Twenty Second Quarterly Progress Report

November1, 2011 to January 31, 2012
Contract No. HHS-N-260-2006-00005-C
Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

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Reporting Period: November 1, 2011 to January 31, 2012

Challenges:

1. During Quarter 22 we lost some functionality in the implant of one of our animals. This change was not associated with infection or with trauma, and did not result in a complete failure of the device. Rather, the device began to produce reduced stimulation intermittently, skipping stimulus pulses or failing to stimulate at lower stimulation frequencies. These changes were seen only with the clinical interface initially, using a behind the ear processor. Later however, the problem began to affect the research NIC-2 interface, and then only the research NIC-2 interface. Since the problem was intermittent, it was difficult to diagnose the underlying cause. In response to this issue, we changed the programming of the device so that the power pulse frequency was independent of the stimulation frequency. We reasoned that the lower stimulation frequencies possibly were resulting in inadequate powering of the implanted receiver stimulator. These changes were successfully implemented and there were minimal improvements in the performance of the device in this animal at low frequencies. We feel however, that this is a more logical strategy for powering the device, and so we have continued to utilize this approach.

We also suspected that the RF communication with the device was compromised by an accumulation of tissue between the surface coil and the receiver coil. We noted that placement of the surface coil was critical to the performance of the device, and pressure applied to the coil changed the performance of the stimulator. We purchased a new, more powerful magnet for the device to try to rectify the problem, but this did not fully resolve the issue. We will still record from this animal in Quarter 23, because we are getting reasonable performance from the device at higher frequencies, but we are interpreting the results with caution. In addition, we are recording the stimulation artifact with surface electrodes, and limiting data collection to periods when the device is producing a normal stimulation artifact.

Successes:

1. During Quarter 22 we obtained further longitudinal data on vestibular evoked compound action potentials (vECAPs) in three of our animals. This data is the subject of an I.E.E.E. submission next quarter and is displayed in the figures below. As is clearly shown in Figure 1, vECAP can be sustained over long durations in individual canals in a single monkey. Figure 1 shows the vECAP responses in three canals in a single monkey 89 days post surgery and 239 days post surgery. The figure shows that in each canal, there was no difference in the waveform or amplitude of the response between the early and late time points. In order to demonstrate the full longitudinal data set for this animal, we calculated the amplitude of the vECAP potential for each current amplitude at each time point after surgery. In Figure 2, this information is displayed graphically as the measured N1-P1 amplitude of the vECAP waveforms versus days post surgery. Again, it can be seen that across the entire period of recording, there was little change in the amplitude of the vECAP.

