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Longitudinal performance of an implantable vestibular prosthesis

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Abstract

Loss of vestibular function may be treatable with an implantable vestibular prosthesis that stimulates semicircular canal afferents with biphasic pulse trains. Several studies have demonstrated short-term activation of the vestibulo-ocular reflex (VOR) with electrical stimulation. Fewer long-term studies have been restricted to small numbers of animals and stimulation designed to produce adaptive changes in the electrically elicited response. This study is the first large consecutive series of implanted rhesus macaque to be studied longitudinally using brief stimuli designed to limit adaptive changes in response, so that the efficacy of electrical activation can be studied over time, across surgeries, canals and animals. The implantation of a vestibular prosthesis in animals with intact vestibular end organs produces variable responses to electrical stimulation across canals and animals, which change in threshold for electrical activation of eye movements and in elicited slow phase velocities over time. These thresholds are consistently lower, and the slow phase velocities higher, than those obtained in human subjects. The changes do not appear to be correlated with changes in electrode impedance. The variability in response suggests that empirically derived transfer functions may be required to optimize the response of individual canals to a vestibular prosthesis, and that this function may need to be remapped over time.

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1. Introduction

The vestibular system provides balance and orientation information that is critical for daily activity. The primary source of vestibular sensory information is in the inner ear, which contains five sensory end organs. In these organs, three semicircular canals (SCC) and two otolith organs, hair cells transduce rotation and/or linear accelerations of the head into neural activity. When these cells die, or experience transient changes in functional integrity due to conditions such as Meniere's disease, patients may experience a range of symptoms, including disequilibrium, oscillopsia, or vertigo. Furthermore, mammalian hair cells show only a small amount of spontaneous regeneration (Forge et al., 1993, 1998; Warchol et al., 1993; Rubel et al., 1995; Walsh et al., 2000; Oesterle et al., 2003; Kawamoto et al., 2009; Wang et al., 2010; Lin et al., 2011; Golub et al, 2012). For this reason, if there is a permanent loss of hair cell function, there is also a permanent loss of natural sensory input to the vestibular system. One strategy for treating hair cell loss is to bypass the missing receptor cells using direct electrical stimulation of the nerves innervating each end organ (Golub et al, 2010, 2013; Fridman and Della Santina, 2012; Merfeld and Lewis, 2012). This strategy has already achieved remarkable success for treating hair cell loss in another comparable sensory modality, hearing, with cochlear implants. For the vestibular system, an electrical stimulator could be used to replace the spontaneous activity of the missing end organ, or using a gyroscope or accelerometer to replace the dynamic modulation of vestibular input that results from head motion.

Much research effort by multiple groups has been spent on the development of an implantable single and multichannel vestibular neurostimulator over the past two decades (Fridman & Della Santina, 2012; Chiang et al, 2011; Cohen et al, 1964; Cohen and Suzuki, 1963; Bierer et al, 2012; Dai et al, 2011b,c, 2013; Davidovics et al, 2011, 2013; Della Santina et al, 2005, 2007; Fridman et al, 2010; Gong and Merfeld, 2000, 2002; Gong et al, 2008; Lewis et al, 2001, 2002, 2010, 2013; Merfeld et al, 2006, 2007; Nie et al, 2011, 2013; Phillips et al, 2011; Rubinstein et al, 2012; Sun et al, 2011; Suzuki and Cohen, 1964, Thompson et al, 2013; Valentin et al, 2013; Phillips et al, 2013; Golub et al, 2013; Perez Fornos et al, 2014; Guyot et al, 2011a, b, 2012; Wall et al., 2007; Van de Berg et al, 2012). The studies have described the efficacy of these devices in driving vestibulo-ocular reflex (VOR) mediated eye movements with electrical stimulation in a range of species, including humans. Stimulation from such a neurostimulator produces robust vestibular nystagmus in association with electrical stimulation trains of brief biphasic pulses, which is comparable to eye movements produced naturally through the VOR (Thompson et al. 2012; Phillips et al, 2011; Davidovics et al. 2013). In addition to VOR, electrical stimulation has been shown to drive other modalities of the vestibular system, including producing postural and head movements (Mitchell et al. 2013, Phillips et al. 2013) and perceptual responses (Lewis et al. 2013). Therefore, initial results in animal models and human subjects have been encouraging.

