Exp Brain Res (2006) 175:471–484
DOI 10.1007/s00221-006-0567-7

RESEARCH ARTICLE

Dynamics of the horizontal vestibuloocular reflex after unilateral labyrinthectomy: response to high frequency, high acceleration, and high velocity rotations

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Received: 13 January 2006 / Accepted: 16 May 2006 / Published online: 29 June 2006

Abstract Loss of vestibular information from one labyrinth results in a marked asymmetry in the horizontal vestibuloocular reflex (VOR). The results of prior studies suggest that long-term deficits in VOR are more severe in response to rapid impulses than to sinusoidal head movements. The goal of the present study was to investigate the VOR following unilateral labyrinthectomy in response to different stimuli covering the full range of physiologically relevant head movements in macaque monkeys. The VOR was studied 1–39 days post-lesion using transient head perturbations (up to 12,000°/s^2), rapid rotations (up to 500°/s), and sinusoidal rotations (up to 15 Hz). In response to rotations with high acceleration or velocity, both contra- and ipsilesional gains remained subnormal. VOR gains decreased as a function of increasing stimulus acceleration or velocity, reaching minimal values of 0.7–0.8 and 0.3–0.4 for contra and ipsilesional rotations, respectively. For sinusoidal rotations with low frequencies and velocities, responses to contralesional stimulation recovered within ~ 4 days. With increasing velocities and frequencies of rotation, however, the gains of contra- and ipsilesional responses remained subnormal. For each of the most challenging stimuli tested (i.e., 12,000°/s^2 transient head perturbations, 500°/s fast whole-body rotations and 15 Hz stimulation) no significant compensation was observed in contra- or ipsilesional responses over time. Moreover, we found that gain of the cervico-ocular reflex (COR) remained negligible following unilateral loss indicating that neck reflexes did not contribute to the observed compensation. VOR responses elicited by both sinusoidal and transient rotations following unilateral labyrinthectomy could be described by the same mathematical model. We conclude that the compensated VOR has comparable response dynamics for impulses and sinusoidal head movements.

Keywords VOR · Unilateral labyrinthectomy · High frequency · High acceleration · High velocity

Electronic Supplementary Material Supplementary material is available to authorised users in the online version of this article at http://dx.doi.org/10.1007/s00221-006-0567-7.

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Introduction

Because of its relative simplicity, the vestibuloocular reflex (VOR) has become an important model system for understanding neuronal mechanisms of motor plasticity and compensation following injury. The response dynamics of VOR compensation have been extensively studied in a variety of mammalian species including humans, monkeys, cats, and guinea pigs (for review see Smith and Curthoys 1989). Most testing has been done for frequencies less than 2 Hz and velocities less than 40°/s (e.g., Mathog 1972; Keller 1978; Bohmer and Henn 1983; Kasteel-Van Linge and Mass 1990; Peterka et al. 1990; Demer et al. 1993). Although there are species differences, there is general agreement that

immediately following the lesion, there is a marked asymmetry in gain characterized by diminished responses to rotations that would be excitatory for the lesioned side. In addition, the recovery of the gain and symmetry of the VOR is relatively complete within ~ 30 days across species (guinea pig: Smith and Curthoys 1988a, b; human: Allum et al. 1988; Curthoys and Halmagyi 1995).

Long-term deficits in VOR performance become more pronounced for rotational stimuli with higher peak velocities (cats: Maioli et al. 1983; squirrel monkeys: Paige 1983b; Lasker et al. 2000; and humans: Paige 1989; Galiana et al. 2001) and frequencies (cats: Broussard et al. 1999; squirrel monkeys: Lasker et al. 2000). For example, for the most dynamic sinusoidal rotations that have been tested (Lasker et al. 2000), response gains decrease by half for ipsilesional rotations, and even contralesional responses show some attenuation relative to normal values. More marked asymmetries can be observed in responses evoked by head impulses with accelerations of 1,500–3,000°/s^2 (guinea pig: Gilchrist et al. 1998; squirrel monkey: Lasker et al. 2000; human: Halmagyi et al. 1990; Crane and Demer 1998). This latter finding has led to the suggestion that deficits in the VOR following unilateral labyrinthectomy are more severe in response to impulses than to sinusoids (Gilchrist et al. 1998).

To date, prior studies of the horizontal VOR following labyrinthectomy have probed only a limited part of the stimulus space that characterizes natural head movements. The frequency content of head movements during activities such as running and gaze shifts approaches 20 Hz in humans and monkeys (Grossman et al. 1988; Armand and Minor 2001; Huterer and Cullen 2002). Moreover accelerations can reach 25,000°/s^2 with velocities up to 400–500°/s (Armand and Minor 2001; Roy and Cullen 2003). In normal monkeys and humans, the VOR is compensatory for frequencies as large as 15–26 Hz (Minor et al. 1999; Huterer and Cullen 2002; Ramachandran and Lisberger 2005), velocities as large as 300–500°/s (Paige 1983a; Huterer and Cullen 2002; Roy et al. 2003; Tomlinson 1990).

Here our primary goal was to characterize response dynamics of the horizontal VOR after unilateral labyrinthectomy, over the full range of physiologically relevant head movements in macaque monkeys. Figure 1a schematically illustrates the stimuli tested in the present study in comparison to previous studies of VOR compensation following labyrinthectomy. In the present study, we tested a far more extensive range of head movements than had been employed in previous studies. Stimuli included sinusoidal rotations with frequencies up to 15 Hz (red), head perturbations with accelerations up to 12,000°/s^2 (blue), and whole-body rotations with velocities up to 500°/s (green).

Materials and methods

Surgical preparation

Three macaque monkeys (*Macaca fascicularis*) were prepared for chronic behavioral experiments under aseptic conditions. All procedures were approved by the McGill University Animal Committee and Johns Hopkins University Animal Care and Use Committee and were in compliance with the guidelines of the Canadian Council on Animal Care and the National Institutes of Health.

Preparation for chronic behavioral recordings

The surgical procedure and postoperative care have been described elsewhere (Sylvestre and Cullen 1999). Briefly, a dental acrylic implant was attached to each animal's skull using stainless steel screws. A stainless steel post was embedded within the implant, which was used to restrain the animal's head during the experiment. Additionally, a 16–17 mm diameter eye coil, consisting of three loops of Teflon-coated stainless steel wire, was sutured to the sclera of the eyes beneath the conjunctiva.

Unilateral labyrinthectomy

Labyrinthectomy was performed as has been previously described (Lasker et al. 2000). A postauricular incision was made and the mastoid bone was removed with an otologic drill and curettes to expose the horizontal and posterior semicircular canals. The petrous bone was removed further anteriorly and superiorly to visualize the superior canal near its union with the common crus. Each of the semicircular canals then was obliterated with removal of the ampulla. The vestibule was entered, and the utriculus and sacculus were removed. The internal auditory canal was opened next, and the distal ends of the ampullary nerve branches were removed. The space created by the labyrinthectomy was packed with muscle and fascia and the postauricular incision was closed.

Data acquisition

The experimental set-up, apparatus, and methods of data acquisition were similar to those that have been