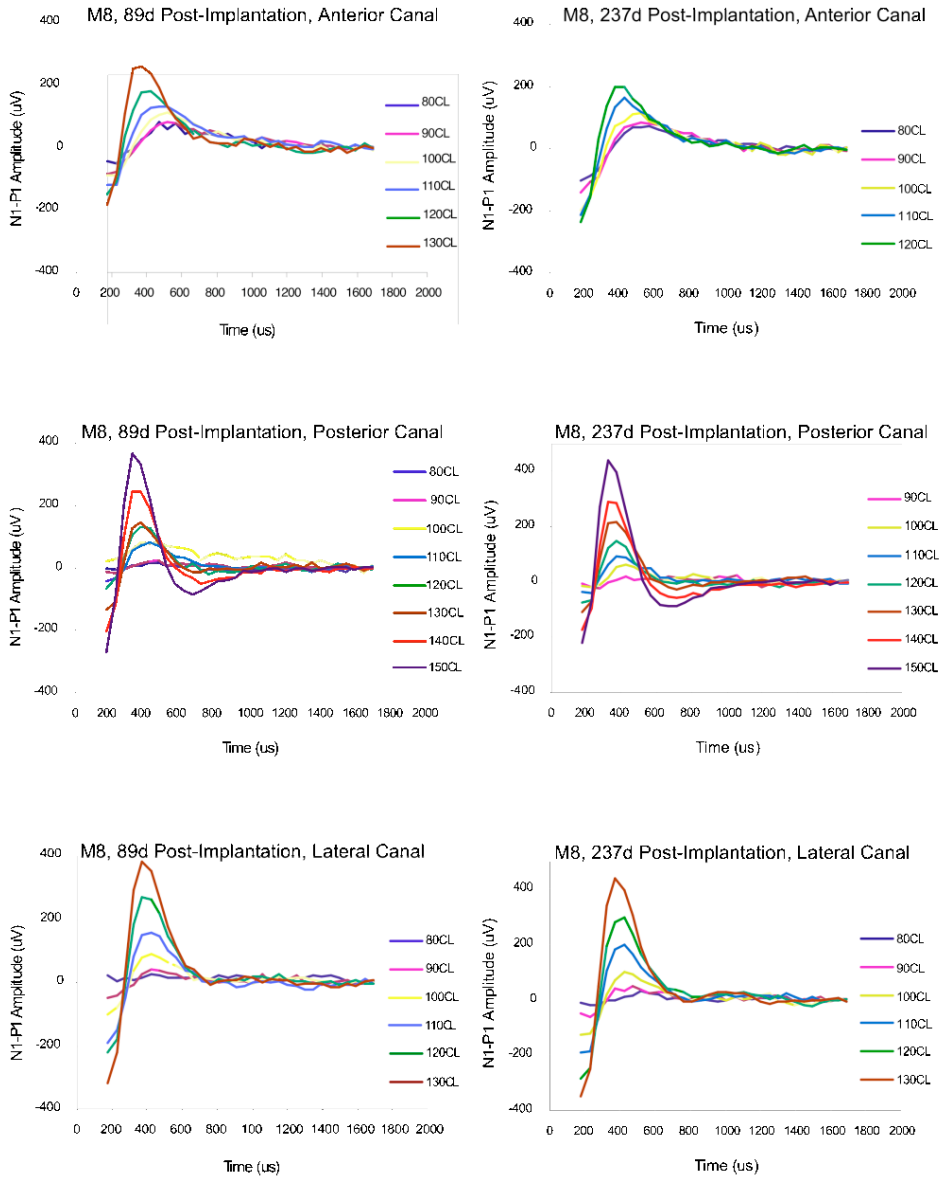


Figure 1. vECAP waveforms at multiple current intensities from three canals in a single monkey at two time points. Anterior canal recordings are from stimulation of the most distal electrode in the anterior canal, and recording in the next most distal electrode in the same canal. Posterior and lateral canal recordings are from stimulation of the most distal electrode in each canal, and recording in the most distal electrode in an adjacent canal. Colors denote the stimulation current used. Currents are specified in clinical level (CL). uA = 17.5 x 100 (CL/255).

