Human Horizontal Vestibulo-Ocular Reflex Initiation: Effects of Acceleration, Target Distance, and Unilateral Deafferentation

BENJAMIN T. CRANE AND JOSEPH L. DEMER
Departments of Ophthalmology and Neurology, University of California, Los Angeles, California 90095-7002

Crane, Benjamin T. and Joseph L. Demer. Human horizontal vestibulo-ocular reflex initiation: effects of acceleration, target distance, and unilateral deafferentation. J. Neurophysiol. 80: 1151–1166, 1998. The vestibulo-ocular reflex (VOR) generates compensatory eye movements in response to angular and linear acceleration sensed by semicircular canals and otoloths respectively. Gaze stabilization demands that responses to linear acceleration be adjusted for viewing distance. This study in humans determined the transient dynamics of VOR initiation during angular and linear acceleration, modification of the VOR by viewing distance, and the effect of unilateral deafferentation. Combinations of unpredictable transient angular and linear head rotation were created by whole body yaw rotation about eccentric axes: 10 cm anterior to eyes, centered between eyes, centered between otoloths, and 20 cm posterior to eyes. Subjects viewed a target 500, 30, or 15 cm away that was extinguished immediately before rotation. There were four stimulus intensities up to a maximum peak acceleration of 2,800°/s². The normal initial VOR response began 7–10 ms after onset of head rotation. Response gain (eye velocity/head velocity) for near as compared with distant targets was increased as early as 1–11 ms after onset of eye movement; this initial effect was independent of linear acceleration. An otolith mediated effect modified VOR gain depending on both linear acceleration and target distance beginning 25–90 ms after onset of head rotation. For rotational axes anterior to the otoloths, VOR gain for the nearest target was initially higher but later became less than that for the far target. There was no gain correction for the physical separation between the eyes and otoloths. With lower acceleration, there was a nonlinear reduction in the early gain increase with close targets although later otolith-mediated effects were not affected. In subjects with unilateral vestibular deafferentation, the initial VOR was quantitatively normal for rotation toward the intact side. When rotating toward the deafferented side, VOR gain remained less than half of normal for at least the initial 55 ms when head acceleration was highest and was not modulated by target distance. After this initial high acceleration period, gain increased to a degree depending on target distance and axis eccentricity. This behavior suggests that the commissural VOR pathways are not modulated by target distance. These results suggest that the VOR is initially driven by short latency ipsilateral target distance dependent and bilateral target-distance independent canal pathways. After 25 ms, otolith inputs contribute to the target distance dependent pathway. The otolith input later grows to eventually dominate the target distance mediated effect. When otolith input is unavailable the target distance mediated canal component persists. Modulation of canal mediated responses by target distance is a nonlinear effect, most evident for high head accelerations.

INTRODUCTION

The vestibulo-ocular reflex (VOR) historically was described as a three-neuron arc activating the extraocular muscles in response to semicircular canal stimulation (Lorente de Nó 1933). Since this initial description, it has been found that the VOR responds to numerous contextual factors such as motor activity and visual feedback (Collewijn 1989) as well as otolith input (Fernandez and Goldberg 1976) and viewing distance (Schwarz et al. 1989; Viirre and Demer 1996; Viirre et al. 1986). This context-dependent behavior implies complexity far beyond a three-neuron arc. One major complexity is highlighted by the VOR response to simultaneous angular and linear motion.

The VOR response to translation increases for proximal as compared with distant targets in both monkeys (Bush and Miles 1996; Paige and Tomko 1991; Schwarz et al. 1989) and humans (Bronstein and Gresty 1988; Busettini et al. 1994; Paige 1991). This behavior is appropriate to minimize image motion on the retina. Angular rotation about an eccentric axis produces a behaviorally relevant combination of angular and linear motion. As geometrically appropriate to gaze stabilization, the VOR gain of monkeys rotated about an axis posterior to the head is greater for proximal than distant targets (Viirre et al. 1986) but is decreased for near targets when the rotational axis is anterior to the head (Sargent and Paige 1991). The prevailing view is that variation in VOR gain with axis eccentricity is mediated by otolith responses modulated by some factor related to target distance, possibly vergence (Paige 1991). It is unclear how responses to linear and angular motion are combined. There is evidence that the interaction is linear during steady-state rotation in both monkeys (Sargent and Paige 1991) and humans (Crane et al. 1997). However, comparisons of sudden linear and angular motion in humans suggest that the otolith and canal inputs may not combine linearly (Anastasopoulos et al. 1996). The basis for these conflicting findings has yet to be determined.

During eccentric rotation, the eyes and otoloths experience different degrees of translation due to their spatial separation. This may result in paradoxical situations. For example, although the eyes are translating when rotating about a pitch axis passing through the otoloths, these organs experience no linear acceleration. Published data are contradictory regarding whether effects of viewing distance on VOR function correspond to eye translation or merely otolith translation: correction for eye position relative to the otoliths has been reported in the monkey during steady state rotation at peak acceleration of 120°/s² with visual feedback (Viirre et al. 1986) and in darkness during transient rotation at a peak acceleration of 500°/s² (Snyder and King 1992). During steady-state oscillation without visual feedback, no correction for otolith position relative to the eyes was observed in humans (Crane et al. 1997). However, in this same study,
correction was observed during transient rotation in darkness. Again, the cause of these discrepancies is unclear.

Although it is well established that the translational (otolithic) contribution to the VOR is scaled according to target distance (Paige 1991; Schwarz and Miles 1991; Schwarz et al. 1989; Yue et al. 1995), there is evidence that the gain of the angular (canal) component of the VOR also is modified directly by target distance. However, such scaling of the canal VOR component has been hard to demonstrate because it has been difficult to separate from confounding otolith input. Evidence of semicircular canal-mediated target distance effects has been found in the monkey during sudden acceleration (Snyder and King 1992). During sinusoidal rotation in darkness about an axis located between the otoliths, a situation that should produce little or no net otolithic response, no effect of target distance on human VOR gain was observed for steady-state sinusoidal yaw rotation (Crane et al. 1997). There was an increased VOR gain for near targets during transient yaw acceleration in these humans when rotated about the same axis. It is unclear why target distance influences the canal VOR response under some conditions but not others.

Study of the early time course of the monkey VOR during transient acceleration at 500°/s² motivated Snyder and King (1992) to propose a linear combination of four channels accounting for the initial VOR. The first channel had a latency of 10 ms from onset of head motion. During the period from 10 to 20 ms, Snyder and King found that VOR gain was not modulated by axis eccentricity or target distance. After 20 ms, VOR gain was modified by viewing distance (channel 2). This effect on viewing distance did not depend on the eccentricity of rotation and was thought to be canal mediated. A third channel was observed in the period from 30 to 45 ms after head rotation, in which linear acceleration and target distance modified VOR gain. The fourth channel was noted after 110 ms, when VOR gain appeared to be corrected for the distance between the eyes and the otoliths. In humans, the onset of the VOR is reportedly ~7 ms from the onset of head motion (Maas et al. 1989; Tabak and Collewijn 1994). The earliest ocular following effects of vision have a latency of 80 ms, although minor earlier modulation of VOR gain with vision has been observed in some human subjects rotated transiently at 284°/s² (Johnston and Sharpe 1994). The early dynamics of other effects that modulate the VOR, as well as the applicability of the Snyder and King model to humans, have not been previously determined. It is unclear why target distance modulation of the semicircular canal VOR (channel 2) and correction of the linear VOR for eye position (channel 4) are evident during sudden acceleration but not during steady-state rotation.

