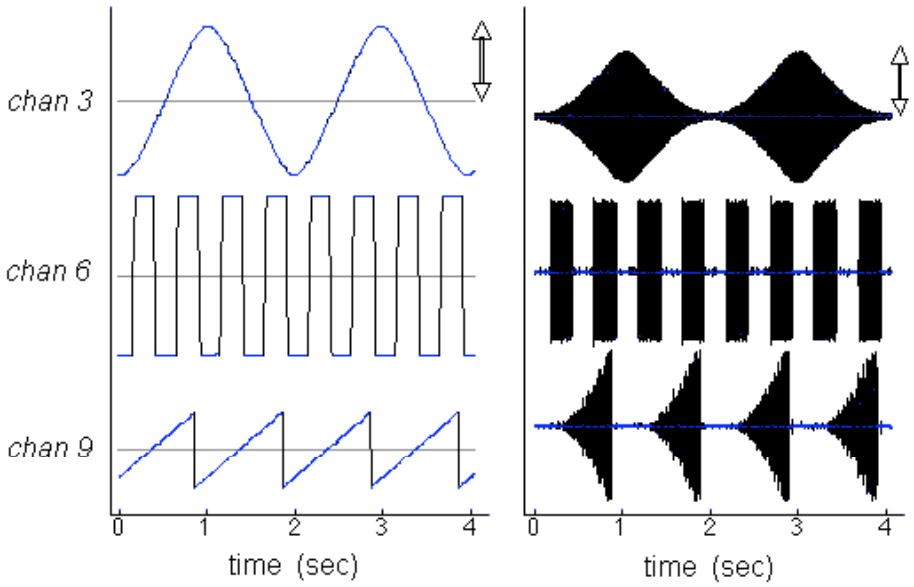

Figure 6. 3 channel independent electrical stimulation assessed with an "implant in a box". The input signals are displayed in the left panels and the output stimulation measured across a resistor is displayed in the right panels. The vertical arrows indicate 10 v and 650 μA, respectively.

Testing of the signal delivery program was performed using an "implant-in-a-box", with each output channel connected to ground via a 10 kOhm resistor. An example of pulse trains modulated simultaneously with three distinct input signals is shown in Figure 6. The input signals (left panel) were generated with separate function generators and the resulting pulse trains (right panel) were delivered to implant channels 3 (top), 6 (middle), and 9 (bottom). Each channel was programmed to produce biphasic pulses with a width of 100 μs per phase, at a rate of 500 pulses per second, and with minimum and maximum

currents at 0 and 650 μA, respectively. The carrier frequencies were 800, 2000, and 5000 Hz, and the analysis bandwidths were at least one-half octaves. Channels 3 and 6 were programmed with a linear transformation for an input range of +/- 10 volts. As a demonstration of the programming flexibility, channel 9 was programmed with a ½-wave rectified transformation for an input range of +/- 5 volts. Comparison of the left and right panels shows that the different input signals resulted in the expected modulation of the three pulse trains.

One drawback of the technique, due mainly to its implementation on Cochlear hardware and software designed for audio signals, is apparent from this example. The pulse-to-pulse amplitudes are somewhat noisy for electrode channel 9 compared to the other two channels (some amount of jitter is expected due to undersampling of the narrow pulses). This noise can be partly attributed to pick-up of environmental acoustic sounds from the microphone, which cannot be turned off in the standard clinical software. The problem is likely compounded by the wider spectral bandwidth for channel 9, which cannot be specified in the clinical software without widening the bandwidth on the other channels. Nevertheless, the signal interface program performs well in separating the three components without cross-talk between channels.