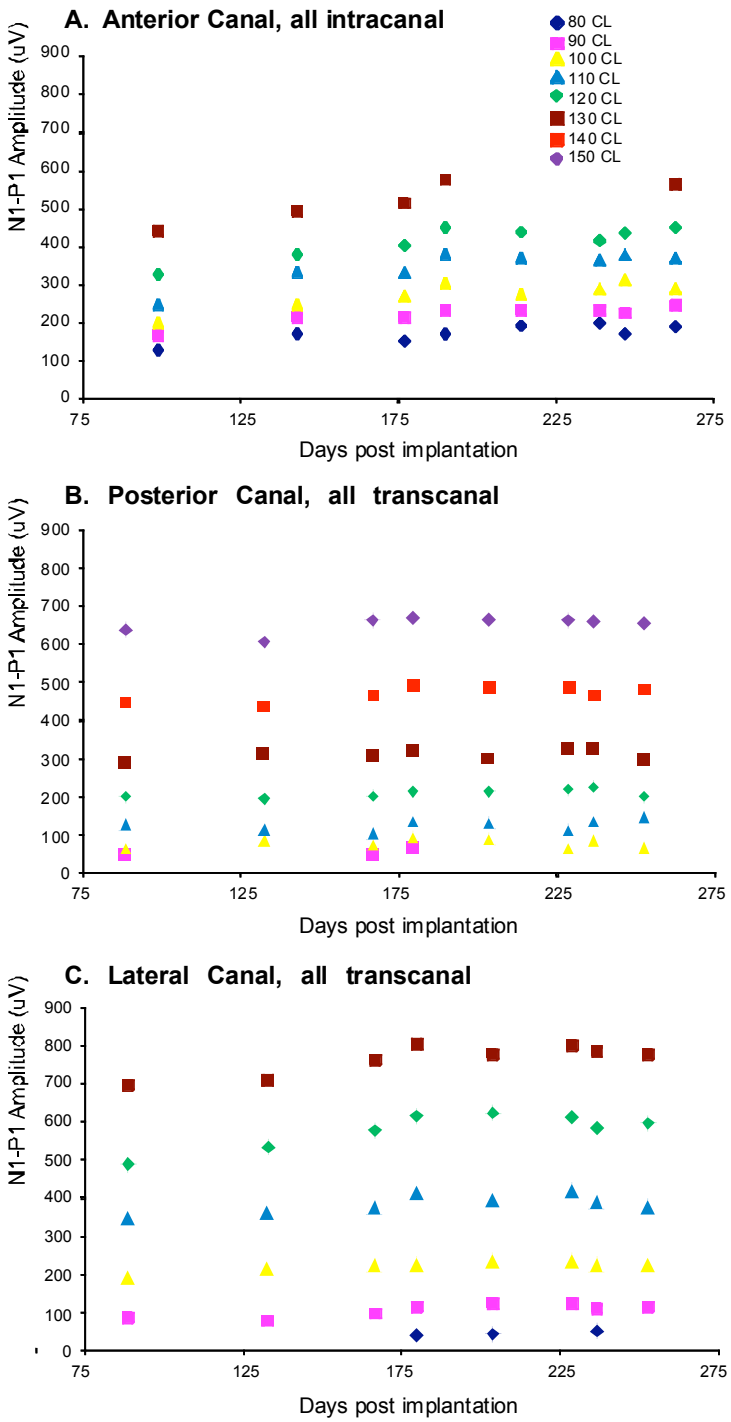


Fig. 2. Longitudinally recorded vECAP amplitudes at multiple current intensities from three canals in the monkey from Figure 1. Anterior canal recordings are from stimulation of the most distal electrode in the anterior canal, and recording in the next most distal electrode in the same canal. Posterior and lateral canal recordings are from stimulation of the most distal electrode in each canal, and recording in the most distal electrode in an adjacent canal. Colors denote the stimulation current used. Currents are specified in clinical level (CL).

vECAP amplitudes were not maintained in all animals. Figure 3 shows that the vECAPs can decrease significantly and precipitously in a single canal while being maintained in another canal in a single animal. In this monkey, the vECAPs became smaller 606 days after implantation in the lateral canal but were maintained in the posterior canal.

