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Longitudinal performance of a vestibular prosthesis as assessed by electrically evoked compound action potential recording.*

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***Abstract*— Electrical stimulation of the vestibular end organ with a vestibular prosthesis may provide an effective treatment for vestibular loss if the stimulation remains effective over a significant period of time after implantation of the device. To assess efficacy of electrical stimulation in an animal model, we implanted 3 rhesus monkeys with a vestibular prosthesis based on a cochlear implant. We then recorded vestibular electrically evoked compound action potentials (vECAPs) longitudinally in each of the implanted canals to see how the amplitude of the response changed over time. The results suggest that vECAPs, and therefore electrical activation of vestibular afferent fibers, can remain largely stable over time following implantation.**

I. Introduction

Vestibular neural prostheses are being developed to treat a range of vestibular pathology from Meniere's disease to bilateral vestibular areflexia. Current devices [1]-[4] electrically activate afferent fibers within the ampullae of individual semicircular canals using biphasic pulse trains that can be modulated in amplitude or frequency by head velocity or acceleration signals. In this way, the device can theoretically bypass the transduction mechanism provided by hair cells of the inner ear when those cells are compromised by injury or disease. For this strategy to succeed, the afferent fibers that carry action potentials from the ampullae to the brain must remain intact and galvanically sensitive, and the implanted electrode array and neural stimulator must remain fully functional.

One measure of functional efficacy for electrical stimulation is the behavioral response that is elicited when vestibular afferents are activated. Nystagmus that is created by electrical stimulation with constant frequency and constant current amplitude trains of stimuli can be used as a measure of the state of an electrically elicited vestibulo-ocular reflex (VOR). Modulated eye velocity resulting from modulation of the frequency or current of electrical stimulation modulated by head velocity, or modulated in the absence of actual head rotation, would provide a similar measure of overall VOR function [5]-[8]. However, these behavioral responses may undergo adaptive change, because the VOR is capable of remarkable adaptive plasticity. Therefore, a progressively weakening input signal from a vestibular prosthesis could produce a response that failed to change substantially over the limited time, perhaps up to a year or two, available for long-term animal experiments. Behavioral measures of VOR could produce an overestimate of the efficacy of electrical stimulation, or an underestimate of changes in the integrity of the electrode arrays or changes in the innervation of the ampullae.

Clearly, a direct measure of effective electrical stimulation of the vestibular afferent fibers at the end organ would provide useful information about the longitudinal integrity of electrical stimulation. Ideally this measure should be minimally invasive, and should produce a reliable estimate of the aggregate neural response to a specific electrical stimulus. In this study, we have used the vestibular electrically evoked compound action potential (vECAP) produced in response to a specific stimulus, to quantitatively assess longitudinal changes in the efficacy of electrical stimulation of afferent fibers in three rhesus monkeys implanted with a vestibular prosthesis.

II. Procedure

A. Vestibular implant design

We constructed a vestibular implant based on the Cochlear Nucleus Freedom cochlear implant. The implanted device could be controlled by either a standard clinical processor or a NIC-2 research processor. The device design has been described previously [4],[9]. It is important to note that this device is constructed with a fine 2.5 mm tip which is inserted into the perilymphatic space adjacent to the ampulla of each implanted canal (the posterior and lateral canals of two monkeys, and all three canals of a third monkey).

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B. Testing, Implantation, and Recording

The animal experiments fully complied with the recommendations of the Society for Neuroscience and the National Research Council (1997, 2003). All animal work exceeded the minimum requirements recommended by the Association for Assessment and Accreditation of Laboratory Animal Care International (AALAC) and the Institute for Laboratory Animal Research (ILAR). All procedures were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Washington.

Monkeys were implanted with the vestibular stimulator device during sterile surgery using a hybrid implantation surgical technique [9]. The monkeys were also implanted with scleral search coils for eye movement recording, and stabilization lugs to maintain head alignment [10]. The precise placement of the electrode array in each semicircular canal was performed with intra-operative recording of vestibular electrically evoked compound action potentials (vECAPs) [11]. One week after implantation of the electrodes, additional vECAP recording was performed, and trains of electrical stimuli were used to characterize the eye movements elicited by electrical stimulation of each canal. A standard stimulus, approximately 300 pps monopolar biphasic pulse train, 100 uA current amplitude, 100 us per phase and 8 us gap with a train duration of 2 seconds was used multiple times per week over the duration of behavioral and neural recording to longitudinally characterize the nystagmus response to short stimulus trains [4],[12]. These experiments suggested that the nystagmus was sustained over time. In addition, a number of experiments were performed in each animal that included awake behavioral recording of eye and head movements in response to modulated and unmodulated electrical stimulation of varying duration, rotational stimulation in multiple canal planes with and without electrical stimulation, optokinetic stimulation, sedated ABR recording, and in one animal, brainstem neural recording with tungsten microelectrodes.

