Vestibulo-Ocular Reflex Responses to a Multichannel Vestibular Prosthesis Incorporating a 3D Coordinate Transformation for Correction of Misalignment

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ABSTRACT

There is no effective treatment available for individuals unable to compensate for bilateral profound loss of vestibular sensation, which causes chronic disequilibrium and blurs vision by disrupting vestibulo-ocular reflexes that normally stabilize the eyes during head movement. Previous work suggests that a multichannel vestibular prosthesis can emulate normal semicircular canals by electrically stimulating vestibular nerve branches to encode head movements detected by mutually orthogonal gyroscopes affixed to the skull. Until now, that approach has been limited by current spread resulting in distortion of the vestibular nerve activation pattern and consequent inability to accurately encode head movements throughout the full 3-dimensional (3D) range normally transduced by the labyrinths. We report that the electrically evoked 3D angular vestibulo-ocular reflex exhibits vector superposition and linearity to a sufficient degree that a multichannel vestibular prosthesis incorporating a precompensatory 3D coordinate transformation to correct misalignment can accurately emulate semicircular canals for head rotations throughout the range of 3D axes normally transduced by a healthy labyrinth.

Keywords: electrical, stimulation, vestibular, prosthesis, VOR, gyroscopes, implant, labyrinth, vestibulo-ocular reflex

INTRODUCTION

Bilateral loss of vestibular sensation can occur as the result of ototoxic drug exposure, ischemia, infection, genetic abnormality, or trauma to the inner ears. Because input from the vestibular labyrinths normally mediates perception of movement and reflexes that stabilize posture and visual gaze, loss of this input causes chronic disequilibrium, postural instability, and visual blur due to illusory movement of the world during head motion (Grunbauer et al. 1998; Minor 1998; Gillespie and Minor 1999). A multichannel neuro-electronic prosthesis that senses rotation of the head in three dimensions and delivers corresponding stimuli to the ampullary branches of the vestibular nerve should restore sensation of head rotation, which in turn should help to stabilize gaze and at least partially restore perception of head movement. Restoring function to just one labyrinth is a reasonable goal for such a device because the adaptive capacity of vestibulocerebellar circuits is sufficient to ensure that individuals with a single, normal labyrinth (e.g., after unilateral injury or infection) typically compensate well enough to suffer little or disability in activities of daily life (Curthoys and Halmagyi 1995; Black et al. 1996).

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Normally, the eyes rotate opposite the direction of head rotation in order to stabilize images on the retinae. This compensatory eye rotation is driven by the angular vestibulo-ocular reflex (aVOR), for which sensory input is provided by three mutually orthogonal semicircular canals (SCC) in each inner ear's vestibular labyrinth. Discharge rates of vestibular afferent fibers in each SCC's ampullary nerve are modulated by the component of head angular velocity about that SCC's axis (Ewald 1892; Wilson and Melvill 1979; Carey and Della Santina 2005; Della Santina et al. 2005b). The resulting eye movements can be measured precisely in 3D, giving insight into relative excitation of the ampullary nerves driving the reflex (Robinson and Murphy 1932; Robinson 1963; Aw et al. 1996a, b; Migliaccio et al. 2005).

Classic experiments by Cohen, Suzuki, et al. (Cohen et al. 1963, 1964; Cohen and Suzuki 1963a, b; Suzuki et al. 1964, 1969; and Suzuki and Cohen 1964) demonstrated that pulses of electrical stimulation delivered to the ampullary nerves via wire electrodes elicit an aVOR about axes of rotation similar to those elicited by the hydrodynamic excitation of the individual canals (Ewald 1892). Merfeld, Gong, Lewis, et al. (Gong and Merfeld 2000, 2002; Lewis et al. 2001, 2002; Merfeld et al. 2006, 2007; and Gong et al. 2008) described a single-channel prosthesis based on the idea of sensing rotational motion using a gyroscope and stimulating the appropriate branch of the vestibular nerve. Della Santina et al. (Della Santina et al. 2005b, 2006, 2007; Chiang et al. 2009; and Davidovics et al. 2009) extended that approach to 3D using a multichannel prosthesis that contains three mutually orthogonal gyroscopes to sense head rotational velocity and deliver electrical stimulus via multiple electrodes to the appropriate nerves. Tests of this device in chinchillas rendered bilaterally vestibular-deficient via gentamicin treatment revealed partial restoration of the 3D aVOR. However, current spread within implanted labyrinths limited the ability to selectively stimulate each ampullary nerve without incurring spurious excitation of adjacent branches of the vestibular nerve. Increasing stimulus current amplitude initially increased aVOR magnitude without changing the aVOR axis, but at higher currents, the eye rotation axis deviated from the ideal as spurious stimulation of other vestibular nerve branches altered the head rotation axis "perceived" by brainstem neurons mediating the aVOR.

In theory, one should be able to overcome the effects of current spread from an electrode targeting one ampullary nerve by adjusting the input delivered via other electrodes targeting two other ampullary nerves in the same (or contralateral) labyrinth. For example, if current intended for the horizontal ampullary nerve spuriously excites the anterior and

posterior ampullary nerves, then head rotation purely about the horizontal SCC axis might be encoded by modulating not only the horizontal electrode input but instead by simultaneously modulating stimuli on all three electrodes to represent a horizontal head rotation via vector summation. If linearity and vector superposition hold, this procedure amounts to a simple linear transformation between two different 3D coordinate systems, analogous to the matrix algebra transformations popularized by Robinson (1982) for analysis of the 3D aVOR. One should be able to characterize this transformation by delivering a set of stimuli $\vec{s}_i$ (with each $\vec{s}_i$ being a 3-vector representing a triplet of stimulus intensities delivered via three electrodes targeting the three ampullary nerves) and measuring the corresponding responses $\vec{r}_i$ (with each $\vec{r}_i$ being a 3-vector representing the axis and speed of observed eye movement responses) for a set of N virtual head movements spanning the range of head movement axes and rotational velocities normally encoded by the labyrinth. A single 3×3 matrix $\mathbf{M}$ can then be found using least-squares techniques such that

$$\vec{r}_i \approx \mathbf{M} \vec{s}_i \quad \text{for } i = 1 \dots N. \quad (1)$$