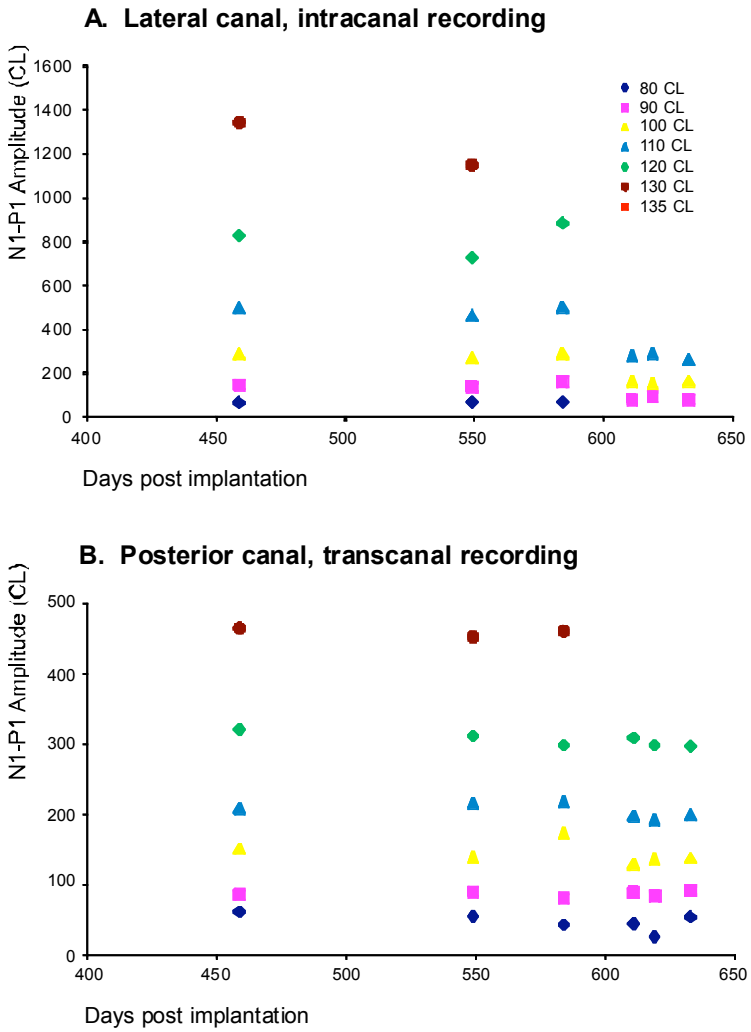


Figure 3. Longitudinally recorded vECAP amplitudes at multiple current intensities from two canals in a second monkey. Lateral canal recordings are from stimulation of the most distal electrode in the lateral canal, and recording in the next most distal electrode in the same canal. Posterior canal recordings are from stimulation of the most distal electrode in the posterior canal, and recording in the most distal electrode in an adjacent canal. Colors denote the stimulation current used. Currents are specified in clinical level (CL).

A third animal showed similar changes in vECAP response over time. In this animal, however, there were also changes in device function with intermittent failures, as described in challenges section above. Figure 4 shows that the device produced lower

vECAP amplitudes later in the stimulation trials, and the threshold for vECAP actually increased.

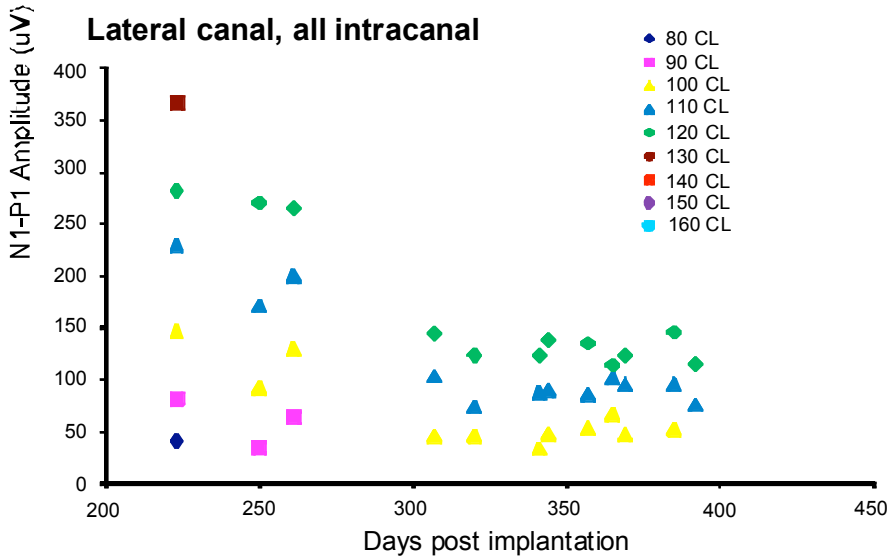


Figure 4. Longitudinally recorded vECAP amplitudes at multiple current intensities from the lateral canal in a third monkey. The recordings are from stimulation of the most distal electrode and recording in the next most distal electrode in the same canal. Colors denote the stimulation current used. Currents are specified in clinical level (CL).