3. We have used single unit recording to evaluate the mechanism of the transient increase in slow phase velocity that accompanies the onset of stimulation during constant frequency stimulation. We have noted previously that there is a brief non-linearity in the slow phase velocity response to constant frequency stimulation. In our reports, we define the velocity response to stimulation in terms of the sustained velocity elicited by the electrical stimulus train. This allows us to use the measured velocities to construct stimulation patterns that produce predictable modulation of eye velocity across a broad frequency range. However, the start of stimulation typically elicits a brief epoch, at least part of a first slow phase, with a velocity that is well above the sustained slow phase velocity. This transient may be responsible for the increase in response velocity that we observed during high frequency, 5 Hz sine wave modulated, stimulation.

To understand the mechanism underlying this phenomenon, we recorded from single vestibular neurons during electrical stimulation, and carefully examined the instantaneous firing rate during the stimulation train. The results of one such stimulation train are illustrated in figure 7. The large open arrow in figure 7 indicates the velocity transient that occurs at the onset of stimulation. Gross inspection of the instantaneous discharge frequency trace of the recorded secondary medial vestibular nucleus neurons suggests that the neuron fires in roughly the same pattern throughout the electrical stimulation. However, a closer inspection reveals a critical difference between the initial epoch and later epochs chosen at random throughout the stimulation train. The onset of stimulation produces a brief period of robust frequency following, where the unit fires with every stimulus pulse. Subsequent epochs show unit discharge that follows the stimulation intermittently, with many periods where the neuron fails to follow every other pulse. Furthermore, the neuron frequently fires in doublets in response to a single stimulus pulse during the first epoch, and does not do so in the other representative epochs. Therefore, the transient increase in velocity appears to be reflected in the discharge of secondary

vestibular neurons. Two mechanisms are suggested. The initial double response for a single stimulus pulse may indicate a post synaptic mechanism where the excitability of vestibular neurons changes with repeated high frequency stimulation. The reduced frequency following after prolonged stimulation may reflect presynaptic mechanism where a loss of neurotransmitter reserves is produced in the vestibular afferents with continued stimulation. At this time, the cellular mechanism is unknown.

