Compensatory and Orienting Eye Movements Induced By Off-Vertical Axis Rotation (OVAR) in Monkeys

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Kushiro, Keisuke, Mingjia Dai, Mikhail Kunin, Sergei B. Yakushin, Bernard Cohen, and Theodore Raphan. Compensatory and orienting eye movements induced by off-vertical axis rotation (OVAR) in monkeys. J Neurophysiol 88: 2445–2462, 2002; 10.1152/jn.00197.222. Nystagmus induced by off-vertical axis rotation (OVAR) about a head yaw axis is composed of a yaw bias velocity and modulations in eye position and velocity as the head changes orientation relative to gravity. The bias velocity is dependent on the tilt of the rotational axis relative to gravity and angular head velocity. For axis tilts ≤15°, bias velocities increased monotonically with increases in the magnitude of the projected gravity vector onto the horizontal plane of the head. For tilts of 15–90°, bias velocity was independent of tilt angle, increasing linearly as a function of head velocity with gains of 0.7–0.8, up to the saturation level of velocity storage. Asymmetries in OVAR bias velocity and asymmetries in the dominant time constant of the angular vestibuloocular reflex (aVOR) covaried and both were reduced by administration of baclofen, a GABA_A agonist. Modulations in pitch and roll eye positions were in phase with nose-down and side-down head positions, respectively. Changes in roll eye position were produced mainly by slow movements, whereas vertical eye position changes were characterized by slow eye movements and saccades. Oscillations in vertical and roll eye velocities led their respective position changes by ~90°, close to an ideal differentiation, suggesting that these modulations were due to activation of the orienting component of the linear vestibuloocular reflex (IVOR). The beating field of the horizontal nystagmus shifted the eyes 6.3°/g toward gravity in side down position, similar to the deviations observed during static roll tilt (7.0°/g). This demonstrates that the eyes also orient to gravity in yaw. Phases of horizontal eye velocity clustered ~180° relative to the modulation in beating field and were not simply differentiations of changes in eye position. Contributions of orientating and compensatory components of the IVOR to the modulation of eye position and velocity were modeled using three components: a novel direct otolith-oculomotor orientation, orientation-based velocity modulation, and changes in velocity storage time constants with head position relative to gravity. Time constants were obtained from optokinetic after-nystagmus, a direct representation of velocity storage. When the orienting IVOR was combined with models of the compensatory IVOR and velocity estimator from sequential otolith activation to generate the bias component, the model accurately predicted eye position and velocity in three dimensions. These data support the postulates that OVAR generates compensatory eye velocity through activation of velocity storage and that oscillatory components arise predominantly through IVOR orientation mechanisms.

INTRODUCTION

Yaw rotation in darkness about axes tilted from the spatial vertical (off-vertical axis rotation, OVAR) induces nystagmus that persists for as long as the rotation continues (Benson and Bodin 1966; Guedry 1965). The nystagmus is present in a wide range of species (humans, Benson and Bodin 1966; Darlot et al. 1988; Denise et al. 1988; Furman and Baloh 1992; Furman et al. 1992; Guedry 1965; Haslwanter et al. 2000; Yagi et al. 2000; monkey, Angelaki and Hess 1996a,b; Cohen et al. 1983; Hess and Angelaki 1997; Raphan et al. 1981; Young and Henn 1975; cat, Correia and Money 1970; Harris 1987; rat, Hess and Dieringer 1991; and rabbit, Janecke et al. 1970; Maruta et al. 2001). The eye position and velocity in three dimensions is composed of a steady-state compensatory horizontal slow phase eye velocity, known as the bias velocity (Benson and Bodin 1966; Guedry 1965), oscillations in horizontal, vertical, and roll eye position and velocity, and vergence eye movements related to head position with regard to gravity (Dai et al. 1996). The direction of the bias velocity is compensatory, being opposite to the direction of head rotation. In the monkey, the bias velocity has substantial gains up to head velocities of ~60–90°/s (Raphan et al. 1981) but is much lower in humans (Benson and Bodin 1966; Guedry 1965). OVAR nystagmus is present for head movements about other axes, as well, and there is a steady-state eye velocity and modulations in eye position in yaw, pitch, or roll whenever the axis of rotation is not spatially vertical and a gravitational component is added (Angelaki and Hess 1996a,b; Hess and Angelaki 1997; Young and Henn 1975).