However, there are several limitations to the current literature. First, the majority of the papers that have been published have actually been reports based on a relatively small number of successful implantations. Indeed, many publications report results from multiple studies of the same animals over a relatively short period. Second, the majority of the papers

have reported on only the initial findings in animals, which are quite promising when an implantation is successful. The long term efficacy of stimulation has only been studied in a few papers, and in these papers the slow phase eye velocities elicited during stimulation were either relatively low, or the duration of the study was relatively short (Merfeld et al, 2007; Lewis et al, 2010, Thompson et al, 2013; Dai et al, 2013). Also, the eye movements were often elicited in a natural rotational context, frequently including intermittent eyes open rotation, where residual vestibular function and adaptation play an important role in modifying the observed responses. Two of these studies were, in fact, specifically designed to elicit an increasingly accurate compensatory VOR response with electrical stimulation or to study adaptive changes in electrically elicited eye movements.

For these reasons, in this paper we describe the first full series of consecutive implantations of a large number of rhesus monkeys with a vestibular implant using a transient stimulation paradigm that was specifically constructed to reduce adaptive changes in the VOR response. This allowed us to evaluate the long-term efficacy of electrical stimulation with a vestibular prosthesis. We evaluated not only the slow phase velocity of the elicited eye movements across different currents and frequencies of stimulation, but also the impedance of the electrodes, over up to 644 days after implantation with the device. These results allow us to directly compare long term intermittent electrical stimulation elicited eye movement behavior across canals in single rhesus monkeys, across monkeys in the consecutive series, and with recently published data from human subjects using identical stimulation parameters, paradigms and devices. This comparison allows us to evaluate the rhesus monkey as a model system for the development of treatments using long-term electrical vestibular stimulation in human patients.

2. Methods

All experiments were performed in accordance with the recommendations of the National Research Council (1997, 2003) and the Society for Neuroscience, and exceeded the requirements recommended by the Institute of Laboratory Animal Resource and the Association for Assessment and Accreditation of Laboratory Animal Care International. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Washington.

2.1 Implantation

Six rhesus macaque monkeys were implanted unilaterally with a vestibular neurostimulator in the right ear (Figure 1A). All animals had normal vestibular function prior to implantation. Detailed descriptions of the implanted device used in this study (Nie et al. 2013), as well as the surgical implantation approach (Rubinstein et al. 2012), have been published previously. Briefly, the UW/Cochlear prosthesis was based on a Nucleus Freedom cochlear implant (Cochlear, Ltd., Sydney). The device contained a chronically implantable neurostimulator, which communicated with an external processor via an RF link. The neurostimulator includes a trifurcated lead. Located on the distal ends of each lead is a 2.5mm electrode array with three stimulation sites ($250\mu\text{m} \times 120\mu\text{m}$). During a sterile surgical implantation, a fenestration was made in the bony labyrinth adjacent to the ampulla

of each semicircular canal, through which the tip of each lead was inserted. The electrode tip was small enough to allow for fluid flow within the membranous labyrinth. As such, the device was designed to preserve the sensitivity of the implanted end organ to natural rotational stimulation. Vestibular evoked compound action potentials and electrode impedance measurements were utilized during surgery to optimize the placement of the stimulating electrode within the canal (Nie et al. 2011). Finally, a remote ground ball electrode was placed under the temporalis muscle. If, following implantation, electrical stimulation failed to elicit behavioral responses, an additional surgery was undertaken to reposition electrode leads. Longitudinal monitoring began following an animal's last implantation surgery. In addition to the surgical implantation of the vestibular neurostimulator, all animals were implanted with scleral eye coils and head stabilization lugs in separate sterile surgeries. Five of the six animals were also implanted with a neural recording chamber.

2.2 Vestibular stimulation

The animals included in this study typically performed stimulation experiments 2-4 times a week beginning one week after implantation. Experiments were performed for up to 644 days following implantation. Each session lasted approximately two hours. Outside of these sessions, the implanted vestibular neurostimulator was always inactive. In addition to the longitudinal monitoring experiments, the animals also participated in various additional experiments. These included electrical stimulation in the dark with sinusoidally modulated stimuli, combined rotation and electrical stimulation in the dark, and unit recording in the vestibular nucleus during electrical stimulation. The longitudinal data reported here were obtained before other experiments in a given test session in order to reduce the interaction between the longitudinally recorded data and other stimulus conditions. During electrical stimulation, the monkeys were always in the dark without visual feedback. During testing sessions, animals were seated in the dark with their heads restrained within a 3-degrees of freedom rotational chair. Horizontal and vertical eye position measurements were collected using a magnetic search coil (CNC Engineering, Seattle, WA). The driver coils for the system were mounted on the multidimensional rotator on which the monkey chair was mounted. Eye and chair position data were recorded online with a sampling rate of 1 kHz with a CED Power 1401 (Cambridge, UK). Prior to the stimulation studies, the animals were trained to track laser point targets that were either stepped or drifted on the interior surface of a drum that moved with the animals. Animals were rewarded for maintaining their gaze within a $2^\circ \times 2^\circ$ position window surrounding the moving target.