In the experiments described here, we performed longitudinal recording of vECAPs in each animal using consistent stimulation parameters across time in each of the implanted canals. The procedure for vECAP recording has been described previously [11]. Briefly, vECAPs were recorded using Neural Response Telemetry (NRT) with Nucleus Freedom Custom Sound EP 1.3™ software (Cochlear Limited). The implanted canal was typically stimulated using monopolar stimulation between the most distal electrode on an implanted array and a remote ground. The resulting compound action potential was recorded from an adjacent electrode, or from an electrode in an adjacent canal, based on the results of initial stimulation trials. A forward masking paradigm was used to reduce stimulation artifact. Stimulation currents of varying intensity were used to elicit an increasing compound action potential. The amplitude of the N1-P1 response at each stimulation current intensity was quantified to determine the response of presumed vestibular afferents to electrical stimulation.

III. Results

vECAP responses were recorded in three monkeys over the course of up to 600 days. The stimulation parameters were optimized for each canal stimulated so as to elicit a robust vECAP response; i.e., stimulation elicited a large N1-P1 amplitude response that increased in amplitude with increasing stimulation current with a minimal current threshold.

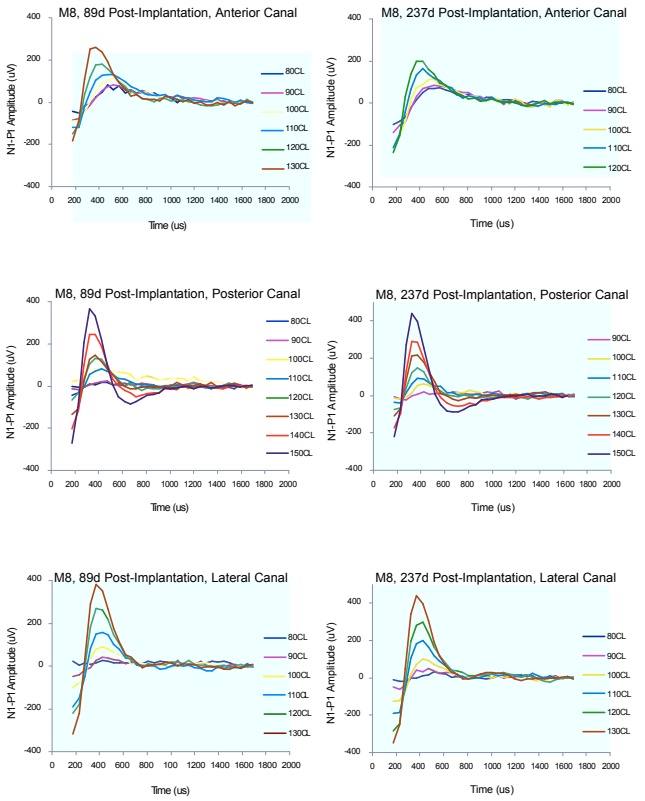

Fig. 1. vECAP waveforms at multiple current intensities from three canals in monkey M8 at two time points. Anterior canal recordings are from stimulation of the most distal electrode in the anterior canal, and recording in the next most distal electrode in the same canal. Posterior and lateral canal 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 $^{(CL/255)}$. Current increments in clinical level are commonly used to achieve equal percentage increases per step.

In all animals, the vECAP response displayed the same waveform shapes and scaling of amplitude with stimulation current throughout the longitudinal trial. Figure 1 displays the vECAP waveforms resulting from stimulation of the three canals in monkey M8 at the start of the longitudinal recording sessions, 89 days post surgery, and late in the longitudinal recording sessions, 237 days post surgery. For each canal, the vECAP amplitude and waveform at every current was quite similar at both time points.

To study longitudinal changes in vECAP amplitude, we measured the N1-P1 response from the waveforms shown in Figure 1, and for all of the other days in the longitudinal trial. The results across days post surgery are displayed in Figure 2.