The basis of the bias component response to OVAR has engendered much interest because it could lead to a better understanding of how the central vestibular system estimates the velocity of continuous head rotation from periodic oscillatory signals coming from the peripheral labyrinth. For small angles of tilt, the magnitude of the bias response at a given velocity of rotation is dependent on the angle of tilt of the rotation axis (Young and Henn 1975). There was initial spec-
ulation that this response was due to a roller pump action of the gravitational field on the semicircular canals (Benson and Bodin 1966; Steer 1970). However, a bias velocity is present even after inactivation of the semicircular canals by plugging (Cohen et al. 1983; Correia and Money 1970; Janecke et al. 1970) and recordings from eighth nerve canal afferents do not contain activity consistent with a bi-directional, steady-state canal response during OVAR (Goldberg and Fernandez 1981, 1982; Raphan et al. 1983). It is, therefore generally accepted that the bias component during OVAR is generated from otolith activation. One model estimates the continuous yaw angular velocity of the head from a correlation of “head jerk” with an orthogonal component of linear acceleration (Hain 1986). A similar approach extracts the jerk signal from response ellipses of neurons, and correlates it with the interaural linear acceleration (Angelaki 1992a,b; Angelaki et al. 1991). While these models can produce continuous estimation of yaw head velocity, it is not clear how computation of jerk is implemented or how it is extracted from response ellipses. Other models utilize sequential activation of the otoliths by the projection of the linear acceleration of gravity onto the horizontal plane (Fanelli et al. 1990; Guedry 1965; Raphan and Schnabolk 1988; Raphan et al. 1981; Schnabolk and Raphan 1992). This estimation of the head velocity from sequential activation of otolith cells activates velocity storage (Cohen et al. 1983; Fanelli et al. 1990; Raphan and Schnabolk 1988; Raphan et al. 1981; Schnabolk and Raphan 1992), which, in turn drives the oculomotor system to produce the nystagmus. The exact manner in which yaw head velocity is estimated has not been definitively determined.

There is general agreement, however, that velocity storage is critical for generating the continuous eye velocity. This is supported by the fact that the bias velocity opposes activity arising in the semicircular canals at the time rotation is stopped, superposing with and canceling canal-induced, postrotatory nystagmus up to the saturation level of velocity storage (Raphan et al. 1981). Vestibular-only (VO) neurons in the vestibular nuclei that are believed to be responsible for producing velocity storage have activity that is not only related to the dominant time constant of the angular vestibuloocular reflex (aVOR) and to optokinetic after-nystagmus (OKAN), but also to OVAR steady-state-eye velocities (Raphan and Cohen 1996; Reisine and Raphan 1992; Yokota et al. 1992). Moreover, the long-dominant time constant of the aVOR, OKAN and the bias velocity of OVAR all disappear when velocity storage is inactivated by lateral semicircular canal nerve section, by midline section, or by administration of baclofen, without affecting the direct aVOR pathways or the pathways for pitch and roll orienting responses (Cohen et al. 1983, 1987; Holstein et al. 1999; Wearne et al. 1997). As yet, there is relatively little quantitative information about how the bias velocity is related to angle of tilt of the axis of rotation or to the velocity of rotation. One purpose of this study was to obtain this information.

The oscillations in horizontal position and slow phase velocity (SPV) as well as the oscillations in vergence have also engendered interest because they represent three-dimensional responses to dynamic otolith activation and give information about the low-frequency behavior of the linear vestibuloocular reflex (IVOR) (Dai et al. 1994, 1996; Furman and Baloh 1992; Furman et al. 1992; Wall and Black 1984). Because there is sinusoidal oscillation of the gravitational acceleration along the interaural and naso-occipital axes during yaw OVAR, it has been hypothesized that the oscillations in yaw eye velocity are related to the compensatory (translational) IVOR (Angelaki and Hess 1996a; Hain 1986; Merfeld et al. 1999; Paige and Tomko 1991). However, the compensatory IVOR operates mainly at higher frequencies of head movement in monkeys and humans, and the IVOR gain drops sharply at &lt;0.5 Hz (Paige and Tomko 1991; Telford et al. 1997), which are the frequencies of rotation at which OVAR nystagmus is usually induced. Moreover, the phases of the yaw oscillations during OVAR are highly variable among monkeys (Angelaki and Hess 1996a). Thus despite the studies that have analyzed the eye-movement responses to OVAR in three dimensions (Angelaki and Hess 1996a,b; Hess and Angelaki 1997), the underlying mechanisms that determine the phase characteristics of the modulation components have not been fully explicated. In particular, the contribution that the compensatory (translational) IVOR makes to the oscillation component of the horizontal eye velocity during OVAR has not been clearly established.