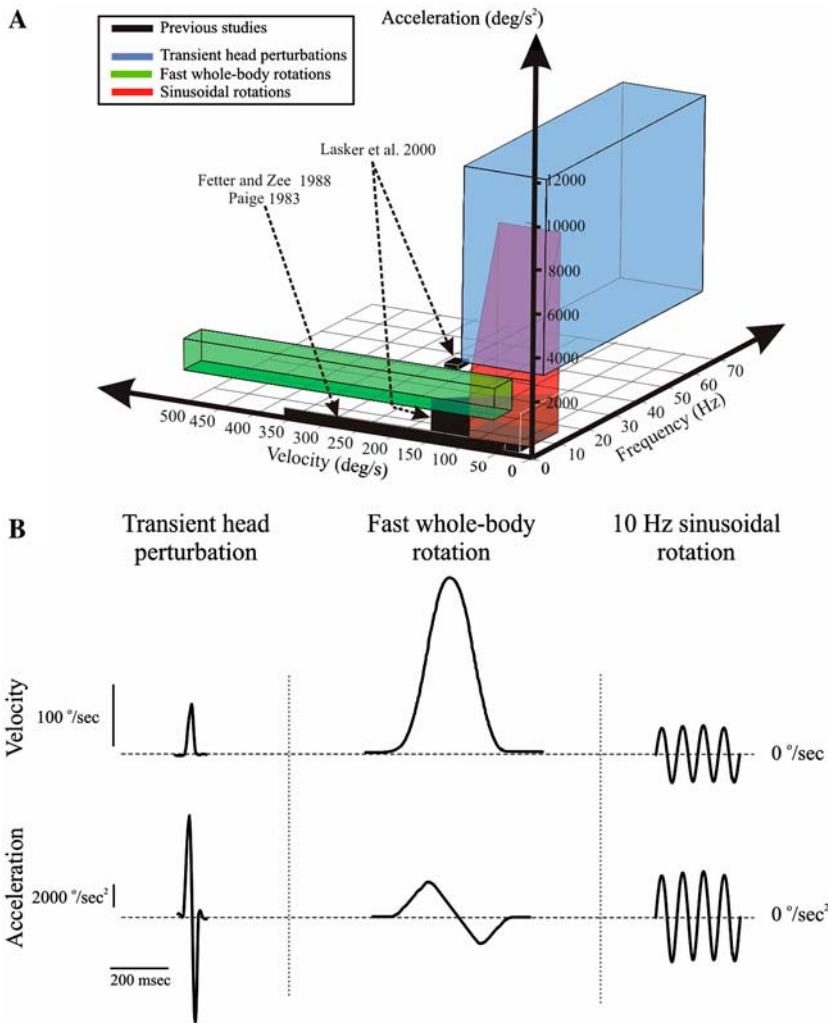

Fig. 1 Rotational stimuli used to investigate compensation of the horizontal VOR after labyrinthectomy. **a** Comparison of stimuli used in the present study with those of previous studies. *Each box* is a three-dimensional representation, which corresponds to the frequency, velocity, and acceleration of the head movements that were applied. Previous studies in nonhuman primates (*black boxes*) have used frequencies of up to 15 Hz, peak velocity of 20°/s (Lasker et al. 2000), accelerations of 3,000°/s with peak velocities of 150°/s (Lasker et al. 2000), and velocities of up to 360°/s with low frequencies of 0.2 Hz (Paige 1983b; Fetter and Zee 1988). The stimuli used in the present study included transient head-on-body perturbations with accelerations of up to 12,000°/s^2 (*blue boxes*), fast whole-body rotations with velocities up to 500°/s (*green boxes*), and sinusoidal rotations with frequencies of up to 15 Hz (*red boxes*). **b** *Examples of the velocity and acceleration profiles produced by the three types of stimuli used in the present study. Left panel: transient head perturbations with acceleration of 8,000*°/s^2 and peak velocity of 80°/s. *Middle panel*: fast whole-body rotation with peak velocity of ~ 400°/s and acceleration of ~ 3,000°/s^2. *Right panel*: sinusoidal rotation at 10 Hz with peak velocity of 40°/s. The three examples are shown using the same time and amplitude scales

described for studies of the horizontal angular VOR in normal macaque monkeys (Huterer and Cullen 2002). During the experiments the animals were comfortably seated in a primate chair and the head was restrained in the stereotaxic position. In this position, the horizontal canals were pitched up 12° from earth horizontal (Reisine et al. 1988). The monkey's head was centered within a 1-m magnetic field system (CNC Engineering). Head and gaze position signals were recorded using the magnetic search coil technique (Fuchs and Robinson 1966). The head coil was mounted within a rigid mould that was bolted to the animal's head implant to minimize the separation of the head and eye coil in the magnetic field (< 5 cm) and leads were embedded in foam to minimize movement (see Fig. 1 of Huterer and Cullen 2002). The head–coil assembly provided the monkey with an unobstructed field of view of ± 30° relative to primary position. Data acquisition and vestibular stimulation (see below) were controlled by a QNX-based real-time data-acquisition system (REX)

(Hayes et al. 1982). Gaze and eye position signals were low-pass filtered at 250 Hz by an 8 pole Bessel filter and sampled at 1 kHz. The sampled signals were digitally filtered at 125 Hz.

Rotational paradigms

Monkeys were tested before the labyrinthectomy to obtain pre-lesion VOR data and then following labyrinthectomy on days 1, 4, 8, 11, 18, 25, 32 and 39. Animals were initially head restrained at the beginning of each session. The monkey's eye coil calibration was verified by having the animal make saccades to a laser target. Monkeys were then left stationary in darkness for 2 min, while their spontaneous nystagmus was recorded. The VOR elicited by rotation in the yaw axis during each of the following stimulation paradigms was then measured in darkness. In order to assure a constant level of behavioral alertness throughout the session, intervals of 1–2 min of target tracking in the light were interleaved between trials of rotational stimuli.

Transient head perturbations

Transient (~ 30 ms), high-acceleration (3,000–12,000°/s^2) head-on-body perturbations were passively applied using a torque motor (Animatics), which was securely coupled (through precision universal joints) to the post implanted on the monkey's head. An example is shown in Fig. 1b (left panel). The most dynamic stimuli applied were comparable to the 'very short perturbation' described in studies of the VOR in normal macaque monkeys (Huterer and Cullen 2002). The command to the torque motor lasted for ~ 10 ms and the amplitude was adjusted empirically for each monkey to reach peak head velocities of 30, 80 and 120°/s (corresponding to 3,000, 8,000, and 12,000°/s^2 accelerations, respectively). These rotations produced changes in head position of 0.9 ± 0.2°, 1.8 ± 0.3°, and 2 ± 0.2°, respectively.

Fast whole-body rotations

Whole-body rotations (Fig. 1b, middle panel) were produced by manually rotating the vestibular turntable. These movements can be considered as steps in position, with displacements of 90–100° and peak velocities of up to 200–500°/s. For the fastest stimuli, peak acceleration reached ~ 3,000°/s^2. This value is comparable to that of the lowest acceleration of the 'transient head perturbations' used in this study as well as that of the head impulses which are commonly used in the clinical 'head-thrust test' (Della Santina et al. 2002).

Sinusoidal rotations

Whole-body rotations were applied by rotating the monkey en-bloc at 0.5 Hz, 40°/s. Head-on-body rotations at 5, 10, and 15 Hz were delivered by a servo-controlled torque motor (Fig. 1b, right panel). The torque applied was systematically adjusted to evoke peak head velocities across the range of 10–100°/s for each animal (see also: Huterer and Cullen 2002). For frequencies of 5 and 10 Hz, ten consecutive stimulus cycles were applied within each trial. In order to minimize the possibility of damage to the monkey's head implant, only five consecutive cycles were applied for 15 Hz stimulation.

Body under head rotations

The status of the cervico-ocular reflex (COR) was assessed by rotating the animals' body under a stationary head and measuring the resultant slow shape eye movement. Sinusoidal rotations in the range of 0.2–3 Hz were applied at velocities of 10, 40, and 80°/s.

Data analysis

To quantify VOR response dynamics, the recorded data were imported into the Matlab (The MathWorks) programming environment for analysis. Horizontal gaze, eye, and head position data obtained during the sinusoidal head oscillations were digitally low pass-filtered using a 51st order finite-impulse-response (FIR) filter (cut-off frequency = 40, 125, and 40 Hz for sinusoidal rotations, transient head perturbations, and fast whole-body rotations, respectively), and differentiated to obtain velocity traces. Segments of the data with saccades were excluded from analysis.

Transient head perturbations

The frequency content of the transient head perturbations was analyzed using a fast Fourier transform (FFT) as previously described (Harris 1998; Huterer and Cullen 2002). At least ten quick phase/saccade-free trials were analyzed for each of the three test profiles (i.e., 3,000, 8,000 and 12,000°/s^2). Since monkeys frequently exhibited a spontaneous nystagmus following labyrinthectomy, a bias velocity (defined as the mean velocity 5–40 ms prior to the onset of the perturbation) was calculated for each trial. The VOR gain was defined as the change in eye velocity (i.e., peak eye velocity–bias velocity), divided by the peak head velocity of the perturbation.

Fast whole-body rotations

Trials with peak head velocities between 200 and 500°/s were grouped into 100°/s bins for rotations in each direction. At least ten trials were included in each bin. The gain and latency of VOR for these high-velocity rotations were calculated as described above for the transient head perturbations.