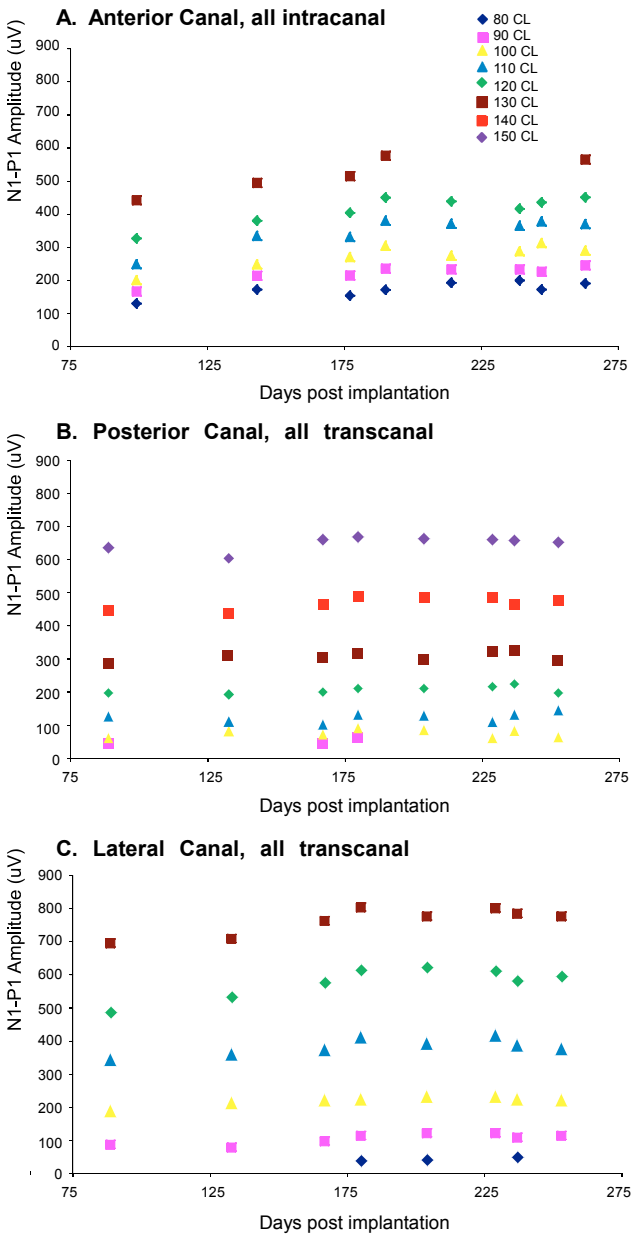

Fig. 2. Longitudinally recorded vECAP amplitudes at multiple current intensities from three canals in monkey M8. Anterior canal recordings are from stimulation of the most distal electrode in the anterior canal, and recording in the next most distal electrode in the same canal. Posterior and lateral 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).

Figure 2 shows the result of vECAP recording for 148 days in monkey M8. When longitudinal recording experiments were initiated, monkey M8 had already been implanted with a vestibular prosthesis for 89 days. It is clear from the figure that the vECAP was stable in all canals in monkey M8 during the duration of the recording experiment. The threshold for eliciting a vECAP remained stable in one canal, went down by 10 CL in one canal, and went up by 10 CL in one canal.

Prior to the recording experiment displayed in Figure 1, the masking and electrode stimulation parameters had been frequently adjusted to optimize the vECAP recordings, making direct comparison with the longitudinal data difficult. However, vECAPs recorded prior to the start of longitudinal data collection had significantly different N1-P1 amplitudes than the longitudinal data. In two animals (M8 and M5), intraoperative and one-week post-operative vECAPs had lower N1-P1 amplitudes across stimulation current levels than those for the longitudinal data. The third animal (M7) displayed vECAPs with varying N1-P1 amplitudes intraoperatively and one-week post-operatively.

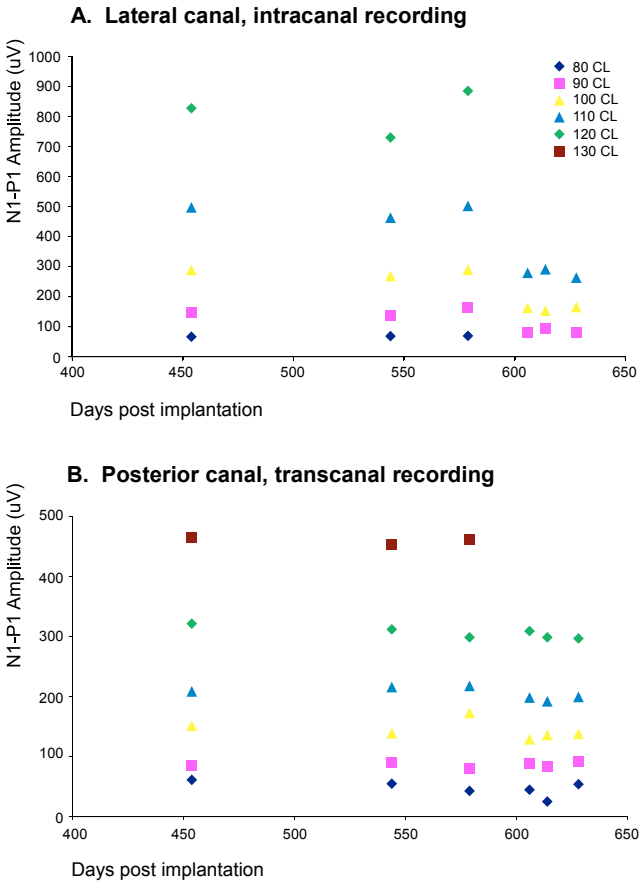

Fig. 3. Longitudinally recorded vECAP amplitudes at multiple current intensities from two canals in monkey M5. Lateral canal recordings are from stimulation of the most distal electrode in the lateral canal, and recording in the next most distal electrode in the same canal. Posterior canal recordings 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).