Once $\mathbf{M}$ has been established, the appropriate pattern of electrode activation $\vec{a}$ the prosthesis should deliver to the three ampullary nerve electrodes during a head rotation eliciting gyroscope signals $\vec{g}$ is

$$\vec{a} = \mathbf{M}^{-1} \vec{g} \quad (2)$$

This procedure would require that $\mathbf{M}$ is computed during an occasional "fitting" session, analogous to fitting required for patients with cochlear implants. For this procedure to work properly, the axes of eye movement responses to individual stimulation of each the three ampullary nerves must be linearly independent with respect to each other. Otherwise, the inverse of $\mathbf{M}$ cannot exist and the matrix pseudoinverse calculation will fail. In this context, linear independence means that the 3D axis of aVOR responses to stimuli delivered via any one electrode alone cannot be in the plane defined by the axes of responses to the other two electrodes. The accuracy with which linear precompensation can correct for current spread also depends on the extent to which the electrically evoked aVOR response is linear and exhibits vector summation.

Observations by Cohen et al. (1964) during electrical stimulation of ampullary nerves alone and in combination demonstrated that the aVOR at least qualitatively exhibits vector summation. Recently, Gong et al. (2008) showed that responses to prosthetic stimuli delivered to electrodes implanted in

coplanar canals on opposite sides of the head show evidence of linear summation. However, significant frequency- and amplitude-dependent nonlinearities are evident in aVOR responses of individuals with a single intact labyrinth (who most closely represent the functional goal of a vestibular prosthesis implanted unilaterally in a bilaterally vestibular-deficient individual; Carey et al. 2002a; Weber et al. 2008, 2009). The 3D aVOR may therefore be more complex than a static vector summation of different ampullary nerve inputs. Furthermore, nonlinearities could arise due to the dynamics of action potential initiation in ampullary nerve fibers spuriously excited or inhibited by current spread. Therefore, linear behavior of the electrically evoked 3D aVOR cannot be assumed.

In the present study, we assessed the linearity of the electrically evoked aVOR and then examined whether incorporating a linear precompensation encoding scheme in a multichannel vestibular prosthesis enables implanted animals to accurately sense and respond to sinusoidal head rotation about any specified 3D axis at any specified velocity within the range typical of normal behavior.

METHODS

Subjects

Adult wild-type 450–650 g chinchillas were used for all experiments, which were performed in accordance with a protocol approved by Johns Hopkins University Animal Care and Use Committee.

Surgical procedures

Surgical procedures were similar to those described previously in detail (Della Santina et al. 2007). Under general anesthesia (isoflurane, 3–5%), a phenolic post was positioned on the skull in the midline, perpendicular to the mean horizontal semicircular canal plane and embedded in dental cement (ESPE ProTemp II, 3M Corp., Minneapolis, MN), forming a rigid connection to the skull. The post served to restrain the animal during aVOR testing. Electrodes were fashioned from pairs of Teflon-insulated 75- μ m Pt-Ir wire (Cooner Wire, Chatsworth, CA) for each of the canal electrodes and 125- μ m Pt-Ir wire for reference electrodes.

To provide reference data on the aVOR of an animal with a single normal labyrinth (against which to compare responses of bilaterally vestibular-deficient animals treated with unilateral prosthetic stimulation), three otherwise normal chinchillas were treated unilaterally via intratympanic injection of ~ 0.5 mL gentamicin (26.7 mg/mL buffered to pH 7.4 with sodium bicarbonate) using a protocol described

previously (Hirvonen et al. 2005). Head posts were placed subsequently as described above.

Electrodes were positioned in the left labyrinth for all four implanted chinchillas. The electrode for the anterior canal ampullary nerve stimulation was positioned via a fenestration in the internal auditory canal exposing the ampullary nerve just medial of the anterior canal ampulla. The electrode for horizontal canal stimulation was positioned via a ~ 100 - μ m fenestration on the anterolateral wall of the horizontal ampulla. The electrode intended for the posterior canal stimulation was inserted into a fenestration in the thin segment of the posterior canal and advanced toward the ampulla until resistance was encountered.

Two reference electrodes were implanted to provide a choice of two possible returns for the monopolar stimulation delivered via any of the stimulating electrodes. A distant return was inserted into neck musculature, and a near return was inserted into the common crus via a fenestration in the superior aspect of the anterior SCC. The distant return was stripped of approximately 5 mm of insulation, and the near return was stripped of approximately 1 mm of insulation. For each stimulating electrode, we selected the reference electrode that yielded the highest velocity aVOR response with lower axis misalignment.

At the time of electrode implantation, the semicircular canals of the right labyrinth were plugged with fascia and bone chips via fenestrations in their thin segments. In order to assess the impact of electrode placement alone, we did not plug the canals in the left labyrinth. Instead, the two animals (ch206 and ch207) that had residual aVOR after the surgery were treated with intratympanic gentamicin on the left side, which ablated all residual sensitivity to head rotation without prosthetic input in each case. (Intratympanic gentamicin kills type I vestibular hair cells and renders type II hair cells insensitive to endolymph motion (Della Santina et al. 2005c; Hirvonen et al. 2005; Lyford-Pike et al. 2007)).

Eye movement measurement and analysis

Real-time, binocular 3D video-oculography (3D VOG) was used for recording eye movements in response to head movement or electrical stimulation. The method we employed is analogous to that described in detail previously (Migliaccio et al. 2005; Della Santina et al. 2007), except for the use of faster cameras yielding a higher sample rate. The system was installed on a dual core 2-GHz 2-GB RAM PC running Windows XP. Firewire cameras (Dragonfly Express, Point Grey Research, Richmond, BC, Canada) retrofitted with 25.0-mm focal length, f/2.0 microvideo lenses were used to acquire 500×400 pixel, 8-bit grayscale images at 180 Hz for each eye. An array of three fluorescent

yellow 0.5×0.5 -mm squares, separated by 0.5 mm and arranged in a 45° right triangle on a black film, was placed on the topically anesthetized cornea of each eye using a small amount of veterinary tissue glue (e.g., VetBond, 3M Corp) after application of proparacaine and saline eye drops. The glue forms a conformal coat over the saline film on the cornea up to the limbus, making a translucent film that remains on the eye and passes under the lids during eye movement. A set of ultraviolet light-emitting diodes (UV LEDs) illuminated each marker, and a UV cut filter on each camera maximized contrast of the markers versus reflections of the LEDs on the conjunctiva. LabVIEW software (National Instruments, Austin, TX) was used to control camera settings, threshold the image, correct lens distortion, and determine the center of each marker using a center of mass algorithm. Each eye's center of rotation was aligned by centering a pattern of corneal reflections from LEDs attached to the camera at points equidistant from the lens axis.

