Twenty Third Quarterly Progress Report

February 1, 2012 to April 30, 2012
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Neurophysiological Studies of Electrical Stimulation for the Vestibular Nerve

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Challenges:

During Quarter 23 we are maintaining 3 test animals, two of which have experimentally induced vestibular loss. The vestibular lesions were produced intentionally by unilateral and then bilateral injection of gentamicin, starting with the implanted ear in each animal. Both of these animals have two implanted canals. One animal has an intermittent failure of the implanted vestibular prosthesis, and must be monitored carefully during stimulation to confirm that the device is functioning properly. The intermittent failure issue makes longitudinal studies in this animal challenging but possible. The other two animals have fully functioning devices that elicit robust slow phase velocity in multiple canals. Both of these animals have recording chambers and both are being used for single cell recording as well as behavioral studies. The non-lesioned animal has three implanted canals, all of which are still fully functional. The challenge that we face is to rationalize the use of this limited resource to maximize the benefit derived from the remaining months of our study.

Our response to this challenge has been to maintain longitudinal recoding at a regular interval in each of the remaining monkeys, with frequent recording of auditory brainstem responses (ABRs), vestibular evoked compound action potentials (vECAPS), electrode impedances, slow phase eye velocity recording during short duration trains of biphasic pulse electrical stimulation, and frequency and amplitude modulated vestibulo-ocular reflex (VOR) responses using both preprogrammed and head velocity modulated stimulation. Some of these results are displayed below.

Successes:

1. We have had one paper published, one paper accepted for publication, and we submitted two manuscripts and one abstract. We have also given one invited presentation, and presented our work at two international meetings.

Rubinstein JT, Bierer S, Kaneko C, Ling L, Nie K, Oxford T, Newlands S, Santos F, Risi F, Abbas PJ, Phillips JO. Implantation of the semicircular canals with preservation of hearing and rotational sensitivity: a vestibular neurostimulator suitable for clinical research. Otol Neurotol. Accepted for publication.

Bierer SM, Ling L, Nie K, Fuchs AF, Kaneko CR, Oxford T, Nowack AL, Shepherd SJ, Rubinstein JT, Phillips JO. Auditory outcomes following implantation and electrical stimulation of the semicircular canals. Hear Res. Epub 2012 Apr 5.

Justin Golub, Leo Ling, Kaibao Nie, Amy Nowack, Sarah Shepherd, Steven Bierer, Elyse Jameyson, Chris Kaneko, James Phillips, Jay Rubinstein. Prosthetic implantation of the vestibular system: monkey and man. Otology and Neurotology, submitted

James O. Phillips, Sarah J. Shepherd, Amy L. Nowack, Leo Ling, Steven M. Bierer, Chris R.S. Kaneko, Christopher M.T. Phillips, Kaibao Nie, Jay T. Rubinstein, Longitudinal performance of a vestibular prosthesis as assessed by electrically evoked compound action potential recording. I.E.E.E., EMBC, submitted

A. Nowack, CRS. Kaneko, L Ling, K. Nie, J.T. Rubinstein, S. Shepherd, J.O. Phillips Adaptation of VOR eye movements through electrical stimulation. Society for Neuroscience Meeting Abstracts, 2012, submitted

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, 2012

James Phillips, Leo Ling, Albert Fuchs, Chris Kaneko, Steven Bierer, Justin Golub, Shawn Newlands, Kaibao Nie, Amy Nowack, Trey Oxford, Christopher Phillips, Sarah Shepherd, Frank Miles, Jay Rubinstein An implantable prosthesis for vestibular loss in humans. AAS Annual Meeting, 2012

James Phillips, Leo Ling, Albert Fuchs, Chris Kaneko, Steven Bierer, Justin Golub, Shawn Newlands, Kaibao Nie, Amy Nowack, Trey Oxford, Christopher Phillips, Sarah Shepherd, Frank Miles, Jay Rubinstein An implantable prosthesis for vestibular loss. NCRAR Monthly Seminar Series, 2012

2. We have performed experiments with the bone anchored sensor array. We used the device to drive a behind the ear processor which in turn communicated with an implant. We recorded the audio frequency output of the sensor array and the current output of the receiver stimulator across a known resistance with a CED Power 1401 digitizer. The results are displayed in Figures 1-3.

Figure 1 shows that the audio output peak amplitude modulation of a single channel of the sensor array is linearly related to the peak velocity of rotation in the plane of the sensor for that channel. The data shown is for rotation in the plane of the right lateral canal. The 5Khz audio carrier modulation increases in depth with increases in the velocity of the rotation, whereas the 2Khz and 800Hz channels are only modulated very weakly, due to a small alignment error of the head mounted device with respect to the rotational axis of the chair.

Figure 2 shows the amplitude modulation of each channel with respect to the three optimal planes of rotation for the device; i.e., horizontal, right anterior (RALP), and right posterior (LARP). The figure shows that each channel is modulated linearly with head velocity in its optimal plane of rotation. The 800 Hz carrier responds to right anterior canal plane (Ant) rotation, the 2KHz carrier responds to right posterior canal plane (Pos) rotation, and the 5Khz carrier responds to horizontal canal (Horiz) rotation. While the slopes of the modulation versus velocity relationships are fully programable and in this case are not equivalent across canals, each relationship is linear.