After a unilateral vestibular deafferentation by nerve section, human VOR gain is decreased during high-acceleration rotation toward the side of the lesion (Cremer et al. 1988; Halmagyi et al. 1990). This effect also has been demonstrated during the first 120 ms of the response in squirrel monkeys (Backous et al. 1996). Sinusoidal VOR gain is decreased immediately after unilateral canal plugging in monkeys but quickly recovers (Paige 1985). Although VOR gain may remain slightly asymmetric after recovery during low-frequency, low-velocity sinusoidal rotation (peak velocity <200°/s), such asymmetries are subtle (Balogh et al. 1977; Katsarkas et al. 1995). The relatively greater loss in VOR function for high acceleration rotation toward the lesion is thought to be caused by inhibitory cutoff of afferents from the intact labyrinth by ampulofugal deflection of the cupula (Goldberg and Fernandez 1971). The effects of target distance and axis eccentricity have not yet been studied in unilaterally deafferented humans.

METHODS

Subjects

Twelve normal paid normal volunteers and four volunteers with right-sided vestibular deafferentation gave written consent to participate in these experiments according to a protocol approved by the University of California, Los Angeles Human Subject Protection Committee in conformity with the tenets of the Declaration of Helsinki. The normal group consisted of five women and six men of average age 25 ± 4 (SD) yr (range 20–32). The unilaterally deafferented subjects consisted of two women and two men of average age 53 ± 8 yr (45–61) who had undergone surgical right VIIIth cranial nerve transections and in two cases labyrinthectomies during the removal of acoustic neuromas. Responses to left-sided bithermal caloric testing as well as neuro-imaging were normal, suggesting normal left vestibular and brain function in each unilaterally deafferented subject. Surgeries had been performed 1–5 yr before testing. All subjects underwent ophthalmologic examination to verify that they were free of ocular disease and would be able to converge and focus the targets clearly without the aid of corrective lenses. Subjects were monitored via infrared closed-circuit television and intercom.

Apparatus

Angular eye and head positions were measured with magnetic search coils, as employed by other investigators (Grossman and Leigh 1990; Grossman et al. 1989). Reference magnetic fields were generated by three pairs of solenoid coils, each 2 m in diameter, and arranged to form the sides of a cube (C-N-C Engineering, Seattle, WA). This configuration placed the center of the cube near eye level. The two vertically oriented coil pairs were driven by 60 kHz sinusoidal currents in phase quadrature (Collewijn et al. 1975). The horizontally oriented coil pair was driven by a 120-kHz sinusoidal current (Robinson 1963). Single-winding scleral magnetic search coil annuli were placed on the right eye of most subjects, except one unilaterally deafferented subject who wore the coil on the left eye, to measure angular position of the eyes in space. Two subjects wore binocular search coils. Angular head position was measured in two ways: with a search coil taped to the forehead and with another search coil mounted on a bitebar, custom molded to the upper teeth of each subject. Because of slippage of the forehead skin, the search coil taped to the head was found to be a less reliable indicator of head position during the onset of rotation so all data presented were obtained with the bite bar coil. The ocular coil was embedded in an annular suction contact lens (Skalar Medical, Delft, The Netherlands) that adhered to the eye under topical anesthesia with proparacaine 0.5% (Collewijn et al. 1975). Search coils were connected to external detectors (C-N-C Engineering, Seattle, WA) incorporating single pole low-pass filters with a cutoff frequency of 167 Hz. Horizontal angular positions were demodulated by a phase angle method that is linear over a range of ±100°.

The homogeneity of the reference magnetic field was directly verified. Gain calibration curves were constant to ±5% within a central cube 58 cm on each side and ±1.6% within a central cube measuring 11 cm on each side. The measured peak-to-peak position...
noise level of the search coil system at a bandwidth of 0–100 Hz was 2 min arc (1/30 of 1°). The root mean square (RMS) horizontal velocity noise of the system over a bandwidth of 0–43 Hz was 0.05 min arc.

Experiment control and data acquisition were performed by a Macintosh compatible computer running the MacEyeball software package (Regents of the University of California). Search coil data (horizontal and vertical gaze and head positions) were displayed on a digital polygraph and low-pass filtered over a bandwidth (4-pole Butterworth) of 300 Hz before simultaneous digital sampling with 16 bit precision at 1.2 kHz.

Subjects were rotated by a 500 N-m stepper motor (Compumotor, Rohnert Park, CA) with a dedicated driver and position feedback digital controller. The motor had a resolution of 425,984 steps per revolution and could reliably reproduce the desired motion. Because the motor’s step resolution was 0.05 min arc, the steps were well below the noise level of the search coil system, making the steps indistinguishable from continuous rotation. Before each trial, the data acquisition computer downloaded a program to the servo controller defining the directions and relative strengths of stimuli to be delivered during that trial. After the program was downloaded, the motor controller awaited a synchronization pulse from the acquisition computer initiating the sequence of precisely determined rotations. By sampling the synchronization pulse, the data-acquisition computer precisely recorded event timing. The presence of the motor did not have a detectable effect on search coil measurements.

Measurement conditions

During each trial, the subject sat in a hardwood chair fabricated with nonmetallic fasteners. The seat, back, and sides of the chair were fit with dense foam cushions. The subject’s body was secured by lap, chest, knee, leg, and ankle belts. Armrests and hand grips on the chair enabled subjects to further stabilize themselves. The head was held against stiff conforming foam within a nonmetallic head holder. The forehead and chin were secured by straps.

During each 50-s trial, 20 directionally unpredictable transient rotations (10 in each direction) were administered in random order. Rotations of 200–1,000 ms duration had an onset varying randomly by ?250 ms. The laboratory was illuminated between rotations to enable subjects to maintain an accurate memory of the target. The fluorescent room lights were extinguished at a random time 50–70 ms before the onset of each head rotation and remained dark until the chair began its return to center ~400 ms later. Subjects were instructed to maintain gaze on target even when the lights were extinguished. Targets were centered directly in front of the right eye at distances of 15, 30, and 500 cm. The target used at 15 and 30 cm distances consisted of a 4-cm black cross surrounded by radiating lines at the center of a white background 50 × 43 cm. The target located at 500 cm was a 14 cm cross on a 102 × 81 cm background. All three target distances were tested in eight subjects. In three subjects, only 15 and 500 cm target distances were tested because performance with the 15 and 30 cm targets was frequently similar.

Eccentricity of the head relative to the axis of rotation was varied by changing the location of the head holder relative to the chair and by sliding the chair on a track attached to the motor hub. Eccentricity of the rotational axis was defined relative to the midpoint between the centers of the eyes with more anterior positions described as negative. Eccentricities of 20 and 7 cm (posterior to the eyes) were achieved with the chair centered over the motor hub while eccentricities of 0 (between the eyes) and –10 cm (anterior to the eyes) were achieved with the chair posterior to the motor hub. For eccentricities of 20 and 0 cm, the head was moved forward by 13 or 10 cm, respectively, relative to the chair. When eccentricity was varied by moving the head holder, the cushioning of the chair was adjusted so that the subject was supported adequately. The eccentricity of 7 cm, the mean distance between the eyes and otoliths (Crane et al. 1997), was designed as an otolith centered rotation.

All subjects were rotated at the peak stimulus acceleration of 2,800°/s² to a velocity of 190°/s, which rotated the head 40° in 250 ms. Four normal subjects also were rotated at three lower peak accelerations. The lower accelerations were used for all axes of rotation except that 20 cm posterior to the eyes. The half intensity peak acceleration was to 1,600°/s² with a peak velocity of 140°/s which rotated the head 30° in 250 ms. The quarter intensity peak acceleration was to 1,000°/s² with a peak velocity of 70°/s which rotated the head 14° in 250 ms. The lowest peak acceleration was to 500°/s² with a peak velocity of 35°/s which rotated the head 7° in 250 ms.