Sinusoidal rotations

The head velocity signal was divided into right and left half cycles based upon zero crossings of the stimulus. At least ten half-cycles were analyzed for each direction. VOR gain and phase were determined by the least-squares optimization of the equation:

$$E'(t) = (\text{gain}) \cdot [H'(t - t_d)] + \text{bias} \quad (1)$$

where $E'(t)$ is eye velocity, $H'(t)$ is head velocity, gain is a constant value, t_d is the dynamic lag time (in ms) of the eye movement with respect to the head movement, and bias is a DC offset. The dynamic lag time (t_d) was used to calculate the corresponding phase ($\phi°$) of eye velocity relative to head velocity. The variance-accounted-for (VAF) of each fit was computed as {1–[var(est–E')/var(E')]}, where var represents variance, est represents the modeled eye velocity, and E' represents the actual eye velocity. VAF values were typically between 0.90 and 1, where a VAF of 1 indicates a perfect fit to the data. Trials for which the VAF was less than 0.7 were rare, and were excluded from the analysis.

Statistical analysis

Data is described as mean ± standard error of the mean (SEM). Differences between responses with respect to frequency and time after labyrinthectomy were analyzed with a two-way ANOVA test, using Tukey's HSD test to evaluate the significance between groups whenever the result of the ANOVA test was significant ($P < 0.05$).

Results

A spontaneous nystagmus was present once the animal had awakened following surgery. The mean slow phase velocity of the spontaneous nystagmus in the dark, for the three animals when the eyes were centered in the orbit (i.e., eye position at 0 ± 5°) was 15 ± 5.2°/s on day 1 and decreased to 5.4 ± 1.4°/s by day 4 ($P < 0.01$ compared to day 1) and then remained stable at this level up to day 39.

VOR response to transient head perturbations and fast whole-body rotations

Transient head perturbations

The three transient head perturbations used in this study are shown in Fig. 2a (red traces). The frequency content of stimuli extended up to about 40, 50, and 70 Hz for the perturbations with accelerations of 3,000, 8,000, and 12,000°/s^2, respectively (see insets). Examples of the eye (blue traces) velocity trajectories elicited by each perturbation are superimposed. Average eye (dark blue traces) and head (dashed red traces) traces were calculated based on a minimum of 20 trials. Responses before labyrinthectomy were similar to those shown in a previous study of normal macaques (Huterer and Cullen 2002), with latencies between 5 and 6 ms and gains close to one for all velocities and accelerations (Fig. 2a). Figure 2b shows the results of the VOR response elicited by the same stimuli on day 39 after labyrinthectomy. During contralesional perturbations, eye velocity followed head velocity with a gain of close to unity. In contrast, in response to ipsilesional perturbations, peak eye velocity was less than peak head velocity for all three stimuli. Findings similar to those shown in Fig. 2a and b for Monkey P were also noted in Monkeys G and W. For the highest acceleration perturbations (i.e., 12,000°/s^2) directed towards the ipsilesional direction, peak eye velocity reached maximum values of about 50–60°/s in all monkeys.

The gain of the VOR evoked in response to transient head perturbations is plotted as a function of days following labyrinthectomy in Fig. 3. Contralesional response gains were not attenuated relative to normal values following labyrinthectomy (Fig. 3a). In addition, there were no significant differences between the mean values of contralesional gains on different days or in response to different head perturbations ($P > 0.1$). In contrast, for ipsilesional perturbations, VOR gain showed marked attenuation on the first day following labyrinthectomy (Fig. 3b). In response to head perturbation with the lowest accelerations (i.e., 3,000°/s^2), responses to ipsilesional rotations showed improvement by day 8 following labyrinthectomy. This improvement resulted in ipsilesional gains on day 11 that were significantly different from that of day 1 ($P < 0.02$). For the two higher acceleration head perturbations, the ipsilesional gain did not change significantly over the time course tested. Thus, the sharp

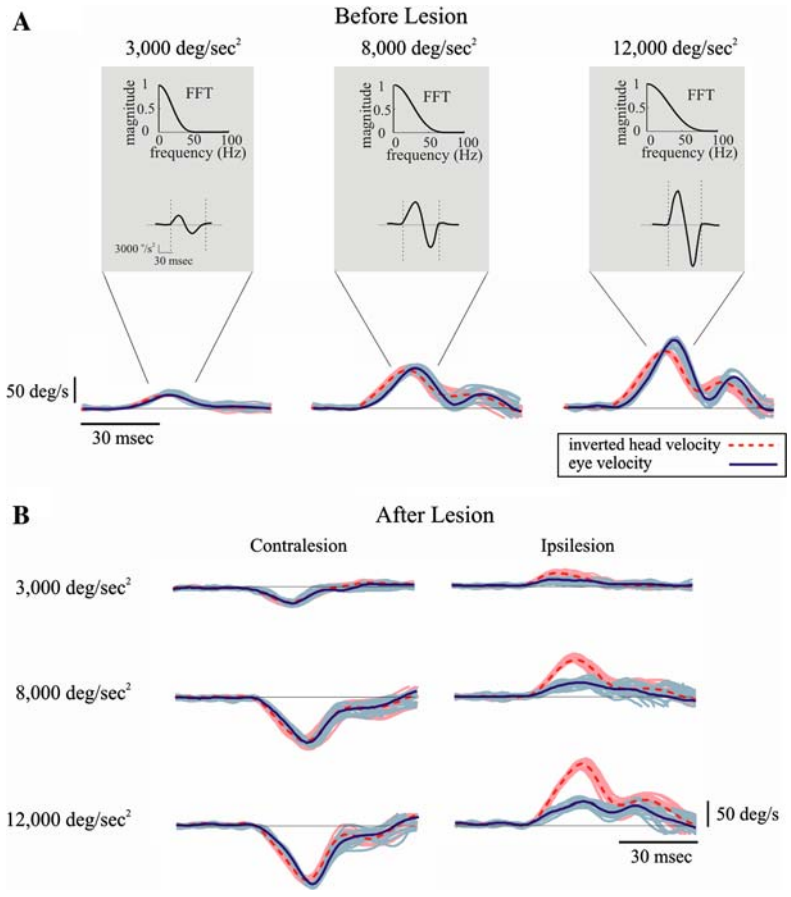

Fig. 2 Response to transient head perturbations with accelerations of 3,000, 8,000, and 12,000°/s^2 in Monkey P. **a** Responses before unilateral labyrinthectomy. Eye (*blue*) and inverted head (*red*) velocities are shown. Each average trace (*solid heavy line* for eye and *broken line* for head) is superimposed on a minimum of 20 trials. *Insets* show acceleration profiles and fast Fourier transform (*FFT*) performed on the velocity profile over the time interval defined by the zero crossings of each stimulus. The example FFTs show energy extending up to 40, 50 and 60 Hz for example stimuli with peak accelerations of 3,000, 8,000, and 12,000°/s^2, respectively. **b** Responses 39 days after unilateral labyrinthectomy. Note the asymmetry in the response leading to lower eye velocities for ipsilesional rotations

decrease that was observed immediately following labyrinthectomy in response to head perturbations with accelerations of 8,000 and 12,000°/s^2 and frequency contents extending to 50–70 Hz persisted until day 39, whereas the contralesional responses remained normal over the period of time that the VOR was tested.

Response to fast whole-body rotations

Figure 4 illustrates the four high velocity head perturbations which were used to characterize compensation of the VOR. Example responses before labyrinthectomy are shown in Fig. 4a for Monkey P in one direction. The eye and head velocity trajectories from a minimum of 20 trials are superimposed for each stimulus. Stimuli had significant power up to frequencies up to only 3–5 Hz for the perturbations with velocities of 200, 300, 400 and 500°/s (see insets). Thus, the frequency content of these transient perturbations was considerably less than that of the transient perturbations that are described above. The peak acceleration of all stimuli remained constant at ~ 3,000°/s^2.

Similar to findings of previous studies in normal macaques (Roy et al. 2003), the gain of the VOR on the day before labyrinthectomy was close to one for responses in both directions. After labyrinthectomy (Fig. 4b), both contra- and ipsilesional responses showed a soft saturation in eye velocity (dashed lines in Fig. 4b) that occurred at head velocities of > 300°/s. For a given velocity of head rotation, eye velocities were less for ipsilesional than contralesional rotations.