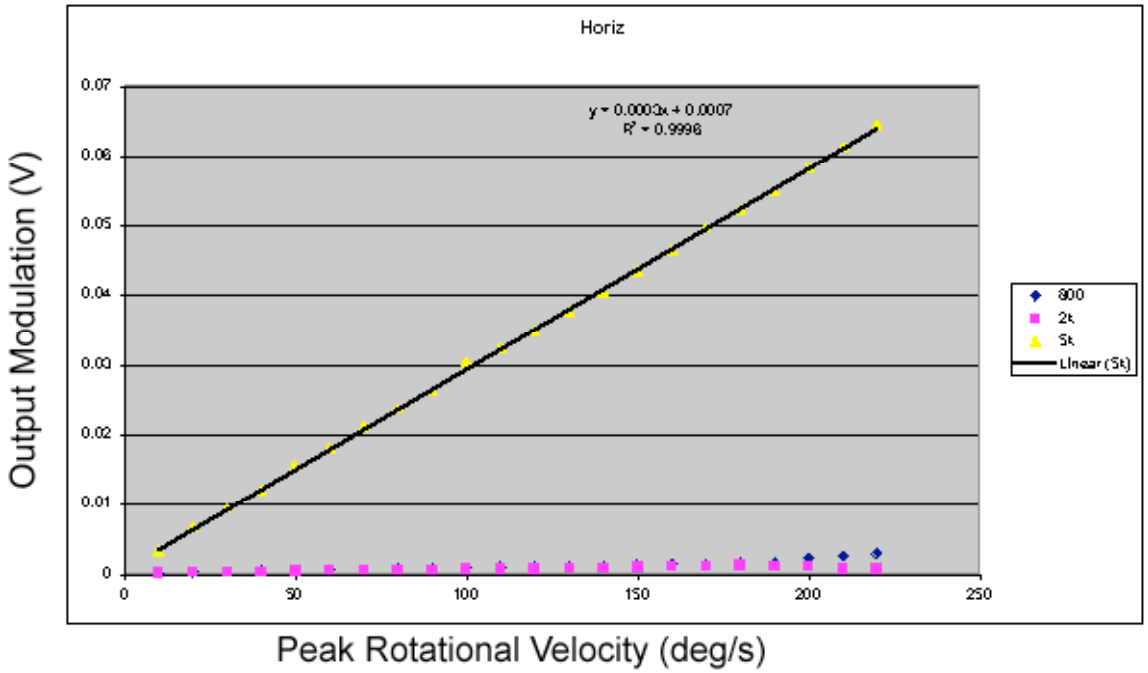

Figure 1. Amplitude modulation versus peak rotational velocity for each of the carrier frequencies in the audio output of the bone anchored sensory array during head rotation in the lateral canal plane, corresponding to the 5Khz carrier.

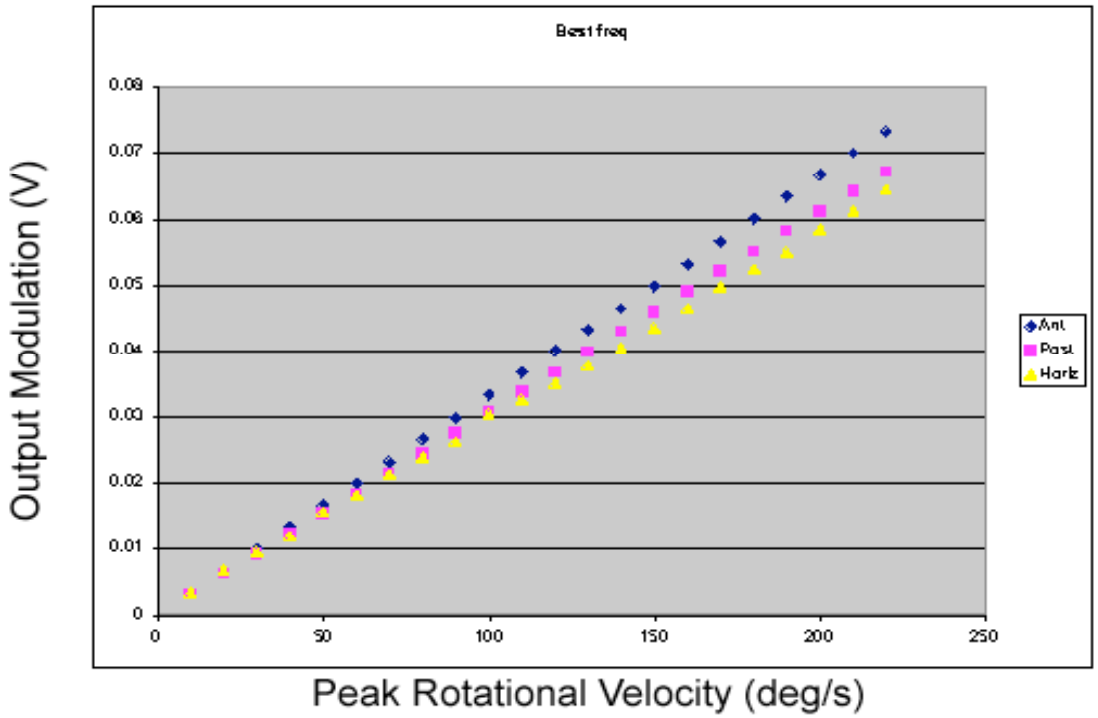

Figure 2. Amplitude modulation versus peak rotational velocity for each of the carrier frequencies in the audio output of the bone anchored sensory array during head rotation in the optimal plane for each carrier.

Figure 3 shows the output of the receiver stimulator in response to chair rotation in the horizontal plane. Figure 3A shows that the device produces a current modulated output of constant frequency pulses at the most distal right lateral canal electrode site (E6) during sinusoidal chair rotation at 0.5 Hz. Figure 3B shows an expanded view of the constant frequency biphasic pulses that are modulated in Figure 3A.

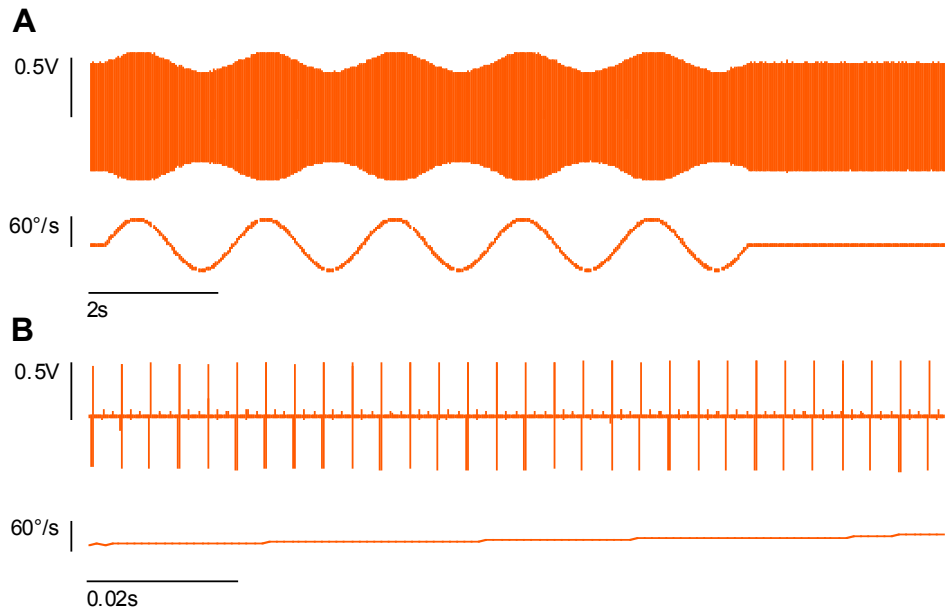

Figure 3. Response of the bone anchored sensor array to sinusoidal rotation in the plane of the right lateral canal. A: Current modulation of one stimulating electrode (channel E6, upper trace) during rotation of the bone anchored vestibular processor in the lateral canal plane (chair tachometer, lower trace). B: Detail showing individual stimulating pulses (channel E6, upper trace) and the chair tachometer output (lower trace) with an expanded time scale.

These data demonstrate that the combined bone anchored sensor array, behind the ear processor, and receiver stimulator respond appropriately to the rotational stimuli when programmed to produce real time head velocity contingent amplitude modulated biphasic pulses in individual channels.