Eye movement data were analyzed using custom software incorporating 3D rotational kinematics. Recordings from each eye indicating horizontal, vertical, and torsional eye rotations in eye coordinates were converted to 3D rotational position in rotation vector form in a right-hand-rule canal-referenced coordinate system. Velocity vectors were calculated from the corresponding rotation vectors, then filtered using a running spline interpolation filter (LabVIEW "Cubic Spline Fit" module with balance parameter 0.99995) applied to data linearly interpolated on a 1-kHz time base. For eye responses to sinusoidal stimuli, each of the three eye movement components [horizontal, LARP (about the mean axis of the left-anterior/right-posterior SCCs), and RALP (right-anterior/left-posterior)] were separately averaged cycle by cycle for cycles free of saccades and blinks. LARP and RALP axes were approximated as being 45° off the midline and in the mean plane of the horizontal SCCs.

Motion stimulation

Whole body rotations about mean SCC plane axes were used for testing aVOR responses to natural stimuli. Each animal was rigidly mounted in a gimbal bolted to a servo-controlled motor positioned so that the center of the animal's skull was aligned with the rotator's Earth-vertical axis. The gimbal was reoriented to bring each axis of interest coincident with the rotator's axis for each of three axes: horizontal, LARP (left ear down nose up) and RALP (right ear down nose up). The horizontal aVOR was tested with the gimbal in its reference position in which the animal's horizontal semicircular canal axes were

approximately Earth-vertical. LabVIEW-based software controlled the motor. Sinusoids included rotations at 2 Hz at peak velocity $50^\circ/\text{s}$. Stimulus duration was sufficient to include at least six cycles at each frequency, and only cycles not corrupted by blinks or other artifacts were analyzed.

Electrical stimulation

The complete dataset for each individual animal was obtained in a single session lasting approximately 3 h. In all experiments, angular velocity of real or emulated head rotation about a semicircular canal's axis was used to modulate the pulse frequency of charge-balanced, symmetric, biphasic current pulses delivered to that canal's ampullary nerve. Pulse rate was modulated between 0 and 400 pps at 2 Hz along a two-segment, piecewise-linear operating characteristic running linearly from 0 pps at $-300^\circ/\text{s}$ (inhibitory head rotation for the left labyrinth) to 60 pps (head stationary) then linearly from 60 to 400 pps at $+300^\circ/\text{s}$ (excitatory head rotation for the left labyrinth). We chose the 60-pps baseline stimulation rate based on preliminary experiments (Davidovics et al. 2009) that revealed much larger responses for lower baseline rates than for the supranormal baseline rates we (Della Santina et al. 2007) and others (Lewis et al. 2001, 2002; Merfeld et al. 2006) have used previously. This rate approximates the mean resting spike rate of vestibular afferent fibers in normal chinchillas (Baird et al. 1988; Hullar et al. 2005) and is about 50% higher than the mean rate in labyrinths treated with intratympanic gentamicin (Della Santina et al. 2005c; Hirvonen et al. 2005).

The current amplitude of biphasic current pulses delivered at $350 \mu\text{s}/\text{phase}$ and 1-Hz modulation between 30 and 230 pps (half-maximal modulation) was slowly increased until signs of facial nerve stimulation were observed or an obvious shift in the eye response axis away from the target axis was detected, then lowered until these gross effects abated, typically resulting in a response amplitude of $25\text{--}50^\circ/\text{s}$ (amplitude of the best-fit single-frequency whole cycle sinusoid fit via single-frequency Fourier transform). The current amplitude and the return electrode used for monopolar stimulation delivered to the electrodes implanted in each canal are listed in Table 1. Charge per phase was kept constant for each animal once it was set during the preliminary stimulation session.

Stimulation current amplitude for each electrode was then downloaded to the multichannel vestibular prosthesis, which has been described in detail elsewhere (Della Santina et al. 2007). Pulse frequency-modulated biphasic pulse trains on the three electrodes were presented concurrently, but asynchronously,

TABLE 1

Stimulation current levels ($\mu\text{A}/\text{phase}$) and reference electrode used for each active electrode in each animal

Animal ID	Stimulation level ($\mu\text{A}/\text{phase}$) and reference electrode		
	LA electrode	LH electrode	LP electrode
ch205	120 (CC)	120 (M)	70 (M)
ch206	350 (CC)	225 (M)	70 (M)
ch207	140 (CC)	130 (CC)	170 (CC)
ch208	35 (CC)	55 (M)	120 (CC)

Amplitude and reference electrodes were determined for stimulating electrode and for each animal at the beginning of the recording session and kept constant for the duration of that experiment

LA, LH, and LP active electrode's target ampullary nerve (left anterior, horizontal, and posterior, respectively), M muscle reference electrode, CC common crus reference

ensuring no overlap in pulse presentations. In the case of a timing conflict between the channels, pulses were queued up and presented in first-in/first-out order so that only one electrode was active at any moment.

To assay eye movement responses during a large variety of prosthetically encoded rotation angles in a precise and repeatable manner and to ensure that responses measured were solely due to prosthetic input, all subsequent experiments were performed with the head stationary. In place of the gyroscope inputs that are normally sampled by the prosthesis central processor, we substituted three analog signals generated by a USB-3103DAQ data acquisition card (Measurement Computing, Norton, MA) controlled by a PC running custom software written in LabVIEW.