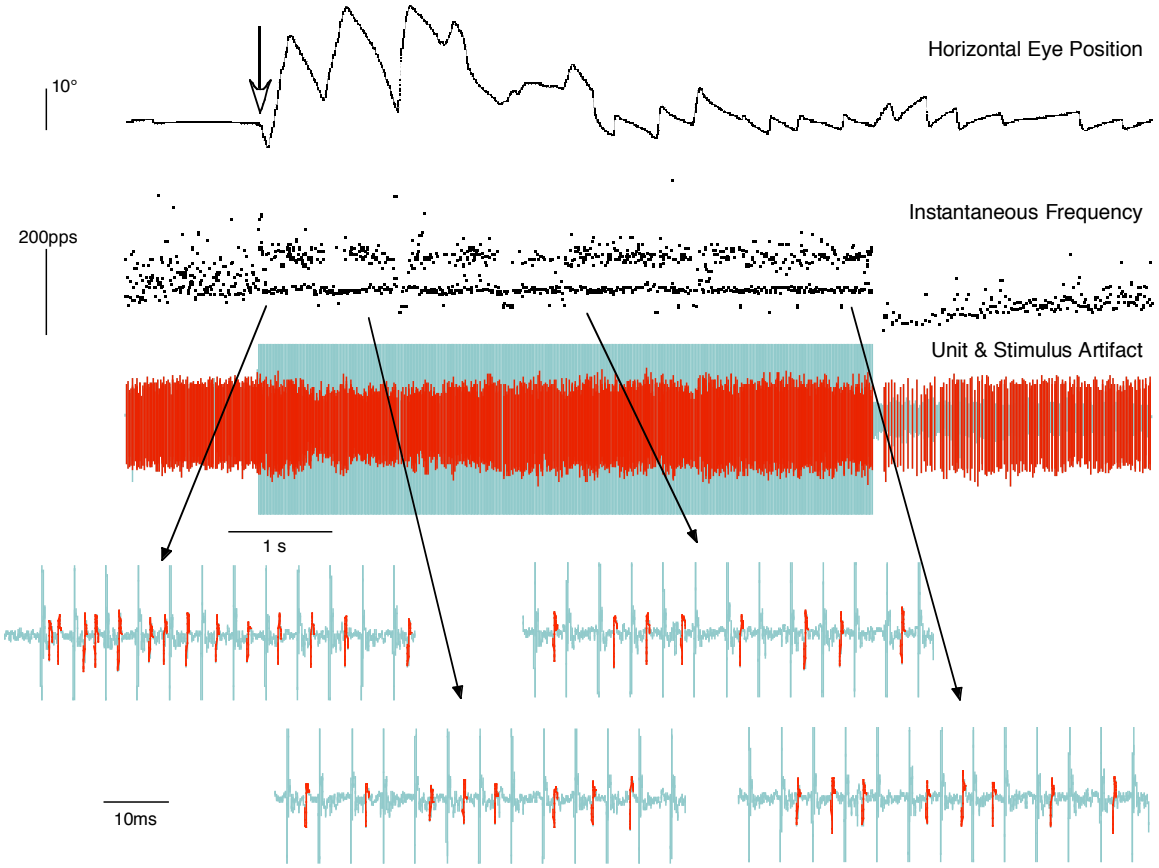

Figure 7: Recording of a single vestibular neuron during constant frequency electrical stimulation of the right lateral canal. The stimulus artifact is displayed in grey and the single vestibular neuron spikes are in red. The filled arrows indicate the portions of the instantaneous frequency trace that are expanded in the insets below. The open arrow indicates the velocity transient at the outset of electrical stimulation.

4. We have used single unit recording to evaluate the mechanism underlying the production of reversed nystagmus following electrical stimulation. As was noted in previous quarterly reports, with frequent high current stimulation, we have been able to produce nystagmus, afternystagmus, and even reversed afternystagmus (after-after nystagmus) in rhesus monkeys. We assumed that this was a reflection of the activation of complex neural circuits in the brainstem, which are responsible for the storage of velocity information. This is likely to be the primary mechanism. However, we have also noticed that the discharge of individual secondary vestibular neurons often reflects the post-stimulation behavior in their resting discharge rate. To study this phenomenon in detail,

we have analyzed the resting discharge of vestibular neurons before and after electrical stimulation. An examination of the resting discharge of the neuron in figure 7 shows that the difference in resting discharge can often be dramatic, and that the changes in resting discharge parallel the changes in the observed behavior. This example, which was chosen for the dramatic transition between nystagmus elicited by electrical stimulation and the rapid development of reversed afternystagmus following electrical stimulation, clearly shows that the onset of reversed afternystagmus is associated with a reduction in resting discharge in this neuron. Indeed, as the resting discharge recovers toward the pre-stimulation levels, the velocity of the reversed nystagmus decreases. Despite the fact that this neuron is a secondary vestibular neuron, and hence activated at monosynaptic latency with electrical stimulation of the vestibular end organ, its discharge clearly reflects the post stimulation eye velocity.

5. We have used evoked potential recording to evaluate the mechanism of eye position related velocity changes in response to brief electrical stimulation. In our last quarterly report, we described the significant changes in the eye velocity evoked by a stimulus train when that train was initiated in different eye positions. The resulting eye velocity was strongly related to the initial eye position. To evaluate the hypothesis that the vestibular input to eye motoneurons scaled with eye position, we recorded evoked field potentials in response to electrical stimulation of the lateral canal in the contralateral abducens nucleus during fixation in different eye positions. The result of a single recording session is displayed in figure 8.