3. In Quarter 23, we examined the relationship between otolith input and observed slow phase eye velocity resulting from changes in head orientation. A single monkey was subjected to en-bloc static tilt in pitch and roll. The stimulation parameters remained constant for all orientations, but the results revealed that slow eye velocity changed with tilt orientation. Data for the pitch tilt experiments are shown in Figure 4.. In this experiment, a single monkey was tilted 45° in the pitch axis in a rotary chair, resulting in three en-bloc orientations; upright, nose down, and nose up. Once the animal was placed in one of the static orientations, a train of biphasic pulses at a frequency of 300 pps with a 100µs pulse width was applied in the dark for two seconds in one of the three semicircular canals in the right ear. Five consecutive stimulations were applied, each separated by an eight-second gap. Four sets of stimulations were performed, resulting in

20 trials for each of the orientation-canal pairs. The current amplitudes for the anterior, posterior and lateral canals were 75, 200 and 150μA, respectively.

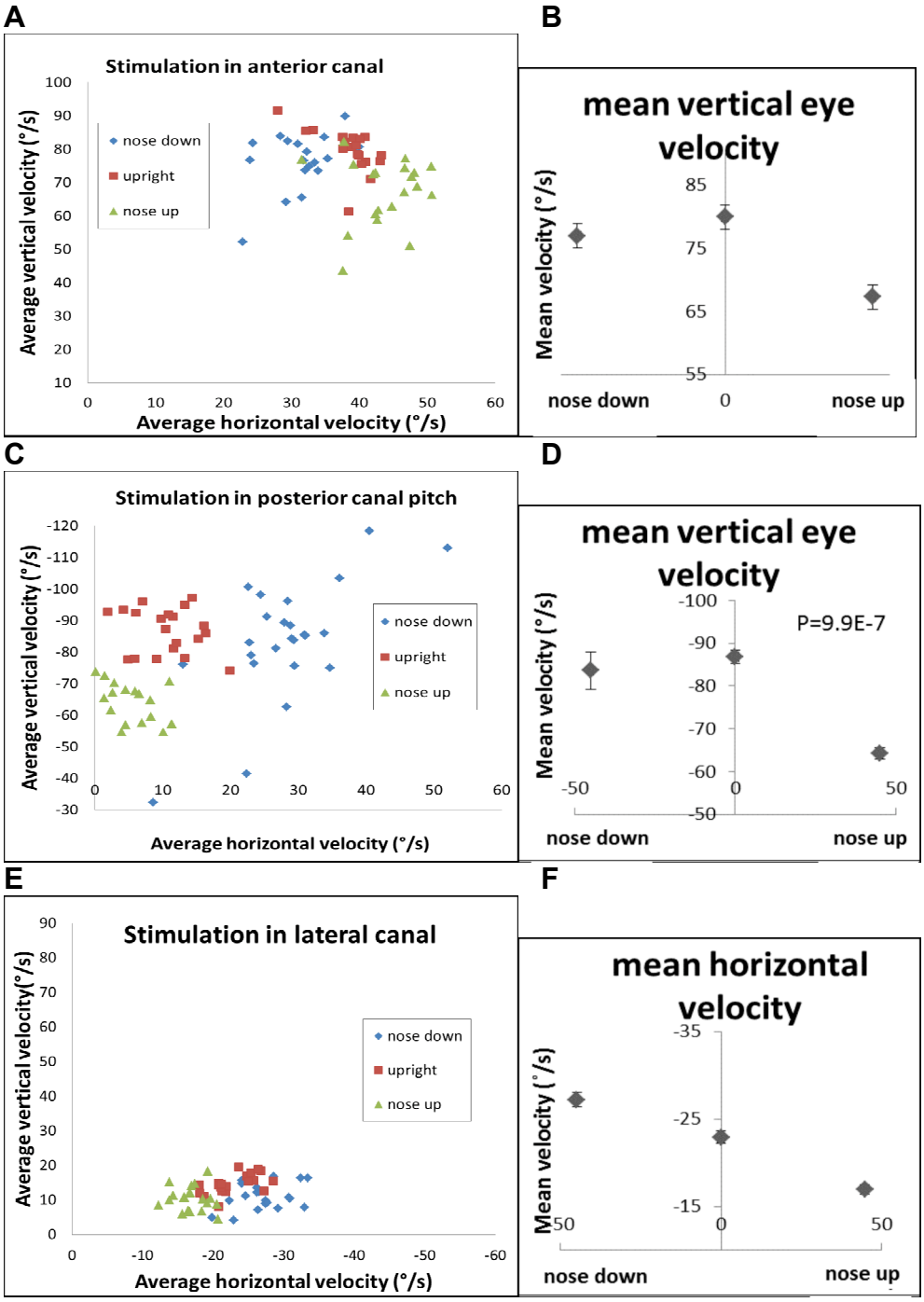

Figure 4. Slow phase eye velocities elicited by electrical stimulation of three canals in a single monkey during pitch tilt. A, C, E, vertical versus horizontal slow phase velocity elicited by electrical stimulation of the anterior, posterior and lateral canals, respectively. B, D, F, mean and standard deviation of the primary eye velocity component resulting from the electrical stimulation.

The data of Figure 4 indicate that pitch rotation results in a significant change in eye velocity elicited by the same electrical stimulation parameters in different head orientations with respect to gravity. Vertical and horizontal slow phase eye velocities are affected by the tilt orientation, but the primary component velocities all decrease in nose up pitch.

For roll tilt a similar result was obtained in that roll tilt produced consistent changes in slow phase eye velocities. However, the vertical velocity changes reversed with anterior and posterior canal stimulation, with roll right orientation producing decreased velocities with anterior canal stimulation and increased velocities with posterior canal stimulation. These results are interesting and suggest an interaction between the otolith organ afferent input and the canal specific electrical stimulation input. The importance of these interactions is that the device is designed to be used in patients with partially preserved vestibular function, and the summation of natural and electrical stimulation seen here parallels our previous observations with natural rotational and electrical stimulation .

4. In Quarter 23 we conducted further experiments examining the longitudinal responses of two monkeys that had received transtympanic gentamicin injection to electrical stimulation with the implanted vestibular prosthesis. Both monkeys received serial transtympanic injections of gentamicin during the experiments, first in the implanted ear and then in the unimplanted ear. We studied a number of parameters to determine if the injections were effective in eliminating the natural vestibulo-ocular reflex (VOR) or hearing, and if there were changes the efficacy of the electrical stimulation with the device. This is a critical issue since many of our experiments have been conducted with animals that are implanted but otherwise intact, but the prosthesis is intended for patients with fluctuating or significantly reduced vestibular function.