In the experiments described here, electrical stimulation was controlled by a NIC-2 research processor (Cochlear, Ltd, Sydney), which sent preprogrammed instructions to the neurostimulator. During stimulation trials, the animal was tasked with making saccades to direct their gaze at a randomly stepping target. At random intervals, the target was moved to a straight-ahead position and then turned off to eliminate fixation suppression of any observed eye movements. A train of electrical stimulation was subsequently delivered from the neurostimulator (Figure 1B). The stimuli were delivered in monopolar mode, stimulating between one of the three implanted canal sites and a combination of the remote and case grounds of the device. The electrode site that was used in these experiments was based on

which site was most effective in eliciting nystagmus. The stimulus was customized for each electrode and animal based on the current and frequency required to produce a measurable slow phase velocity nystagmus in the plane of the stimulated canal. An average best stimulation current and frequency were then established for each animal so that comparable results could be obtained longitudinally. In all cases, this standard stimulation consisted of a two second constant current, constant pulse rate train of biphasic pulses 100 μ s per phase with an 8 μ s interphase gap. In order to determine the relationship between stimulation pulse rate and current amplitude and the elicited slow phase eye velocities, a set of stimulation trains of differing pulse rates and amplitudes were also tested multiple times longitudinally. The number of two second stimuli delivered within a two hour testing session varied between animals and test session, depending on the number of electrodes, stimulation currents, and stimulation pulse rates tested on that date. The maximum number of two second stimulation trains delivered within a single testing session was 127 (less than five minutes of total stimulation) across all animals and all longitudinal testing sessions. All responses of like stimulation parameters within a single testing session were averaged for the purposes of longitudinal measurements.

Impedance data from each electrode was collected prior to stimulation testing sessions at multiple time points longitudinally. Impedance measurements were collected between each stimulating electrode and the common ground using Nucleus Freedom Custom Sound EP software (Cochlear, Ltd., Sydney).

2.3 Data analysis

Analysis of eye movement recordings was conducted offline using purpose written Spike2 (CED, Cambridge, UK) and MATLAB (Mathworks, Natick, MA) scripts. First, a measurement of any spontaneous nystagmus of the animal was taken from a period of recording taken during each testing session in the absence of electrical stimulation while the animal was in the dark. Eye position records from this period were marked, based on a settable velocity criterion with manual adjustment, to indicate the location of saccades or fast-phase eye movements. Marked portions of the eye position trace were removed. A linear regression using a least-squares method was applied to each resultant segment of accepted eye-position samples, each of which constituted a slow phase, to calculate a velocity. A time weighted average of the horizontal and vertical eye velocity of these slow phases was used as a measure of the animal's underlying spontaneous drift on that day.

For stimulation trials, the same technique was used to calculate a time-weighted average of the slow-phase velocity of all slow phases during a stimulation train (Figure 1B). All slow-phases from stimulation trains of the same stimulation parameters (electrode, pulse rate, and pulse current amplitude) on a given test date were averaged to calculate a single measure for that date. The spontaneous drift value for the same session was then subtracted from the resultant average slow-phase velocity for that date. Thus, the velocity values reported in this study indicate the change in slow-phase velocity produced by electrical stimulation above any spontaneous drift.

Within sessions where stimulation parameters were parametrically varied to examine the relationship between pulse rate, pulse current amplitude, and the slow-phase velocity of

electrically elicited nystagmus, gains and thresholds were calculated. The relationship between pulse current amplitude at a fixed pulse rate and the slow-phase velocity of electrically elicited nystagmus was fit with an exponential function. The relationship between pulse rate at a fixed pulse current amplitude and slow-phase velocity was fit with a linear function. Fits were calculated for any session in which more than three pulse current amplitudes or pulse rates were collected at a fixed pulse rate or pulse current amplitude, respectively. These fits described the gains of the relationship. Throughout this report, the threshold was defined as the current or pulse rate required to elicit a slow-phase velocity greater than $10^\circ/\text{s}$ in the canal-plane. Fits and statistical analyses were performed in MATLAB.

