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AUTHOR MANUSCRIPT

Accepted for publication in a peer-reviewed journal

Published as: *J Neurophysiol.* 2005 April ; 93(4): 2028–2038.

Normal Performance and Expression of Learning in the Vestibulo-Ocular Reflex (VOR) at High Frequencies

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Abstract

The rotatory vestibulo-ocular reflex (VOR) keeps the visual world stable during head movements by causing eye velocity that is equal in amplitude and opposite in direction to angular head velocity. We have studied the performance of the VOR in darkness for sinusoidal angular head oscillation at frequencies ranging from 0.5 to 50 Hz. At frequencies of 25 Hz, the harmonic distortion of the stimulus and response were estimated to be <14 and 22%, respectively. We measured the gain of the VOR (eye velocity divided by head velocity) and the phase shift between eye and head velocity before and after adaptation with altered vision. Before adaptation, VOR gains were close to unity for frequencies 20 Hz and increased as a function of frequency reaching values of 3 or 4 at 50 Hz. Eye velocity was almost perfectly out of phase with head velocity for frequencies 12.5 Hz, and lagged perfect compensation increasingly as a function of frequency. After adaptive modification of the VOR with magnifying or miniaturizing optics, gain showed maximal changes at frequencies <12.5 Hz, smaller changes at higher frequencies, and no change at frequencies larger than 25 Hz. Between 15 and 25 Hz, the phase of eye velocity led the unmodified VOR by as much as 50° when the gain of the VOR had been decreased, and lagged when the gain of the VOR had been increased. We were able to reproduce the main features of our data with a two-pathway model of the VOR, where the two pathways had different relationships between phase shift and frequency.

INTRODUCTION

The rotatory vestibulo-ocular reflex (VOR) helps maintain stable gaze in the face of head turns. When the object of regard is far from the observer, the VOR generates eye rotation of a velocity that is nearly equal in amplitude and opposite in direction to angular head velocity (Fuchs and Kimm 1975; Keller 1978). For vestibular stimuli consisting of sine waves of head motion in darkness, the performance of the VOR is quantified by computing two measures: the gain, defined as peak-to-peak smooth eye velocity divided by peak-to-peak head velocity, and the phase shift, defined as the phase difference between the actual eye velocity and that required to compensate perfectly for the head motion. In normal monkeys, for frequencies <4 Hz, the gain of the VOR in darkness is close to 1, and the phase shift is close to 0° (e.g., Keller 1978).

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The VOR is a highly modifiable reflex. When head turns are consistently associated with image motion across the retina, the VOR undergoes changes in gain or phase shift that are in the correct direction to improve the compensatory nature of the eye movements (Melvill Jones 1977; Miles and Fuller 1974; Robinson 1976). For example, if monkeys view the world through spectacles that magnify or miniaturize the visual scene, the VOR in darkness undergoes adaptive increases or decreases in gain. Prior analyses of adaptive modification of the VOR have shown that the VOR consists of parallel modified and unmodified components (Broussard et al. 1992; Khater et al. 1993; Lisberger 1984; Lisberger and Pavelko 1986). Recordings from neurons in the brain stem and cerebellar circuits for the VOR have mapped these two components onto largely separate neural pathways that receive inputs from different subpopulations of vestibular afferents (e.g., Boyle et al. 1992; Hirata and Highstein 2002; Lisberger 1994; Lisberger and Pavelko 1986; Lisberger et al. 1994a,b).

One approach to the analysis of sensory-motor behavior is to explore the parameters of sensory stimuli in search for the limits of system performance. In prior studies of the VOR that tested a wide range of stimulus parameters, Keller (1978) studied the performance of the VOR for frequencies 8 Hz, and Huterer and Cullen (2002) showed that the VOR remains approximately compensatory up to frequencies of 25 Hz. However, neither study challenged the limit of VOR performance or looked at effects of adaptive modification of the VOR. Lisberger et al. (1983) reported the frequency response of the VOR after adaptive modification with natural head turns, but also did not challenge the limits of VOR performance. In more recent studies, Clendaniel et al. (2001) have studied the expression of adaptive modifications for frequencies 15 Hz, but were concerned with responses to large amplitude stimuli as a means of exploring what they called the “linear” and “nonlinear” components of the VOR and relating them to nonlinear properties of vestibular afferent responses, such as cut-off at zero firing rate.

Our goal has been to push the frequency range of vestibular stimuli used to test the VOR to a limit that might reveal further properties of the modified and unmodified components of the VOR. We chose to use high-frequency stimuli even though they do not comprise a natural stimulus for the VOR (Armand and Minor 2001; Grossman et al. 1988), because we wanted to use stimuli that might evaluate the VOR in a regimen where neural signaling comprises a temporal code rather than a rate code (Rabbitt et al. 1996). For example, when the stimulation frequency starts to approach the resting rate of the neurons, we might expect to see “phase locking” in which afferents emit only one or two spikes at consistent phases of the sinusoidal stimulus, instead of steady firing frequencies that are modulated smoothly around a baseline (Dickman and Correia 1989; Rabbitt et al. 1995). We have kept the amplitude of the vestibular stimuli below 20°/s, partly to avoid the complications of cut-off at zero firing rate in vestibular afferent responses at low frequencies (Clendaniel et al. 2001), and partly to make it practical to deliver oscillations to an awake monkey over a frequency range from 0.5 to 50 Hz. Our data show that adaptive modification of the VOR is expressed only at frequencies of 25 Hz or below, while the VOR is not modified but has a very high gain at higher frequencies.

METHODS

Experiments were conducted on three male rhesus macaque monkeys (*Macaca mulatta*) that had been prepared for chronic experiments using techniques described in detail elsewhere (Lisberger and Pavelko 1986; Lisberger et al. 1994b). All procedures were approved by the Institutional Animal Care and Use Committee at UCSF and were in strict compliance with the guidelines for animal research established by the National Institutes of Health.