Unilateral injections in the implanted ear had different effects depending on whether there was residual hearing in that ear at the outset of the experiments. Hearing was minimally affected by the gentamicin administration in one monkey (monkey M2) with normal hearing before administration. The click evoked auditory brainstem response changed ≤15 dB for this animal through the full series of transtympanic injections. The other monkey (Monkey M1) was profoundly deaf in the implanted ear prior to gentamicin administration. Figure 5 shows that monkey M2, with intact hearing, showed a small but significant loss of sinusoidal VOR gain with unilateral injection of gentamicin, whereas monkey M1, with profound hearing loss in the implanted ear, did not. The gain changes in monkey M2 were most notably present at the lowest rotational frequency of 0.01 Hz. Finally, both animals showed a dramatic decrease in VOR gain with injection of gentamicin in the unimplanted ear. Therefore, bilateral injection produced the desired reduction in vestibular function.

As expected, there were no changes in the electrode impedances in either monkey as a result of transympanic gentamicin injection. This can be seen in the data of Figure 6, which displays representative longitudinal impedance measures in the lateral canal of monkey M2. Although the impedance measurements differ with the different return

configurations, there is no change in the impedance in any configuration over the duration of the injection experiments.

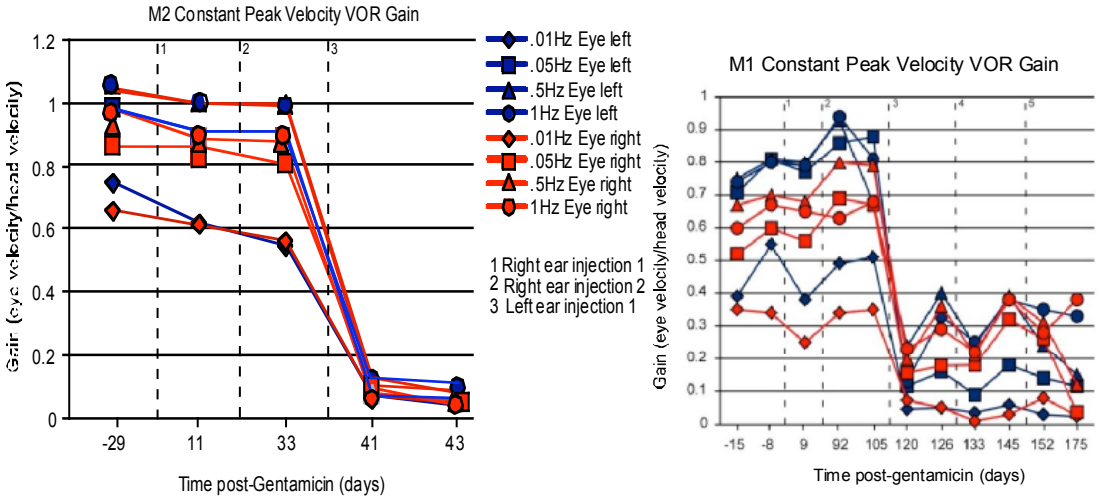

Figure 5. Longitudinal VOR gain in response to horizontal sinusoidal rotation at different frequencies across three trans-tympanic injections of gentamicin in a rhesus monkey. The gain of the response is plotted versus the days post injection 1. The first two injections were in the right (implanted) ear, and the third injection was in the left (unimplanted) ear. Inset: Comparable data for a second monkey with unilateral hearing loss in the implanted ear. In this monkey, injections 1 and 2 were in the implanted ear, and injections 3-5 were in the left ear or bilateral.

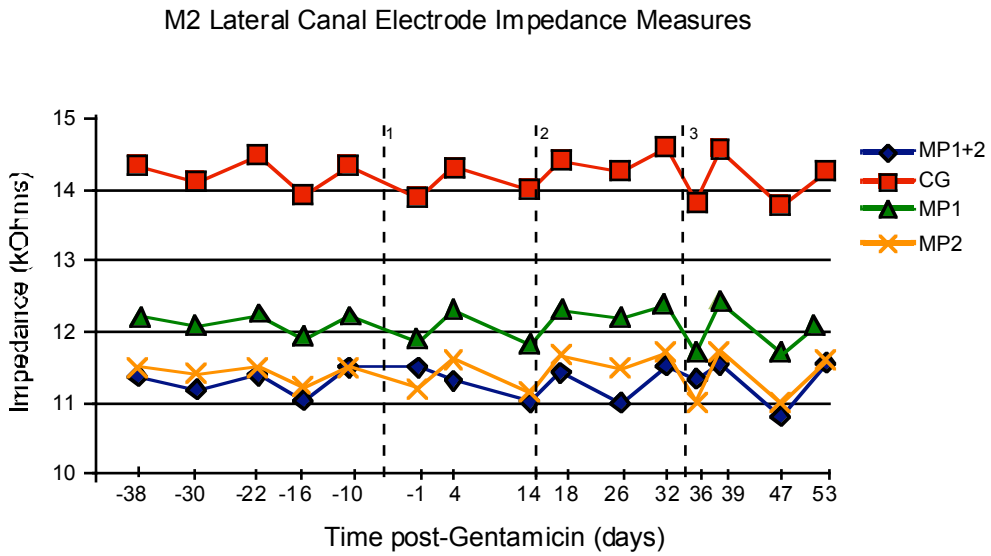

Figure 6. Longitudinal changes in electrode impedance measured in the most distal lateral canal electrode in a single rhesus monkey. Several return configurations are displayed.