3. Results

3.1 Implantation

Six rhesus macaque were included in this study. Three additional animals were excluded from this study either because stimulation following implantation failed to elicit any behavioral responses and the animals had other implant failures (2 animals) or because they were treated with intratympanic gentamicin shortly after implantation for a different experimental protocol (1 animal). All animals were implanted with a vestibular neurostimulator in their right ear. Three animals (M1, M3, and M4) underwent revision surgeries to reposition electrode leads within the canal. All animals were implanted with electrodes in the lateral canals. Four of the animals were implanted with electrodes in the posterior canal (M2, M4, M5, M6). Two animals were implanted with electrodes in the anterior canal (M1, M2). In total, 12 out of 18 possible canals were implanted.

The early relationships between stimulation current, pulse rate, and the elicited slow-phase eye velocity for the horizontal and vertical canals in all animals are presented in Figures 2 and 3, respectively. Stimulation of all implanted lateral canals and 5 of 6 total implanted vertical canals initially elicited sustained nystagmus. Stimulation of the lateral canal elicits nystagmus with a predominantly leftward directed slow-phase (Figure 2). For vertical canal stimulation, slow-phases of the elicited nystagmus were directed appropriately for the canal stimulated: upward for anterior canal stimulation (Fig 3B) and downward for posterior canal stimulation (Fig 3C-F). The average velocity of this nystagmus typically increases as a function of both pulse current amplitude and pulse rate. Optimal combinations of pulse rates and currents were capable of eliciting nystagmus of very high velocities. For lateral canal stimulation, horizontal components were greater than $150^\circ/\text{s}$ in some animals (eg., M3 150 pulses per second, $250\mu\text{A}$, Fig 3C). Typically, the relationship between stimulation current and the slow-phase velocity of the elicited eye movement is well fit with an exponential function for horizontal and vertical components. With respect to pulse rate, increasing the pulse rate above 300 pulses per second (PPS) at a fixed current may yield increases, no changes, or decreases in nystagmus velocity, depending on the animal and canal. The current and pulse rate thresholds and gains varied between animals and canals. At 300 PPS, the current threshold, defined as the current required to elicit a nystagmus with a velocity greater than $10^\circ/\text{s}$, ranged from $29\mu\text{A}$ – $122\mu\text{A}$ in the lateral canals and $62\mu\text{A}$ – $129\mu\text{A}$ in the vertical canals. At $150\mu\text{A}$, the pulse rate threshold ranged from 35 (M5) – 227 PPS (M2)

in the lateral canals and 105 PPS (M2: anterior) - >600PPS (M1,M6) in the vertical canals. It was not the case that animals with lower lateral canal stimulation thresholds had lower vertical canal thresholds (cf. Fig 2B,F and Fig 3B,F). Finally, elicited eye velocities were not entirely in the plane of the stimulated canal. Because torsion measurements were not collected, it is not possible to assess completely the variability in the direction of nystagmus elicited by stimulation. In 5 of the 6 animals, the nystagmus elicited by lateral canal stimulation contained a significant upward vertical component. In M1, the vertical component was directed downwards. Across all animals, the vertical component was reduced in velocity from the horizontal component. Averaged across all stimulation trains eliciting horizontal velocities greater than 10°/s, the velocity of the vertical component ranged from 17% (M4) to 61% (M3) of the velocity of the horizontal component. For vertical canal stimulation, the velocity of the horizontal component ranged from 16% (M5) to 45% (M4) of the velocity of the vertical component.

3.2 Longitudinal changes

While a trial-to-trial and day-to-day variability in the response is clearly present, relatively clear trends emerge in the eye movement response to a standard stimulus over many months of stimulation. This can be seen in Figure 4A, which plots the average horizontal slow-phase velocity of eye movements elicited over time, for a standard stimulation frequency and current applied to the lateral canal of each animal. Because the frequency of stimulation was consistent (300 PPS) in all animals, and the currents were comparable (100µA-125µA), Figure 4A also shows the relative efficacy of a standard stimulus across animals. There is significant variability in the efficacy of a standard stimulus train across animals initially following implantation. Average slow-phase velocities range from 6°/s (M2) to 65°/s (M3) across animals during the first 50 days following implantation. An examination of the linear regression trend lines suggests that there are large differences in the changes in slow-phase velocity with stimulation over time. Three of the animals (M1, M3, and M6) showed a decrease in slow-phase velocity with stimulation over time, suggesting that stimulation was becoming less effective in driving the vestibular system over the first 234 (M3) to 401 (M1) days of recording. One animal (M5) showed an increase in slow-phase velocity over time, suggesting that stimulation was becoming more effective over 455 days of recording. The two remaining animals (M2 and M4) showed no clear trend over 622 (M2) to 644 (M4) days of recording. It should be noted that linear regression does not fully capture the progression of the elicited slow-phase velocities over time. Specifically, in several animals there was a rapid change in the efficacy of the electrodes over the first 100 days, and then the response velocities showed a slow progression. This can be seen in monkey M1, where velocities fall from 60°/s to 20°/s in the first 100 days, and then show a slow but steady decrease over the next 300 days. In monkey M2, velocities increase rapidly over the first 100 days and subsequently decrease slightly over the next 500 days.