An alternate hypothesis is that the horizontal modulations during OVAR are produced by the orienting components of the IVOR that operate in a range of frequencies encountered during OVAR (Raphan and Cohen 1996). There is little information about horizontal orienting movements in primates, but it has been postulated that the eyes orient similarly in three dimensions in frontal-eyed as well as lateral-eyed species (Cohen et al. 2001). The best known of the ocular orienting movements is ocular counter-rolling (Benjamin 1918; Collewijn et al. 1985; Diamond et al. 1979; Hannen et al. 1966; Lichtenberg et al. 1982; Magnus 1924; Van Der Houwe and De Kleijn 1918), but there are also vertical orienting movements (Angelaki and Hess 1996b, Cohen et al. 1991; Dai et al. 1994; Haslwanter et al. 1992). Ocular counter-pitch and counter-roll occur when subjects are tilted statically or slowly rotated and can be substantial, commonly reaching values of &gt;15°/H11350 in lateral-eyed animals (Benjamin 1918; Magnus 1924; Morita et al. 2001; Van Der Houwe and De Kleijn 1918). In humans and monkeys, counter-pitch and counter-roll are generally &lt;10°/H11349 (Cohen et al. 2001; Collewijn et al. 1985; Dai et al. 1994; Diamond et al. 1979; Hannen et al. 1966; Lichtenberg et al. 1982) and are of relatively constant amplitude across stimulus frequencies up to ~0.2 Hz (Telford et al. 1997). An orienting system could produce the vertical and roll modulation components and the modulations in horizontal eye velocity as a function of eye orientation during OVAR. The orienting system could also be responsible for the spatial-orientation properties of velocity storage and the convergence that occurs at the low frequencies of rotation encountered during OVAR (Dai et al. 1994). Orienting mechanisms are known to modify the time constants (inverse of eigenvalues) and orientation vectors (eigenvectors) of velocity storage (Arai et al. 2002; Dai et al. 1991; Raphan and Sturm 1991; Raphan et al. 1996; Wearne et al. 1999), but whether the changes in time constant as a function of head position relative to gravity are important in determining the phase of the modulations in horizontal slow phase eye velocity during OVAR is not known.

A second purpose of this study was to develop and test a model of orientation that includes roll, pitch, and yaw responses to a changing gravitational environment. By combining the orientation model with models of bias velocity gener-
eight monkeys (7 rhesus and 1 cynomolgus monkeys) were tested in this study. Data from five rhesus monkeys that were obtained preflight as part of the COSMOS 2229 space-flight study of 1992–1993 (Dai et al. 1994) were included as part of the database for this study. Three additional monkeys were tested specifically for this study. Because the dynamic vestibulo-oculomotor responses of rhesus and cynomolgus monkeys are similar, data from both species were combined in this study. The experiments conformed to the Guide for the Care and Use of Laboratory Animals (National Research Council) and were approved by the Institutional Animal Care and Use Committee.

Surgical procedures

Eye coils were implanted using sterile surgery under anesthesia. The monkeys were initially anesthetized with a ketamine (7.0 mg/kg)-xylazine (1.8 mg/kg) mixture, which was followed with a ketamine (4.0 mg/kg) and xylazine (1.0 mg/kg) every 30 min. The animal’s condition was continuously monitored by heart rate and electrocardiograph. Two search coils were placed on one eye to record its orientation in three dimensions. The frontal coil was sutured under the conjunctiva in the frontal plane. This coil was aligned with the optic axis and recorded horizontal and vertical eye positions (Judge et al. 1980; Robinson 1963). Another coil was placed around the superior rectus muscle to measure roll eye movement (Dai et al. 1994). In two monkeys (M9865 and M9866), frontal plane coils were implanted on both eyes for binocular recording of horizontal and vertical eye position. Screws secured to the skull were embedded in a 90-mm acrylic head-mount ring to fix the monkey’s head during experiments (Sirota et al. 1988; Yakushin et al. 2000). Postoperatively, the animals were treated with analgesics, antibiotics, and steroids to relieve pain and inflammation.