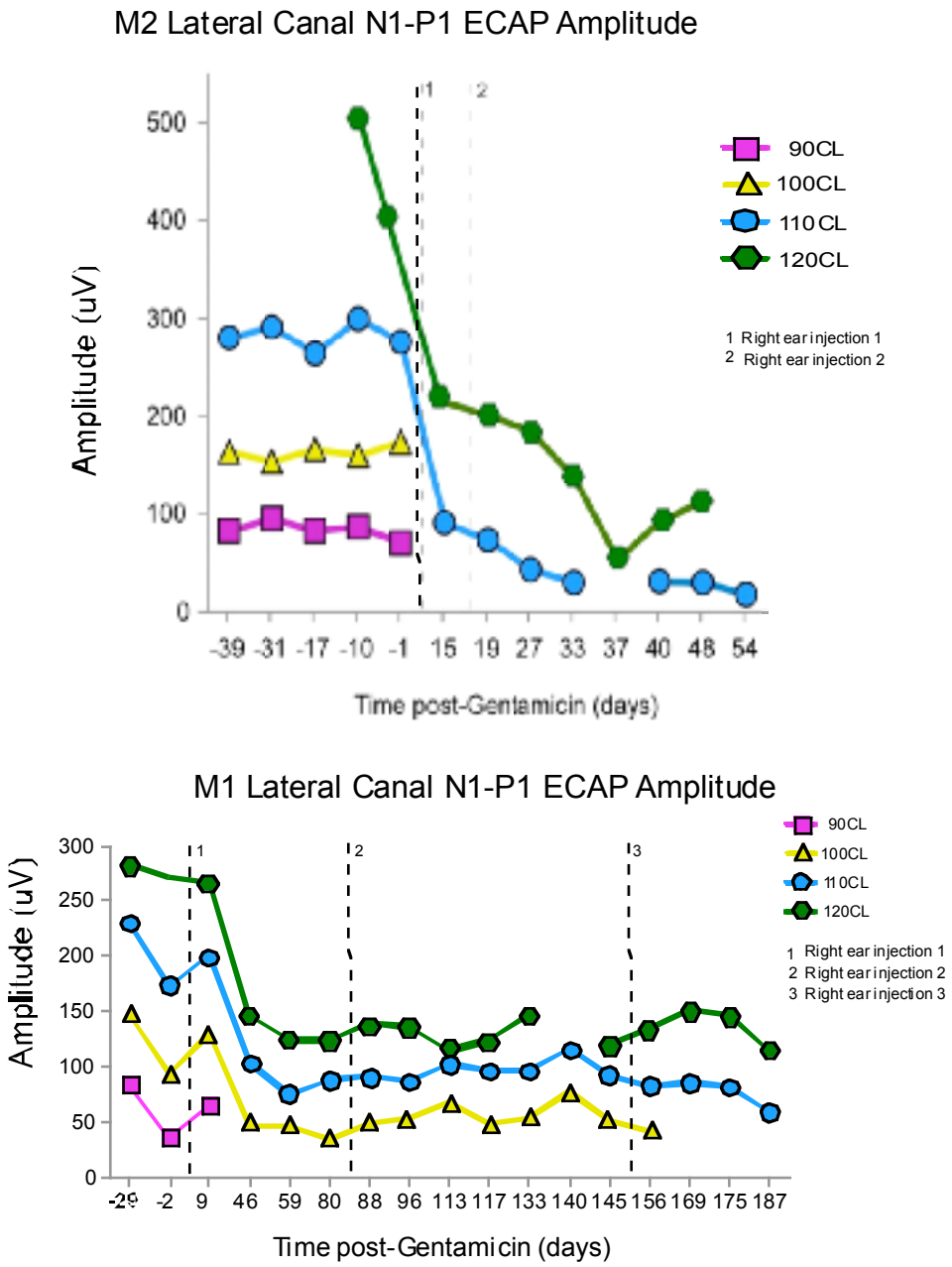

Figure 7. Longitudinal vECAP recording from two monkeys following injection of gentamicin in the implanted ear. Currents are reported in clinical level in both animals.

Surprisingly, there was a significant decrease in the vECAP response with transtympanic injection of gentamicin. This can be seen in the representative traces shown in Figure 7, which displays the longitudinal vECAP data from both monkeys. Figure 7 shows that both animals displayed both a decrease in vECAP amplitude for a given current, and an increase in vECAP threshold overall in response to intra-tympanic gentamicin injection. This was a somewhat surprising result.

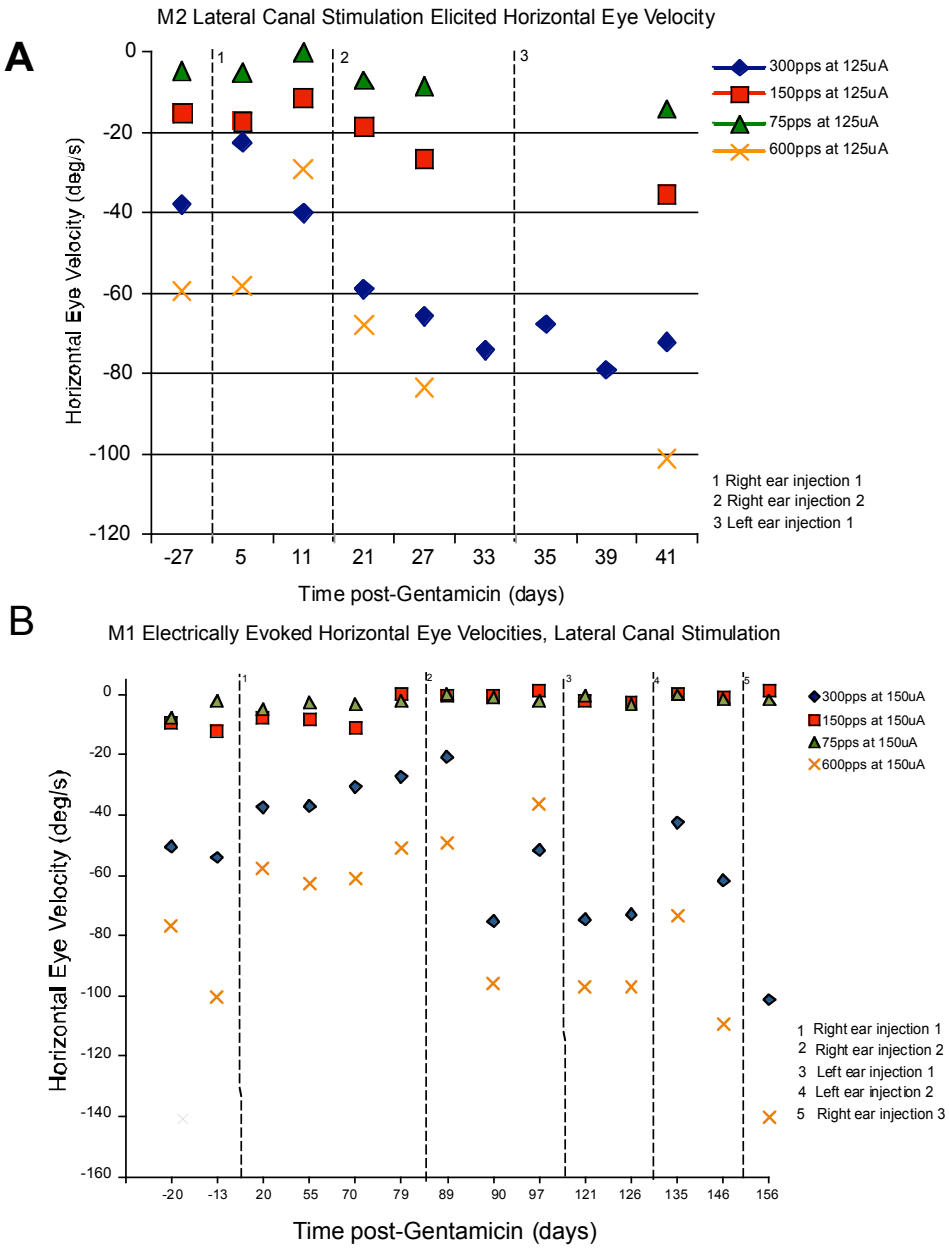

Figure 8. Horizontal slow phase velocity elicited by a 2s train of biphasic pulse stimuli versus number of days post first transtympanic gentamicin administration. Different pulse frequencies are represented by different symbols. Vertical lines denote the timing of gentamicin administration in the implanted ear.