In Fig. 5, the relationship between peak eye velocity and the peak velocities of the transient head perturbations (black filled circles) and fast whole-body rotations (gray filled circles) are plotted for each of the three animals. Similar findings are noted for each of the animals. Ipsilesional responses showed a soft saturation in eye velocity at lower head velocities compared to contralesional responses. The mean VOR gain (mean of the peak eye velocity/peak head velocity across all animals) at a peak head velocity of 400°/s was 0.8 ± 0.04 for contralesional rotations and 0.45 ± 0.05 for ipsilesional rotations. At 500°/s, the mean gain fell to 0.75 ± 0.05 for contralesional rotations and 0.4 ± 0.1 for ipsilesional rotations. Thus in response to ipsilesional rotations, the apparent saturation observed in peak eye velocity of ~ 60°/s for highest acceleration transient head perturbations (Fig. 2b, bottom right

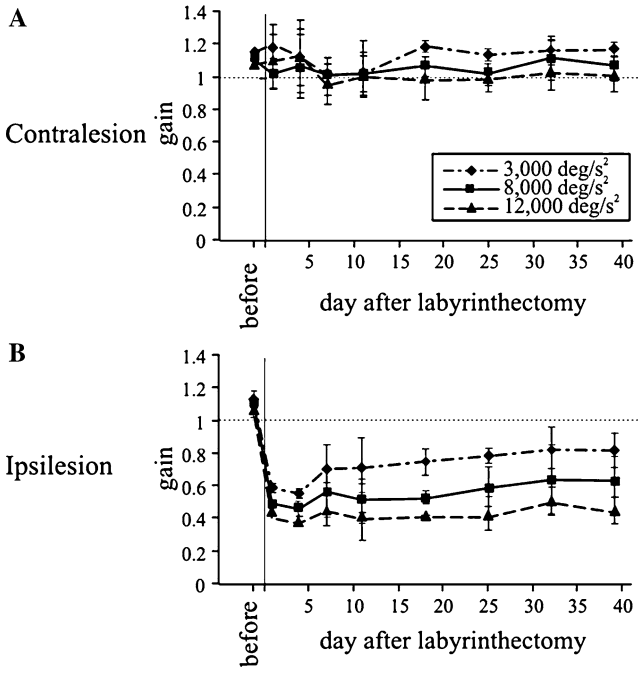

Fig. 3 Mean VOR gain before and at different days after labyrinthectomy for responses elicited from transient head perturbations at accelerations of 3,000, 8,000, and 12,000°/s^2. Responses reach steady-state levels by around day 18 after the labyrinthectomy. *Error bars* represent standard error of the mean

panel) was not observed in response to rotations with lower accelerations (~ 3,000°/s^2) but higher velocities (Fig. 4b, right panel).

VOR response to high frequency sinusoids

The experiments described above suggest that VOR responses after compensation are dependent on the velocity as well as the acceleration of stimulation. In these studies, however, the frequency content of the transient perturbation versus the fast whole-body rotations varied greatly. In order to investigate the dependence of VOR compensation on stimulus frequency and velocity, we next applied sinusoidal rotations before and following labyrinthectomy. This approach allowed more control over the acceleration, frequency, and velocity of the rotation, and extended our test stimuli to regions of stimulus space (Fig. 1a) that were not probed by transient head perturbations and fast whole-body rotations (see above). For example, our highest frequency stimulus was a 15 Hz sinusoidal rotation. The peak velocity of the stimulus was varied from 10 to 100°/s, resulting in a range of accelerations from ~ 940 to ~ 9,400°/s^2.

Figure 6a shows example responses evoked when sinusoidal rotations were applied to Monkey P. Prior to

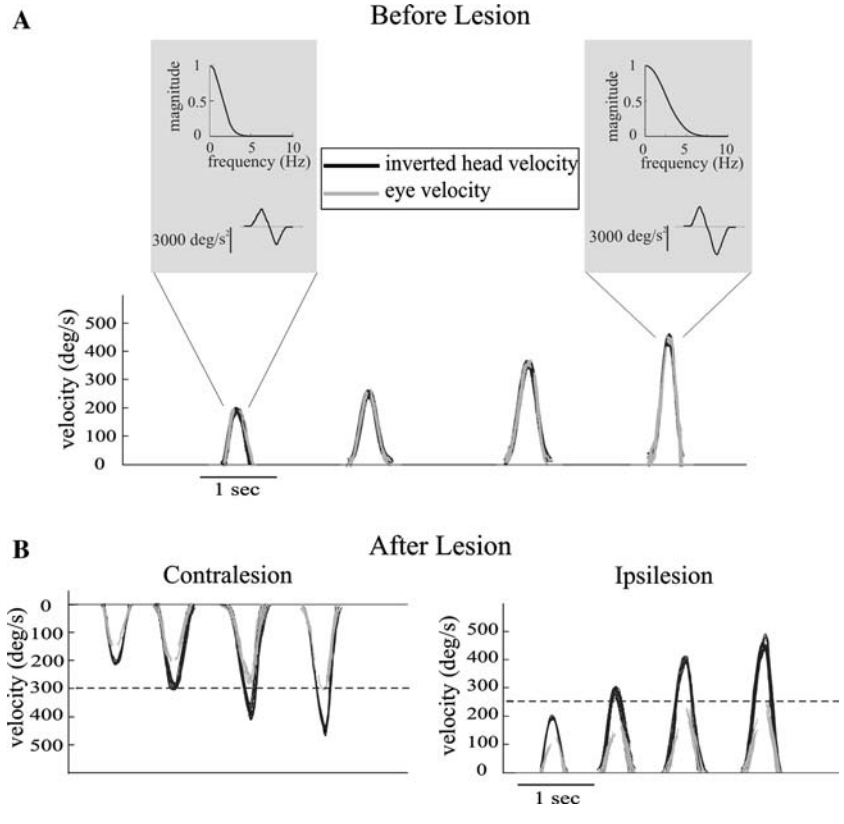

Fig. 4 Response to fast whole-body rotations in Monkey P. Inverted head velocity (*black lines*) and eye velocity (*gray lines*) are superimposed for multiple (10–20) trials with peak head velocities of about 200, 300, 400, and 500°/s. **a** Responses before unilateral labyrinthectomy. *Insets* show the acceleration profiles and FFT results for the lowest (200°/s) and highest (500°/s) velocities with energy extending up to 3–5 Hz. **b** Responses 39 days after unilateral labyrinthectomy. Note the soft saturation in eye velocity (*dashed lines*) for peak head velocities > 300°/s for both contra and ipsilesional rotations

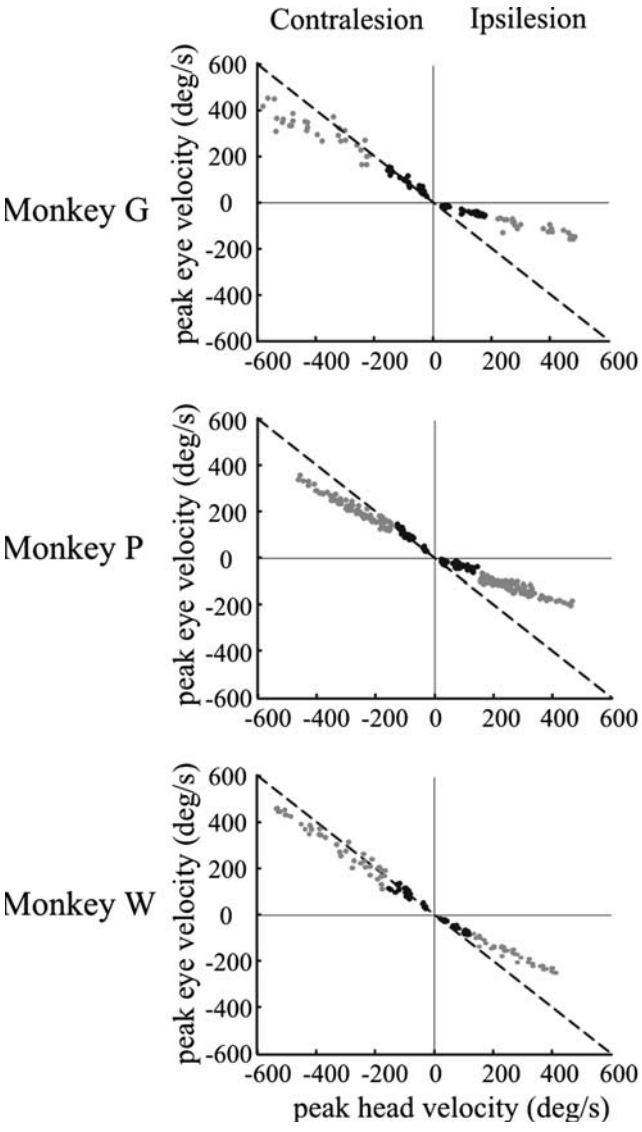

Fig. 5 Peak eye versus peak head velocity from transient head perturbations (*black symbols*) and fast whole-body rotations (*grey symbols*) for the three animals. Eye velocity in response to ipsilesional rotations reached a maximum of ~ 200°/s for the highest head velocities. Decreases in contralesional gain were noted for rotations > 200°/s

the lesion (Fig. 6a, left column), eye and inverted head velocity traces were nearly identical. After unilateral labyrinthectomy, there was an asymmetry in VOR response that was dependent on the side of rotation as well as the stimulus intensity. For rotations at 0.5 Hz (± 40°/s) eye velocities approximated head velocities, however slightly lower velocities were observed for ipsilesional half cycles. More pronounced asymmetries between ipsi- and contralesional responses were noted in response to higher frequency sinusoidal rotations. Eye velocities for contralesional half cycles well matched head velocities whereas those for ipsilesional half cycles were substantially lower (Fig. 6a, right column).