Assessment of linearity of electrically evoked aVOR

To assess the degree of linearity for responses to stimuli targeting a given ampullary nerve, we measured eye rotation velocities during 2-Hz sinusoidal modulation of the pulse rate at various stimulus intensities (SI) about baseline on that ampullary nerve's electrode, while pulse rates on electrodes targeting the other two ampullary nerves were kept constant at 60 pps. Changes in pulse rate encode head angular velocity, so SI is analogous to the amplitude of a sinusoidal head velocity. Down-modulating pulse rate from 60 toward 0 pps effectively encodes head rotation in the inhibitory direction, while up-modulating from 60 toward 400 pps encodes excitatory head rotation about the axis of the stimulated ampullary nerve's SCC. Using the piecewise linear mapping of the gyro-signal to pulse rate, SI of 0% delivered a steady 60 pps. SI of 50% modulated between 30 and 230 pps so that for half of the sinusoidal cycle, the pulse rate changed from 60 to 30 pps and back, and

for the second half of the cycle, the pulse rate changed from 60 to 230 pps and back. SI of 100% modulated the pulse rate from 60 to 0 pps and back during the inhibitory half of the cycle and from 60 to 400 pps during the excitatory half of the cycle. Eye responses were recorded during sinusoidal modulation stimuli presented with SI of 20%, 40%, 60%, 80%, and 100%, in random order on each of the three electrodes.

Finding parameters for precompensation matrix

To determine the linear precompensation matrix for a given animal, we first tuned pulse current as described above, typically resulting in response velocities of approximately $25\text{--}50^\circ/\text{s}$ (amplitude of best-fit whole cycle sinusoid) for 50% SI on each of the three electrode channels activated individually. We then presented a series of stimulus combinations on each of the three active electrodes, with each triplet representing an axis of head rotation in a 3D space defined by the mean horizontal, LARP, and RALP semicircular canal axes. The stimulation vector comprised three parameters, each indicating the SI on each of the individual electrodes after precompensatory remapping. Sixty-five evenly spaced stimulus vectors spanning the space of possible rotation axes in 3D were initially presented at corresponding ratios of 50% SI about the 60-pps baseline on each electrode, typically producing aVOR response velocity amplitudes in the range $25\text{--}50^\circ/\text{s}$. Using the complete set of aVOR velocity vectors in response to all commanded stimulus vectors, we then computed an optimal mapping matrix M for each animal using QR decomposition (Matlab, Mathworks, Cambridge, MA). This matrix described the least squares optimal linear 3D remapping relationship between the set of stimulus vectors and corresponding response vectors. The inverse of this matrix was then used for subsequent experiments to compute SI commands for each electrode given an arbitrary desired aVOR rotation axis and velocity. A similar approach was independently described in a recently awarded patent that included claims to the use of linear algebraic coordinate transformations in the setting of prosthetic vestibular stimulation (Merfeld 2008).

Preliminary experiments revealed that using SI other than 50% produced matrices which were similar to the one derived from using the SI of 50%. For consistency, we used 50% SI to derive the optimal mapping matrix M for each of the animals used in these experiments.

Assessing aVOR responses to precompensated stimuli

To assay the response to precompensated prosthetic stimuli for a given desired head rotation axis, a ten-

cycle burst of 2-Hz sinusoidal pulse frequency modulation was presented with the relative SI on each of the three active electrode channels set according to the appropriate output of Eq. 2. This was repeated in random order for 65 axes chosen to span a hemisphere at 22.5° intervals. For each axis tested, stimulation was presented at different SI, corresponding to 12.5, 25, 37.5, 50, 75, and $100^\circ/\text{s}$ desired peak eye rotation response at 2 Hz. Assuming a normal chinchilla aVOR gain of ~ 0.4 , these correspond approximately to head rotations at peak velocity 32, 62, 94, 125, 188, and $250^\circ/\text{s}$. An analogous set of responses was measured on each animal using frequencies of 0.2, 0.5, 2, and 5 Hz at $25^\circ/\text{s}$ desired peak eye rotation velocity. The aVOR responses about each of the three spatial components (horizontal, LARP, and RALP) were measured in terms of the amplitudes of the best-fit whole cycle sinusoid at the same frequency as the stimulus. Measured aVOR responses were compared to the expected eye rotations, defined as being about the same axis as the intended virtual head rotation and with speed equal to that predicted for a normal chinchilla undergoing a true head rotation about the specified axis. We assumed a mean aVOR gain and phase of 0.5° and 0° , respectively, for normal chinchillas at 2 Hz (Della Santina et al. 2007).

Statistical methods

Linearity of single-channel responses was quantified using the Pearson correlation coefficient for a least mean square error linear fit. To determine whether misalignment and error in eye velocity were significantly different between the uncompensated and precompensated paradigms, we used a multivariate general linear model constructed and analyzed using SPSS 16.0 software (SPSS Inc., Chicago IL).

RESULTS

When a normal chinchilla is rotated sinusoidally at 2 Hz and $50^\circ/\text{s}$ peak about the mean axis of each coplanar pair of semicircular canals, normal aVOR responses are only partially compensatory for the head rotation, with the resulting eye movements being opposite the direction of head rotation but at only about half the head velocity (Fig. 1A, column 1). After unilateral gentamicin treatment, responses to sinusoidal head rotation become asymmetric, with a near-normal aVOR response during rotation toward the normal ear and attenuated response during ipsilesional rotation (Fig. 1A, column 2). After canal plugging, electrode insertion, and gentamicin treatment resulting in bilateral vestibular deficiency, no aVOR response is observed for head rotation in either

direction (Fig. 1A, column 3). When the same animal (ch207) is electrically stimulated at 50% SI on individual SCCs' electrodes, current spread to non-targeted branches of the vestibular nerve is evident in that the aVOR response axis does not align well with the intended axis (especially for that RALP case of Fig. 1A, column 4). Precompensatory adjustment of the stimuli attenuated the undesired response components and normalized both the axis and amplitude of the response (Fig. 1A, column 5). Asymmetry was observed in the responses for all four animals, indicating that unilateral prosthetic stimulation restores a bilaterally vestibular-deficient animal to a state similar that of an animal with a single normal labyrinth (i.e., Fig. 1A, column 2).