There are several potential explanations for this. One possibility is that that the galvanic sensitivity of the afferent fibers to electrical stimulation with the implanted device is significantly influenced by the resting rate of the fibers. This in turn is influenced by the synaptic activity in the end organ, and the number of surviving hair cells. Curiously however, there was little change in the vestibular response of monkey M1 following unilateral injections, but a dramatic change in the vECAP. A second possibility is that the gentamicin directly affects the afferent fibers, reducing their sensitivity to stimulation or their survival. Such a process could affect the response to electrical stimulation

without changing the sensitivity to rotational stimulation if, in monkey M1, the vestibular hair cells were already lost in the non-hearing ear. Although the mechanism remains uncertain, these data suggest that transtympanic gentamicin injection reduced the compound action potential produced by electrical stimulation, and presumably the number of afferent fibers driven by the electrical stimulus.

Since the electrically elicited afferent input was reduced by injection of gentamicin, we assumed that the behavioral response to electrical stimulation would be proportionately reduced. The data of Figure 8 show that the opposite effect actually occurred. In monkey M2, the initial administration of gentamicin produced a transient reduction in electrically elicited slow phase velocity. The timing of this reduction was inconsistent for the different frequencies of biphasic pulse stimulation. After the second administration, however, there was a consistent increase in the leftward (negative) slow phase velocities produced by electrical stimulation. This was consistent with timing of the initial decrease in natural VOR rotational gain in this animal, as seen in Figure 5. This process continued, so that after bilateral injection there was a both a dramatic decrease in natural rotational VOR gain and an equally dramatic increase in the gain and efficacy of electrical stimulation, with low frequencies of stimulation producing higher velocities of slow phase eye movement, and increases in stimulation frequency producing proportionally greater increases in slow phase velocity.

Figure 8 also shows a similar result in monkey M1 with the exception that there was not an initial decrease in the electrically elicited slow phase velocity after the first gentamicin administration. Rather, in this monkey, there was a consistent increase in slow phase velocity over time with serial gentamicin administration, corresponding to a decrease in natural VOR gain as seen in Figure 5. This animal was deaf in the implanted ear prior to gentamicin administration, and therefore may have sustained a loss of hair cells prior to gentamicin administration, thereby eliminating the transient initial decrease in slow phase velocity.

We hypothesize that the gentamicin results reveal a process of peripheral and central changes in vestibular processing of the electrical stimulation. The gentamicin appears to be effective in reducing the natural VOR, presumably largely by eliminating vestibular hair cells. The small reduction in VOR gain with unilateral administration of gentamicin in the implanted ear occurred only in the animal with hearing in that ear, consistent with the idea that the implantation preserved both hearing and at least some vestibular function. The animal with no hearing and reduced vestibular responses in the implanted ear before injection, showed no such reduction in gain. Bilateral injection, reduced VOR gain in both animals. Gentamicin injection did not change electrode impedances, suggesting that the electrodes were still delivering comparable currents post injection. Gentamicin injection did consistently decrease vECAP response amplitudes and increases vECAP thresholds. This suggests that the implanted device drove fewer afferents following the loss of hair cells, or perhaps due to direct effects of gentamicin on vestibular afferents. Despite this reduction in the total afferent response to electrical stimulation, the behavioral response increased over time so that the slow phase velocity that was produced by the stimulation was much greater after the gentamicin

administration and subsequent loss of natural VOR. This result was presumably due to central adaptation. The nervous system was increasing the gain of the VOR in response to a loss of peripheral input, and the behavioral response to electrical stimulation was more robust because there was a disproportionate loss of hair cells as opposed to the decrease in afferent galvanic sensitivity. It remains to be seen how long these changes will persist in the gentamicin lesioned monkey.

5. In quarter 23 we completed our experiments on the behavioral effect of electrical stimulation of vestibular afferents during natural gaze shifts. We had previously shown in Quarter 17 that there were changes in eye velocity associated with brief electrical stimulation of the vestibular end organ during active gaze shifts. These changes were consistent with an on going utilization of vestibular head velocity information during a gaze shift. In Quarter 23, we completed a parametric study exploiting this phenomenon to better understand the mechanism of head unrestrained gaze shifts, and presented the results at an international meeting. In two rhesus monkeys, we perturbed horizontal gaze shifts with brief constant frequency electrical stimulation of the right lateral canal. The electrical stimulation elicited a change in eye (eye in head), gaze (eye in space), and head velocity. An example of these results is displayed in Figure 9.