The gain and phase of VOR measured in response to sinusoidal rotations in the three animals before labyrinthectomy were consistent with values that have been reported in previous studies (Minor et al. 1999; Huterer and Cullen 2002). Specifically, the gain for rotations in either direction remained close to unity (Fig. 6b, top panels) and the phase of the response showed a lag that increased with frequency up to a peak of 10–15° at 15 Hz (Fig. 6b, bottom panels). Data are shown from day 39 after labyrinthectomy, since compensation had stabilized by this time (see Fig. 3, as well as Fig. 7 below). In general, gains for ipsilesional rotations were lower than for contralesional rotations. This trend was most robust for higher frequencies (i.e., 5 Hz and greater). The gain for contralesional half cycles on day 39 was not different from that of day before labyrinthectomy for frequencies of 0.5–10 Hz, while response gains at 15 Hz remained lower than before labyrinthectomy. Moreover, the phase of the response to contralesional rotations was not altered following labyrinthectomy. In contrast, ipsilesional gains were lower than control values over the range of frequencies tested and decreased with increasing frequency of rotation, reaching values of 0.5–0.7 at 15 Hz, in all animals. The phase of the ipsilesional responses increased with increasing frequencies and was not significantly different from those recorded prior to the lesion.

Changes in VOR gain measured at different times during compensation

Figure 7 shows the mean and standard error of the averaged VOR response gain measured at days 1, 4, 8, 11, 18, 25, 32, and 39 after labyrinthectomy. The gains for half cycles in each direction did not differ before labyrinthectomy ($P > 0.1$). Following labyrinthectomy, the gain for ipsilesional half cycles decreased to values that were less than normal. Most of the compensation that occurred in subsequent days was in responses to lower frequency rotations. In contrast, no significant recovery was noted in the response to 15 Hz rotations, in any of the animals. Responses to rotations at 5 and 10 Hz were intermediate between those for 0.5 and 15 Hz and for clarity, only data for 0.5, 5, and 15 Hz are shown. Contralesional gains recovered more rapidly than did ipsilesional gains. Within 8 days of the labyrinthectomy, response showed substantial recovery across all frequencies, relative to response on day 1 after the lesion. Interestingly, the gains for 15 Hz rotations

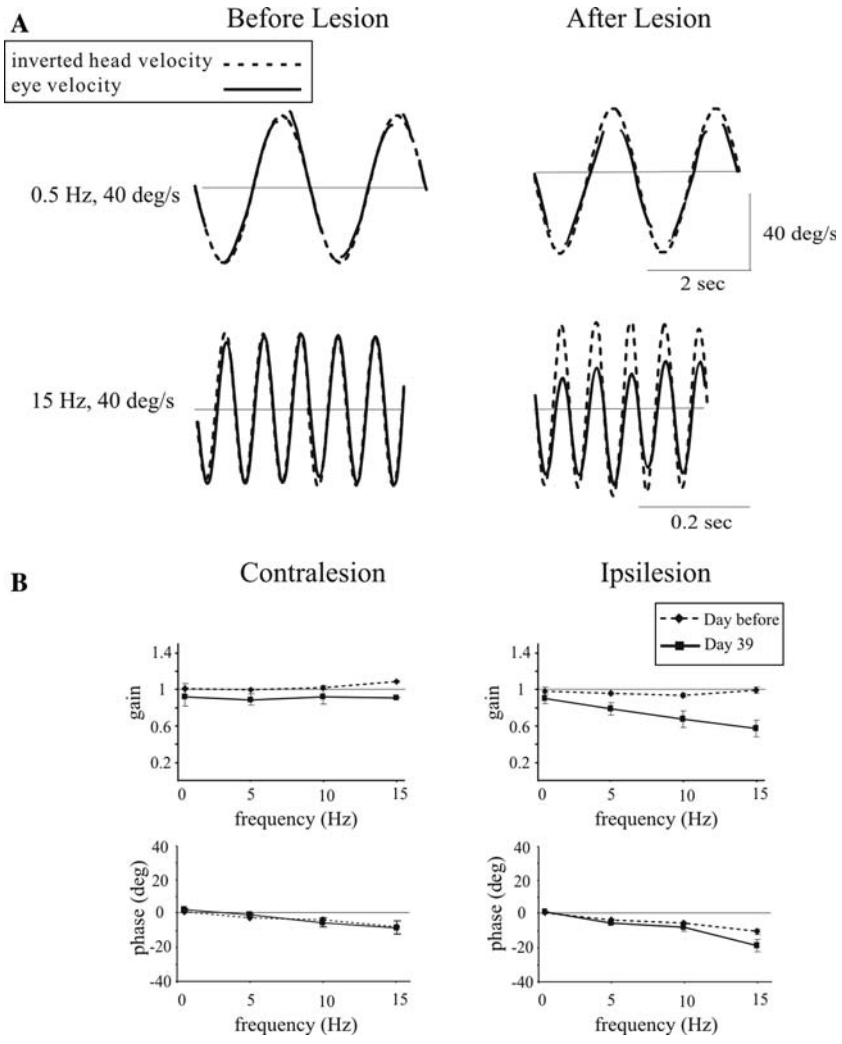

Fig. 6 Response to sinusoidal rotations. **a** Eye velocity and inverted head velocity traces for sinusoidal rotations at 0.5 and 15 Hz with peak velocity of 40°/s before and on day 39 after labyrinthectomy in Monkey P. For data after labyrinthectomy, downward direction on the head velocity trace represents rotations toward the contralesional side. Note that fast phases have been removed from the eye velocity traces for 0.5 Hz rotations. **b** Mean value of gain and phase for responses to sinusoidal rotations from 0.5 to 15 Hz at 40°/s for the three monkeys before labyrinthectomy and day 39 post-labyrinthectomy. Half-cycle gains and phases are shown for contralesional and ipsilesional rotations in the left and right columns, respectively. *Error bars* represent standard error of the mean. Note that after labyrinthectomy gain decreases with rising frequency for ipsilesional half-cycles

were higher at this time, but decreased by day 39 to values similar to those of 0.5, 5, and 10 Hz rotations.

The effect of velocity of rotation on VOR response during steps of position was mentioned in the previous sections. We also addressed whether the gain of the VOR changed as a function of head velocity during sinusoidal rotations. We found that both contra- and ipsilesional gains decreased with increasing head velocity from 10 to 100°/s. For 15 Hz rotations, ipsilesional gain decreased by 31% when velocity was increased from 10 to 100°/s. The contralesional response decreased by only 15% over this range. Difference between response gains to 5 versus 15 Hz rotations were significant for velocities > 20°/s. This was the case for both contra and ipsilesional rotations.