Coordinate frame for eye-movement measurements

Eye movements were measured in a head-based coordinate frame (Fig. 1H). This coordinate frame was defined by the naso-occipital or roll (X_h) axis, the interaural or pitch (Y_h) axis, and the dorso-ventral or yaw (Z_h) axis. The coordinate frame of the eye was defined by the roll (X_e), pitch (Y_e), and yaw (Z_e) axes (Fig. 1A). The roll axis is the visual axis. The reference position of the eye occurs when the head is upright with its yaw axis (Z_e) aligned with gravity and the visual axis (X_e) is parallel to the naso-occipital axis (X_h). Positive directions for head and eye rotations were defined by a right-hand rule. Positive roll (+X) is clockwise from the animal’s point of view along the naso-occipital
axis, positive pitch (+Y) is downward, and positive yaw (+Z) is to the left. Positive directions for head and eye velocities were similarly defined. Eye position components can be given as Euler angles (Yakushin et al. 1995) or as axis-angle (Maruta et al. 2001). For angles of rotation less than \(\sim 20° - 25°\), these components of eye rotation are close to the angles obtained directly from the coil voltages (Yakushin et al. 1995). Thus angles obtained directly from coiled voltages were used in this study.

**OVAR stimulation**

Animals sat in a primate chair with their heads fixed in the center of a 26-cm square box that held the field coils. The horizontal stereotaxic plane was orthogonal to the yaw axis. Therefore the lateral canals were tilted up \(\sim 30°\) from the horizontal stereotaxic plane (Blanks et al. 1985; Yakushin et al. 1995). The apparatus, a multiaxis vestibular and optokinetic stimulator [Neurokinetics, Pittsburgh, PA (Dai et al. 1994)] allowed independent control of four axes. Three axes were for vestibular stimulation (an outer horizontal axis, a nested horizontal per-rotatory axis, and a doubly nested roll axis). The fourth axis drove an optokinetic sphere that provided full-field visual stimulation. To produce OVAR, animals were first rotated in yaw about the earth vertical axis at a constant velocity of 10–150°/s in darkness. This induced horizontal per-rotatory nystagmus that declined to zero as the rotation continued. The rotation axis was then tilted from 5 to 90° with respect to earth vertical at a velocity of 5–15°/s while the animal was still rotating. The axis was then held stationary at the tilted position for 6–20 cycles of rotation while data were collected.

**Roll tilt stimulation**

Orienting yaw responses were studied in two monkeys by tilting them in the roll plane at a low constant velocity (0.5°/s) to side-down positions. The monkeys were first tilted from the upright to one lateral position, then back to the upright, followed by tilt to the opposite side and return to the upright. At this stimulus velocity, it took 360 s to go from +90 to -90°, which was slow enough so that no nystagmus was generated at any portion of the tilt cycle. Several stimulus cycles were recorded in one session, and the data were combined to determine if there was a consistent tilt-related, horizontal eye deviation.

**Optokinetic stimulation**

The effect of head position with regard to gravity on the velocity storage integrator was studied in three monkeys using OVAR. Animals were tilted 30, 60, or 90° from the upright position. In tilted positions, the head was oriented in 1 of 12 static positions separated by 30° about the yaw axis. Optokinetic nystagmus (OKN) was produced by rotating the visual surround around the animal’s yaw axis at a velocity of 30°/s. The visual surround was a sphere (107-cm diam) that surrounded the animal and filled its field of vision with alternating black and white stripes 10° apart. The shell of the sphere was 54.5 cm from the animal. After 60 s of OKN, the lights were turned off to generate OKAN, which was recorded until the nystagmus disappeared. Two to five trials were done in each position. The sequence of the head orientations was randomized. For each head orientation, the time constant of OKAN was calculated by fitting the horizontal slow phase velocity with a first-order exponential (Cohen et al. 1977; Raphan et al. 1979).