Data analysis

Data were analyzed automatically using custom software written using the LabView package (National Instruments, Austin, TX). For each subject, rotational events were grouped based on target distance, eccentricity, stimulus intensity, and direction. Events where eye position varied by >0.2° in the 80-ms preceding head rotation were discarded as failures of fixation and not considered for further analysis. Events also were discarded when saccades occurred within 250 ms after onset of head rotation.

Most results were analyzed in terms of angular VOR gain, the ratio of eye velocity to head velocity. After differentiation, eye and head data were filtered using a third-order low-pass Butterworth filter (0–50 Hz). Gain was determined by dividing compensatory eye velocity by head velocity. This approach normalizes the effect of small variation in the head stimulus. Variation in head movement was common for the strongest stimulus where there was greater decoupling of the head from the rotator and where the motor approached torque limits for heavier subjects rotating about eccentric axes. Decoupling could not be physically eliminated because the skin slides independently of the skull despite tight placement of head straps. We chose not to use a bite bar to couple subjects to the rotator to avert dental injury and because the search coil on the upper teeth provided an accurate indication of skull movement.

The onset of motor rotation occurred consistently ~60 ms after the synchronization pulse was delivered to the motor controller. The onset of head motion was consistent for each subject for rotations about the same eccentricity. However, there was variation in onset of head rotation relative to the onset of motor rotation between subjects and between eccentricities. The onset of head rotation was determined by finding the time when the head position moved 1° from the center, then subtracting an interval depending on the strength of the stimulus. A threshold head displacement of 1° was used because by the time it had occurred, head position was free of early decoupling artifacts. The time subtracted was empirically determined to be 40, 47, 70, and 75 ms for the strongest to weakest stimuli, respectively. Using this criterion, head motion in the intended direction usually began within 5 ms of the onset time as determined by visual inspection of position tracings. A slight decoupling artifact occurred early in the response when the axis was located 20 cm behind the head. This artifact unavoidably complicated comparison of data collected at various axis eccentricities but was considered in data interpretation.

Right eye position was defined as zero before the chair began moving because the target was directly in front of the right eye. In the two subjects where left eye also was measured, the left eye position was calibrated based on the angle required to foveate the target (Crane et al. 1997).

Onset of eye movement relative to head movement was determined by an automated cross-correlation technique, an automated
threshold by cross-correlating eye position in the head with head position in space during the period from 20 ms before to 30 ms after onset of head rotation. The time (between a 0- and 30-ms eye delay) giving the maximum cross-correlation was taken as the VOR latency. The second technique measured the standard deviation of eye and head position during a 50-ms period when no eye or head rotation occurred. The onset of eye or head motion was determined by finding the time at which values exceeded three times the standard deviation during rest. The latency was determined by subtracting the eye onset time from the head onset time. Values more extreme than a 10-ms eye lead or a 50-ms eye lag were not considered for further analysis. A similar technique has been used to determine the onset of the linear VOR in the monkey (Angelaki and McHenry 1997).

Differences in gains between conditions were considered significant when the standard error of the mean (SE) did not overlap for the two conditions for a period of ≥30 ms. The onset of these gain differences was defined as the time at which the SEs no longer overlapped. This conservative criterion tends to bias recognition of significant differences to later times than the more liberal criteria employed by others (Khater et al. 1993).

RESULTS

Target distance, eccentricity of the axis of rotation, and head acceleration all significantly influenced the initial VOR. No significant differences were seen for left versus right rotations (except in the few cases noted below), so data from both directions were pooled. Representative data from a single normal subject rotated at maximum acceleration under various testing conditions are shown in Fig. 1. Traces shown are averages of 5–10 rotations under identical conditions. Figure 1A shows representative eye and head velocities in response to three different target distances while the head was rotated about an axis 20 cm behind the eyes. More proximal targets elicited higher eye velocities that were manifest almost immediately on onset of the VOR response. Figure 1B presents the same data as in Fig. 1A but represented as VOR gain. Because of relatively small head velocities in the first 25 ms of the response that were near measurement noise level, relatively large variability was introduced into the early gain values, as reflected by the width of the early SE bands (Fig. 1, B and D). Despite this gain in the first 25 ms was greater for more proximal than for distant targets. For the subject’s data in Fig. 1B, VOR gain rose to 1.8 with the most proximal target while remaining near 1.0 for the distant target. An increase in VOR gain is geometrically appropriate under these conditions. The effect of rotational axis on head and eye velocity for a target 15 cm away are shown for a representative subject in Fig. 1C. Head velocity was slightly lower for the posterior axis eccentricities. As seen in Fig. 1D, gain for this subject was altered over a threefold range in a dynamically complex manner by variations in axis eccentricity. Such differences generally occurred later than differences due to target distance. Control experiments were done in which targets remained illuminated during rotation. The presence of visual feedback under these conditions had no effect for the first 80 ms of the response after which a correcting influence of vision was observed. The remainder of this paper evaluates the onset times of these modulations in the VOR responses observed during rotations in darkness.

Latency of the VOR

The onset of head movement was often ambiguous because of decoupling of the skull from the rotator during the early portion of the response. The forehead coil, which moved with the skin, usually began to do so 25 to 50 ms before the dental coil began to rotate. Because the skin was better coupled to the chair via the straps than the skin was coupled to the skull, the skull did not accelerate with the chair during the initial 25 ms. When the center of mass of the head was forward of the axis of rotation, a small head rotation opposite the direction of the chair often occurred in the initial 30 ms, after which head rotation reversed to follow the chair. This effect was especially noticeable at an eccentricity of 20 cm (Fig. 2A) but also was present at an eccentricity of 7 cm (Fig. 2B).

It was necessary to define precisely the onset of skull rotation. The criterion described in METHODS was effective because by the time the head had moved 1°, decoupling effects were stabilized and the skull had reached a velocity that was independent of the rotational axis. Temporal comparisons of trials conducted at different eccentricities were based on this onset time. For an eccentricity of 20 cm, the average onset of oppositely directed rotation was 30 ms before criterion onset time (the 0 point shown in Fig. 2A) due to skull decoupling resulting from the relatively large linear head acceleration.

Despite decoupling, it was usually possible to determine the latency of the VOR following skull rotation. Average latency across all subjects by visual inspection appeared to be 5–10 ms (Fig. 2, range indicated by double headed arrows). Latency of the VOR was also determined by cross-correlation, giving a mean of 10.8 ± 0.3 (SE) ms (n = 2,430 events).

By subtracting the onset of the eye motion from the onset of head motion as defined by the moment when position exceeded three times the standard deviation of the noise, the VOR latency was found to be 8.9 ± 0.2 ms (averages of 11 subjects) with the 2,800°/s² stimulus. Longer latencies were found at 9.2 ± 0.5, 11 ± 1, and 14 ± 1 ms with the 1,600, 1,000, and 500°/s² stimuli, respectively.