Discussion

Unilateral labyrinthectomy results in profound changes in the dynamics and symmetry of the VOR. The purpose of the present study was to evaluate the performance of the horizontal VOR, after unilateral labyrinthectomy, for the full range of head movements that are encountered during natural activities (Fig. 1). In response to sinusoidal rotations at low frequencies and velocities, contralesional response gain and phase recovered to normal values in ~ 4 days. However, the VOR never fully compensated in response to rotations with higher frequency, velocity, and acceleration. In response to transient head perturbations or fast whole-body rotations, both contra and ipsilesional gains decreased with increasing peak acceleration and velocity, respectively. We found that for the most challenging stimuli (i.e., head-on-body perturbations with accelerations of ~ 12,000°/s^2, whole-body rotations with velocities of ~ 500°/s, and sinusoidal rotations at 15 Hz with a peak velocity of 100°/s) the gain for contra- and ipsilesional rotations decreased to minimum values of 0.7–0.8 and 0.3–0.4, respectively. Moreover, for these stimuli no significant compensation was observed in

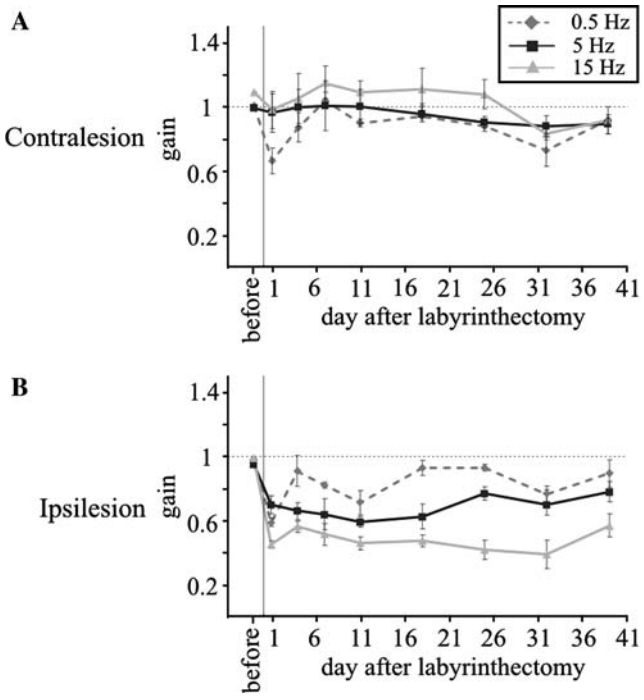

Fig. 7 Gain for contralesional and ipsilesional half-cycles of rotations at 0.5, 5 and 15 Hz (± 40°/s) averaged between the three animals. Data are presented at different time points during the first 39 days after the labyrinthectomy. Note there is little recovery of gain for ipsilesional half-cycles at 15 Hz. *Error bars* represent standard error of the mean

contra- or ipsilesional responses over time relative to day 1.

In the following sections, we will first compare our findings to those of previous behavioral studies. We will then consider these results in relation to recent studies that have recorded the responses of single neurons in the VOR pathways. Finally, we show that the same model structure can describe the VOR responses elicited by both sinusoidal and transient rotations following unilateral labyrinthectomy.

Relationship to previous behavioral studies

Immediately upon awakening from anesthesia after unilateral labyrinthectomy, all monkeys had a spontaneous nystagmus with fast components directed towards the contralesional side. This finding is similar to that observed in previous studies (rhesus monkeys: Fetter and Zee 1988; squirrel monkeys: Lasker et al. 2000; gerbils: Newlands and Perachio 1990a; Newlands and Perachio 1990b; cats: Precht 1987; guinea pigs: Smith and Curthoys 1988a, b; Gilchrist et al. 1998). Although the velocity of the slow component of spontaneous nystagmus decreased by day 4 after labyrinthectomy, the nystagmus never completely disappeared. Lasker et al. (2000) saw no reduction in spontaneous nystagmus when animals were kept in darkness. This finding indicates that visual fixation and/or retinal slip introduced by head motion in light are required for the compensation that is normally observed following labyrinthectomy.

Dynamics of the horizontal VOR after unilateral labyrinthectomy

Our findings characterize the compensation that occurs in macaque monkeys over the range of stimulus accelerations, velocities, and frequencies that closely resemble the dynamics of naturally occurring head movements. VOR gain decreased as a function of both increasing stimulus acceleration and velocity. This trend was evident in response to both ipsilesional and contralesional rotations. As expected, responses to rotations that would be excitatory for the lesioned side (i.e., ipsilesional rotations) were more dramatically affected. In addition, consistent with previous studies of VOR compensation following unilateral labyrinthectomy, compensation was stable within ~ 10 days.

In the present study both passive head-on-body and whole-body rotations were used to probe the status of the VOR following labyrinthectomy. For example, higher frequency stimuli were applied by rotating the head on the body (5–15 Hz), while lower frequency stimuli (0.5–4 Hz) were applied using whole-body rotations. Thus the question arose as to whether the passive stretching of neck proprioceptors during these higher frequency rotations might activate the COR as well as the VOR. To explicitly address this possibility, we verified the lack of a COR response before and following unilateral loss in two of the three animals described in this report even in this lower range of 0.2–3 Hz (10–80°/s peak head velocity) by rotating the animals' body under an earth-fixed head and recording the evoked eye movements (see Materials and methods). This result is consistent with findings from other studies showing that (1) the gain of the COR is negligible in normal humans and rhesus monkeys (Barlow and Freedman 1980; Bohmer and Henn 1983; Bronstein and Hood 1986; Jurgens and Mergner 1989; Sawyer et al. 1994; Roy and Cullen 2002), and (2) following unilateral vestibular loss, significant COR responses are only observed in humans > 60 years old (Schubert et al. 2004). Moreover, regarding the latter study, the gain decreases to negligible values with increasing frequency and velocity of rotation even in older subjects, such that it remains negligible at frequencies > 1 Hz. Thus, taken together these results suggest that the COR does not make a significant

contribution to the eye movements evoked by the high frequency sinusoidal head-on-body rotations or transient head-on-body perturbations which were used in the present study. It is worth noting that in contrast, the gain of the COR does increase following bilateral labyrinthectomy in both humans (Kasai and Zee 1978; Goebel et al. 2000) and monkeys (e.g., Dichgans et al. 1973) and contributes to the functional recovery of eye–head coordination.

Responses to transient head perturbations and fast whole-body rotations

In humans, the 'head thrust test' is commonly used for clinical assessment of VOR deficits. Head rotations are applied by manually rotating the patient's head-on-body resulting in movements with peak accelerations of ~ 3,000°/s^2 and peak velocities of 150–200°/s. In the present study, the status of the VOR following unilateral labyrinthectomy was probed using stimuli with much greater accelerations than are achieved in the clinical 'head thrust test' (i.e., up to 12,000°/s^2, Fig. 1a). In response to these high-acceleration transient head perturbations, we observed a decrease in ipsilesional gain on day 1 after labyrinthectomy. While ipsilesional gain did show a slight improvement for the lower acceleration stimuli of 3,000°/s^2 (30°/s peak velocity), ipsilesional gains did not show any improvement by day 39 for perturbations with the highest accelerations of 8,000°/s^2 (80°/s peak velocity) and 12,000°/s^2 (120°/s peak velocity). In contrast, contralesional gains remained normal up to day 39.

Understanding the dynamics of the compensated VOR at these higher accelerations is critical, since the dynamics of natural head movements can extend well into this range (e.g., Armand and Minor 2001; Cullen and Roy 2004). Overall, ipsilesional gains decreased as a function of acceleration, reaching a minimum value of ~ 0.3 for the most challenging stimulus (Fig. 3). At higher accelerations (8,000°/s^2 and higher) VOR responses saturated at ~ 60°/s (Fig. 2b). Response asymmetry was striking under these stimulus conditions since contralesional gains did not differ from the gains measured prior to the lesions for even the most challenging stimuli tested.

We investigated the possibility that the saturation in eye velocity at 50–60°/s that was observed for high-acceleration perturbations was a fixed limitation inherent to the compensated VOR pathways. We found that this was not the case. We were able to evoke responses up to 200°/s when stimuli with relatively lower accelerations (~ 2,000–3,000°/s^2) but higher velocities (up to 500°/s) were applied. VOR gain for ipsilesional rotations decreased as a function of stimulus velocity, reaching values as low as ~ 0.3 for the highest velocities (~ 500°/s). In addition, contralesional gain decreased relative to pre-lesion values for velocities above ~ 200°/s. As a result, contralesional gain values were as low as ~ 0.7 for rotations of 500°/s. Our results extend those of previous studies of high velocity rotations in primates (Paige 1983b; Fetter and Zee 1988). Comparison of our results from transient head perturbations and fast whole-body rotations show that the ipsilesional gain is reduced to a minimum value of ~ 0.3 not only by increasing the acceleration of a stimulus, but by increasing its velocity.

Our observation that contralesional gains decreased as function of head velocity for these stimuli is compatible with our findings regarding the relationship between contralesional gain and velocity for sinusoidal stimuli (Fig. 5). However, this result differs from that of Lasker et al. (2000) in squirrel monkeys, who observed the opposite trend following compensation. We suggest that this difference is consistent with previous findings regarding the VOR responses dynamics of normal macaque and humans in comparison to squirrel monkeys (see Huterer and Cullen 2002). We consider this point more extensively in our discussion of VOR responses to sinusoidal stimulation (see below).