We also examined the longitudinal efficacy of stimulation of the vertical canals in the same animals. This can be seen in Figure 4C, which plots the average absolute vertical slow-phase velocity of eye movements elicited over time, for a standard stimulation frequency and current applied to the lateral canal of each animal. In this figure, the frequency of stimulation was consistent (300 PPS) in all animals, but the standard currents were not

comparable across animals (100 μ A-200 μ A). The linear regression trend lines suggests that for the vertical canals there are also large differences in the changes in slow-phase velocity with stimulation over time. Two of the animals (M2 and M6) showed a decrease in slow-phase velocity with stimulation over time in their anterior (M2) and posterior (M6) canals, suggesting that stimulation was becoming less effective in driving the vestibular system. Three animals (M2, M4, and M5) showed an increase in slow-phase velocity over time in their posterior canals, suggesting that stimulation was becoming more effective. The remaining animal (M1) showed a very weak increase in slow phase velocity over time in response to stimulation of the anterior canal. It should be noted that linear regression again did not fully capture the progression of the elicited slow-phase velocities over time, with rapid changes occurring early in the longitudinal series.

We also compared the lateral and vertical canal stimulation elicited longitudinal eye velocity measurements with longitudinal measurements of electrode impedance. Figure 4B shows the longitudinal measurements of the lateral canal electrode impedances for all 6 animals. Figure 4D shows comparable data for the vertical canals of those animals. The large points at day 0 denote electrode impedances obtained intraoperatively during the implantation procedure. In all cases, there was a large increase in electrode impedances between the intra-operative recording and the first post surgical recording. In 5 of 6 animals, a linear regression showed a relatively steady decline in lateral canal electrode impedance over time after implantation. In one animal, M3, the electrode impedance remained relatively stable over the first 144 days. In 3 of 6 vertical canals (2 of 5 animals) the linear regression suggested a decline in impedance. However, 3 animals showed an increase in vertical canal impedance over time. If we compare the changes in electrode impedance with the changes in slow phase velocity over time, no obvious relationship emerges between impedance changes and changes in velocity. Animals M1 and M4 showed comparable decreases in lateral canal electrode impedances over time, while one showed a decrease in the stimulation elicited slow phase velocity and the other showed no change in the elicited slow phase velocity over time. From this data, it appears that electrode impedance is not the primary factor in determining the longitudinal efficacy of electrical stimulation as measured by elicited nystagmus.

While Figure 4 presents an overview of the efficacy of lateral canal stimulation to elicit nystagmus over time, the observed changes from a standard stimulus conflate changes occurring in the underlying relationship between stimulation parameters and behavior. As was shown above, varying pulse rate or pulse current amplitude both parametrically vary the velocity of the elicited nystagmus. Changes in the threshold, gain relationship, or both with respect to either pulse rate or pulse current amplitude may contribute to observed changes in response to standard stimuli. In addition to presenting initial eye velocity data, Figures 2 and 3 also present the relationships between stimulation current and eye velocity at 300 PPS at early and late time points for all implanted canals (compare open diamonds for early time points with filled stars for late time points). Across all implanted canals, it is possible to see that a variety of changes occur, including changes in threshold (Fig 2A, 3D), gain (2D,F), or both (3C).

In two animals, it was possible to examine longitudinal changes in these relationships for lateral canal stimulation. Figure 5A plots the slow phase velocity of eye movements elicited by 300pps stimulation at different currents in M1. In this animal, longitudinal data at multiple currents was only collected during a 180 day period starting 220 days after implantation. Over this time period, there was a slow decrease in slow-phase velocities elicited by the standard stimulus. However, modulation of eye velocity with current remained intact for this frequency of stimulation. The gain of the relationship remained constant over this period (Figure 5C). The decrease in elicited velocities appears to be largely a consequence of a gradual increase in threshold. This data does not address the question of what happens to the modulation of velocity during periods of rapidly changing slow-phase velocity in response to the standard stimulus. Figure 5B presents comparable data from M2. In this animal, velocities increase over the first 100 days and then remains relatively constant over the subsequent 160 days. The increase in velocity is a consequence of both an increase in gain and a slight decrease in threshold (Figure 5C). Figure 6 presents the slow-phase eye velocity of eye movements elicited by 180uA and 100uA stimulation at different pulse rates over the same period of time for both animals. A similar trend is observed in both animals. In M1, there is a small decrease in eye velocities over the 180-day period, but modulation of eye velocity with stimulation pulse rate remained intact (Figure 6A). As with current, the gain relationship with respect to pulse rate remains relatively constant, while the threshold decreased (Figure 6C). With monkey M2, an increase in velocities is observed over the first 100 days (Figure 6B). During this period there is an increase in the gain relationship and a decrease in threshold (Figure 6C), similar to the relationship observed with current.