Briefly, two surgical procedures were required to prepare monkeys for behavioral experiments. Both surgeries were conducted during anesthesia with isoflurane and using sterile procedure. In the first surgical procedure, dental acrylic was used to secure a stainless steel head post to materials used in human orthopedic surgery: 5-mm-wide orthopedic straps secured to the skull by 8-mm-long screws (Synthes). The head post was used to fix the monkey's head to the chair during experiments, so that sinusoidal head velocity inputs could be imposed. In the second surgery, a 16-mm-diam coil of extremely lightweight, Teflon-coated stainless steel wire (Cooner Wire) was sutured to the sclera using a modification of the technique of Judge et al. (1980). Viewing through an operating microscope, tenotomy scissors were used to make a circular incision in the conjunctiva leaving about 1-mm of conjunctiva attached at the limbus and to dissect bluntly between Tenon's capsule and the sclera. Once the sclera had been exposed and cleaned, the coil was placed on the sclera and sutured at ~1:30, 4:30, 7:30, and 10:30 using 6-0 vicryl with a spatula needle to place sutures part of the way through the sclera. A large loop of the lead from the coil was placed deep in the lateral side of the orbit between the sclera and Tenon's capsule, and a needle was used to run the lead out of the orbit and subcutaneously to a connector on the head-restraint implant. The loop in the lateral side of the orbit was finalized by pulling on the end of the wire while visualizing the loop in the orbit. One additional scleral suture then was taken to secure the twisted pair of leads from the coil just as they left the coil itself to course down into the lateral side of the orbit. Finally, the circular incision in the conjunctiva was closed by taking 8-10 simple sutures of 6-0 gut, leaving the cut ends about 5 mm long. We find that this surgical technique has two advantages. 1) The signal-to-noise ratio of these eye coils was usually about twice as good as we had experienced in coils that were not sutured to the sclera. 2) The healed eye is not distinguishable from the control eye and remains in seemingly perfect condition for years. Postsurgically, analgesics were administered, and the monkey was monitored carefully.

Training and experimental data collection started no sooner than 1 wk after the last surgical procedure. Initially, monkeys were conditioned to head restraint and trained to fixate for fluid reward on a spot of light (0.1° diam) projected on a translucent tangent screen located 114 cm away. Later training involved maintaining gaze near the center of the orbit during vestibular stimulation, even if the spot was turned off in an otherwise darkened room. Monkeys also were trained to track the spot if it moved smoothly across the screen.

Physical setup for vestibular stimulation

During experiments, the monkeys were seated comfortably in an acrylic primate chair that was specially reinforced to transmit high frequencies faithfully. The monkeys' heads were fixed to the chair by means of the post implanted on their head and were positioned so that the axis of rotation of the chair matched the position of the head-post. In two of the three monkeys, an 18-in electromagnetic field coil (CNC Engineering) was coupled rigidly to the primate chair, and the monkey, chair, and field coil were bolted to a servo-controlled turntable (Contraves-Goertz model 820) that provided sinusoidal oscillations about the vertical axis. In a third monkey, the same 18-in field coils were secured by a metal and plastic frame to the floor so that they did not impose a load for the turntable. There were some quantitative differences between the data obtained with the field coils attached to the floor or the chair, but the qualitative features of our results did not depend on the mechanical arrangement. The only exception was that the responses at 40 Hz with the coils secured to the chair showed a phase shift that did not fit into the smooth function defined according to the responses at neighboring frequencies. We assume that this reflects an artifact with the stimulus, and we have not placed heavy weight on the responses at 40 Hz in those two monkeys, even though full disclosure dictates that we keep those data in our figures.

The major issue in applying sinusoidal head oscillation at high frequencies is testing whether the oscillations of the turntable are faithfully applied to the monkey's vestibular apparatus. To assess the exact head stimulus applied to the vestibular apparatus and the real eye movement response, we measured the position of a series of three carefully calibrated search coils that resided within the magnetic field provided by the field coils bolted to the chair. One coil was secured to the floor or ceiling of the experimental room and suspended rigidly within the moving field coils to measure the position of the magnetic field with respect to the stationary world (F_W). A second search coil was cemented to the head implant in the coronal plane and measured the position of the head relative to the magnetic field (H_F). The third search coil was implanted on the eye and assessed the position of the eye with respect to the magnetic field (E_F). The world stationary coil and the head coil were placed as close to each other and the eye coil as possible. The output of the eye-coil electronics was calibrated by rewarding the monkey for fixating targets placed at known positions along the horizontal meridian. The head-coil and world-stationary coil were calibrated by aligning the coils with known angular displacements of the monkey's head and of the magnetic field itself. We differentiated the position output from each coil with the same analog circuits and then used the following equations to compute the two parameters we needed to measure: eye velocity with respect to the head ($\dot{E}_H$) and head velocity with respect to the world ($\dot{H}_W$)

$$\dot{H}_W = \dot{H}_F + \dot{F}_W \quad (1)$$

$$\dot{E}_H = \dot{E}_F + \dot{F}_W - \dot{H}_W = \dot{E}_F - \dot{H}_F \quad (2)$$

Note that these equations apply equally when the field coils are secured to the oscillating chair and to the stationary floor. However, $\dot{E}_F$ indicates eye velocity relative to the head when the field coils are secured to the chair, and eye velocity relative to the world when the field coils are secured to the floor. The dots over the main symbols in Eqs. 1 and 2 indicate the derivatives of the position signals defined in the previous paragraph.

We verified the appropriate calibration of the coils by determining that the results of Eqs. 1 and 2 for low-frequency head oscillations agreed with our direct measurements of head and eye velocity using a tachometer attached to the shaft of the turntable and the coil implanted on the monkey's eye. Direct assessment of the angular velocity of the monkey chair with an accelerometer secured to the top of the chair revealed good agreement with the angular velocity resulting from Eq. 1 when the field coils were fixed to the chair. Finally, we checked for artifacts by implanting a block of wood the size of a monkey's head with the same head-restraint hardware and eye coils used in the monkey, weighting the primate chair with a lead brick, and securing all leads exactly as we did when measuring the VOR of a monkey. A full VOR test on the block revealed that artifacts from the mechanical system contributed at most a VOR gain of 0.04, even at the highest test frequencies. This assessment would have revealed any artifacts introduced by the rotation of metallic components of the implants and the primate chair when the magnetic field coils were bolted to the floor.