Responses to sinusoidal stimuli

In the present study, asymmetries between the gain of contra- and ipsilesional responses were noted on day 1 and were most prominent at frequencies between 5 and 15 Hz, ± 40°/s (18–24 h after the lesion). An increase in the gain of the VOR for ipsilesional half-cycles in responses to lower frequency stimuli was noted over the course of the first 39 days after the lesion (Fig. 7). In contrast, response gains to 15 Hz stimulation showed no improvement over the time period of this study. This finding extends that of previous studies that have shown greater recovery in ipsilesional gain for rotations at lower frequencies with low to mid peak velocities in contrast to responses for stimuli that are higher frequency, acceleration, and velocity (macaque: Fetter and Zee 1988; squirrel monkey: Paige 1983b; Lasker et al. 2000; cat: Broussard et al. 1999; guinea pig: Gilchrist et al. 1998). Responses to contralesional rotations also showed changes with time over the initial 39 days after the lesion. The mean value of the compensated contralesional gain for the three animals was less than normal by day 39 for 10 and 15 Hz rotations.

Once compensation had stabilized, all animals showed a more prominent asymmetry of the response with increasing velocities of head rotation. At higher

frequencies, both contra- and ipsilesional gains decreased as a function of increasing velocity, and larger asymmetry was due to a smaller decline in the gain in response to contralesional compared to ipsilesional rotations. This finding is similar to that previously described in humans (Della Santina et al. 2002). In contrast, Lasker et al. (2000) observed that in squirrel monkeys response to contralesional rotations at 10 Hz increased as a function of velocity. It is important, however, to note that in normal animals, VOR response dynamics show some differences for squirrel monkeys and macaques (see Discussion in Huterer and Cullen 2002).

Relationship to in vivo single unit studies

The neural basis of the spontaneous nystagmus that is observed immediately following labyrinthectomy is well understood. The loss of afferent input to the ipsilesional side results in an imbalance in the resting activity of neurons in the vestibular nuclei on each side (see for example: Smith and Curthoys 1989; Newlands and Perachio 1990a, b; Ris et al. 1995). In addition to the changes in resting rate, neurons in the vestibular nuclei also show changes in their sensitivity to head velocity immediately following unilateral labyrinthectomy. Type I neurons show a decrease in their sensitivity to head rotations by 70–100% and ~ 40% in the ipsi- and contralesional vestibular nuclei, respectively (Smith and Curthoys 1989; Newlands and Perachio 1990a, b; Ris et al. 1995). The range of frequencies tested in these studies varies from 0.13 to 1.3 Hz. Thus, these findings can be most directly related to our behavioral data at 0.5 Hz.

The results of these single unit recording experiments can be easily related to the VOR response to contralesional rotations in the acute stage: the ~ 50% decrease in VOR gain on the day following unilateral labyrinthectomy correlates very well with the ~ 40% observed reduction in sensitivity of neurons in the contralateral vestibular nuclei. On the other hand, the findings of the single-unit recording experiments would predict a greater reduction in VOR gain for ipsilesional rotations than the 50% reduction that we observed. It is important to recognize that a limitation of these prior studies has been that neurons were not characterized either in terms of their physiological discharge properties or central projections.

It is yet more difficult to relate the results of single unit studies to the VOR responses recorded in the chronic stage. Our results as well as those of previous studies (Fetter and Zee 1988; Lasker et al. 2000) show that responses to contralesional rotations show considerable compensation, approaching pre-lesion values for 0.5 Hz rotations at lower velocities. In order for this to occur, the modulation of the premotor input to the extraocular motorneurons must be the same as that seen under normal conditions. Surprisingly, the acutely reduced head sensitivity of contralesional Type I cells shows only marginal improvement following compensation (Newlands and Perachio 1990a, b; Ris and Godaux 1998), even 1 year following labyrinthectomy (Smith and Curthoys 1988a, b). These results are paradoxical when viewed in relation to the impressive behavioral compensation that is observed. As has been noted above, a better understanding of the specific cell types recorded at various stages in the compensation process is needed in order to better understand the changes that occurred.

Concluding remarks

Compensation in VOR response provides a simple model for studying plasticity and its neural correlates. Previous studies have looked at VOR compensation following unilateral lesions in a variety of mammalian species including humans, monkeys, cats, and guinea pigs, using stimuli with different frequencies, accelerations, and velocities (Smith and Curthoys 1989; Fetter and Zee 1988; Maioli et al. 1983; Paige 1983a, b, 1989; Lasker et al. 2000; Galiana et al. 2001). Although these studies agree that rotations towards the lesioned side result in a decreased VOR gain that is not fully compensated, there are differences across studies. For example, in humans, rotations towards the contralesional side result in slightly reduced gains (Halmagyi et al. 1990), whereas in squirrel monkeys (Lasker et al. 2000) and guinea pigs (Gilchrist et al. 1998), contralesional gains increase relative to control levels as a function of velocity for frequencies > 4 Hz. In addition, finding more marked asymmetries in responses to head impulses in guinea pigs has led to the suggestion that deficits in the VOR are more pronounced in response to impulses than to sinusoids (Gilchrist et al. 1998).

Here we were able to address these apparent discrepancies by testing an extensive range of stimulus dynamics, which extended over the full range of natural head movements, in the same subjects (i.e., three macaque monkeys). We found that the contralesional as well as ipsilesional responses decreased with increasing intensity of the stimulus. This finding is consistent with Ewald's second law, which states that excitatory responses for the angular VOR are greater than inhibitory responses. As a result, loss of excitatory inputs following unilateral labyrinthectomy during

ipsilesional rotations have a greater effect than loss of inhibitory signals during contralesional rotations, which explains the lower gains for ipsilesional responses. This said, the vestibular system is not able to fully compensate for the loss of inhibitory signals and this is evident for the most challenging contralesional rotations.

We then addressed whether a single model could predict responses over this extended range of frequencies, accelerations, and velocities (as described in the Appendix which accompanies the electronic version of this paper). To do this, we adapted a previously published model for the squirrel monkey VOR (Lasker et al. 2000) to our data (see electronic supplementary material for more detail). The model accounted for VOR responses to different paradigms using the same parameters. Together, these findings provide evidence that there are no fundamental differences between responses to transient head rotations and sinusoidal head movements. We conclude that intrinsic dynamics of the neural components mediating the VOR and compensatory changes that occur following unilateral ablation of vestibular function account for responses observed for a wide range of head movements. These studies of the horizontal VOR in macaques provide a set of data that are critically important for future studies of vestibular-nerve afferents and central vestibular neurons in this species following unilateral labyrinthectomy.

Acknowledgements In this study, David Lasker implemented the mathematical model described in the Appendix that accompanies this paper electronically. This model had been previously developed by him for the squirrel monkey horizontal VOR (Lasker et al. 1999; Minor et al. 1999). He optimized the parameters used in this model from the data for the macaque VOR and prepared the figures for the simulated responses. We thank Dr. Charles Della Santina, Mathieu Beraneck, Marion Van Horn, and Ariana Andrei for critically reading the manuscript. This work was supported by the Canadian Institutes of Health Research (CIHR) and NIH R01 DC02390.

References

Allum J, Yamane M, Pfaltz C (1988) Long-term modifications of vertical and horizontal vestibulo-ocular reflex dynamics in man. I. After acute unilateral peripheral vestibular paralysis. Acta Otolaryngol 105:328–337

Armand M, Minor LB (2001) Relationship between time- and frequency-domain analyses of angular head movements in the squirrel monkey. J Comput Neurosci 11:217–239

Barlow D, Freedman W (1980) Cervico-ocular reflex in the normal adult. Acta Otolaryngol 89:487–496

Beraneck M, Hachemaoui M, Idoux E, Ris L, Uno A, Godaux E, Vidal P, Mooew L, Vibert N (2003) Long-term plasticity of ipsilesional medial vestibular nucleus neurons after unilateral labyrinthectomy. J Neurophysiol 90:184–203

Beraneck M, Idoux E, Uno A, Vidal P, Moore L, Vibert N (2004) Unilateral labyrinthectomy modifies the membrane properties of contralesional vestibular neurons. J Neurophysiol 92:1668–1684

Bohmer A, Henn V (1983) Horizontal and vertical vestibuloocular and cervicoocular reflexes in the monkey during high-frequency rotation. Brain Res 277:241–248

Bronstein AM, Hood J (1986) The cervico-ocular reflex in normal subjects and patients with absent vestibular function. Brain Res 373:399–408

Broussard D, Bhatia J, Jones G (1999) The dynamics of the vestibulo-ocular reflex after peripheral vestibular damage. I. Frequency-dependent asymmetry. Exp Brain Res 125:353–364

Cartwright A, Curthoys IS, Gilchrest D (1999) Testable predictions from realistic neural network simulations of vestibular compensation: integrating the behavioural and physiological data. Biol Cybern 81:73–87