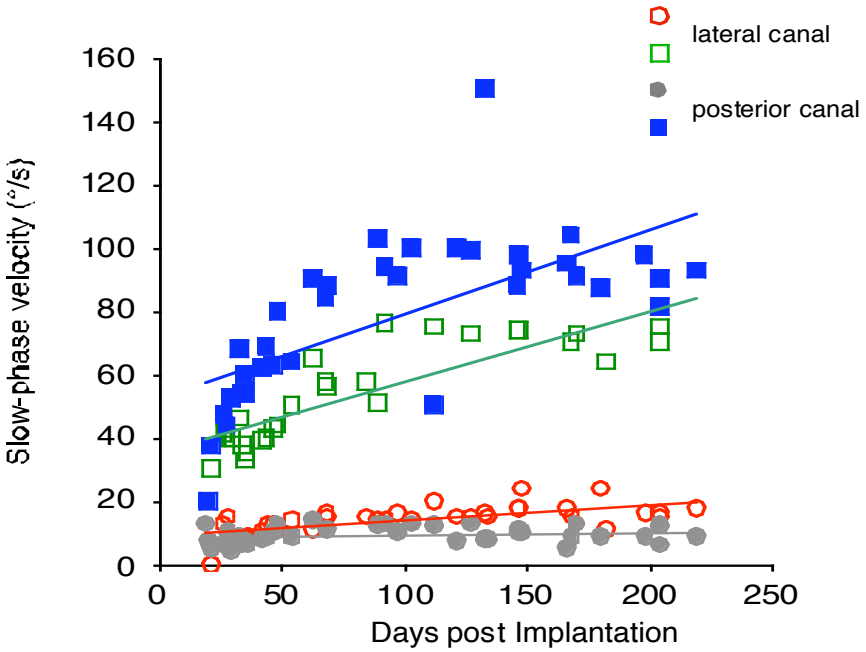


Figure 5. Slow phase velocity measured at two current levels in the lateral and posterior canal of the monkey in figures 1 and 2 versus days post surgery. The circles represent approximately 90 CL stimulation and the squares represent approximately 130 CL stimulation currents.

The significance of the vECAP measure is that it can be used to monitor the effect of electrical stimulation on the afferent fibers at the vestibular end organ. It is possible that the effects of electrical stimulation measured behaviorally are distorted by central adaptation of the response. Direct comparison of the central and peripheral responses should provide a clue as to whether this is the case. To provide such a comparison, we obtained the slow phase velocity versus stimulation current relationship for the lateral canal and posterior canals of the monkey with longitudinal vECAP amplitudes displayed in Figure 2. The slow phase velocity data, which is displayed in Figure 5, was obtained over a longer period than the data displayed in Figure 2. Figure 5 shows that the efficacy of electrical stimulation in response to two stimulation currents actually increases over time, but that it reaches a plateau at the time that the vECAP data collection began, starting at 89 days post implantation. Therefore, both the vECAP amplitudes (in Figure 2) and the measured slow phase velocities at two currents remain relatively stable across the full duration of the longitudinal vECAP study.

2. We have now developed two working prototypes of our bone anchored sensor array and we have tested these in response to rotational stimuli. The prototype is pictured in Figure 6, which displays the device sealed in an epoxy coating for primate experiments. The case is computer fabricated using a polymer extrusion process and then coated with epoxy after the electronics have been inserted. The device has a battery life of 48 hours.