Similar improvement in the axis alignment was evident for all four experimental animals when we compared observed and actual axes of aVOR response for modulation of each SCC's electrode individually (Fig. 1B).

To assess whether the relationship between single-channel SCC stimulation intensity and aVOR response velocity is sufficiently linear to justify use of a linear precompensation scheme, we assayed aVOR response amplitude for each animal as a function of SI amplitude (Fig. 2). The Pearson correlation coefficient for a linear fit between the SI amplitudes and the corresponding aVOR response amplitudes was >0.93 in all cases.

Observed aVOR responses matched desired amplitude and axis better when precompensation was used to correct for axis misalignment than did responses to stimuli presented without precompensation. Figure 3 compares desired and actual aVOR responses for 16 stimulus vectors without (panel A) and with precompensation (right panel B). In the first case, stimuli without precompensation were presented at 50% SI. In the second case, precompensation was used to correct for axis misalignment and to specify desired $25^\circ/\text{s}$ peak eye velocities. Misalignment is clearly reduced by precompensation. This reduction of misalignment is also apparent in (Fig. 3C, D), which shows misalignment without and with precompensation for all 65 head rotation axes emulated during the experiment. Precompensation also reduced errors in the speed of eye movement responses (Fig. 3E, F).

To discern whether animal tested, order of stimulus presentation, axis of desired response, and/or combinations of these factors significantly affected misalignment and amplitude error of responses, these factors were included in the multivariate general linear model as independent variables. Order of presentation was defined by binning data acquired within each of two test sessions (either uncompensated at 50% SI and 2 Hz or precompensated at $25^\circ/\text{s}$ desired velocity and 2 Hz), each of which comprised

FIG. 1. **A** Precompensatory 3D remapping improves both axis and amplitude of prosthesis-encoded head velocity percept. *Column 1* Mean head and eye velocity for a normal chinchilla during 50°/s peak 2-Hz whole body rotations in darkness about the axis of each coplanar pair of semicircular canals (SCC): horizontal (*top row*), left anterior/right posterior (LARP, *middle row*), and right anterior/left posterior (RALP, *bottom row*). For clarity, only mean responses are shown; the standard deviation for each trace was <6°/s. Eye traces are inverted to compare with head. Normal chinchillas exhibit good alignment with head rotation axis and symmetric gain (eye velocity/head velocity) of about 0.5 (data from Della Santina et al. 2007). *Dashed curves* indicate mean responses for all animals studied. *Column 2* aVOR responses for chinchillas treated with intratympanic

gentamicin (ITG) in one ear are attenuated during ipsilesional rotation. *Column 3* Head rotation of a bilaterally vestibular-deficient animal (ch207) after ITG and canal plugging elicits no response for any axis when prosthesis is off. *Column 4* Responses for the same animal when pulse rates on individual electrodes implanted in the left labyrinth SCCs are modulated *without precompensatory 3D remapping*. Misalignment due to current spread is evident for all three axes of rotation. *Column 5* aVOR responses of the same animal to stimuli *with precompensatory 3D remapping* are like those of animals with a single working labyrinth (*column 2*). **B** 3D aVOR responses to prosthetic stimuli encoding head rotation about each of the three SCC axes *without* (B1) and *with* (B2) precompensatory 3D remapping for each of four implanted animals.

measurements of 65 different desired axes presented in random order divided into ten epochs. The first epoch comprised responses from the first ten presentations, the second epoch had the responses from the second ten, and so on. Desired eye rotation axis was similarly binned into four sectors of space to determine whether misalignment and velocity error varied systematically with desired axis.

Responses to precompensated stimuli were significantly better than uncompensated responses, inde-

pendent of all other factors, yielding smaller misalignment ($p < 0.001$) and smaller error in eye velocity amplitude ($p < 0.001$). This was true for every animal, although differences between animals were significant for both misalignment and velocity error ($p < 0.001$). Order of presentation had no significant effect alone on misalignment or velocity error ($p = 0.91$ and 0.55 , respectively), nor did it have any significant effect in combination with other factors, suggesting that adaptation and central compensation did not occur to

FIG. 2. Amplitude of best-fit whole cycle sinusoid velocity of aVOR response to stimuli delivered on an electrode near the horizontal (A), anterior (B), and posterior (C) semicircular canals of the left labyrinth in each of four chinchillas. Velocity varies almost linearly with stimulus intensity (pulse frequency depth of modulation as defined in text). $R^2 > 0.93$ for linear fit in each case.

a substantial degree during an experiment. The 3D orientation of the desired eye rotation axis (i.e., the inverse of the head rotation axis being encoded) did not significantly affect misalignment ($p=0.21$), but did have a significant effect on velocity error ($p < 0.001$), which was lowest for desired eye rotation axes within the sector for which inputs to all three SCCs were excitatory. This reflects asymmetry of responses to unilateral prosthetic stimulation, which are evident in Fig. 1A, column 5.

Pooling responses to all 65 vectors over a range of simulated head velocities for each of the four animals, the misalignment error between the desired axes of rotations and the corresponding aVOR responses was $27.5 \pm 14.4^\circ$ (mean $\pm$ SD) for the 50% SI stimuli prior to precompensation. After precompensation, misalignment decreased to $16.5 \pm 9.6^\circ$. For each animal, misalignment and velocity errors were lower with precompensation than without. This reduction in error was most pronounced for stimuli representing faster head rotations (Fig. 4A).

For each of the animals, the aVOR response velocity after precompensation increased as expected with increases in the desired aVOR velocity (Fig. 4B). Pearson correlation coefficient for a linear fit between the desired and recorded aVOR response amplitudes was 0.8014.