Vergence angle

The instantaneous vergence angle (left eye minus right eye) was determined in two subjects in whom binocular recordings were made. Change in vergence during 2,800°/s² head rotation is shown in Fig. 3 for each target distance for a single subject. These recordings are representative of both subjects and all conditions of rotation. With near targets (15 and 30 cm), the vergence angle decreased with head rotation as geometrically required to maintain foveation of the target. With near targets, the vergence achieved during head rotation was generally slightly greater than that theoretically required to foveate the target. The vergence angle was averaged over the period from 155 to 165 ms after the onset of head rotation. With a target 15 cm away, the vergence in this period came closest to the theoretical requirement during rotation about an eye centered (eccentricity 0 cm) axis, being 0.1 ± 0.8° (mean ± SE) less than the theoretical level. Vergence exceeded the theoretical level during this period.
FIG. 1. Effects of rotational axis and target distance on the initial vestibulo-ocular reflex (VOR) of a representative normal subject. Data shown average responses to 10 leftward rotations at the highest head acceleration ($2,800^\circ/s^2$). Data collected at 1,200 Hz from a dental search coil registering head position and a scleral search coil on the right eye. Symbols are shown at intervals to help differentiate gain traces (B and D). Zero time corresponds to onset of head motion not including any early decoupling artifacts. Fine dotted lines represent ±1 SE for each condition. A: eye velocity and head velocity for 3 target distances. The axis of rotation was 20 cm behind the eyes. There was a reduction in eye velocity after 150 ms as the eye reached the end of the oculomotor range. B: VOR gain calculated from the data shown in A. Gain was increased throughout the entire response for nearer targets. C: eye velocity and head velocity for 4 rotational axis eccentricities relative to the eyes (negative numbers anterior). Target distance was 15 cm. Head velocity took longer to reach asymptote for more posterior axes of rotation. D: VOR gain calculated from data shown in C. Gain was reduced late in the response for more anterior axis eccentricities.

With a 15-cm target at anterior and posterior axes of rotation. With a 15-cm target, measured exceeded that predicted by $1.7 \pm 1.9^\circ$, $2.4 \pm 0.3^\circ$, and $3.9 \pm 0.8^\circ$ for axes 10 cm anterior, 7 cm posterior, and 20 cm posterior to the eyes, respectively. Because vergence errors were even smaller for more remote targets, we did not regard vergence error as a likely confounding factor and did not measure vergence in the other subjects.

Effect of viewing distance

In the first 80 ms of the response, VOR gain for the maximum acceleration stimulus was always greater with nearer than remote targets regardless of the eccentricity of rotation (Fig. 4). This was even the case when the axis was centered on (eccentricity 0 cm, Fig. 4C) or anterior to the eyes (eccentricity −10 cm, Fig. 4D). For the most anterior axis, gain for the near target was appropriately reduced to less than that for the far target later in the response. Increased gain with near targets was within the first 10 ms of the VOR eye movement for both axes. The first significant difference in gain associated with target distance occurred 10 ms after the onset of head movement at an axis 20 cm posterior to the eyes, 8 ms at an axis 7 cm posterior to the eyes (otolith centered), 18 ms at an eye centered axis (0 cm), and 14 ms with the axis 10 cm anterior to the eyes (−10 cm). With the axis forward of the otoliths (0 and −10 cm), the latency of viewing distance effects was slightly but significantly longer than the latency of the first measurable VOR.

Viewing distance influenced the ocular response throughout the trial for each eccentricity tested. The only time in the response when VOR gain did not depend on target distance was transiently 125 and 90 ms after stimulus onset at eccentricities of 0 and −10 cm, respectively. After these times, the initially greater gains with the near target declined to become less than gains with the far target (Fig. 4).

Effect of rotational axis location

Eccentricity of the rotational axis affected VOR gain later in the response than did changing target distance.
Nonlinear effect of head acceleration

In addition to the data collected using maximum head acceleration presented up to this point, three lower accelerations also were employed in some subjects. For each stimulus, the peak acceleration was reached during the first 50 ms of head rotation, after which acceleration declined. Nearly constant head velocity was reached 90 ± 125 ms after the onset of head motion. The signal-to-noise ratio was lower with less intense stimuli, making significant differences more difficult to detect and potentially delaying the threshold of their detection. Despite this, not only were many significant effects found for lower peak accelerations, but some effects occurred earlier than with higher accelerations.

In the first 75 ms of the response, VOR gain was less with lower acceleration stimulation than with higher (Fig. 6). There were some scattered gain values before 40 ms when the lower intensity stimulation resulted in a higher VOR gain than the full intensity stimulus; these effects were not consistently observed in opposite directions and are thought to be artifacts of the lower signal to noise ratio early in the response and the relatively small total number of trials with the lower stimulus intensities. The difference in VOR gain was greater for near (Fig. 6) than for far targets (not shown). The reduction in VOR gain from the 2,800 and 1,000°/s² peak accelerations observed 60 ms after the onset of head rotation was computed. With an otolith centered axis (Fig. 6A), the reduction in gain was 0.23 ± 0.06 (mean ± SE) for the near and 0.20 ± 0.03 for the far target. At the eye centered axis (Fig. 6B), the reduction in gain was 0.31 ± 0.08 for the near and 0.11 ± 0.05 for the far target. When the axis was anterior to the eyes (Fig. 6C), the reduction in gain was 0.34 ± 0.04 for the near and 0.10 ± 0.03

**FIG. 2. Onset of head and eye motion.** Data sampled at 1,200 Hz shown are averaged across multiple trials in each of 11 normal subjects during leftward rotations with target at 15 cm. Head velocity traces are shown as a solid line with circles and eye traces are shown as a dashed line with open squares. Horizontal arrow shows the estimated range VOR onset latency. Zero (0) point on each graph is the onset of head motion as identified by the automated technique described in METHODS. Narrow dotted lines represent ±1 SE for each condition. A: head and eye velocity traces with rotational axis 20 cm eccentric behind the eyes. Notice that ~27 ms before the identified onset of head rotation (vertical arrowhead), decoupling of skull from the rotator caused the head to rotate slightly opposite to final head rotation. This type of decoupling was greatest at this axis. B: head and eye velocity traces with the axis located 7 cm behind the eyes (centered between the otoliths). Negligible decoupling occurred before the onset of head rotation. Other axes of rotation (eccentricity 0, −10 cm) gave responses with no opposite direction decoupling.

alone (Fig. 5). Gain was lower for axes of rotation anterior to the otoliths (eccentricity 0, −10 cm) than for axes posterior to the otoliths (eccentricity 20 cm). Variation in axis eccentricity had a greater effect on VOR gain when the target was located at 15 cm than at 500 cm. Latency of VOR gain changes associated with eccentricity are given from the time of motion onset in Table 1. The tabulated time of motion onset for the 20 cm posterior axis has been corrected by appropriately subtracting the ~30 ms duration of decoupled head motion.

When the axis of rotation was located anterior to the otoliths, late VOR gain with the near target declined to below the gain for the far target. With the eye centered axis and the strongest stimulus intensity, this crossover occurred at 129 ms. With the axis 10 cm anterior to the eyes, the crossover occurred at 107 ms (Table 2).

**FIG. 3. Change in vergence angle after the onset of 2,800°/s² leftward rotation is shown for a single subject (same subject as Fig. 1, interpupillary distance of 70 mm) rotated about an axis 20 cm behind the eyes for 3 target distances.** Response theoretically required to foveate the target as the head rotates is shown as a thin dashed line. Solid lines represent the actual response. Data represent the average of 10 trials. Error limits of ±1 SE are too small to be seen on the plot.
FIG. 4. VOR gain sampled at 1,200 Hz during the initial 150 ms of head rotation for 2,800°/s² peak head acceleration and 2 target distances. Each plot represents the average of 10 rotational trials in each of 11 normal subjects. VOR gain was higher with the 15-cm target distance before 80 ms in each response independent of eccentricity. Time 0 represents the onset of head motion. Thin dotted lines represent ±1 SE. A: axis located 20 cm behind the eyes. Gain was increased for the near target throughout the trial. B: axis located 7 cm behind the eyes (centered between the otoliths). Initial gain increase with the near target was greatly reduced after 80 ms. C: axis centered between the eyes. Gain for the near target declined below that for the far target after 130 ms. D: axis located 10 cm anterior to the eyes. Gain with the near target declined below that for the far target 90 ms after the onset of head rotation.

for the far target. Hence a significant reduction in gain with reduced peak head acceleration occurred at 60 ms for every condition tested, although these differences did not remain significant and often reversed later in the response (80–180 ms).