VOR modification and testing

To obtain adaptive changes in the VOR, monkeys were fitted with goggles that contained either magnifying or miniaturizing optics. Goggles were form-fitted to each monkey's face using procedures that have been described elsewhere (Lisberger and Pavelko 1986; http://keck.ucsf.edu/~sgl/top_goggles.htm). Increases in gain were induced by having the monkeys view the world through $\times 2.2$ telescopic lenses, and decreases in VOR gain were induced with $\times 0.25$ lenses. Once the monkeys were fitted with goggles and lenses, they were

returned to their cages where adaptation occurred through spontaneous, natural head movements. Adaptation proceeded for 5 days before we tested the VOR to obtain the data reported here. Goggles were removed daily for cleaning and to ensure that there was no contact between the goggles and the monkey's face.

VOR performance was tested during passive sinusoidal oscillation in total darkness. Sinusoidal oscillations had peak velocities of 15 to 20°/s and frequencies ranging from 0.5 to 50 Hz (see Table 1). During testing, the monkey's head was fastened securely to the chair and field coil, and the spectacles were removed. Care was taken that the couplings between the turntable and the primate chair, and between the field-coil and the primate chair were as rigid as possible, and that the head was fixed as tightly as possible to the primate chair. Motion of wires used to lead signals to the electronics was minimized by stabilizing all wires at multiple places on the coil and the chair, and also at the connector on the monkey's implant.

Data acquisition and analysis

The behavioral paradigms, data acquisition, and stimulus triggering were controlled by a real-time data acquisition program that ran under Windows NT using the real-time kernel RTX (VenturCom). The signals from the three field coils were differentiated in real-time by an analog differentiator with a 100-Hz upper-frequency cut-off. The coil position and velocity traces, along with the head velocity from a tachometer on the shaft of the turntable, were sampled at 500 Hz per channel and stored on hard disk for later analysis, when we compensated for the filtering characteristics of the analog differentiator. The compensation procedure was based on assessment of the gain and phase of the differentiator as a function of frequency and therefore ensured that the frequency responses we report for the VOR are features of the biology, not of the differentiators.

To analyze the VOR evoked by sinusoidal head oscillation, we averaged the head and eye velocity for 20 stimulus cycles at each frequency. At frequencies <4 Hz, saccades were removed from the eye velocity traces, and data were analyzed under two conditions: 1) when eye velocities during the saccade were interpolated between the immediate presaccadic and postsaccadic velocity, and 2) when the data for the duration of the saccade were not used. The differences between the two conditions were negligible (see also Churchland and Lisberger 2001), so the values presented here were computed the second way. At higher frequencies, the cycles were discarded if they contained saccades, and the stimuli were used for analysis only if there were 20 consecutive full cycles that did not include any saccades. The averages were subjected to Fourier analysis by fast Fourier transform (FFT), and the gain of the VOR was estimated as the ratio of the amplitudes of the fundamental components of eye and head velocity. The phase of the VOR was determined as the difference between the phase values of the fundamental components of head and eye velocity. The VOR was defined as having zero phase-difference when eye velocity was 180° out of phase with head velocity. Finally, the total harmonic distortion of the head and eye velocity traces was computed as

$$THD = \frac{\sum_{i=2}^n A_i^2}{A_1^2} \quad (3)$$

where A_i is the amplitude of the i th harmonic, and n was 7 for frequencies ≤ 25 Hz and was 6 and 5 for 40 and 50 Hz, respectively.

RESULTS

Normal performance in the VOR

Figure 1 shows the measurements we made from search coils that estimated magnetic field angular velocity with respect to the stationary world ($\dot{F}_w$), head velocity with respect to the magnetic field ($\dot{F}_F$), and eye velocity with respect to the magnetic field ($\dot{E}_F$). When combined (see Eqs. 1 and 2), these three signals estimated the real vestibular stimulus, head velocity with respect to the stationary world ($\dot{H}_w$), and the traditional measure used to assess the VOR, eye velocity with respect to the head ($\dot{E}_H$).

The top half of Fig. 1 shows data obtained with the field coils fixed to the floor, so that field velocity relative to the world was stable. The stimuli and responses were approximately sinusoidal 25 Hz (0.5 and 10 Hz shown in Fig. 1, *A* and *B*, respectively), and remained periodic but with some irregularities at 40 and 50 Hz (Fig. 1, *C* and *D*). For the example day shown in Fig. 1, *A-D*, the gain of the VOR was 1.03, 1.04, 2.97, and 2.76 at testing frequencies of 0.5, 10, 40, and 50 Hz, respectively. Eye velocity led a perfect VOR by 0.1 and 5.9° at 0.5 and 10 Hz and lagged by 28.4 and 62.2° at 40 and 50 Hz. Note that the measurement of eye position with respect to the field coils was not modulated for the lower two frequencies in Fig. 1, because gain of the VOR was close to 1, and the field coils were fixed to the floor so that the monkey's eye coil measured gaze rather than eye position.

The bottom half of Fig. 1 shows data obtained when the field coils were fixed to the oscillating chair. With this mechanical arrangement, the field is supposed to move with respect to the chair, but the head is supposed to remain stationary with respect to the field, as shown for the lower frequencies (Fig. 1, *E* and *F*). Thus the most troubling aspect of the stimuli provided with the field coils fixed to the chair is the modulation of head velocity with respect to the field at 40 and 50 Hz (Fig. 1, *G* and *H*). This modulation indicates either that the monkey's head was moving with respect to the chair or, more likely, that the field coils were flexing under the stress of the high-frequency oscillation. Still, our estimate of head velocity with respect to the world was sinusoidal and had lower harmonic distortion at 50 Hz than when the field coils were fixed to the floor. Furthermore, our estimates of the gain and phase of the VOR were similar to those obtained with the field coils fixed to the floor: in Fig. 1, *E-H*, the gain of the VOR was 0.89, 0.99, 2.97, and 3.65 at 0.5, 10, 40, and 50 Hz, and eye velocity led a perfect VOR by 1-2° at 0.5 and 10 Hz and lagged by 65 and 61° at 40 and 50 Hz, respectively. Good agreement at 50 Hz between the values we computed for $\dot{H}_w$ and chair angular velocity derived from an accelerometer indicates that the data at 50 Hz were valid even when the field coils were attached to the rotating chair. Our greatest concern was the data at 40 Hz, where the phase shift of the VOR was out of line with those obtained at neighboring frequencies and where the stimulus shows very large head motion with respect to the field.