Response dynamics evaluated for all 65 vectors spanning the possible 3D head rotation axes for each of four frequencies (0.2, 0.5, 2, and 5 Hz) at $25^\circ/\text{s}$ desired eye velocity amplitude showed a high-pass characteristic somewhat similar to that of the normal aVOR (Della Santina et al. 2007; Fig. 4C). The cutoff frequency, f_c , for a least squares fit of a single-order high-pass filter to the frequency response data in Fig. 4C (averaged across all animals in decibels at

each frequency) was 0.42 Hz, corresponding to a time constant, τ , of 0.38 s. This is between the values we observed for normal chinchillas ($f_c \sim 0.05\text{--}0.1$ Hz; $\tau \sim 1.6\text{--}3.2$ s) and prosthetically stimulated animals ($f_c \sim 2$ Hz; $\tau \sim 0.08$ s) in our previous study (Della Santina et al. 2007). It is different from values reported previously for normal chinchillas by Merwin et al. (1989) ($f_c \sim 0.02$ Hz; $\tau \sim 7.5$ s). However, the present study's result must be considered in light of variability across animals, asymmetry of responses, and the fact that because our focus here was on eye movement alignment (which was evaluated in each case for multiple replicates of 65 different directions), the evaluation was repeated for only four frequencies in the range for which aVOR dominates gaze stabilization. None of those frequencies tested was low enough to unambiguously identify an inflection point in the frequency responses. Comparison to frequency response data from Gong et al. for the electrically evoked aVOR in guinea pig is complicated by their use of response normalization and a high-pass filter to condition gyro output signals (Gong and Merfeld 2002); however, their data revealed a similar high-pass shape, $f_c \sim 0.5$ Hz and a somewhat steeper fall in gain with decreasing frequency.

DISCUSSION

Our observations confirm that prosthetically evoked aVOR responses exhibit linearity and vector summation to sufficient extent that a precompensation strategy incorporating a linear coordinate system transformation computed from a set of desired and actual response amplitudes can significantly correct misalignment of 3D aVOR responses (and presumably

FIG. 3. When precompensatory 3D remapping is employed, axis and speed of observed aVOR eye rotation responses align better with desired responses for virtual head rotations about any 3D axis as compared to the responses to uncompensated rotations. **A** Desired and actual eye velocity for 16 different directions tested prior to precompensation, each at 2 Hz and 50% stimulus intensity (*SI*, defined in text). Axis and speed are represented by orientation and length, respectively, of plotted vectors. *Dashed lines* define a head-based coordinate system comprising the horizontal, left anterior/right posterior (LARP) and right anterior/left posterior (RALP) axes; the length of each denotes 50°/s peak head velocity which would evoke

an eye velocity of approximately 25°/s in a normal chinchilla. **B** Results for the same 16 desired rotations after precompensation (again 2 Hz, desired peak velocity 25°/s). *Thick lines* indicate error between response and stimulus. Errors are significantly smaller after precompensation. **C** Misalignment (angle between desired and actual eye rotation axis) for each of the 65 virtual head rotations tested without precompensation. Azimuth and elevation of each axis is as defined in **B**. **D** Misalignment is significantly smaller after precompensation. **E, F** Peak velocity for same cases as in **C** and **D**. Responses to precompensated stimuli are significantly closer to the desired velocity of 25°/s.

of head movement percepts) that would otherwise occur due to current spread from each electrode to axons outside its target nerve branch. This optimal transformation, which effectively encodes both a reorientation and a rescaling of stimulus intensities, significantly corrected both the axis and amplitude of eye rotational velocity, with the degree of correction greatest at the largest amplitudes tested. Incorporating this correction allowed us to maintain 3D aVOR alignment while reliably achieving larger peak eye

movement response velocities than we and others have reported previously (Gong and Merfeld 2000; Lewis et al. 2001, 2002; Della Santina et al. 2005a, b; Merfeld et al. 2006, 2007; Della Santina et al. 2007; Gong et al. 2008; Lewis et al. 2008, 2009). Responses to unilateral prosthetic stimulation exhibited excitation–inhibition asymmetry both before and after precompensation, similar to responses of animals with a single normal labyrinth experiencing natural head rotation stimuli.

FIG. 4. **A** Misalignment angle for aVOR responses to prosthetic input is less with precompensation than without and smallest for high velocity head rotation. **B** The relationship between desired and observed aVOR responses with precompensation clusters around equality for all four implanted animals. **C** As for normal animals (Della Santina et al. 2007), a high-pass characteristic is noted for each animal's aVOR response as a function of the modulation frequency encoding virtual 50°/s head rotations.

Asymmetry of responses to unilateral prosthetic stimulation

Prior studies of prosthetic stimulation using unilaterally implanted, head-mounted devices have tried to achieve symmetric eye movement responses to sinusoidal head rotations by modulating stimuli about a baseline rate that is well above that of most normal vestibular afferents. For example, we previously used

baseline rates of 100 pps in chinchillas (Della Santina et al. 2005a, b, 2007), while Gong et al. have used baseline rates of 150 pps in guinea pigs (Gong and Merfeld 2000), 200 pps in squirrel monkeys (Gong et al. 2008), and 250 pps in rhesus monkeys (Lewis et al. 2008), greater than or equal to two times the mean resting rate of normal vestibular afferents in each case. The rationale underlying this has been to expand the dynamic range over which a unilaterally implanted prosthesis can use downward modulation of pulse rate to encode inhibitory head rotations.

We departed from that approach in the present study, choosing instead a lower baseline pulse rate closer to spontaneous discharges rates measured in normal vestibular afferents. This change was motivated by our recent observation that while supernormal baseline rates result in roughly symmetric responses, those responses are almost invariably smaller in amplitude than those we can achieve when using baseline rates that better approximate the mean spontaneous firing rate of normal vestibular afferents. A baseline rate of 60 pps was selected based on results of a previous study of chinchillas treated unilaterally with intratympanic gentamicin that found spontaneous rates of 55 ± 20 (mean $\pm$ SD) spike/s for 62 control side vestibular afferent fibers and 36 ± 15 for 122 treated side afferents (Della Santina et al. 2005c), consistent with prior studies by others (Hullar and Minor 1999; Hirvonen et al. 2005).