Contrary to expectations based on signal-to-noise ratio considerations, axis eccentricity effects often appear significantly earlier as head acceleration was reduced (Table 1). The largest decrease in latency was between peak accelerations of 2,800 and 1,600°/s². For the two stimuli with peak accelerations <1,600°/s², eccentricity effects were seen slightly later than with the 1,600°/s² stimulus.

With decreasing stimulus intensity, VOR gain decreases with near targets at axes forward of the otoliths occurred earlier (Table 2). With the most anterior axis (eccentricity −10 cm), gain increases for the near target were no longer observed with peak head accelerations <1,600°/s² (Fig. 7C). At the otolith centered axis (eccentricity 7 cm), an initial VOR gain increase for the near as compared with the far target was observed at every peak head acceleration (Fig. 7A). Under conditions when near target gain exceeded far target gain, the onset of this difference occurred later with lower head acceleration (Table 2). Representative data are shown in Fig. 7 for the peak acceleration of 1,000°/s².

Effect of unilateral vestibular deafferentation

In addition to 11 normal subjects, 4 subjects with isolated right-sided vestibular deafferentation were tested. When rotated to the left (contra-lesional), these subjects (Fig. 8) exhibited a response almost indistinguishable from that of the normal controls (Fig. 4). During contra-lesional rotation, patients showed a significant gain enhancement in the first 80 ms for near relative to distant targets that was independent of location of the rotational axis. For further posterior axes (Fig. 8, A and B), early near target gain enhancement persisted until 150 ms. For the eye-centered axis, the significant gain enhancement for the near target persisted only until 80 ms, after which gains were the same for the near and distant targets. For the axis located anterior to the eyes, gain after 80 ms was lower for the near than the far target (eccentricity −10 cm, Fig. 8D).

VOR gain was markedly lower for rotation in the ipsilesional than in the contra-lesional direction. For ipsi-lesional rotation, gain generally remained <0.5 for at least the first 55 ms of the response regardless of viewing distance or eccentricity. The exception is an initial response occurring near 15 ms at eccentricity 20 cm with near targets, which may be an artifact of the low signal-to-noise ratio early in the response (Fig. 8E). In the first 55 ms, a slightly increased...
FIG. 5. Effects of peak head acceleration on average VOR gain for various rotational axis eccentricities while normal subjects regarded a target at 15 cm. For all conditions, gain was greater with more posterior axes at 150 ms from onset of head rotation (time 0). This difference prevailed until the end of the analyzed interval except during 2,800°/s² stimulation when gain declined at the end of the oculomotor range for axes posterior to the eye (eccentricity 7, 20 cm). Data shown for leftward rotation. Thin dotted lines represent ±1 SE. A: stimulus with peak head acceleration of 2,800°/s². Average of responses of each of 11 normal subjects. Eccentricity of 20 cm was tested only at this stimulus intensity. For eccentricity of 20 cm, time 0 represents onset of decoupled head motion to the right, which was later followed by intended rotation to the left (Fig. 2A). To avoid displaying an artifact when head motion became recoupled to the rotator at ~30 ms, the eccentricity of 20 cm is plotted only after 45 ms. B: stimulus with a peak acceleration of 1,600°/s². Average of responses in each of 4 subjects. Differences among eccentricities occurred earlier than those in A. C: stimulus with a peak acceleration of 1,000°/s². Average of responses in each of 4 subjects. D: stimulus with a peak acceleration of 500°/s². Average of responses in each of 4 subjects.

VOR gain was observed for near as compared with far targets; however, the difference was much smaller than during contra-lesion rotation and was often insignificant. For each axis of rotation and target distance, gain increased between 55 and 80 ms, coincident with the reduction in acceleration of the head rotation stimulus. This increase was especially notable for the near target condition during rotation about the axis located anterior to the head (eccentricity of −10 cm, Fig. 8H). In this case, the lower gain during the initial period was closer to the geometrically ideal value (0.3) than the higher gain occurring later in the ipsi-lesional response.

A saturating nonlinearity was observed for the VOR during ipsi-lesional rotation. The early VOR gain during ipsi-lesional rotation was higher with lower head accelerations. This effect was first significant with 1,000°/s² compared with 2,800°/s² peak acceleration starting 30 ± 4 ms after onset of head motion (mean ± SE, range 14–55 ms). Averaging across all target distances and axes (except otolith centered rotation with a far target), gain remained significantly higher for the lower acceleration ipsi-lesional stimulus until 83 ± 5 ms after motion onset (mean ± SE, range 67–99 ms). For otolith-centered ipsi-lesional rotation with far target, gain for the lower acceleration stimulus remained higher indefinitely. This lower gain with a higher head acceleration is opposite the behavior observed in the normal group (Fig. 6). However, rotation of unilaterally deafferented subjects in the contra-lesional direction produced results similar to those of the control group. Although VOR gain for the 1,000°/s² peak acceleration eventually exceeded gain for 2,800°/s² acceleration during contra-lesional rotation, this did not occur until 190 ± 30 ms (mean ± SE, range 137–239 ms) after motion onset and was probably due to reaching the limit of the oculomotor range at the higher velocity.

DISCUSSION

The current experiments exploited a substantially more powerful (500 N-m) rotational stimulator than heretofore available for human use, able to deliver peak head accelerations ±2,800°/s² with peak otolith tangential acceleration up to 0.6 g at an axis eccentricity of 20 cm and 0.8 g in the opposite direction at an axis eccentricity of −10 cm. Previ-
TABLE 1. Effect of peak head acceleration on latency of axis-related VOR gain differences with a 15-cm target

<table>
<thead>
<tr>
<th>Peak Head Acceleration (m/s²), deg/s²</th>
<th>Latency, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,800</td>
<td>1,600</td>
</tr>
<tr>
<td>1,000</td>
<td>500</td>
</tr>
<tr>
<td>Rotational axis pairs</td>
<td></td>
</tr>
<tr>
<td>7 and 0 cm</td>
<td>91.2</td>
</tr>
<tr>
<td>7 and -10 cm</td>
<td>55.8</td>
</tr>
<tr>
<td>0 and -10 cm</td>
<td>44.5</td>
</tr>
<tr>
<td>20 and 7 cm</td>
<td>54.5</td>
</tr>
<tr>
<td>20 and 0 cm</td>
<td>62.8</td>
</tr>
<tr>
<td>20 and -10 cm</td>
<td>52.0</td>
</tr>
</tbody>
</table>

Effect of peak head acceleration on latency of axis-related vestibulo-ocular reflex (VOR) gain differences with a target 15 cm from the eyes. Differences with axis posterior to the head (eccentricity 20 cm) are not shown because rotations at this eccentricity were performed only at maximum stimulus strength. Data were averaged from the onset of differences determined separately in each of 11 subjects although not every subject participated in every condition shown. Values were determined using an automated method in the gain domain. Times shown are the average of the earliest significant differences found between stimuli at the two axes. Values are averages for left and right rotations.

Previous studies have used accelerations of 500 m/s² in the monkey (Snyder and King 1992) and 284 m/s² (Johnston and Sharpe 1994), 600–1,000 m/s² (Crane et al. 1997), or 300 m/s² (Anastasopoulos et al. 1996) in humans. With capability for precisely delivering higher acceleration stimuli, we found that the initial VOR depends not only on viewing distance and axis of rotation but also both qualitatively and quantitatively on the magnitude of head acceleration. Recognition of this nonlinear behavior reconciles previously conflicting observations.