**Baclofen injection**

Baclofen, a GABA\(_A\) agonist, is known to reduce the time constant of the OKAN, which is a direct representation of the velocity storage integrator (Cohen et al. 1987). Baclofen was used to study the relationship between the bias velocity of OVAR and the velocity-storage integrator. After pretesting, the animals received a first injection of 0.5 mg/kg of a 1.0 mg/ml baclofen solution into the dorsal neck muscle. Thirty to 45 min later, the animals were again tested with yaw axis rotation about a spatial vertical axis at 30°/s and with OVAR about an axis tilted 90° from the vertical. One hour after the first injection, the animals received 1.0 mg/kg of the drug again (2nd injection). Thirty to 45 min after the second injection, the animals were tested with the same stimuli.

**Data acquisition and processing**

Eye-position-related analog signals were amplified with a bandwidth of DC to 40 Hz and sampled at 600–750 Hz with 12-bit resolution. Eye-position voltages were digitally differentiated. Fast phases of nystagmus were removed from the differentiated signal using a maximum likelihood ratio criterion (Singh et al. 1981). Eye movements were calibrated by rotating the animals about an earth vertical axis in light at 30°/s. Animals were positioned upright, on side, or supine to calibrate the yaw, pitch, and roll components of eye movement, respectively. It was assumed that horizontal and vertical velocity gains were close to unity in this condition (Crawford and Vilis 1991; Dai et al. 1991; Raphan et al. 1979; Skavenski and Robinson 1973). The roll velocity gain was assumed to be 0.6. Similar roll gains have been obtained for monkeys by using other techniques (Crawford and Vilis 1991; Henn et al. 1992). Eye-position calibrations were obtained from velocity calibrations. Because the animals were not trained to fixate points in space, absolute eye position in the orbit was not known. This was not an impediment, however, because we were primarily interested in relative changes of eye position during OVAR and particularly in the amplitude and phases of the sinusoidal modulations in eye position as a function of head position with regard to gravity.

Vergence and divergence were defined as disconjugate changes in yaw eye position and were determined by subtracting the relative position of the right eye from the position of the left. We did not have a position calibration for each eye, but it was assumed that the distance between the eyes was 3 cm and that the animals were looking at the shell of the sphere, which filled their visual surround. Thus it was assumed that the resting position of the eyes in dark verged at \(\sim 54.5\) cm from the center of the head, the distance of the sphere to the animal (Dai et al. 1996; Paige 1991). When looking straight ahead, this corresponded to a vergence angle of \(\sim 3°\). The vergence measurement was the modulation about this position. Therefore when we refer to divergence, we mean that the eyes were diverged relative to this resting position. A vergence amplitude of \(\sim 2°\), which is the range of vergence about the dark state vergence found in our study, implies that the verged position of the eyes varied from 84 to 42 cm in front of the head. This value could vary among monkeys (Dai et al. 1996).

The horizontal nystagmus and the vertical and roll components induced by OVAR were analyzed during the steady state. Position and velocity signals were averaged over 3–20 cycles of rotation and fitted by a least-square sinusoid, \(y = A \cdot \cos(at + B) + C\), where \(a\) is the radian frequency corresponding to the velocity of rotation. From the fits to the data, we determined the bias component \((C)\) as well as the amplitude \((A)\) and phase \((B)\) of the modulation component. Because the dominant time constant of the VOR and of velocity storage can be different for nystagmus in different directions, slow phase velocities to the right and left were treated as independent conditions. The amplitude and phase were considered as a vector from which an average vector was obtained over all trials. The phase of the average vector was given relative to the nose-down position with positive values as leading.

To obtain average horizontal eye position during the roll tilt paradigm, horizontal eye position was averaged over 1-s epochs to minimize the effect of the saccadic eye movement, and this value was represented as a function of head position. A randomized one-way ANOVA was used for statistical analyses.
RESULTS

General characteristics

Constant velocity rotation at 10–150°/s about axes tilted 5–90° from the earth vertical produced continuous horizontal nystagmus as well as oscillations in horizontal, vertical and roll eye position and eye velocity that were related to head position with regard to gravity (Fig. 1). The slow phases of the horizontal nystagmus were compensatory in that they opposed the direction of rotation with a continuous eye velocity bias (Fig. 1A, solid line), oscillated as a function of head position with regard to gravity and was defined as the beating field. Changes in vertical eye position were achieved by a combination of slow phases and saccades (Fig. 1B) (Angelaki and Hess 1996a; Dai et al. 1996). Together the slow and rapid eye movements oriented the vertical position of the eyes in phase with the acceleration along the naso-occipital axis. The eyes also were modulated in roll over each cycle (Fig. 1C). At low velocities of rotation (<90°/s), small roll quick phases of nystagmus opposed the slow position changes (Fig. 1C). Forward saccades, i.e., in the direction of the roll slow phases, were less common but were present at higher velocities of rotation (>120°/s). Vertical slow phase velocity was offset in the negative direction (Fig. 1E), reflecting the weak spontaneous nystagmus of the monkey in darkness with upward slow phases (Rude and Baker 1996). Roll velocities, on the other hand, modulated approximately around zero (Fig. 1F).