The frequency response of the VOR over the frequency range from 0.5 to 50 Hz appears for three monkeys in Fig. 2 under control conditions, before adaptive modification of the VOR. Over the frequency range from 0.5 to 10 Hz, the gain curves were flat and stayed close to 1.0, and eye velocity was very nearly in phase with inverted head velocity. At 12.5 Hz, monkeys U and S showed a slight elevation in gain that returned to 1 at 16.67 and 20 Hz before reaching values in excess of 3 in the frequency range from 25 to 50 Hz. Monkey W, who was tested with the field coils secured to the floor, showed a VOR gain that was near 1 to 16.67 Hz and then reached a value of 3 at 40 and 50 Hz. In monkeys U and S, phase lag increased steadily as frequency increased from 10 to 40 Hz and decreased at 50 Hz. In monkey W, phase showed a lead of almost 20° that peaked at 12-16 Hz before turning to a

phase lag of more than 60° at 50 Hz. Based on the more reliable data of monkey W, we suspect that the discontinuity in phase shifts at 40 Hz in monkeys U and S was an artifact of the lower quality vestibular stimulus when the field coils were affixed to the rotating chair. However, the data of monkey W confirm that the gain of the VOR indeed achieves very high values at frequencies of 40 and 50 Hz. We cannot be sure whether the phase lead around 15 Hz or the slightly lower VOR gain at 50 Hz should be taken as individual differences (cf. Huterer and Cullen 2002), the result of using a better-quality vestibular stimulus in monkey W, or a consequence of minor brain stem damage caused by electrode penetrations.

A phase lag of 80° at 50 Hz would correspond to a time delay of 4.4 ms, in reasonable agreement with other estimates of the delay in the VOR pathways for high values of head acceleration such as the $6,280^\circ/\text{s}^2$ imposed by our 50-Hz stimulus (Clendaniel et al. 2001; Huterer and Cullen 2002; Tabak et al. 1997). Our finding that the gain of the VOR increases as a function of stimulus frequency agrees with previously reported values for the performance of the VOR for frequencies > 30 Hz in humans (Gauthier et al. 1984) and for frequencies > 25 Hz in one of the three rhesus monkeys tested by Huterer and Cullen (2002), although the two other monkeys in the latter study did not show the same gain enhancement at high frequencies.

Frequency response after adaptive modification of the VOR

Figure 3 shows superimposed averages of the five relevant signals for the VOR measured in darkness at 0.5, 10, and 50 Hz after spectacles had been used to cause adaptive increases (black traces) or decreases (gray traces) of the gain of the VOR. Comparison of the signals used to monitor the stimulus ($\dot{H}_F$ and $\dot{F}_W$) and their combination to yield the actual head motion ($\dot{H}_W$) revealed success in applying the same vestibular stimuli on a daily basis.

Comparison of the eye movements evoked by the VOR ($\dot{E}_H$) shows the expected consequences of adaptive modification when measured at 0.5 and 10 Hz, and no effects of adaptive modification when measured at 50 Hz. Note that these data were obtained with the field coils bolted to the floor so that the trace showing eye velocity with respect to the field is measuring gaze velocity. As a result, adaptive increases or decreases in the gain of the VOR result in traces that are 180° out of phase, even though eye velocity with respect to the head is always out of phase with head velocity with respect to the world. For these 2 days, the gain of the VOR ranged from 0.58 to 1.61 at 0.5 Hz, from 0.74 to 1.43 at 10 Hz, but only from 2.73 to 2.84 at 50 Hz. The phase difference between eye velocity with respect to the head (lowest traces) and inverted head velocity was unrelated to the gain of the VOR at when the test frequency was 0.5 Hz (phase leads of 0.2 and 1.5°), but depended on the gain of the VOR at higher frequencies. At a test frequency of 10 Hz, eye velocity lagged inverted head velocity by 3.3° when the gain of the VOR was high and led by 19° when the gain of the VOR was low. At a test frequency of 50 Hz, eye velocity lagged inverted head velocity by 59.9 and 62.7° when the gain of the VOR was high and low.

To summarize the performance of the VOR as a function of testing frequency, we first allowed the monkey to adapt to the modified vision imposed by the spectacles for 5 days, and we measured the performance of the VOR in darkness for 10 consecutive experimental sessions. Figure 4 plots the means and SD of VOR gain and phase across experimental day as a function of testing frequency. The results were qualitatively similar for the three monkeys, shown in the *left*, *middle*, and *right panels*. At testing frequencies of 10 Hz and below, the gain of the VOR was uniformly increased after adaptation with $\times 2.2$ goggles and decreased after adaptation with $\times 0.25$ goggles. The phase of the VOR shows increasing lead and lag as a function of frequency for decreases in gain ($\bullet$) and increases in gain (Δ),

respectively. For testing frequencies in the range from 10 to 25 Hz, the amount of change in the gain of the VOR decreased as a function of frequency, but the differences from control ($\square$) remained statistically significant ($P < 0.05$, Mann-Whitney U test). The effect of spectacle adaptation on the phase shift of the VOR was greatest over the frequency range from 10 to 25 Hz. For a testing frequencies of 50 Hz, the gain of the VOR after adaptation was not different from control conditions ($P > 0.5$, Mann-Whitney U test), and eye velocity lagged inverted head velocity by 60–100° both before and after spectacle adaptation.