Using this lower baseline rate has reliably resulted in peak excitatory responses exceeding 100°/s (Fig. 4B). While lower baseline rates leave less room for encoding inhibitory head rotation and thus result in an obvious excitation–inhibition asymmetry (e.g., Fig. 1A, column 5), the degree of asymmetry is similar to that observed in animals that have one normal labyrinth and one gentamicin-treated labyrinth (Fig. 1A, column 2; also see (Jones et al. 2003; Della Santina et al. 2005c)). Since the latter animals represent our goal with a unilateral prosthesis (i.e., to restore one implanted labyrinth to near-normal function after bilateral vestibular sensory loss), we consider this degree of asymmetry acceptable. Clinical experience demonstrates that patients with one remaining normal labyrinth typically compensate very well after unilateral gentamicin treatment (Carey et al. 2002b) or labyrinthectomy (e.g., Diaz et al. 2007), ultimately becoming essentially asymptomatic during most head movements typical of daily life. This occurs despite the fact that afferent firing rates do not rise to supernormal levels in the intact labyrinth after contralateral gentamicin treatment (Hullar and Minor 1999; Della Santina et al. 2005c; Hirvonen et al. 2005) or labyrinthectomy (Sadeghi et al. 2007a).

We used single-valued measures of best-fit whole cycle sinusoid amplitude for stimulus intensity and

response velocity rather than half-cycle measures because we sought to design a single optimal pre-compensation matrix for each animal. Excitation–inhibition asymmetry was explicitly incorporated via the piecewise-linear, two-segment mapping from gyro input to pulse rate on the corresponding electrode channel. As evident from Fig. 3, this approach was successful in reducing misalignment and correcting amplitude. It might be possible to improve response alignment and amplitude fidelity even further by devising a more elaborate scheme that involves different matrices for excitatory and inhibitory inputs. However, using different matrices for excitatory and inhibitory inputs would be cumbersome, because one could then require eight matrices to account for all possible combinations of excitatory and inhibitory inputs on three gyro input channels.

The ideal shape of the mapping from gyro input to pulse rate has yet to be determined, and further optimization to maximize both response amplitude and symmetry might be possible. Apart from yielding large-amplitude responses with asymmetry similar to that observed during natural stimulation of animals with a single normal labyrinth, the simple piecewise-linear mapping used in the present study allowed us to examine the linearity of physiologic responses without the potential confounding effect of the multiple degrees of freedom available when specifying the shape of a sigmoidal mapping curve.

Key differences between natural and prosthetic ampullary nerve stimulation

Each normal ampullary nerve contains ~1,500 asynchronously firing afferent fibers (Boord and Rasmussen 1958) with a diversity of spontaneous rates, baseline firing rate variability, thresholds, sensitivities, excitation/inhibition asymmetries, and terminal locations in the cristae (Goldberg 2000). This allows an ampullary nerve to convey much more information than could be conveyed by a single axon. For example, a group of afferents with a wide range of thresholds and sensitivities can provide a quasi-linear ensemble signal over a wide dynamic range of head velocities. Similarly, afferents with different response dynamics (e.g., due to crista location and morphology of their synapses with hair cells) can encode different frequency components of transient and sustained head movements. Stochastic independence between fibers further increases the amount of information carried by the ensemble (Sadeghi et al. 2007b).

In contrast, pulsatile prosthetic stimuli like those we currently use probably evoke nearly synchronous action potentials in all afferent fibers for which the pulse is above threshold. Our present inability to controllably excite different subpopulations of axons

that normally have different thresholds for head rotation probably restricts the dynamic range over which we can accurately encode head velocity. The pattern of fiber activity presented to vestibular nuclei is probably further distorted by the fact that fibers with irregular spontaneous discharge are more sensitive to applied currents than are regular fibers (Goldberg et al. 1984), and larger caliber axons tend to be more sensitive to applied current than are thinner fibers. Irregular, large-caliber fibers tend to terminate in calyceal synapses with type I hair cells in the central zone of the crista, and their natural responses tend to be more phasic (i.e., more nearly in phase with head acceleration than velocity) and less linear than those of regular afferents terminating on boutons. Thus, near-threshold prosthetic electrical stimuli might initially be “interpreted” by vestibular nuclei as representing a head rotation with different frequency content than that measured by the gyros. Refinements of pulse shape may help us semi-selectively exploit differences in activation dynamics of different classes of fibers, but for now, the signal we can present to the brainstem is a relatively crude facsimile of normal.

Another difference between the prosthetic stimuli we provide and sensory signals reported by a single normal labyrinth during natural head movement is that prosthetic/electrical input to targeted ampullary nerves may be incongruent with activity (or lack thereof) on the ipsilateral macular nerves. For example, during a head roll about an Earth-horizontal axis (EHA), aVOR responses to ampullary nerve activity are normally augmented by responses to macular nerve inputs driven by the utricle and saccule. This effect is most prominent for low-frequency EHA movements (as shown by Dickman et al. 2000 for pigeon and Hess and Angelaki 1997 for rhesus monkeys), while canal-mediated components dominate for all Earth-vertical axis (EVA) rotations and for EHA rotations at frequencies above about 0.1 Hz. Otolith-mediated contributions were probably minimal for the data we present, because all our stimuli were ≥ 0.2 Hz, all our mechanical stimuli were EVA, and we kept animals stationary during electrical-only stimuli. However, an animal wandering around in its cage while using a prosthesis would experience some EHA rotations at <0.1 Hz. Under those conditions, lack of macular nerve modulation during EHA low-frequency rotations would be incongruent with prosthetic ampullary nerve stimuli (and conversely, any residual otolith endorgan mechanosensitivity would probably augment the aVOR).

Our data confirm that congruence among all ampullary and macular nerves is not a prerequisite for eliciting an aVOR sufficient to stabilize gaze, at least over the frequency range for which the aVOR is most essential for maintaining stable gaze. Many

examples of nystagmus elicited by incongruent labyrinthine inputs exist (e.g., benign paroxysmal positional vertigo; Tullio phenomenon in superior canal dehiscence; unilateral stimulation studies by Ewald, Cohen, Suzuki, and others; see Carey and Della Santina 2005 for review). In the case of the prosthetic electrical stimulation experiments presented here, the unimplanted labyrinth is not reporting any movement at all (via canals or otolith endorgans) in a stationary animal receiving prosthetic electrical stimuli via one implanted ear, yet this did not preclude eliciting VOR responses that align well with the 65 desired axes we tested. Therefore, we conclude that congruent mechanical input via the contralateral macular nerves is not needed to evoke VOR responses that can stabilize gaze.