Data from a second animal shows that vECAP amplitudes can change relatively quickly in a single canal, while another canal in the same animal can display relatively constant response amplitudes. Figure 3 displays the vECAP amplitude data from the lateral and posterior canals in monkey M5 for 174 days starting on day 454 post implant surgery. Both canals show robust vECAP responses at the outset of the longitudinal trial, but the response to stimulation of the lateral canal shows a large decrease in amplitude across lower stimulation currents starting at day

606. The threshold stimulation currents also increase from 80 to 90 CL. At this time point, the behavior of the animal in response to electrical stimulation of the right lateral canal changed dramatically, so that higher currents now elicited facial twitches whereas before they only elicited right-beating nystagmus. Therefore, we stopped higher current stimulation in this canal in this animal. The change in response to stimulation in the lateral canal was not matched by a change in the response to stimulation in the posterior canal. The vECAP amplitudes remained constant for stimulation currents between 120 CL and 80 CL in the posterior canal.

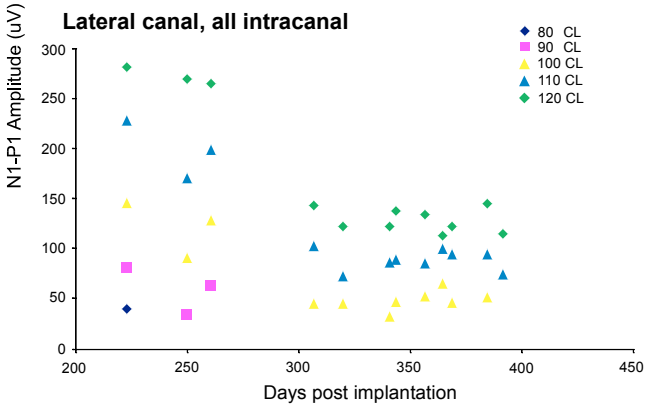

Fig. 4. Longitudinally recorded vECAP amplitudes at multiple current intensities from the lateral canal in monkey M7. The recordings are from stimulation of the most distal electrode and recording in the next most distal electrode in the same canal. Colors denote the stimulation current used. Currents are specified in clinical level (CL).

A similar change in vECAP response amplitudes was seen in monkey M7. In this animal, as seen in Figure 4, stimulation currents elicited large amplitude vECAP responses with low thresholds at the start of the longitudinal trial at day 223 post surgery in the lateral canal. However, by day 310 there was a roughly 50% reduction in vECAP amplitudes and an increase in vECAP threshold from 80 to 100 CL. These changes were associated with a concurrent device failure in this animal. The implanted device failed to produce stimuli at lower frequencies of stimulation, as assessed by recordings of stimulation artifact with surface electrodes. However, interestingly, at higher stimulation frequencies, there was no change in the slow phase velocity of the eye movements that were elicited by electrical stimulation of the lateral canal. For example, a 300pps, 150µA, 2s train, 100µs pulse width and 8µs gap elicited a slow phase velocity of 63º/s at 240 days post surgically, and a slow phase velocity of 67º/s at 388 days post surgically, a net increase in velocity of 4º/s.

IV. Conclusion

We have presented data suggesting that longitudinal vestibular electrically evoked compound action potential recording can be used to monitor the efficacy of electrical stimulation in rhesus monkeys implanted with a vestibular prosthesis. In two animals, significant changes in vECAP amplitudes occurred at 156 and 107 days into the longitudinal trial, corresponding to 606 days and 330 days post implantation, respectively. In one animal, there was a change in behavior associated with a change in the vECAP amplitude in one electrode. The vECAP response of the other canal remained unchanged. In the other animal, there was a change in the behavior of the device during low frequency stimulation trials, but no change in the eye movement behavior elicited by short high frequency trains of biphasic pulses. In a third animal, there was no clear change in vECAP amplitude over the entire 124-day trial, which ended 288 days after implantation. In this animal, the electrodes continued to produce large amplitude vECAPs with low current thresholds in all implanted canals. Taken together, these data suggest that vECAP provides unique information about the ability of the vestibular implant to drive vestibular afferent fibers peripheral to the adaptive mechanisms that control the gain of the electrically elicited vestibulo-ocular reflex.

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