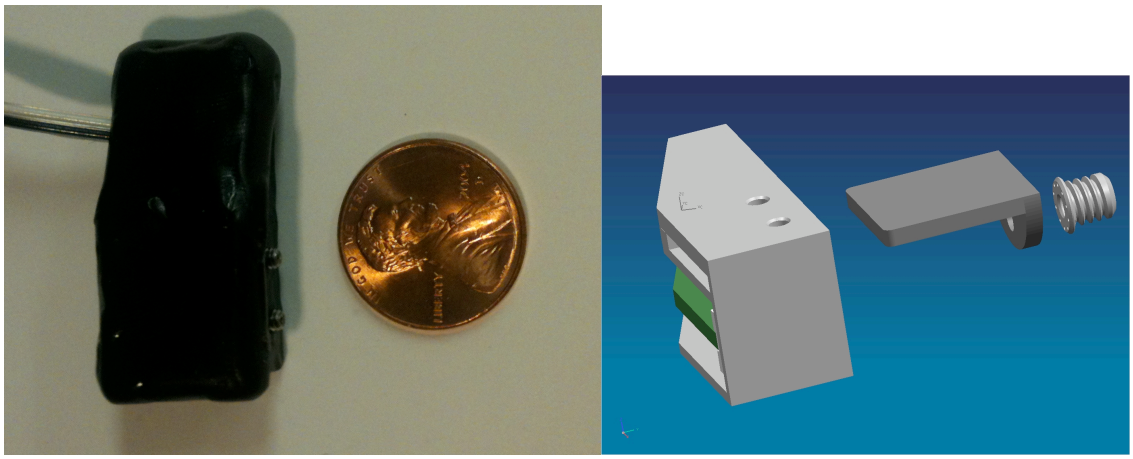


Figure 6. Bone anchored sensor array: The actual device in black is pictured with the lid facing up, rotated 90 deg relative to the schematic drawing. The pressure attachment points adjacent to the bone anchored slot are filled with stops in the actual device, and are shown as open holes in the schematic. The power and audio output cables are pictured to the left of the array processor on the actual device, and are not pictured in the schematic. The attached orientation of the device is displayed in the schematic.

To evaluate the functional prototypes of the device, we rotated the attached device in different planes corresponding to the canal planes of the monkey. The stimuli were sinusoidal rotations at fixed frequencies and velocities. We monitored the output of the device directly by inputting the audio signal produced by the device into the analog

channel inputs of a CED Power 1401 digitizer. The resulting waveforms are displayed in figure 7.

As can be seen in figure 7, the device outputs an audio signal that is the combination of three carriers. These three carriers are modulated in amplitude by rotational velocity in one of three planes corresponding to the planes of the semicircular canals. To generate the lower traces in figure 7, 30 ms of the audio signal was band pass filtered at the frequency of each carrier to show the contribution of that carrier alone. During the recording, the device was being rotated in the plane of the right posterior canal (the LARP plane with respect to the head of the monkey).