We compared longitudinal changes in elicited nystagmus that occurred in different implanted canals within the same animal. Figure 7 presents the slow-phase velocity of nystagmus elicited by 300 PPS stimulation of the lateral and posterior canals at two currents for the four animals implanted in these canals. In two animals, M1 and M4, both canals were followed for comparable 600-day periods starting shortly after implantation. In M1, the rapid changes in the velocity of eye movements elicited by lateral canal stimulation over the first 100 days (cf. Figure 5B) are paralleled by similar changes in the posterior canal (Figure 7A). Both canals exhibit an increase in gain over this period. Subsequently, both canals exhibit a slow decrease in response over the following 500 days. The changes observed in M1 can be compared with those from M4 (Figure 7C). In M4, lateral canal responses decrease immediately in the first weeks after implantation but then remain relatively unchanged over the remainder of the study. In contrast, posterior canal responses show a gradual increase over the same time period (cf. Figure 2D, 3D). Over shorter time periods, M5 and M6 show a pattern that is similar to that of M1 and M4. In M6, the responses to posterior canal stimulation increase slightly over a period of 100 days, while those to lateral canal stimulation decrease (Figure 7B). In M5, over a 200-day period, the responses to stimulation of both the lateral and posterior canals increase at comparable rates. Taken together, these results illustrate that canal independent changes in stimulation efficacy can occur within an implanted animal.

4. Discussion

4.1 Stimulation efficacy following implantation

The purpose of this study was to longitudinally evaluate the eye movements evoked from electrical stimulation of semicircular canal afferents in a large number of consecutively implanted animals. Implantation in these animals, when successful, produced initial slow phase eye movements with velocities and directions that were either comparable to those of previous studies (eg., Dai et al, 2013), or in some cases the velocities exceeded those in previous studies. These “slow phase” velocities could be quite high, reaching up to 240°/s for 2s at high currents and optimal pulse rates. However, this study suggests that such eye movements were highly variable between implanted canals, both in terms of the velocities obtained and the direction of the movements. There was also considerable variability in the efficacy of stimulation between animals in the series. Furthermore, such movements were only produced in a subset of animals without revision surgery. 50% of the animals in this study had revision surgeries because one or more canal failed to produce responses in the original implantation. This suggests a limitation to our current surgical techniques in rhesus monkeys, where the end organs and structure of the labyrinth are quite small, and the anterior canal approach is somewhat more difficult than in humans.

Modulation of pulse frequency or current amplitude produced robust modulation of slow phase velocity in all but one of the implanted canals. The modulation gain was not consistently related to the threshold for evoking eye movements across canals. In some cases the pulse frequency or current threshold was relatively high for evoking eye movement, but slow phase velocity increased dramatically with further increases in either parameter. In other cases, the opposite was true. This initial, canal specific, variation in elicited behavior is likely an inevitable challenge with this type of prosthetic stimulation. Small variation in the location of the stimulating electrode within the labyrinth may significantly impact the charge density on the desired sensory tissue, as well as current spread to other areas within the labyrinth. Because of this, empirically derived maps with perhaps very different transfer functions between pulse rate and pulse current amplitude and behavioral responses may have to be developed for each implanted canal within a patient.

4.2 Longitudinal changes

Long-term intermittent stimulation in each animal produced a variable course between animals, with decreasing, increasing or stable eye velocities produced by comparable stimuli over time. There was not a clear relationship between the efficacy of the standard pulse rate 300 pps stimulus in producing eye velocity at the outset of stimulation and the resulting efficacy of stimulation at the later time point. Again, in Figures 2 and 3, in some canals the current or frequency threshold shifted by the later time point, in some animals the slope of the relationship between slow phase eye velocity and current shifted, and in some animals the responses remained essentially unchanged. Ultimately, prosthetic vestibular stimulation will be continuously delivered. The changes in the efficacy of stimulation that we observed here might be expected to be offset by adaptive changes in the behavioral response to continuous stimulation when visual feedback is present, but such adaptive mechanisms do have limitations and it is as yet unknown the extent to which this will be fully successful. A

study by Lewis and colleagues (Lewis, 2010) in two animals showed that relatively low velocity slow phase compensatory eye movements are generated up to 290 days in monkeys implanted with vestibular prostheses, intermittently delivering continuous, modulated stimulation, and such mechanisms may have played a role in the maintenance of the response in those studies.