Onset of the VOR

The latency of the VOR was measured using two quantitative techniques. A cross-correlation technique was used to measure the eye-head latency. This technique had the advantage of being insensitive to possible differences in slope between the eye and head response. The weakness of this technique was that the values it determined varied widely across trials because of low correlation due to the signal-to-noise ratio at the onset of eye and head movement. However, reasonable values for VOR latency were obtained when data were averaged across multiple subjects and trials. To verify the latency found by this technique, a position threshold technique was employed. When the times at which the

TABLE 2. Latency of target distance effects on VOR gain

<table>
<thead>
<tr>
<th>Stimulus</th>
<th>Near &gt; Far</th>
<th>Eye-Centered Axis, ms</th>
<th>Axis 10 cm Anterior to Eyes, ms</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,800 m/s²</td>
<td>8</td>
<td>18</td>
<td>129</td>
</tr>
<tr>
<td>1,600 m/s²</td>
<td>21</td>
<td>26</td>
<td>142</td>
</tr>
<tr>
<td>1,000 m/s²</td>
<td>32</td>
<td>38</td>
<td>140</td>
</tr>
<tr>
<td>500 m/s²</td>
<td>71</td>
<td>51*</td>
<td>127*</td>
</tr>
</tbody>
</table>

Latency of target distance effects on VOR gain. Near targets were located 15 cm and far targets at 500 cm from the eyes. At the otolith centered axis, there was no condition in which gain for the far target significantly exceeded gain for the near target so no such column is shown. Latencies were determined using an automated technique from data as in Figs. 4 and 7. Times are averages for both directions of rotation. E = 7, 0, and -10 cm for otolith-centered axis, eye-centered axis, and axis 10 cm anterior to eyes, respectively. § Effect was not observed in either direction; * Effect was only observed in one direction.

FIG. 6. Effects of peak head acceleration on early target distance dependent VOR gain increase for leftward rotation at 3 rotational axis eccentricities. Solid line with dots represent data collected at 2,800 m/s² peak head acceleration (11 control subjects). Dashed line with open squares represent data collected at 1,000 m/s² peak head acceleration (4 control subjects). Zero time represents the onset of head rotation. Thin dotted lines represent ±1 SE. A: axis centered between otoliths. There was a slight and inconsistent increase in VOR gain in the early response (<80 ms) with the higher stimulus. B: axis centered between eyes. There was a VOR gain increase with increased stimulus intensity from 45 to 90 ms. C: axis located 10 cm anterior to eyes. Higher gain with greater stimulus intensity occurred from 40–100 ms.
values between trials was determined. Although the values found by the threshold technique seemed more reliable, this technique makes the assumption that the eye and head move equal amounts during the early VOR. The cross-correlation technique indicated the latency of the VOR to be $10.8 \pm 0.3 \text{ ms}$. The threshold technique indicated the latency to be slightly less during the highest acceleration at $8.9 \pm 0.2 \text{ ms}$, although when averaged across all accelerations the threshold latency was $10.6 \pm 0.7 \text{ ms}$. From this analysis, we can conclude that the latency of the human VOR is near 10 ms, consistent with previous human findings (Maas et al. 1989; Tabak and Collewijn 1994).

**Performance of the VOR**

Modulation of VOR gain with target distance and rotational axis location were generally as demanded by geometric considerations by 150–200 ms following the onset of head motion. Predictably, when the axis was posterior to the eyes proximal targets caused an increase in VOR gain; when the axis was anterior to the eyes proximal targets caused decrease in VOR gain. However, there was a result not predicted by the geometry during rotation about an axis midway between the eyes. Here geometric calculations of ideal gain (Crane et al. 1997) predict a slight increase in gain for the near target condition when rotating in a clockwise direction and a slight decrease in gain when rotating in the opposite direction, with magnitude depending on the distance rotated and the interpupillary distance. However, for the eye centered axis, we consistently observed a decrease in VOR gain for near targets late in the response independent of the direction of rotation. This presumably occurs because the otoliths are located behind the axis of rotation and their linear stimulation acts to decrease VOR gain.

Gain of the VOR was generally not ideal for proximate targets. For targets at 15 cm, the gain only reached 70% of the ideal value with the axis posterior to the head (eccentricity 20 cm). When the axis was anterior to the eyes (eccentricity 0 cm), VOR gain was 187% of the ideal value. This is consistent with steady-state eccentric rotation VOR data in humans showing that VOR gain tended to be closer to unity than to ideal (Crane et al. 1997). At a distance of 500 cm, the observed gain and ideal gain were usually both within 5% of each other and near unity 150 ms into the response.

During head rotation, vergence was maintained within a few degrees of the angle theoretically required. As the head rotated, the required vergence angle generally decreased. For the nearest target (15 cm), the vergence angle closely matched the required angle only during rotation about the axis centered between the eyes (eccentricity 0 cm). At other axes, the vergence angle was usually greater than required. This finding implies that although the brain can determine that vergence angle decreases during turning because the eyes become closer together in the plane of the target, the brain apparently does not consider that target distance changes when the axis is not colocated with the eyes. Insufficient vergence during the initial VOR can be excluded as a cause of geometrically suboptimal VOR gain under all conditions.
Comparison with monkey VOR

Snyder and King have proposed a model to describe the initiation of the VOR based on the response of the monkey to sudden onset head rotation (Snyder and King 1992). This model contains four channels: an unmodulated canal-mediated response, a canal-mediated response modulated by target distance, an otolith-mediated response modulated by target distance, and a mechanism that corrects for the position of the eyes relative to the otoliths. In the monkey, these channels are recruited in sequence with the first channel starting at 10 ms and the fourth becoming important 45–110 ms after onset of head rotation.

The current data do not support the existence in humans of a canal response, corresponding to Snyder and King’s first channel, not modulated by target distance. With the most intense stimulus (2,800°/s² peak acceleration 190°/s peak velocity) when the signal-to-noise ratio was most favorable to detect small differences in VOR gain, significant gain increases for proximal targets were seen as early as 8–18 ms after onset of head rotation, depending on the axis eccentricity. These increases were even observed during otolith-centered (7 cm) rotations that would minimize otolithic stimulation, and anterior axes (0 and –10 cm) for which otolithic responses would decrease rather than increase VOR gain. Because the onset of these presumably canal-mediated gain increases with target proximity are indistinguishable from the latency of the VOR itself, we could not demonstrate a period during which gain is independent of target distance. Because of the low single-to-noise ratio at the instant of eye motion onset, we cannot exclude the existence of a brief period (<8 ms) when VOR gain does not depend on target distance. It is conceivable that decoupling of the head from the rotator or a sensory cue such as pressure to the skin near the onset of rotation might confound our interpretation of the effect of target distance on the first few milliseconds of the VOR response. However, because an effect of target distance can be discerned as early as reliable responses can be recorded, we cannot exclude the interpretation that the VOR depends on target distance from its very onset. If so, this suggests that properties of neurons in the basic three neuron arc of the VOR are directly modulated by target distance. Target distance dependent gain increases were observed later with lower head acceleration in the present study. Snyder and King employed a peak head acceleration of only 500°/s² as compared with the maximum value of 2,800°/s² employed here, perhaps accounting for Snyder and King’s differing observation. Thus it is concluded that at lower head accelerations either differences in VOR gain with target distance are concealed in the noise and only detectable later or the effect of target distance on early VOR gain is physiologically more prominent with large head accelerations.

The third channel of Snyder and King’s model, an otolith-mediated response modulated by target distance, also was found here in humans 30 ms after the onset of head rotation. The earliest significant difference in gain attributable to otolith influence was at 23 ms during peak head acceleration of 1,600°/s² having peak tangential acceleration of 0–0.5 g (Table 1), but under most stimulus conditions, otolith effects could not be consistently detected until near 40 ms. Otolith-ocular response latencies as short as 16.2 ms have been measured during 0.7 g free-fall in monkeys (Bush and Miles 1996), but ~38 ms in humans during 0.24 g transient horizontal linear motion (Bronstein et al. 1991). These differences in estimates of latency are likely to be due in part to differences in signal-to-noise ratio and to the chosen criterion for significance but also might be due to real physiological variations in VOR latency with the magnitude of acceleration.