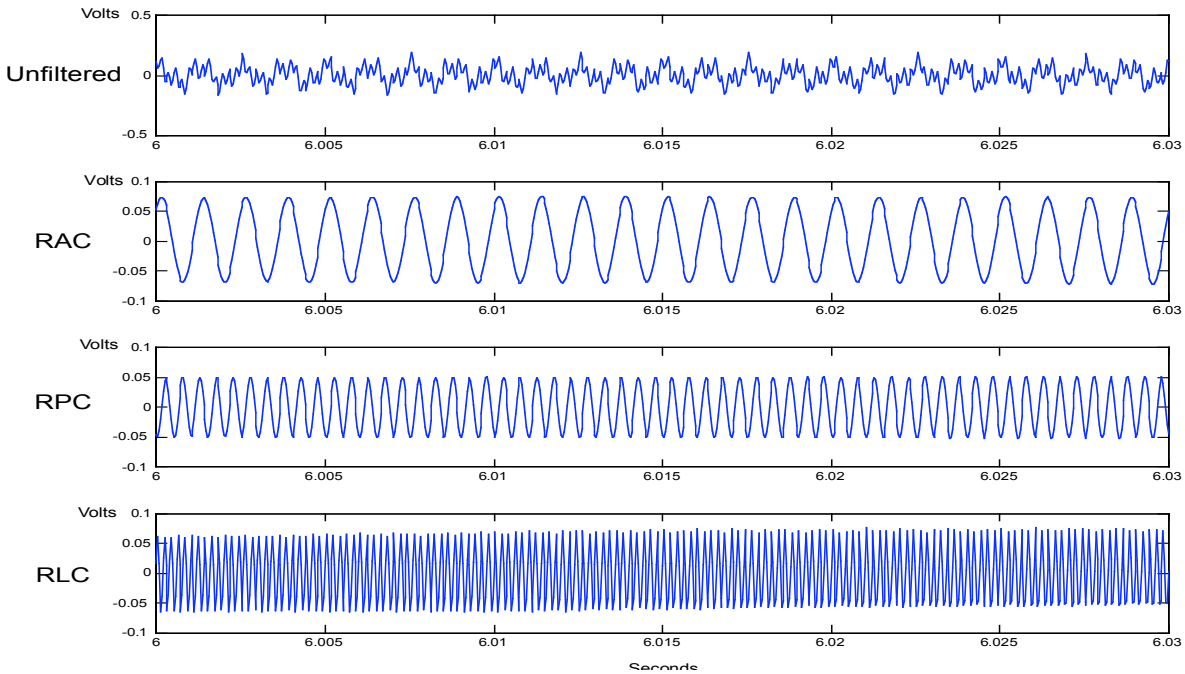
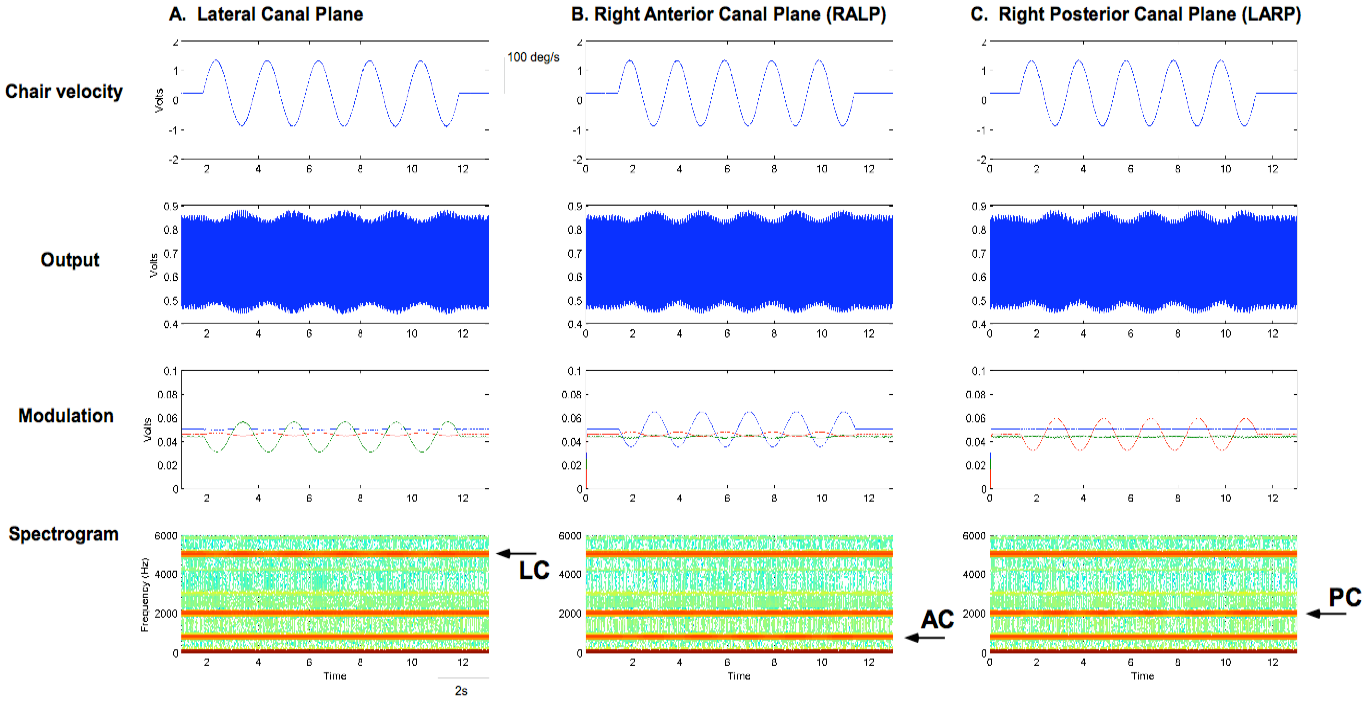