Horizontal bias velocity

The bias velocity was dependent on both the velocity of rotation and the tilt of the rotation axis. For tilt angles from 5° to 15° (0.09–0.26 g projected onto the horizontal plane), there were monotonic increases in the bias velocity for increases in tilt angle (Fig. 2, A–C). For tilts >15–20°, (>0.26–0.34 g projected onto the horizontal plane), the bias velocity was independent of tilt angle and was only affected by head velocity (Fig. 2, A–C). We refer to the bias velocity over this range of tilt angles as the “normalized” value.1 Bias velocities varied among animals and with the direction of the nystagmus. In the three animals, the bias velocity normalized at 9.2 ± 3.4°/s (mean ± SD) for rotation at 15°/s (gain = 0.61; Fig. 2, A–C, triangles; Fig. 2D) and at 24.9 ± 3.4°/s for rotation at 30°/s (gain = 0.83; Fig. 2, A–C, circles; Fig. 2D). Normalization occurred at smaller angles of tilt when the animals were rotated more rapidly. Thus it took a rotating gravity vector of 0.5 g (30° of tilt) to produce normalization at 15°/s, whereas a rotating vector of only 0.26 g (15° of tilt) produced normalization at 30°/s (Fig. 2, A–D). The larger the normalized level of bias velocity, the more steeply the bias velocity increased (Fig. 2, A–D). Similar to previous findings (Raphan et al. 1981), the normalized bias velocities increased monotonically as a function of rotational velocity =50–60°/s with a gain of ~0.7 (Fig. 2E). The curve saturated at slow phase velocities between 40°/s and 75°/s for individual animals, close to the estimated saturation velocity of velocity storage (Cohen et al. 1977; Raphan et al. 1979, 1981). There was variation among monkeys, however, and one animal (M9866), reached bias velocities of ~110°/s for rotations to the left (Fig. 2E, open squares). These data indicate that the rate at which the gravity

1 A steady-state velocity that does not increment further with increases in tilt of the axis of rotation has essentially saturated. However, we chose not to use this term for this relationship because the mechanism producing the relationship has a true saturation value beyond which it is no longer capable of responding to increases in velocity at any tilt angle (Cohen et al. 1977; Raphan et al. 1981; Waespe et al. 1983). For this reason, we have used the terminology “normalized” velocity (Fanelli et al. 1990) to refer to the limitation of the velocity produced by any particular head tilt and velocity during OVAR.
vector rotates about the head plays a significant role in generating signals from which head velocity can be estimated even for small gravitational fields rotating in the horizontal plane. It also shows that the sensitivity for estimating and responding to orientation changes of the head is higher at higher rates of turning.

The dominant time constant of the angular VOR (aVOR) is largely determined by the central vestibular time constant, i.e., the time constant of velocity storage (Raphan et al. 1979). Consistent with the dependence on velocity storage, asymmetries in the bias velocity were reflected in corresponding asymmetries in the aVOR time constant in each animal (Fig. 3, A–C). There was a correlation between directional differences in bias velocity and corresponding differences in time constant of the aVOR (Fig. 3D; $r = 0.63$). Thus animals with a larger asymmetry in their aVOR time constant had a proportionally larger asymmetry in bias velocity induced by OVAR (Fig. 3D). The close relationship between bias velocity and the time constant of the velocity storage integrator was also demonstrated through the use of baclofen (Fig. 3E), which causes dose-related reductions in the aVOR time constant (Cohen et al. 1987). After a parenteral injection of 0.5 mg/kg of baclofen, the aVOR time constant dropped from an average of 27.8–21.7 s with a concomitant decrement in the bias velocity from 25.9 to 18.9°/s. A second injection of 1.0 mg/kg further reduced the aVOR time constant to 10.0 s and the bias velocity to 8.0°/s. The correlation between reduction in time constant and reduction in slow phase velocity as a function of dose of baclofen was significant (ANOVA; $P < 0.01$).