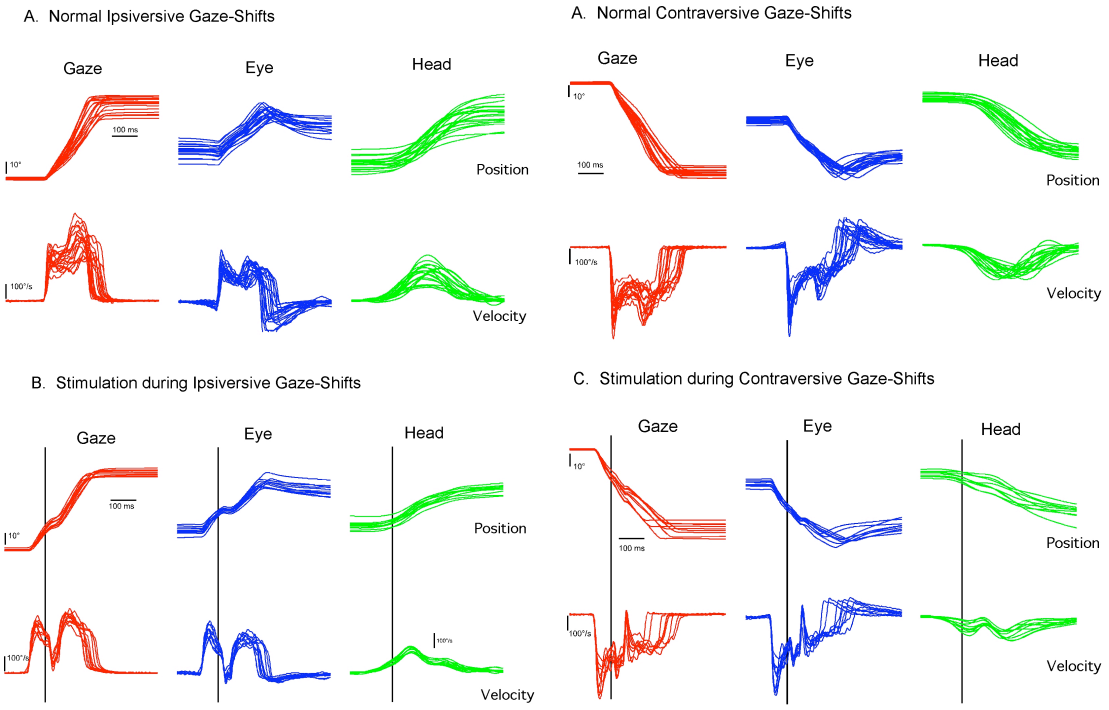

Figure 9. Eye, head and gaze position and velocity during natural head unrestrained gaze shifts, and gaze shifts in which there was electrical stimulation of the right lateral semicircular canal at 165 μA. Lines denote onset of a 50 ms biphasic pulse train. A. Natural gaze shifts. B. Perturbed ipsiversive gaze shifts. C. Perturbed contraversive gaze shifts.

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Figure 9 shows that for ipsiversive gaze shifts toward the implanted ear there was a decrease in eye and gaze velocity, but an increase in head velocity. This is a startling

finding, consistent with some recent models of gaze movement control, but inconsistent with many others including models from our laboratory. Contraversive gaze shifts produced the opposite effect, producing an increase in gaze and eye velocity but a decrease in head velocity. The effects of stimulation were immediately compensated for by the nervous system. Decelerations in gaze and eye with electrical stimulation during ipsiversive gaze shifts, produced an immediate acceleration of gaze and eye after the end electrical stimulation. Accelerations in gaze and eye velocity with electrical stimulation during contraversive gaze shifts produced a compensatory deceleration after the end of stimulation. The head showed comparable compensatory changes.

To be certain that these changes were indeed due to the vestibular input and not simply an alerting stimulus from the electrical stimulation, we systematically varied the stimulation current to see whether we could parametrically control the perturbation of the eye and gaze movement. Figure 10 shows the result of such an experiment.

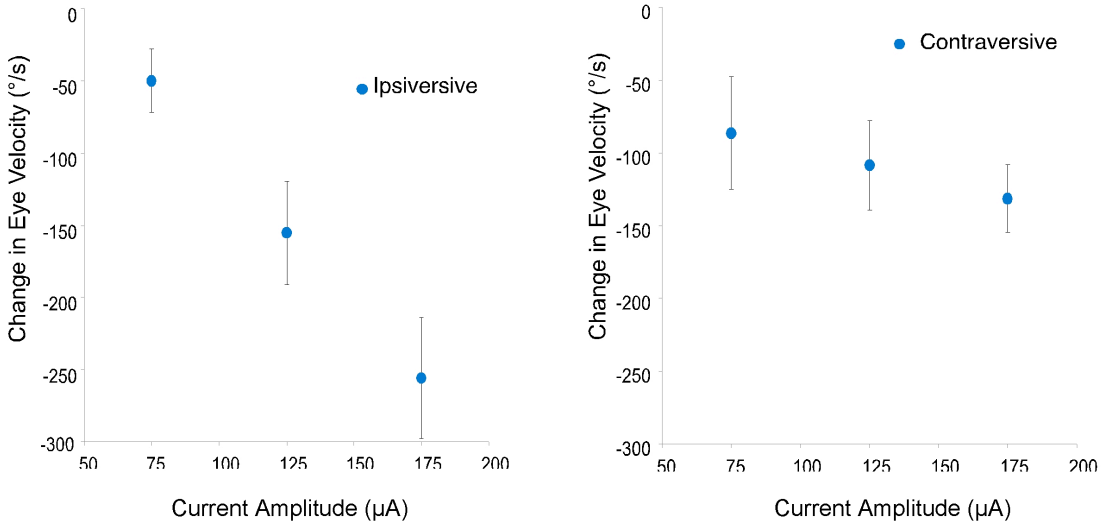

Figure 10. Change in eye velocity during ipsiversive and contraversive gaze shifts with biphasic pulse electrical stimulation of different current amplitudes.

Figure 10 shows that electrical stimulation during both ipsiversive and contraversive movements produces changes in eye velocity that scale with stimulation current. This parametric relationship suggests that the changes in velocity are a direct result of the activation of vestibular afferents, which are recruited in increasing numbers with increasing stimulation current. However, there is a significant difference between the velocity changes produced by ipsiversive and contraversive stimulation. Presumably, this is because during contraversive stimulation the saccadic burst generator and motoneurons are discharging at very high rates and are unable to respond fully to increased drive from the electrically elicited vestibular input; the drive is essentially saturated. On the other hand, during ipsiversive movement the electrically elicited vestibular input reduces the drive to the motoneurons, which is still possible under this scenario.

As we suggested from a single example in Quarter 17, the timing of stimulation also plays an important role in the effects of the electrical stimulation of the vestibular end

organ during gaze shifts. Figure 11 shows the change in eye velocity during gaze shifts elicited by a 50 ms train of biphasic pulses at a single stimulation current but presented at different times during the gaze shift.