There also were some quantitative differences between the VOR measurements from monkey W versus monkeys S and U. The control VOR in monkey W, before adaptive modification, showed more phase lead in the frequency range surrounding 20 Hz and had smaller SD. Furthermore, he underwent smaller changes in VOR gain and phase than did monkeys U and S. Other studies also have shown some differences between monkeys (e.g., Huterer and Cullen 2002), and we do not know the basis for any of these differences. However, we note that monkey W underwent smaller changes in VOR gain and phase even before he was used for brain stem recordings, so this seems unlikely to be the cause. Instead, we assume that the quantitative differences between monkey W and monkeys S and U can be attributed partly to real individual differences and partly to the difference in the mechanical arrangement of the field coils.

We further quantified the effect of adaptive modification on the frequency response of the VOR by computing the ratio of the VOR gain after adaptation relative to the control value before adaptation (Fig. 5A) and the phase shift caused by adaptation (Fig. 5B) for each frequency, direction of adaptation, and monkey. We found symmetry in the effects of adaptive increases and decreases in the gain of the VOR, and good qualitative agreement among the three monkeys (circles, triangles, and squares). Again, adaptive modification caused showed smaller changes in gain and less phase shift in monkey W than in the other two monkeys. The gain changes were largest in the low-frequency range, without clear maxima, and the phase shifts peaked between 16.67 and 25 Hz. In monkeys S and U, the change in phase caused by adaptive modification of the VOR conformed with the values expected if increases or decreases in the gain of the VOR had the effect of causing a 5-ms time lag or lead in the VOR, respectively (Fig. 5, dashed curves). In monkey W, they were equivalent to a 2.5-ms time lag or lead (curves not shown).

DISCUSSION

We have found three novel properties of the VOR by studying its responses at high frequencies of vestibular oscillation. First, the gain of the VOR is unexpectedly high when tested at 40 or 50 Hz. Second, the VOR at frequencies above 25 Hz does not express the adaptive changes in the VOR that appear at lower test frequencies after monkeys wear magnifying or miniaturizing spectacles. Third, adaptive changes in the gain of the VOR cause changes in the phase of the VOR that are especially large at higher frequencies.

Technical issues of imposing high-frequency stimuli

Imposing vestibular stimuli at high frequencies introduces the possibility of potentially serious artifacts because the linkage from the motor that imposes head oscillations to the head itself is inherently unrigid. We have used three approaches to verify that our measurements were good estimates of the real performance of the VOR at high frequencies. 1) We have devised a method that used three coils to measure the motion of the eye with respect to the magnetic fields, the head with respect to the magnetic fields, and the field with respect to the stationary world. Because of the physical relation between these variables, they can in principle be combined to estimate the two physical variables that are important for the VOR: head velocity with respect to space and eye velocity with respect to the head.

2) In the third monkey, we secured the field coils to the floor rather than to the chair, producing stimuli that were of higher quality at most frequencies. Detaching the field coils from the chair removed a major cause of mechanical resonance and improved our vestibular stimulus at all frequencies. Because of the qualitative similarity of the data from all three monkeys, the data from the better vestibular stimulus in the third monkey persuade us that the qualitative findings listed in the first paragraph of the *DISCUSSION* are real. 3) We tested the VOR of an inanimate substitute for the monkey, revealing only very small contributions from artifacts to our measurements of the gain and phase of the VOR. Still, we suspect that the estimates of VOR gain and phase at 40 Hz had a significant contribution from artifacts when the field coils were secured to the rotating chair, in the first and second monkeys, and we retain a healthy skepticism toward this feature of our data.

In an earlier analysis on baboons, Vercher et al. (1984) concluded that the “VOR” at high frequencies was caused passively by the inertia of the globe and not actively by signals passed through neural pathways. We do not think that the inertia of the globe is responsible for the large VOR gains recorded in our monkeys. We think that the active eye muscles of our awake monkeys will create a stiff system that would resist compensatory counter rotations because of inertia, especially compared with the very limp system created by inactive eye muscles during local anesthesia with lidocaine. Our view is supported by the fact that neither we nor others (Huterer and Cullen 2002; Minor et al. 1999) find the short latency counter-rotations that would be expected in response to transient vestibular stimuli if compensatory eye movements were due to inertia rather than neural pathways and active muscle contraction.

A two-pathway model of the VOR

We have made a two-pathway model of the VOR to formalize the predictions of our data in a way that is relevant to the hypothesis that there are separate modified and unmodified VOR pathways in the brain stem. Each pathway in the model (Fig. 6A) consists of a transfer function [$F_m(f)$, $F_u(f)$], a frequency-dependent gain [$G_m(f)$, $G_u(f)$], and a time delay (ΔT_m , ΔT_u), where the subscripts u and m refer to the unmodified and modified pathways, respectively. In the modified pathway, the transfer function was taken from the model that described the vestibular primary afferents with regular discharge in Hullar and Minor (1999)

$$F_m = \frac{s(0.0042s+1)}{4.4s+1} \quad (4)$$

In the unmodified pathway, the transfer function (F_u) was modeled as a time advance of 17 ms. The standard models of intermediate and irregular afferents (e.g., Fernandez and Goldberg 1971; Wilson and Melvill Jones 1979) are based on data at frequencies up to only 8 Hz and could not be used because their phase leads saturate at 90° at high frequencies; our model required much higher phase leads to reproduce the gain and phase of the VOR at high frequencies. We chose to use a pure time advance because it provided a good fit to the phase shifts of primary afferents with intermediate discharge regularity over the range where there are data from intact canals (Hullar et al. 2003) and also provided the high-frequency phase lead we needed. However, we do not mean to imply that the brain is capable of negative latencies. Instead, we are making the testable prediction that there is a progressive increase in the phase lead of intermediate afferents at high frequencies. Figure 6B graphs the relationships between phase and frequency for F_m (○), F_u (△), and the model (dashed curve) used to fit the intermediate afferents by Hullar et al. (2003)

$$\frac{(1+0.006s)(1+sT_2)}{(1+5.7s)(1+0.003s)} \quad (5)$$

where $\log(T_2) = 0.76\log(CV) - 1.06$ and we used $CV = 0.14$.