Figure 7. The output of the bone anchored sensor array during sinusoidal rotation at 0.5 Hz in the plane of the right posterior canal. 30 ms of output are displayed. The device produces an unfiltered output as pictured in the upper tracing. This output is the summation of the three amplitude-modulated carriers as displayed in the lower three traces. The amplitude of each carrier is modulated by the rotational velocity in the plane coded by that carrier (RAC, right anterior canal; RPC, right posterior canal; RLC, right lateral canal).

The modulation of each carrier in its plane of rotation is shown below in Figure 8 for several cycles of 100 deg/s peak velocity sinusoidal rotation at 0.5 Hz. The chair rotation was in the plane of the right lateral canal in column A, the right anterior canal in column B and the right posterior canal in column C. The output of the device is displayed, as is the modulation of each carrier frequency. The figure shows that each canal plane rotation

produces primarily modulation in one carrier alone. The small modulations in the out of plane carriers are a result of imperfect alignment of the device relative to the canal planes. The spectrogram shows that the output is represented by three frequency bands, with the lateral canal at the highest frequency, the posterior canal at an intermediate frequency, and the anterior canal at the lowest frequency carrier. The spectrogram also shows a modulation of the color in the appropriate carrier as the amplitude of the carrier is modulated by head velocity in the plane of its canal. Only one carrier is modulated in color for rotation in a single canal plane.



Figuure 8. Modulation of each carrier during sinusoidal rotation of the bone anchored sensor array in the planes of the associated semicircular canals. A, right lateral canal plane; B, right anterior canal plane; C, right posterior canal plane

3. We have performed trans-tympanic gentamicin injections to study the effects of hair cell loss on the longitudinal response of the animals to electrical stimulation of the vestibular end organ. During this quarter a monkey was injected twice in the implanted ear. The animal displayed transient disequilibrium and an asymmetry in the response to rotation. However, there was no change in the response to electrical stimulation of the implanted ear post injection. We are currently following the responses of two animals following gentamicin injection to determine if there are changes in the auditory brainstem response (ABR), vECAP, rotational vestibular response, electrode impedance, or the electrically elicited slow phase eye velocity in response to this intervention.

4. We have submitted one meeting abstract and presented one poster this quarter.

Ling, L.; Bierer, S, Fuchs, A,F., Kaneko, CRS, Newlands, S.D., Nie, K., Nowack, A., Rubinstein, J.T., Phillips, J.O. Transient and sustained components in response to electrical stimulation of vestibular end organ. Society for Neuroscience Annual Meeting, November 15, 2011

James Phillips, Leo Ling, Trey Oxford, Amy Nowack, Chris Kaneko, Albert Fuchs, Steven Bierer, Kaibao Nie, Jay Rubinstein, Control of gaze shifts in monkeys with vestibular prostheses. Neural Control of Movement Annual Meeting Abstract, 2012

Objectives for Quarter 23

1. In the next quarter we will continue recording longitudinal eye movement responses to electrical stimulation at different frequencies and current amplitudes.

2. We will perform a series of longitudinal experiments characterizing the response of two monkeys to electrical stimulation following elimination of vestibular function with unilateral and bilateral transtympanic gentamicin injection.

3. We will continue recording from the brainstem of our existing monkeys.

4. We continue to test the newly developed bone anchored sensor array and processor.

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