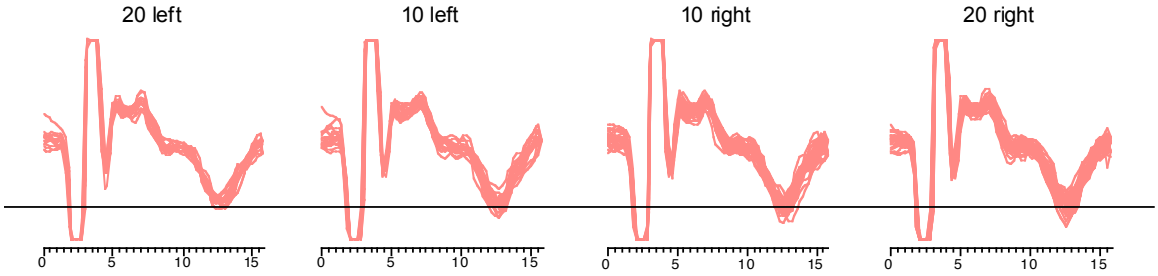

Figure 8. Superimposed evoked field potentials recorded in the left abducens nucleus during 10 Hz electrical stimulation of the right lateral semicircular canal with the eye in various horizontal eye positions. Time in milliseconds is displayed below each set of traces. Stimulus artifact and resulting field potentials are displayed.

Figure 8 clearly shows that the amplitude of the evoked potentials in the contralateral abducens nucleus do not change with eye position. We interpret the preliminary results of these experiments to indicate that the abducens nucleus receives the same electrically evoked vestibular input in different eye positions. Therefore, the eye position related evoked eye velocity changes are related either to intrinsic properties of the abducens neurons and their summation of vestibular inputs with other inputs, or to properties of the oculomotor plant.

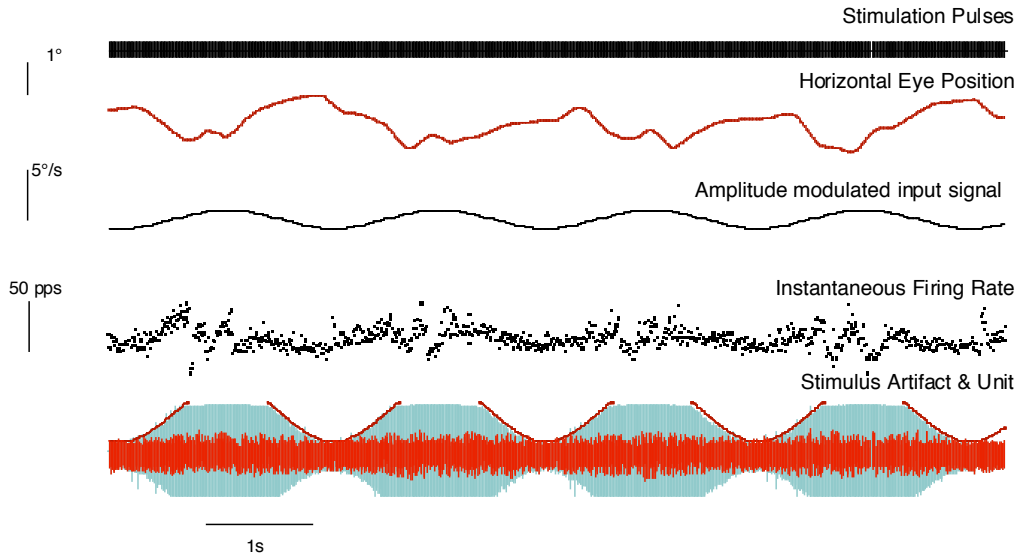

Figure 9. Modulation of a left abducens neuron during sinusiodally amplitude modulated constant frequency electrical stimulation of the right lateral semicircular canal. Stimulus artifact is displayed in grey and neuron spikes are displayed in red.