The other parameter that was fixed when we fit the model to our data were the gain of the unmodified pathway

$$G_u(f) = -0.0000386f^3 + 0.0033f^2 - 0.024f + 0.547 \quad (6)$$

Equation 6 was selected so that its value at low frequencies would remain consistent with our prior conclusion that the value of $G_u(f)$ in the model was $\sim 50\%$ of the control VOR at frequencies < 4 Hz (Lisberger 1994). The higher order terms caused the value of $G_u(f)$ to increase as a function of frequency. High values of $G_u(f)$ were needed to allow the net output of the full model to reproduce the very high gain of the VOR at high frequencies, in the face of large phase differences between the high-amplitude signals transmitted by the modified and unmodified pathways.

We fitted our model to the data for each monkey by finding the values of ΔT_u , ΔT_m , and the gains in the modifiable pathway [$G_m(f)$] that provided the least squared difference between the gain and phase of the data and the model. The fit was done for all frequencies at once, but the value of $G_m(f)$ was optimized separately for each frequency, so that we would not have to make any assumptions about the function that related the gain of the modifiable pathway to frequency. Because of our concern about the validity of data obtained at 40 Hz with the field coils fixed to the oscillating chair, we have not included 40 Hz in our optimization. The optimization weighted errors in gain 10 times more heavily than errors in phase to normalize for the larger values of the changes in phase and allow gain and phase to be fit equally well. Figure 6, *C* and *E*, shows that our model was able to reproduce the effect of VOR adaptation on the relationship between phase and frequency, and Fig. 6, *D* and *F*, shows that it did so with smooth relationships between G_m and frequency. Even though there were some differences in the size of the changes in the gain of the VOR for monkeys W, S, and U, the model did a good job of fitting the data for each monkey, with only minor quantitative differences between the fits: for monkeys W, S, and U, the mean squared error in the gain of the VOR was 0.04, 0.17, and 0.13, and the mean squared error in the phase of the VOR was 30.3, 57.5, and 52.7, respectively. In the best-fitting models for monkeys W, S, and U, the values of ΔT_m were time lags of 7.7, 11.9, and 12.0 ms; the values of ΔT_u were time lags of 12.9, 13.4, and 13.2 ms.

Figure 6, *D* and *F*, shows good agreement between the gain of the modified pathway of the model and available data on the effect of adaptive modification of the VOR on the responses of neurons in the modified brain stem VOR pathways. At low frequencies, G_m was near zero or negative after adaptive decreases in the gain of the VOR (Fig. 6, *D* and *F*, triangles), as found in floccular target neurons under the same conditions (Lisberger et al. 1994b). At high frequencies, G_m did not change as a function of adaptive changes in the gain of the VOR, to account for the absence of any expression of adaptive changes in the VOR when tested with vestibular stimulation at 40 and 50 Hz. Even though its gain is not modified at the highest frequencies, we think that it is appropriate to call this pathway “modified” because it is responsible for the entire change in the gain of the VOR over the frequency range where adaptive modification is expressed. In attempting to reconstruct the gain of the VOR from the values of G_u and G_m at high frequencies, it is essential to recall that the different phase shifts in the modified and unmodified pathways will prevent these two values from simply adding to produce the gain of the VOR.

Our data place serious constraints on the model. To allow increases and decreases in the gain of the VOR to cause symmetrical changes in the phase of the VOR, we had to assume that the modified and unmodified pathways in the model had different relationships between

phase and frequency (Fig. 6B). When the time delays were taken into account, this amounted to phase lead in the unmodified pathway and phase lag in the modified pathway. Then, decreasing and increasing the gain of the modified pathway allowed it to contribute either less or more phase lag, causing the behavioral output to show more lead or more lag. To account for the large effects of changes in the gain of the VOR on the phase of the VOR, we had to assume that increases in stimulus frequency caused large changes in phase of both pathways (Fig. 6B). Future experiments will determine how well the parameters in our model map onto the responses of neurons in a modified VOR pathway that uses floccular target neurons as interneurons (Lisberger and Pavelko 1988), and an unmodified pathway that uses traditional VOR interneurons known as “position-vestibular-pause” or “PVP” neurons (King et al. 1976; Pola and Robinson 1978; Scudder and Fuchs 1992). At this stage, however, we can state with confidence that a two-pathway model like that in Fig. 6 can account well for the data of all three monkeys included in this paper.

Comparison with prior studies

Our results and modeling agree with many of the points made by prior studies of the VOR at high frequencies. First, we agree that adaptive changes in the gain of the VOR are associated with changes in the phase of the VOR, even when the broadband waveform provided by natural head turns is used as the vestibular stimulus during adaptation (e.g., Clendaniel et al. 2001; Lisberger et al. 1983). Second, we agree that the phase lag exhibited by the VOR at frequencies ~ 25 Hz is considerably less than predicted on the basis of a time delay of 5–7 ms (Huterer and Cullen 2002; Minor et al. 1999). For example, a 5-ms delay predicts a phase lag of 45° at 25 Hz, whereas phase lag was $<20^\circ$ in two of our monkeys, and there was a phase lead in one monkey. In this regard, it is important not to confuse *phase leads* with *time leads*. The steady-state performance of dynamical systems often shows *phase lead* even when the system is a causal physical system that has finite *time delay*. Indeed, our model is able to produce phase leads in the VOR even though both pathways have time delays. This is because the unmodified pathway is assumed to receive vestibular inputs that have considerable phase lead with respect to head velocity, especially at high frequencies. We have modeled the phase lead as a time advance, for computational convenience, but we imagine it exists in the brain as a dynamical element that creates increasing phase lead as a function of frequency.