Our results using a standard pulse rate and current stimulus (300 PPS, 100 – 125 uA) over a large number of days showed some very interesting features of the response over time. Most importantly, all of the animals maintained a slow phase eye velocity response to electrical stimulation over the duration of the study. However, there was considerable variability in the course of longitudinal changes over time. Early response velocities did predict the course of the changes in eye velocity at the extremes, with the highest two initial velocities obtained in lateral canals which produced decreasing responses over time, and the lowest 4 initial velocities obtained in canals that increased or maintained their responses over time. Second, most of the change in response velocity occurred in the first 100 days of recording, with more gradual changes occurring later in the response. Third, there was considerable variation in the day to day velocities obtained from the stimulation of individual canals. Such changes are missed by many studies of the effects of stimulation with such devices. These changes may result from fluctuations in the state of the implanted end organ, changes in the alertness of the animal, or changes in the adaptation state of the animal. While these stimuli were uniformly obtained at the outset of the experiments in a particular animal on a particular day, and we used only very brief stimulus presentations in the dark to reduce adaptation to electrical stimulation, Merfeld, Lewis and colleagues (Merfeld et al, 2006, 2007; Lewis et al, 2010, 2013) have shown that adaptive changes do occur with more protracted stimulation and we can not entirely rule out such effects. Fourth, the changes in stimulation efficacy do not seem correlated with changes in the impedance of the electrodes. This would seem to argue that whatever is causing slow changes in stimulation efficacy, it is not related to the micro-environment immediately surrounding the electrodes, nor decay of the electrodes themselves.

4.3 Study limitations

Our study has several limitations, which are important to consider in the context of the changes that we observed. First, the animals in this study were not canal plugged or ototoxically lesioned. This means that the animals may have had different levels of intact hair cell function across the period over time over which they were studied. The changes that we observed may have been related to the relative integrity of natural VOR in these animals. Another limitation of the study is that we performed additional experiments in these animals. These experiments included neural recording and brief head velocity modulated electrical stimulation experiments. However, these experiments were always performed after the data for this study were obtained on any recording day. Furthermore, data was not recorded within 18 hours of the preceding recording session. Although the experiments were largely comparable across animals, the precise timing of these additional studies varied from animal to animal. Finally, the study was conducted exclusively on animals that had electrodes that elicited responses at the outset of the study. Those that did not were either excluded or reimplanted before the study began. Since some animals showed

a rather impressive increase in function with time in this study, we do not know if those animals with what appeared to be failed electrode placements would have developed responses over the course of a longitudinal trial. We presumed that they would not, but this assumption may not have been valid. These results illustrate how difficult it may be to assess the exactly what it means to have a failed implantation. This has some ramifications for how we approach clinical implantation strategies where revision surgeries like those employed here are undesirable or unavailable.

4.4 Human studies

One thing that this study allows us to do is to compare the longitudinal results of this study in monkeys with similar results obtained in human subjects (Phillips et al, 2013; Golub et al, 2014). In those experiments, identical electrodes were implanted in human subjects with Meniere's disease and similar measures were obtained. There are several important differences between the results reported here and the findings in those other papers. The slow phase eye velocities elicited were far higher in this study than in the human studies, and the current thresholds for effective stimulation were lower in monkeys than in humans . All animals maintained eye movement responses over long periods in this study, but in humans the lower velocity eye movements were eliminated in some canals over comparable time periods. Current amplitude and pulse frequency modulation produced very robust changes in eye velocity in this study, but pulse frequency appeared less effective in modulating responses in the human studies above. It should be noted, however, that a recent report by Perez Fornos and colleagues (2014) demonstrated effective modulation of eye velocity with pulse frequency modulation at high frequency in bilateral vestibular loss patients using a very similar device. Differences in the size and fluid volume of the implanted canals, in the placement of the electrodes, or in the condition of the implanted canals (diseased human ears versus healthy monkey ears) may have been responsible for many differences that we observed between monkey and human studies with the same device. Importantly, the data set presented in this report allows us to put in a better context future results obtained in human subjects with vestibular loss of differing etiologies.