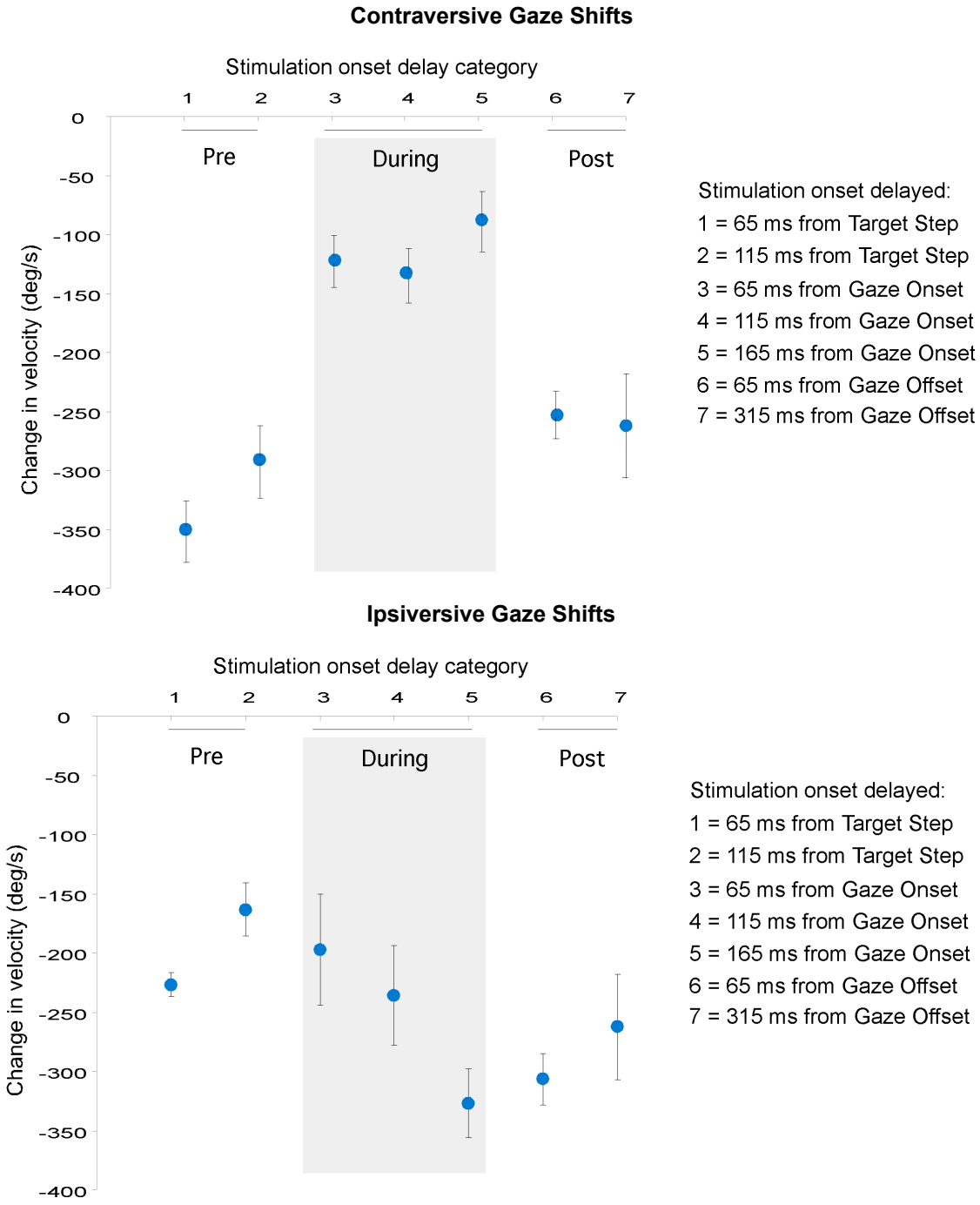

Figure 11. Change in eye velocity produced by during gaze shifts by 50 ms electrical stimulation (175 µA, 100 µs per phase, 8 µs gap) presented at different times relative to the beginning and end of the gaze shift.

The results in Figure 11 show that the effects of stimulation change during the execution of a gaze shift. For contraversive gaze shifts there is a reduction in the stimulation-induced change in gaze velocity during the gaze shift (shaded). For ipsiversive gaze shifts there is a decrease and then a progressive increase in the stimulation induced change in gaze velocity as the gaze shift progresses. These changes suggest that the vestibular information from an individual canal is modified centrally during gaze shifts in the plane of that canal, but directed either toward or away from the canal. It was not possible before these experiments to unambiguously establish these relationships through mechanical perturbation or neural recording studies.

Finally, we examined the overall effect of electrical stimulation on the amplitude of gaze shifts. One might assume that the false head velocity information and the observed eye and gaze velocity changes associated with the electrical stimulation of the vestibular end organ would change the overall amplitude of the observed gaze shift. Most models of gaze control, including our own, explicitly predicted this outcome. However, this was not the case.

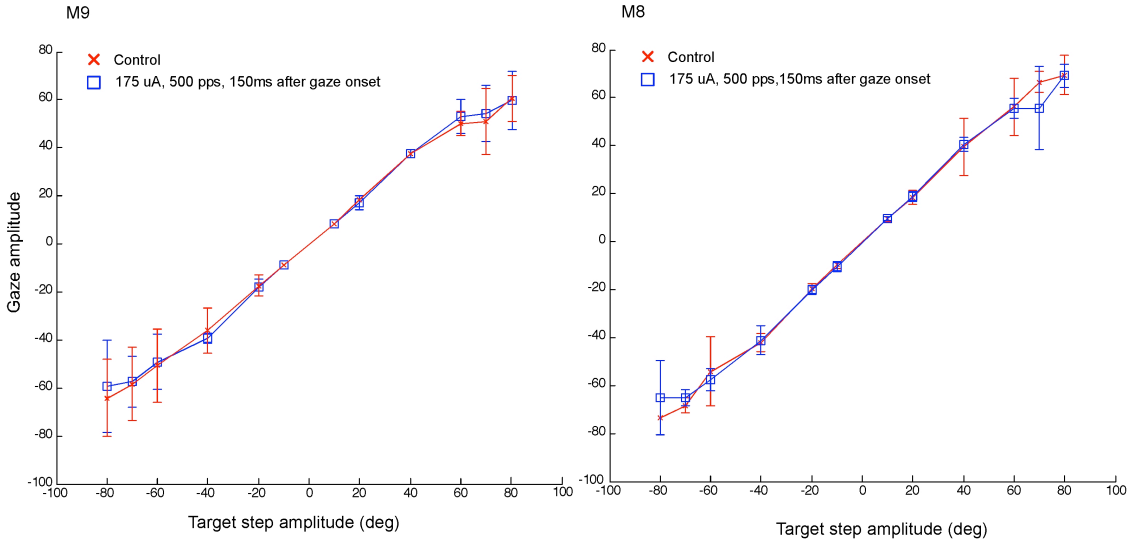

Figure 12. Gaze amplitude versus target step amplitude for natural gaze shifts (control) and gaze shifts perturbed by 50 ms electrical stimulation (175 µA, 100 µs per phase, 8 µs gap). Data from 2 monkeys is displayed. Error bars indicate 1 sd.

The data of Figure 12 demonstrates that for both animals and for both ipsiversive (rightward) and contraversive (leftward) gaze shifts there was no change in the overall amplitude of the gaze shift with electrical stimulation, despite the significant changes in the trajectory of the movements as demonstrated earlier. This stunning result suggests that there are multiple sources of information available to the gaze control system to control the amplitude of gaze shifts. In this case the information is not visual, because the target was extinguished as soon as the gaze shift was initiated.

Objectives for Quarter 24

1. In the next quarter we will continue recording longitudinal eye movement responses to electrical stimulation at different frequencies and current amplitudes in our three animals. In addition, we will record ABR, vECAP, and impedance data at regular intervals to complete our longitudinal observations.

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

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

4. We will perform adaptation experiments to characterize the time course and magnitude of changes in the response to electrical stimulation during and after prolonged trains of electrical stimulation in the light and in the dark.

5. We will perform experiments characterizing the eye position effects on the slow phase velocity of electrical stimulation. Specifically, we will investigate whether prolonged stimulation produces different eye position effects than short stimulation. We hypothesize that prolonged stimulation will produce little if any eye position effect, unlike the 50 and 100 ms stimulation trains that we employed previously.

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