There also are some points of real or apparent disagreement. For example, our finding that the gain of the VOR is above 3 for head oscillation at 40 and 50 Hz disagrees with a finding of Huterer and Cullen (2002). For two of their three monkeys, the gain of the VOR was near 1 for brief pulses of head velocity, even though the gain should have been >1 because the pulses had some frequency content at 40 and 50 Hz. However, our data are consistent with their finding of VOR gains larger than one for brief pulses of head velocity in one monkey. Furthermore, the magnitude of the disagreement is not as large as it might seem. Inspection of the frequency content of their stimuli shows that ~ 75 –80% of the power lies in frequencies of 25 Hz or below, where we also found that VOR gain was little above one. Therefore their measurements would be dominated by the VOR gain at low frequencies. If we assume that 20% of the frequency content of their stimulus is above 40 Hz, where VOR gain is 3 for sinusoidal stimuli, this should contribute only a gain elevation of 0.4 (20% of $3 - 1$) to their results, predicting a gain of 1.4 instead of 1.0. The apparent difference between their study and ours may be attributable to methodological differences: they provided stimuli that rotated the head with respect to the body and used considerably larger values of head velocity (± 50 or $\pm 100^\circ/\text{s}$ in their study vs. $\pm 20^\circ/\text{s}$ in ours).

We do not think that the apparent difference between our conclusions and those of Minor and colleagues (Clendaniel et al. 2001; Minor et al. 1999) is as large as it might appear. They have modeled the VOR in terms of “linear” and “nonlinear” pathways, with the

conclusion that the “nonlinear” pathway receives inputs from irregular afferents and is unmodifiable. We have modeled the VOR in terms of “modified” and “unmodified” pathways, where the modified pathway receives inputs from regular afferents. Their inclusion of linear and nonlinear pathways is inspired by their finding that the gain of the VOR increases as a function of the peak head velocity of the stimulus. Our inclusion of modified and unmodified pathways is based on physiological evidence showing that adaptive modification of the VOR causes little or no change in the brain stem pathways through PVP neurons but large changes in the brain stem pathways through FTNs (Lisberger et al. 1994b). However, our experiments differed both in the species we used (rhesus vs. squirrel monkeys) and in the amplitude of the vestibular stimuli. Clendaniel et al. (2001) point out that stimulus velocities in excess of the $\pm 20^\circ/\text{s}$ we used are needed to cross the threshold for their “nonlinear” pathway, implying that our stimuli would reveal the function of the “linear” pathway only. Of course, it is possible that their nonlinear pathway is activated at very low velocities for the ultra-high stimulus frequencies in our experiments. Still, we do not think that our data or conclusions conflict with theirs, although our analysis of the system may be incomplete in the sense that they have identified a component of the VOR that may not be activated by our stimuli.

Rationale for studying the VOR with high-frequency vestibular stimuli

We see the behavioral experiments presented here as a prelude to analysis of the neural basis for VOR adaptation that would build on prior reports from us and others (e.g., Hirata and Highstein 2002; Lisberger 1984, 1994; Lisberger and Pavelko 1986). Thus we started from a view of the neural substrate for the VOR as two parallel brain stem pathways. One pathway is not subject to modification and appears to use the “PVP” neurons in the vestibular nucleus as an interneuron. The other pathway is modifiable and appears to use floccular target neurons (FTNs) in the vestibular nucleus as interneurons. Our premise in choosing to study the VOR at high frequencies was that frequencies as high as 50 Hz might cause central neurons to become phase locked to the stimulus, as occurs for primary afferents (Rabbit et al. 1995). Phase locking might cause the expression of learning to be different, in both neural responses and VOR behavior. We want to emphasize that our goal was to study the expression of an adapted VOR for stimuli that might prove useful for *analyzing* the neural system. Thus we think it is immaterial that our high-frequency vestibular stimuli are far outside the range encompassed in natural head turns (Armand and Minor 2001; Grossman et al. 1988). Furthermore, we are aware that visual error signals for the VOR would be useless at such high frequencies. Our experiments were not intended to address the identity of the error signals that guide VOR adaptation, but rather the expression of the adapted VOR across a wide and admittedly unnatural range of vestibular stimuli.

The absence of any expression of the adapted VOR at 40 or 50 Hz suggests that the rationale for our approach is sound. Indeed, our data and model raise a number of questions for future analysis. First, does the fact that the phase of the VOR is modified substantially and symmetrically by increases and decreases in the gain of the VOR make accurate predictions about the relationship between phase shift and frequency in vestibular primary afferents? In the modified and unmodified pathways? Second, is there no expression of VOR adaptation at high frequencies because 1) the modified pathways simply do not respond to such high frequencies, 2) they respond, but in a phase locked mode of signaling that allows the signals to bypass the cellular mechanisms of adaptation, or 3) because there are temporal frequency channels in the VOR and the highest frequency channels were not activated during the natural head turns used for adaptation (e.g., Lisberger et al. 1983 for the species used in this study)?

We doubt the explanation based on temporal frequency channels in the VOR simply because it is hard to imagine a convergence of visual and vestibular information that could signal

whether the gain of the VOR needed to increase or decrease at frequencies in excess of about 10 Hz (Raymond and Lisberger 1998). The explanation based on phase-locked signaling would be consistent with burgeoning evidence of cellular plasticity in the generation of trains of action potentials in FTNs, in vitro. For example, if the mechanism of plasticity resided in an ion channel that was critical for determining the interspike intervals of FTNs during repetitive firing (Smith et al. 2002), the timing and probability of occurrence of single action potentials in phase-locked responses might be unaffected by plasticity. Still, the behavioral data in the present paper cannot distinguish the first two possibilities without physiological data on the responses of vestibular afferents, brain stem vestibular neurons, and extraocular motoneurons during high-frequency oscillation.

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FIG. 1.

Representative records showing the output from 3 search coils in our system and performance of the vestibuloocular reflex (VOR) under control conditions before adaptation for 4 frequencies: 0.5 (*A* and *E*), 10 (*B* and *F*), 40 (*C* and *G*), and 50 Hz (*D* and *H*). Data in *A-D* are from monkey W and were obtained with the field coils fixed to the floor. Data in *E-H* are from monkey S and were obtained with the field coils fixed to the oscillating chair. From *top to bottom*, records show velocity of the magnetic field with respect to space, velocity of the head within the field, eye velocity with respect to the field, computed head velocity in the world, and computed eye velocity within the orbit. Each trace was sampled every 2 ms, accounting for the difference in the coarseness of the traces at different frequencies. Calibrations apply to all traces to the *left* of the calibration marker, up to the point where another calibration marker appears. Note that the scales in *G* and *H* are different from those in the rest of the figure and that different traces in *G* and *H* can be on different scales.