5. Conclusions

This study suggests that robust eye movement velocities can be obtained in a consecutive series of vestibular prosthesis implantations in rhesus monkeys. The behavioral response, as quantified by electrically elicited VOR eye movements, varies considerably from animal to animal, canal to canal, and over time. Central adaptive mechanisms will adjust the gain and direction of the elicited responses over time with continuous stimulation in a setting where visual feedback is available. However, it may also be necessary to optimize stimulation on an individual canal basis, using the observed transfer functions between current amplitude or pulse frequency and slow phase eye velocity both initially and at various times after implantation.

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List of Abbreviations

SCC	Semicircular canal
VOR	Vestibulo-ocular reflex
SPV	Slow-phase velocity
PPS	Pulses per second

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Highlights

Study of a large consecutive series of vestibular prosthesis implantations.

Animals exhibit high variability in threshold and gain of response over time.

Animals exhibit larger responses than seen in human subjects.

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Figure 1.

The implantable portion of a multichannel vestibular neurostimulator based on a modified cochlear implant with a trifurcated lead for implantation into the three semicircular canals (A) and electrically evoked eye movement position traces (B). Eye position is plotted such that a negative value indicates a leftward eye movement for horizontal (H. Eye) and a downward eye movement for vertical (V. Eye) eye position traces.

Figure 2.

Mean slow-phase velocity (SPV) plotted against stimulation current for electrically evoked nystagmus during 2-second trains of stimulation delivered to the lateral canals at multiple pulse rates for each animal. Data plotted with filled star markers is 300 pulses per second (PPS) data from a late longitudinal time point. All other data is from an early longitudinal time point. Specific dates expressed in days post implantation are given in parentheses adjacent to the animal name, with the late time point data given beside the star marker. Negative values denote rightward or downward velocities for the horizontal and vertical SPV, respectively. Error bars are +/- 1 standard deviation for all slow phases recorded on that test date.

Figure 3. Mean slow-phase velocity (SPV) plotted against stimulation current for electrically evoked nystagmus during 2-second trains of stimulation delivered to the anterior (A,B) and posterior (C,D,E,F) canals. Data plotted with filled star markers is 300 pulses per second (PPS) data from a late longitudinal time point. All other data is from an early longitudinal time point. Specific dates expressed in days post implantation are given in parentheses adjacent to the animal name, with the late time point data given beside the star marker. Negative values denote rightward or downward velocities for the horizontal and vertical SPV, respectively. Error bars are ± 1 standard deviation for all slow phases recorded on that test date.

Figure 4.

Longitudinal plot of mean slow-phase velocity (SPV) of electrically evoked nystagmus during 2-second trains of standard stimulation current delivered to the lateral canal (A) and vertical canals (C) for all animals and longitudinal plot of electrode impedances for the lateral (B) and vertical canals (D). Only the horizontal or vertical component of the SPV is plotted for the lateral and vertical canals, respectively. Standard stimulation current consisted of 300 pulses / second (PPS) stimulation at 100uA or 125uA pulse current amplitudes. Positive horizontal SPV values indicate leftward eye velocity (A). Positive vertical SPV values indicate either upward eye velocity for the anterior canal stimulation or downward eye velocity for posterior canal stimulation (C). Lines denote linear regressions over all SPV measurements (A,C) or all postoperative electrode impedance measurements (B,D). Electrode impedance measurements located at day 0 indicate intra-operative measurements.

Figure 5.

Longitudinal plots of the relationship between stimulation pulse current amplitude and mean slow-phase velocity (SPV) of electrically evoked nystagmus during stimulation of the lateral canal at a fixed pulse rate (300 PPS) in two animals (A,B) and the gain and threshold relationships for three selected dates (C) in both animals. Vertical lines in A and B denote the dates for data in C. Positive values indicate a leftward velocity.

Figure 6.

Longitudinal plots of the relationship between stimulation pulse rate and mean slow-phase velocity (SPV) of electrically evoked nystagmus during stimulation of the lateral canal at a fixed pulse current amplitude (180 μ A for M1, 100 μ A for M2) in two animals (A,B) and the gain and threshold relationships for three selected dates (C) in both animals. Vertical lines in A and B denote the dates for data in C. Positive values indicate a leftward velocity.

Figure 7.

Longitudinal comparison of mean slow-phase velocity (SPV) of electrically evoked nystagmus during stimulation of the lateral and posterior canals at two currents at a fixed pulse rate (300 PPS) in four animals. Lines denote linear regressions over all (B,C,D) or a subset (A) of measurements. For ease of comparison, positive values here indicate leftward and downward velocities for lateral and posterior canal stimulation, respectively.