How ipsilateral macular nerve input is integrated with prosthetically evoked ampullary nerve input is an interesting question. Using the prosthesis should allow partial decoupling of parts of the labyrinth to facilitate answering this question in future studies. To the extent that electrical stimulation intended for ampullary nerves spreads to excite the utricular and/or saccular nerves, the compensation procedure we used could be extended to leverage that current spread and improve misalignment during Earth-horizontal rotations.

Fortunately, neural signal pathways mediating the vestibulo-ocular reflex are highly adaptive, and prosthetic electrical stimulation can clearly elicit aVOR responses similar to those evoked by a normal labyrinth over a fairly wide range of head velocity and frequency. Nonetheless, we continue exploring approaches to optimization of stimulus encoding to reduce the burden on central compensatory mechanisms and expand the dynamic range over which prosthetic stimuli can accurately encode head rotation (Davidovics et al. 2010)

Translating the approach toward human application

Although linear precompensation works well to correct alignment and amplitude of the electrically evoked 3D aVOR in chinchillas, the extent to which this approach will be necessary and effective when vestibular prostheses are applied to humans is difficult to predict with certainty. Distances between neighboring ampullary nerves in the human labyrinth are larger than those in chinchillas, while precision of surgical positioning should be about the same, so the amount of current spread to non-target nerve branches might be less in humans and might be low enough that precompensation becomes unnecessary. The few data available are inconclusive: recent attempts to selectively stimulate the posterior ampul-

lary nerve intraoperatively in alert humans apparently did not result in eye rotations purely about the desired axis (Wall et al. 2007), whereas the posterior ampullary nerve is usually the easiest branch of the chinchilla vestibular nerve to stimulate intensely with high selectivity and low misalignment. Tests of vestibular prosthetic stimulation in rhesus monkeys, which are intermediate in size between chinchillas and humans, suggest that misalignment may be slightly better than in chinchillas implanted using similar techniques (Lewis et al. 2009; Dai et al. 2010).

Years of clinical and research experience with cochlear implants suggest that the success of vestibular prostheses intended for human use will depend on multiple other factors. Cochlear implant users vary widely in their ability to perceive speech (Firszt et al. 2004; Zeng 2004; Wilson and Dorman 2008). Much of that variability is apparently due to differences in the survival and plasticity of neural substrates available to electrodes (e.g., cochlear nerve axons, the cochlear nucleus neurons upon which they synapse, and other brainstem and midbrain nuclei en route to auditory cortex), prompting efforts to preserve those substrates through anticipatory pharmacologic protection from ototoxic agents (Chen et al. 2007); intralabyrinthine delivery of growth factors, stem cells, and gene therapy (Hendricks et al. 2008); and, when no better alternative exists, prompt implantation and delivery of neuroprotective prosthetic input (Ryugo et al. 2005; Stakhovskaya et al. 2008).

Beyond optimizing the neuronal milieu, multiple design and rehabilitative techniques might be enlisted to further optimize responses to prosthetic stimulation beyond the results achieved using linear algebraic precompensation. These include:

1. Improvements in electrode design and surgical technique could help place cochlear electrodes nearer to their neural targets and further from neighboring axons (e.g., Gstoettner et al. 2001; Middlebrooks and Snyder 2007). Similar efforts may help optimize electrode-nerve coupling for vestibular prostheses.
2. Multipolar stimulation paradigms can provide more selective cochlear nerve stimulation by “steering” the current toward target axons between adjacent electrodes (Bonham and Litvak 2008); a similar approach may help to steer current toward one ampullary nerve and away from another (Chiang et al. 2009).
3. Optimization of stimulation parameters (e.g., pulse shapes, durations and intensities) might exploit the differential sensitivity of irregular and regular vestibular afferent fibers to electrical stimuli, allowing implant designers better control over the constellation of activity delivered to vestibular

nuclei by different classes of vestibular afferent (Gorman and Mortimer 1983; Goldberg et al. 1984; Goldberg 2000; Merrill et al. 2005). If it can be achieved, semi-selectively addressing irregular afferents and regular fibers via different pulse shapes or amplitudes might enable the prosthesis to better encode quick, transient head rotations.

4. Cross-axis adaptation mechanisms should help trim up responses to prosthetic vestibular nerve stimuli distorted by spurious stimulation of non-target branches. Multiple studies suggest this should occur but also demonstrate that there are limits to cross-axis adaptation (e.g., Hay 1968; Miles and Fuller 1974; Miles et al. 1980; Viirre et al. 1998; Ma et al. 2000; Lewis et al. 2001). The closer we can bring the initial response to our desired outcome, the more likely it is that central adaptive mechanisms can finish the job (Schubert et al. 2008). Vestibular rehabilitation exercises enhance vestibular compensation after unilateral labyrinthine injury by enlisting adaptive vestibulocerebellar circuits to improve gaze and postural stability (Szturm et al. 1994; Scherer et al. 2008; Schubert et al. 2008). After unilateral labyrinthectomy, the central nervous system is quite adept at asymmetric adaptation during visuo-vestibular conflict exercises designed to augment aVOR gain during head rotations toward the deficient side (Ushio et al. 2009). Analogous exercise regimens might be harnessed to help implant users to adapt to prosthetic input.
5. In the work presented here, we focused on creating a single compensation matrix based on the best-fit whole cycle sinusoid. While the aVOR responses to precompensated stimulation clearly show reduced misalignment between the desired and actual responses, it may be possible to reduce this error further by taking into account the response asymmetry between the excitatory and inhibitory phases of sinusoidal stimulation. This could be accomplished in future studies by creating more elaborate precompensation scheme based on two sets of coefficients in which one set would correspond to the aVOR responses to excitatory stimulation delivered to a particular electrode and the second to the inhibitory stimulation. Further experiments that investigate adaptation to chronic stimulation should elucidate the need for developing a more complex precompensation scheme.

Developers of vestibular prostheses may need to enlist all of the approaches above to achieve the desired result of restoring gaze stability and more normal perception of head movement to individuals disabled by bilateral loss of labyrinthine function.

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