The fourth channel of Snyder and King was proposed to correct for the differential location of the eyes relative to the otoliths. The present data did not suggest the existence of this channel in humans. If it existed, we would have expected VOR gain for rotation about the eye-centered axis to remain independent of target distance within some range of time. Such an equivalence did occur instantaneously between 120 and 150 ms (Figs. 4C and 7B) when VOR gain for the near target declined to become equal to that for the far target. Later, however, VOR gain continued to decrease so that gain for the near target was lower than for the far target. If only the interval between 120 and 150 ms were examined, then a correction for eye position might appear to occur, but with the perspective provided by the data obtained at later times, this “correction” may be seen to be merely a canal-otolith interaction shifting from an early canal mediated gain increase to a later otolith-mediated gain decrease.

Transient versus steady-state rotation

Gain of the human VOR as assessed in darkness during steady-state sinusoidal rotation between 0.8 and 2.0 Hz was found to be increased by near targets for axes of rotation posterior to the otoliths and decreased for axes anterior to the otoliths (Crane et al. 1997). This trend also was observed in the current data after transient effects stabilized, usually within 150 ms of the onset of the highest head acceleration, although it sometimes took longer with weaker stimulation. The significant difference between the current transient data and the earlier steady-state data is that during steady-state rotation about an axis between the otoliths (eccentricity 7 cm), there was no effect of target distance on gain (Crane et al. 1997). In the current study, a significant gain enhancement with near targets was observed for the otolith centered rotational axis. Significant differences were seen ≥250 ms after the onset of head rotation, the latest time analyzed in this study. The differences between these two studies can be reconciled if it is assumed that the target distance dependent canal gain increase decays with a time constant on the order of one second.

Conceptual model of the human VOR

We propose an alternative to the four-channel model of Snyder and King to describe the initial human VOR. The proposed conceptual model has canal and otolith inputs and simplifies to only two channels (Fig. 9). The model accounts for four important features in the current data: first there is an initial gain increase for near targets relative to far targets that is independent of eccentricity and occurs as soon as the eye starts to rotate (Fig. 4). Second, in cases when the otoliths...
are located posterior to the axis of rotation (eccentricity 0, −10 cm), this initial gain increase is eventually reversed for proximal targets (Fig. 4, C and D). Third, when the axis of rotation is centered between the otoliths, gain increases with near targets do not reverse later in the response (Fig. 4B, Table 2). Fourth, the magnitude of the initial eccentricity-independent gain increase for near as compared with far targets is greater with increased stimulus strength (Fig. 6). This larger initial gain increase is also likely to explain the earlier differences in latency of gain changes at varied eccentricity with near targets (Fig. 5, Table 1).

The model incorporates several features of the underlying physiology. First, the output of the semicircular canals is scaled by a factor inversely proportional to target distance. This scaling is likely to occur in the neurons involved in the fastest VOR pathway because the initial enhancement of gain with near targets has a latency indistinguishable from that of the VOR itself. Second, the otolith organs produce an effect on VOR gain depending on the direction of otolith stimulation relative to the direction of rotation as sensed by the semicircular canals. Rotation about axes anterior to the otoliths decreased gain, whereas rotation about axes posterior to the otoliths increased gain. This second observation is consistent with other eccentric rotation experiments in both humans (Bronstein and Gresty 1991; Crane et al. 1996; Viirre and Demer 1996) and animals (Snyder and King 1992; Telford et al. 1996; Viirre et al. 1986).

In the present data, the output of the canals dominated the early response, whereas the later response was dominated by otolith input. Initial VOR gain increases were observed with close targets even when the otoliths were located posterior to the axis of rotation (Fig. 4, C and D), a situation for which geometry would require a gain decrease. The otoliths presumably dominated target distance modulation later in the response because by 200 ms after onset of head movement, VOR gain was greater with near targets when the axis was located behind the otoliths (eccentricity 20 cm) and gain was less with near targets when the axis was located anterior to the otoliths (eccentricity 0, −10 cm). When the axis of rotation was located directly between the otoliths (eccentricity 7 cm), otolithic stimulation was likely negligible and in opposite directions for the left and right organs. At this axis, a gain increase occurred with near targets that persisted throughout the rotation. This gain increase is interpreted as a canal-mediated gain enhancement. This suggests that although the target distance mediated gain enhancement was dominated by antagonistic otolith effects late in the response, the canal mediated effect can persist in absence of otolith input.

The data are consistent with the canal-mediated target distance effect being more important during higher than lower acceleration rotations. The peak accelerations employed here, ±2,800°/s², are more than sufficient to evoke nonlinear behavior in vestibular circuits; an acceleration of only 700°/s² is required for inhibitory cutoff of type II vestibular neurons (Fuchs and Kimm 1975). For rotation about axes forward of the otoliths (eccentricity 0, −10 cm), it is likely that a period of time exists when antagonistic otolith and target distance dependent canal effects are competing with one another, the former to decrease VOR gain and the latter to increase it. For lower acceleration stimuli, the otolith-mediated effect dominates the VOR gain earlier as measured by the latency for near target VOR gain to fall below far target VOR gain (Table 2). Significant otolith-mediated effects between axis locations occurred earlier with decreased stimulus acceleration (Fig. 5). There are three possible explanations for this. The first may be that the canal-mediated target distance effect itself is relatively weaker with the lower velocity stimuli. The second maybe that otolith effect is relatively stronger at lower velocities. Last, the otolith effect may be better able to inhibit the target distance mediated canal effect at low velocities if such an inhibition occurs. By comparing data collected at each axis eccentricity with different stimulus intensities, it is possible to rule out
the first possibility as an explanation of the entire effect. For the otolith-centered axis (eccentricity 7 cm), only a slight gain decrease due to stimulus strength can be found in the initial response (Fig. 6A, first 70 ms); this indicates there is only slight decline in canal influence in the absence of otolith effects. However, more significant decreases in VOR gain were observed when rotating about axes associated with otolith translation (Fig. 6, B and C, eccentricity 0, −10 cm). The second possibility, that otolith effects are stronger during weaker stimulation, is unlikely because 120 ms into the response when otolith effects dominate little or no gain difference is observed between high and lower intensity rotation (Fig. 6, B and C). Evidence that the canal-mediated target distance VOR gain increase is inhibited in a nonlinear manner by otolith effects at lower accelerations is found by comparing early canal mediated gain increases during stimulation <1,600°/s² (Table 2). A canal-mediated gain increase with near over far targets was observed at the eye centered axis (eccentricity 0 cm) but not at the further forward axis (eccentricity −10 cm). A plausible explainable is that at eccentricity −10 cm the otoliths received enough stimulation to gate out the canal-mediated gain increase. During the smaller translation of the otoliths that occurs at the eye centered axis (eccentricity 0 cm), otolith stimulation might not have reached threshold to overcome the canal-mediated gain increase. This canal-otolith interaction is probably nonlinear at its onset.

A model is presented in Fig. 9 to summarize possible canal-otolith interactions consistent with the current data. The semicircular canals act rapidly (with a slight delay of ≈10 ms) via parallel target distance dependent and target distance independent pathways. The semicircular canals have an influential target distance independent pathway because even with remote targets a VOR gain near 1.0 is required and observed. The effect of target distance dependent canal pathway also decreased with head acceleration (not shown in diagram). The otolith-mediated effects begin a minimum of 20 ms later than the canal-mediated effects (as determined by the earliest otolith-mediated differences that can be observed) and become more prominent with time. This increased otolith prominence may occur as a result of nonlinear inhibition of the target distance dependent canal pathway (dashed line) and/or increasing otolith-mediated effects at later times.