FIG. 2.

Quantitative summary of the performance of the VOR under control conditions before adaptation. Each column of graphs plots the gain of the VOR in *A-C* and the phase difference between eye and head velocity in *D-F*, both as a function of the frequency of the sinusoidal vestibular stimulus. *A* and *D*: data for monkey U. *B* and *E*: data for monkey S. *C* and *F*: data for monkey W. Symbols show mean values across several experimental days and dashed traces indicate $\pm$ SD. Positive and negative values of phase indicate phase lead and lag. A perfect VOR would have a gain of 1 and a phase difference of 0° . Each point shows averages of the gain and phase of the VOR for 10 days of recording, and comprises >500 stimulus cycles at frequencies from 0.5 to 8 Hz and $>1,000$ for higher frequencies.

FIG. 3.

Representative records showing output from 3 search coils in our system and performance of the VOR after adaptive modification of the VOR for 3 frequencies: 0.5 (*A*), 10 (*B*), and 50 Hz (*C*). Gray traces show data acquired after the monkey had worn miniaturizing spectacles. Black traces show data acquired after the monkey had worn magnifying spectacles. From *top to bottom*, records show velocity of the magnetic field with respect to space, velocity of the head within the field, eye velocity with respect to the field, computed head velocity in the world, and computed eye velocity within the orbit. Each trace was sampled every 2 ms, accounting for the difference in the coarseness of the traces at different frequencies. Data are from monkey W and were obtained with the field coils bolted to the floor.

FIG. 4.

Quantitative summary of the performance of the VOR before and after adaptive modification. Each column of graphs plots the gain of the VOR in *A-C* and the phase difference between eye and head velocity in *D-F*, both as a function of the frequency of sinusoidal vestibular stimulus. *A* and *D*: data for monkey S. *B* and *E*: data for monkey U. *C* and *F*: data for monkey W. Symbols show mean values across several experimental days. ●, □, and △ show responses after adaptation to magnifying spectacles, under control conditions, and after adaptation to miniaturizing spectacles, respectively. Dashed traces indicate $\pm$ SD. Positive and negative values of phase indicate phase lead and lag. Each point shows averages of the gain and phase of the VOR for 10 days of recording and comprises >500 stimulus cycles at frequencies from 0.5 to 8 Hz and >1,000 for higher frequencies.

FIG. 5.

Quantitative summary of the change in VOR performance after adaptive modification. *A*: ratio of gain after adaptation to before adaptation as a function of stimulus frequency. *B*: change in phase as a consequence of adaptation as a function of stimulus frequency. Circles, triangles, and squares show data from monkeys S, U, and W. Open and filled symbols show results after increases and decreases in the gain of the VOR. Dashed lines in *B* show the phase shift expected of a 5-ms time lag or lead.

FIG. 6.

Interpretation of the effect of adaptive modification on the performance of the VOR in the context of a model with modifiable and unmodifiable pathways. **A:** architecture of a model that was used to fit our data. Rectangles contain transfer functions in which gain and/or phase shift vary as a function of frequency. Open circle is a summing junction. Head velocity inputs flow from *left to right* in the model to produce the eye velocity of the VOR. **B:** circles and triangles show phase shift as a function of frequency for the transfer functions $F_m(f)$ and $F_u(f)$. Dashed line shows the model of afferent phase shifts from Hullar et al. (2003) for afferents with intermediate discharge regularity. **C** and **E:** phase shift as a function of frequency for monkeys W and S. Circles, squares, and triangles show data obtained when the gain of the VOR was high, normal, or low. Different lines show the output of the best fitting model. **D** and **F:** pathway gain is plotted as a function of frequency for monkeys W and S. Filled circles, open squares, and open triangles show values of $G_m(f)$ when the gain of the VOR was high, normal, or low, respectively. Dashed curve shows the value of $G_u(f)$, which did not vary as a function of the gain of the VOR. Subscripts *u* and *m* refer to unmodified and modified pathways of the model, respectively.

TABLE 1

Properties of vestibular input and eye velocity output across the full range of stimulus frequencies in the data taken with the field coils fixed to the rotating chair

Frequency	Head				Eye				Position excursion	
	Velocity (°/s)		THD (%)		Velocity (°/s)		THD		Head (°)	Eye (°)
	S,U	W	S,U	W	S,U	W	S,U	W	S,U	S,U
0.5	15	15	<1	<1	14.2	15.3	1	1	4.77	4.52
1	15	15	<1	<1	13.4	15	1	1	2.39	2.14
2	15	15	1	1	13.8	15.3	3	1.8	1.19	1.1
3.3		15		1		15.4		2.2		
4	15.6	15	1	1	14.1	15.4	6	4.6	0.62	0.56
5		15		1.4		15.3		4.2		
8	16.2	15	1	1.3	15.9	14.7	6	5.2	0.32	0.31
10	16.6	15	2	1.8	17.2	14.8	9	6.8	0.27	0.27
12.5	17	15	6	2.5	20.2	14.7	11	6.9	0.22	0.26
16.67	16	15	29	6	13.1	16	34	8.4	0.15	0.12
20	14	14.8	18	8	12.9	18.8	27	8.8	0.11	0.10
25	14	14.8	11	8	17.1	22	22	11	0.09	0.11
33.3		14.5		8		30.5		10.08		
40	19	14.2	10	11	74.1	38.3	19	12.5	0.08	0.29
50	24.8	14	10	14	122.2	39.2	15	12.6	0.08	0.39

THD refers to Total Harmonic Distortion, computed from the 1st 7 harmonics for frequencies up to 20 Hz and from the 1st 6 and 5 harmonics for 40 and 50 Hz. Harmonics available for the highest frequencies were limited by the 2-ms data sampling rate. Columns headed by S,U and W indicate values for stimuli used when the field coil was secured to the turntable or the floor, respectively. Empty cells are for frequencies that were not tested in monkeys S and U. Position excursions are given only for monkeys S and U, for whom the field coil was secured to the turntable.