6. We have used single unit recording in the abducens nucleus to understand the mechanism of amplitude modulated electrical stimulation with a vestibular prosthesis. In previous progress reports, we have discussed the relationship between amplitude modulation of electrical stimulation with a vestibular prosthesis and both eye velocity and single vestibular neuron firing rate. In summary, slow phase eye velocity is well modulated with amplitude modulated stimulus current, but single neuron firing rate is not. However, we proposed that recruitment of increasing numbers of vestibular neurons could underlie the modulation of slow phase eye velocity. This proposal suggests that somewhere downstream of the vestibular nucleus neurons that we have recorded, there is a summation of inputs from individual vestibular neurons. We are using single unit recording in individual abducens neurons to determine if that summation takes place in the abducens nucleus. Figure 9 shows the result of one such experiment, in which a burst tonic neuron at the location of the abducens nucleus is recorded during constant frequency, amplitude modulated, electrical stimulation of the contralateral lateral semicircular canal. The amplitude modulated stimulus artifact is displayed, as is the input signal. The eye movements that are evoked have a very roughly sinusoidally modulated eye position, which is reflected in the discharge frequency of the abducens motoneuron. The most interesting relationship in this figure is between the amplitude modulated electrical stimulus artifact and the frequency of the abducens neuron. Although the abducens neurons discharge frequency is phase shifted with respect to the amplitude modulation, as expected from the underlying anatomy and physiology of the vestibulo-ocular reflex, the abducens neuron is clearly modulated by the stimulation. Therefore, for this neuron and others that we have recorded, amplitude modulated electrical stimulation produces frequency modulation of single abducens neurons.

7. We have presented our results in scientific meetings during this quarter. The presentation titles and authors are listed below.

Ling, L., Bierer, S., Fuchs, A.F., Kaneko, C.R.S., Nie, K., Nowack, A., Rubinstein, J.T., Phillips, J.O. Parallel channels of signal processing in the vestibular pathway. Society for Neuroscience, 583.16, 2010

Phillips JO, Ling L, Fuchs AF, Oxford T, Bierer SM, Nie K, Kaneko C, Newlands S, Rubinstein JT Recording of secondary vestibular neurons during electrical stimulation with a vestibular implant for the treatment of Meniere's disease, 6th International Symposium on Meniere's Disease and Inner Ear Disorders, Kyoto, Japan, 2010

Rubinstein J.T., Phillips, J.O. A Vestibular Implant for the Treatment of Meniere's Disease, 6th International Symposium on Meniere's Disease and Inner Ear Disorders, Kyoto, Japan, 2010

Objectives for Quarter 19

1. In the next quarter we will continue our neural and behavioral recording in rhesus monkeys to elucidate the mechanism of action of electrical stimulation with the vestibular prosthesis. We will continue to record from electrically driven neurons and quantify their responses during constant amplitude and frequency stimulation, and during amplitude or frequency modulated stimulation across a range of modulation frequencies. We are targeting neurons in the vestibular nucleus and the abducens nucleus.

2. We will extend the analysis of our data by analyzing the resting rate discharge of neurons immediately before, at the onset, and after electrical stimulation with the vestibular prosthesis. In particular, we will look for changes in discharge that are related to changes in eye velocity. In addition, we will quantify the coefficient of variation (CV and CV*) of vestibular neurons recorded on comparable tracks, and compare the variability of discharge for neurons that are driven with those that are not. This strategy may provide indirect evidence as to the type of vestibular inputs we are driving with our electrical stimulation. We hypothesize that two mechanisms, proximity to the stimulating electrode and galvanic sensitivity of individual afferents, will determine the fibers that we activate, and that the regularity of the discharge of the fibers may be reflected in the regularity of the discharge of the vestibular neurons that we record.

3. We will use the three-channel real time program described above to produce independent real time activation of different semicircular canals in our implanted monkeys. We will explore the stimulation encoding parameters that produce optimal multichannel stimulation.

4. We will perform further laboratory testing on our first human subject, including repeated electrical stimulation at different stimulation frequencies and currents, and both repeated clinical vestibular assessment and a repeated audiogram. In addition, we anticipate implanting a second subject with the vestibular prosthesis.

5. We will perform very high frequency stimulation studies on rhesus monkeys. Our objective will be to see if we can produce changes in slow phase direction as a result of depolarization block with electrical stimulation.