Insights from unilateral vestibular deafferentation

In subjects with unilateral vestibular deafferentation, the transient VOR was normal for rotation opposite the side of the lesion but was severely impaired for rotation toward the lesioned side. This difference provides insight into the organization of the central VOR pathways. Rotation in the contra-lesional direction results in ampulopetetal deflection of the intact cupula and drives a two-synapse excitatory pathway by which increased firing rate in the intact hair cells of the horizontal semicircular canal disynaptically simulates the contra-lesional medial rectus and the ipsi-lesional lateral rectus muscles. Rotation in the ipsi-lesional direction results in ampulofugal deflection of the intact cupula, inhibiting the firing of primary vestibular neurons and driving at least four synapses to stimulate extraocular muscle contraction. The high acceleration used in this study was likely to drive the vestibular afferents (Goldberg and Fernandez 1971), and also the type II vestibular neurons (Fuchs and Kimm 1975), into a domain when their activity no longer accurately represents head motion. This may explain the lower gain in the first 55 ms of the when rotating in the ipsi-lesional direction. However, afferent physiology for the stimuli used is incomplete and interpretation of these findings awaits a more detailed understanding of the physiology. The relatively higher gain with lower peak acceleration ipsi-lesional stimulation, and ipsi-lesional stimulation late in the rotation, may be due to less inhibitory saturation at lower head acceleration.

Despite this early inhibitory cutoff, some compensation occurs later in the response because ipsi-lesional VOR gain increased toward the normal levels 55–80 ms after the onset of head rotation. A later increase in VOR gain also has been observed in patients with unilateral vestibular lesions during sudden head thrusts (Halmagyi et al. 1990). Halmagyi et al. suggested that this late compensatory response might be a small saccade or represent cervico-ocular reflex. Although unilaterally deafferented patients often used saccades as a compensatory strategy, in the current study trials with saccades were removed from analysis. Because the subjects here underwent whole-body rotation, the cervico-ocular reflex cannot be responsible for the late gain increase we observed. Higher gains are probably achieved due to decreased head acceleration during this period releasing primary afferents and type II neurons from inhibitory cutoff. Comparison of stimuli of different peak accelerations demonstrated that higher gains occur earlier for lower peak acceleration.

The subjects with unilateral vestibular deafferentation had lost both canal and otolith afferents from one side. Each utricular macula is sensitive to acceleration in both directions along the transaural axis because of the opposing orientations of its hair cells (Lempert et al. 1996; Spoendlin 1966), which perhaps explains why, by a week after unilateral labyrinthectomy, subjects demonstrated directionally symmetrical latency of the transaural linear VOR (Bronstein et al. 1991). However, the finding in acutely labyrinthectomized humans of a selective loss of the linear VOR for ipsi-lesional translations motivated Lempert et al. (1996) to propose that the linear VOR might be activated only by the midlateral region of the utricle, which is activated by ipsilaterally directed acceleration. Such a mechanism would explain the marked blunting of the early target distance related gain increase observed here for ipsi-lesional but not contra-lesional rotations in our chronically deafferented subjects. Nevertheless after 50 ms there was a nearly normal gain increase for the near as compared with remote target for ipsi-lesional rotation and the most posterior axis eccentricity of 20 cm (Fig. 8). This normalization of the later part of the response may be due to the lower stimulus intensity prevailing after that time or to a late acting compensatory mechanism.

An early canal-mediated, target-distance-dependent VOR gain change occurred both in normal subjects and in patients being rotated in the contra-lesional direction. However, this effect seems significantly blunted in the ipsi-lesional direction (Fig. 8), suggesting that neurons modulated directly by target distance are found primarily in the basic three-neuron arc rather than in the cross-commissural pathway. Although...
this interpretation is consistent with our findings, it is possible that some modulation dependent only on target distance occurs also in the cross-commisural pathway but was not significant due to the lower signal in the initial response during ipsi-lesional rotation. It is also possible that target distance effects occur primarily at excitatory synapses active during ampulopetal but not ampulofugal rotation.

Mechanisms of canal-otolith interaction

It is unclear why the otolith response of the VOR acts later than canal-mediated response. Recordings from utricular afferents in the monkey (Fernandez and Goldberg 1976) and chinchilla (Goldberg et al. 1990) during steady-state stimulation suggest that in both these animals the regular units have a phase lag that increases at higher frequencies (1–2 Hz). In these studies, the irregular units exhibited a slight phase lead at higher stimulus frequency. Modeling of the human VOR under steady-state conditions has shown that otolith input to the VOR correlates most closely with the pattern of firing observed in the irregular units of monkeys (Crane et al. 1997). Although the steady-state otolith response studied by Fernandez and Goldberg was not ideal for detecting small delays in the otolith output, the transfer functions they provided predict no delay to a step response (Fernandez and Goldberg 1976). Based on the data available, the delay in otolith effects seen in the VOR response cannot be attributed to the dynamics of the otolith organs or their primary afferents. This suggests that the delay in the otolith-mediated effects lies in the central circuits of the VOR. When the VOR of monkeys adapted chronically to magnifying or minifying spectacles is tested in response to a velocity step, VOR gain approaches the trained value only after an initial unmodifiable period (Lisberger and Pavelko 1988). Although otolith gain enhancement may share a similar end mechanism, there are significant differences. The effect of otolith input can be modified over seconds as target distance is changed; conversely a VOR gain change in response to motor learning requires minutes to hours of training with altered visual and vestibular inputs.

It is unclear why the canal response of the VOR should depend at all on target distance. The natural axis of head rotation during active movement is on average located 8.8 cm behind the eyes—slightly behind the otoliths (Hine and Thorn 1987). When rotating about this axis, the ideal gain with a near target would be greater than unity even though the otoliths would be receiving relatively little stimulation. Canal-mediated gain increases could be useful in achieving the ideal response under these conditions. However, there are reasons why the natural axis of head rotation is not likely to be a significant factor in determination of ideal VOR gain. First, the secondary vestibular afferents show entirely different firing pattern during voluntary head movement when compared with passive head movement. This suggests that during voluntary head movement, slow phase eye movements are controlled by other mechanisms such as motor efferent copy (McCrea et al. 1996). Second, during commonly occurring movements in humans such as walking and running, a counterphase behavior exists between head translation and head rotation such that the effective axis of ‘‘rotation’’ actually would be anterior to the head (Bloomberg et al. 1992; Crane and Demer 1997). During this situation, the canals and otoliths would be acting in an antagonistic manner. Head movement has been shown to play an active role in gaze stabilization and movement patterns have been observed to change as demanded by conditions such as near targets or magnified vision (Crane and Demer 1997). In light of this, a target distance dependent canal input to the VOR might not play an important role in real-world gaze stabilization unless the function is to cancel out a larger than necessary otolith input. Any ‘‘errors’’ in VOR performance caused by failure to correct for the position of the eyes relative to the otoliths or target distance dependence of canal gain are probably ‘‘corrected’’ by head movement or other adaptive behavior.

This work was supported by United States Public Health Service Grant DC-02952. B. Crane was supported by National Institute of Health Medical Scientist Training Program grant and National Eye Institute Training Grant EY-07026. J. Demer was recipient of a Research to Prevent Blindness Lew R. Wasserman Merit Award.

Address for reprint requests: J. L. Demer, Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095-7002.

Received 16 October 1997; accepted in final form 22 May 1998.

REFERENCES


Cremer, P., Henderson, C., Curthoys, I., and Halmagyi, G. Horizontal