Crane B, Demer J (1998) Human horizontal vestibuloocular initiation: effects of acceleration, target distance, and unilateral deafferentation. J Neurophysiol 80:1151–1166

Cullen KE, Roy JE (2004) Signal processing in the vestibular system during active versus passive head movements. J Neurophysiol 91:1919–1933

Curthoys IS, Halmagyi GM (1995) Vestibular compensation: a review of the oculomotor, neural, and clinical consequences of unilateral vestibular loss. J Vestib Res 5:67–107

Della Santina C, Cermer P, Carey J, Minor LB (2002) Comparison of the head thrust test with head autorotation test reveals the vestibule-ocular reflex is enhanced during voluntary head movements. Arch Otolaryngol Head Neck Surg 128:1044–1054

Demer JL, Oas JG, Baloh RW (1993) Visual-vestibular interaction in humans during active and passive, vertical head movement. J Vestib Res 3:101–114

Dichgans J, Bizzi E, Morasso P, Tagliasco V (1973) Mechanisms underlying recovery of eye-head coordination following bilateral labyrinthectomy in monkeys. Exp Brain Res 18:548–562

Fetter M, Zee DS (1988) Recovery from unilateral labyrinthectomy in rhesus monkey. J Neurophysiol 59:370–393

Fuchs AF, Robinson DA (1966) A method for measuring horizontal and vertical eye movements in the monkey. J Appl Physiol 21:1068–1070

Galiana HL, Smith HL, Katsarkas A (2001) Modelling non-linearities in the vestibulo-ocular reflex (VOR) after unilateral or bilateral loss of peripheral vestibular function. Exp Brain Res 137:369–386

Gilchrist DP, Curthoys IS, Cartwright AD, Burgess AM, Topple AN, Halmagyi M (1998) High acceleration impulsive rotations reveal severe long-term deficits of the horizontal vestibulo-ocular reflex in the guinea pig. Exp Brain Res 123:242–254

Goebel JA, Isipradit P, Hanson JM (2000) Manual rotational testing of the vestibulo-ocular reflex. Laryngoscope 110:517–535

Grossman GE, Leigh RJ, Abel LA, Lanska DJ, Thurston SE (1988) Frequency and velocity of rotational head perturbations during locomotion. Exp Brain Res 70:470–476

Halmagyi GM, Curthoys IS, Cremer P, Henderson C, Todd M, Staples M, D'Cruz D (1990) The human horizontal vestibulo-ocular reflex in response to high-acceleration stimulation before and after unilateral vestibular neurectomy. Exp Brain Res 81:479–490

Harris C (1998) The Fourier analysis of biological transients. J Neurosci Methods 83:15–34

Hayes A, Richmond B, Optican L (1982) A UNIX-based multiple process system for real-time data acquisition and control. WESCON Conf Proc 2:1–10

Huterer M, Cullen KE (2002) Vestibuloocular reflex dynamics during high-frequency and high-acceleration rotations of the head on body in rhesus monkey. J Neurophysiol 88:13–28

Jurgens R, Mergner T (1989) Interaction between cervico-ocular and vestibulo-ocular reflexes in normal adults. Exp Brain Res 77:381–390

Kasai T, Zee DS (1978) Eye-head coordination in labyrinthine-defective human beings. Brain Res 144:123–141

Kasteel-Van Linge A, Mass A (1990) Quantification of visuo-vestibular interaction up to 5.0 Hz in normal subjects. Acta Otolaryngol 110:18–24

Keller EL (1978) Gain of the vestibuloocular reflex in monkey at high rotational frequencies. Vision Res 18:311–315

Lasker D, Backous D, Lysakowski A, Davis G, Minor L (1999) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. II. Responses after canal plugging. J Neurophysiol 82:1271–1285

Lasker D, Hullar T, Minor L (2000) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. J Neurophysiol 83:2482–2496

Maioli C, Precht W, Ried S (1983) Short- and long-term modifications of vestibulo-ocular response dynamics following unilateral vestibular nerve lesions in the cat. Exp Brain Res 50:259–274

Mathog R (1972) Testing of the vestibular system by sinusoidal angular acceleration. Acta Otolaryngol 74:96–103

Minor LB, Lasker DM, Backous DD, Hullar TE (1999) Horizontal vestibuloocular reflex evoked by high-acceleration rotations in the squirrel monkey. I. Normal responses. J Neurophysiol 82:1254–1270

Newlands S, Perachio A (1990a) Compensation of horizontal canal related activity in the medial vestibular nucleus following unilateral labyrinth ablation in the decerebrate gerbil. I. Type I neurons. Exp Brain Res 82:359–372

Newlands S, Perachio A (1990b) Compensation of horizontal canal related activity in the medial vestibular nucleus following unilateral labyrinth ablation in the decerebrate gerbil. II. Type II neurons. Exp Brain Res 82:373–383

Paige G (1983a) Vestibuloocular reflex and its interactions with visual following mechanisms in the squirrel monkey. I. Response characteristics in normal animals. J Neurophysiol 49:134–151

Paige G (1983b) Vestibuloocular reflex and its interactions with visual following mechanisms in the squirrel monkey. II. Response characteristics and plasticity following unilateral inactivation of horizontal canal. J Neurophysiol 49:152–168

Paige G (1989) Nonlinearity and asymmetry in the human vestibulo-ocular reflex. Acta Otolaryngol 108:1–8

Peterka R, Black F, Schoenhoff M (1990) Age-related changes in human vestibuloocular reflexes: sinusoidal rotation and caloric tests. J Vestib Res 1:49–59

Precht W (1987) Recovery of some vestibuloocular and vestibulospinal functions following unilateral labyrinthectomy. Prog Brain Res 64:381–389

Ramachandran R, Lisberger SG (2005) Normal performance and expression of learning in the vestibule-ocular reflex (VOR) at high frequencies. J Neurophysiol 93:2028–2038

Reisine H, Simpson J, Henn V (1988) A geometric analysis of semicircular canals and induced activity in their peripheral afferents in the rhesus monkey. Ann NY Acad Sci 545:10–20

Ris L, Godaux E (1998) Neuronal activity in the vestibular nuclei after contralateral or bilateral labyrinthectomy in the alert guinea pig. J Neurophysiol 80:2352–2367

Ris L, de Waele C, Serafin M, Vidal P, Godaux E (1995) Neuronal activity in the ipsilateral vestibular nucleus following unilateral labyrinthectomy in the alert guinea pig. J Neurophysiol 74:2087–2099

Ris L, Hachemaoui M, Vibert N, Godaux E, Vidal P, Moore L (2001) Resonance of spike discharge modulation in neurons of the guinea pig medial vestibular nucleus. J Neurophysiol 86:703–716

Roy JE, Cullen KE (2002) Vestibuloocular reflex signal modulation during voluntary and passive head movements. J Neurophysiol 87:2337–2357

Roy JE, Cullen KE (2003) Brain stem pursuit pathways: dissociating visual, vestibular, and proprioceptive inputs during combined eye-head gaze tracking. J Neurophysiol 90:271–290

Roy JE, Sadeghi S, Cullen KE (2003) Vestibuloocular reflex dynamics: neuronal correlates of behavioural responses during high frequency and velocity head rotations. Soc Neurosci Abstr 29:593–595

Sawyer RJ, Thurston SE, Becker K, Ackley C, Seidman S, Leigh RJ (1994) The cervico-ocular reflex of normal human subjects in response to transient and sinusoidal trunkrotations. J Vestib Res 4:245–249

Schubert M, Das V, Tusa R, Herdman S (2004) Cervico-ocular reflex in normal subjects and patients with unilateral vestibular hypofunction. Otol Neurotol 25:65–71

Smith H, Curthoys IS (1988a) Neuronal activity in the contralateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy. Brain Res 2:295–307

Smith H, Curthoys IS (1988b) Neuronal activity in the ipsilateral medial vestibular nucleus of the guinea pig following unilateral labyrinthectomy. Brain Res 444:308–319

Smith P, Curthoys IS (1989) Mechanisms of recovery following unilateral labyrinthectomy: a review. Brain Res Rev 14:155–180

Sylvestre PA, Cullen KE (1999) Quantitative analysis of abducens neuron discharge dynamics during saccadic and slow eye movements. J Neurophysiol 82:2612–2632

Tomlinson RD (1990) Combined eye-head gaze shifts in the primate. III. Contributions to the accuracy of gaze saccades. J Neurophysiol 64:1873–1891