**Modulation components**

**AMPLITUDE.** The effect of gravitational acceleration on the amplitude of the modulation components was tested by rotating animals at 30°/s about axes tilted 15–90°. This projected a sinusoidally varying acceleration of amplitude 0.26–1.0 g along each axis in the horizontal ($X_hY_h$) plane. In each instance, the average modulations in eye position per cycle of rotation increased with increases in the amplitude of the rotating gravity vector (Fig. 4, A–C). To estimate the relative sensitivities of the amplitude of the horizontal beating field and the roll eye position changes to acceleration, modulation amplitude versus net gravitational acceleration were approximated by a linear least-squares fit (not shown). These sensitivities were 6.4°/g (horizontal beating field; Fig. 4A) and 9.9°/g (roll; Fig. 4C), respectively. Vertical eye position modulations increased non-linearly, reaching 18.9° at 1 g (Fig. 4B).

Amplitude of modulations in slow phase velocity also increased monotonically as a function of magnitude of the gravitational acceleration in the horizontal ($X_hY_h$) plane (Fig. 4, D–F).
To determine the relative contribution of the slow and rapid eye movements to the vertical and roll position changes, vertical and roll slow phase eye velocities were integrated after saccades were removed. The difference between the extrapolated slow phase amplitudes, estimated from this integration (Fig. 4, B and C, ○) and the observed amplitudes (Fig. 4, B and C, ●), shown by the shaded areas, represents the contribution of saccadic eye movements to the observed changes in eye position. For pitch, the estimated contribution of saccades increased as the gravitational acceleration became larger and was as large as 20° in response to a 1 g rotating vector (Fig. 4B, □). In contrast, the estimated and observed amplitudes of roll (Fig. 4C, ○ and ●) approximately overlay each other. Small differences between the estimated and actual amplitude of roll (Fig. 4C, □) were probably due to small beats of nystagmus, present for tilts ≤45° (Fig. 1), and to the small forward saccades that appeared at larger tilt angles.

Thus the contribution of slow and quick phase eye movements to the vertical and roll components were different from each other with saccades contributing more to changes in vertical eye position. Horizontal position was not analyzed in this fashion because the beating field is an average of eye position during nystagmus over both slow and quick phases. Thus it was a smooth function of head position and could not easily be attributed to the slow phase horizontal eye velocity.

The effect of rotation velocity on the amplitude of the modulations was tested with the axis of rotation tilted 90° from the spatial vertical to produce a rotating gravitational field of 1 g, well above the level at which the response to OVAR normalized. Modulations in the position of the horizontal beating field (Fig. 5A, ●) and in roll eye position (Fig. 5A, ■) were stable in three animals across all rotation velocities. They were ~6° for yaw and 11° for roll. The amplitude of the vertical position changes increased with the velocity of rotation, however, reaching ~25° at higher rotational velocities (Fig. 5A; ▲; P < 0.01). Changes in velocity were somewhat different. The amplitude of the velocity modulations of all three components

![Graphs showing amplitude of OVAR modulation components](image-url)
increased with increases in the speed of rotation (Fig. 5B; \(P < 0.01\), although horizontal (●) and vertical (▲) slow phase velocities increased only slightly, whereas the modulations in roll velocity increased steadily from \(\sim 3.6/\text{s}\) at the lowest rotation velocity to \(17.8/\text{s}\) at the highest velocities (●). In this case, the apparent disparity between the position and velocity modulations in roll was due to the nystagmus present in the roll components (Fig. 1C).

The relative contributions of slow phases and saccadic eye movements to the position amplitudes were analyzed by differentiation of the position waveforms after saccade removal as in the previous section. As would be predicted from Fig. 4B, the estimated amplitudes of vertical eye position due to the slow phases was considerably less than the actual amplitude at all velocities \(>15/\text{s}\). This was due to the contribution of saccades to the eye position changes. In contrast, the estimated amplitude of the roll modulations was slightly larger than the actual amplitude of the modulation in position for velocities \(\leq 90/\text{s}\), where the two reversed. Thus saccades were a dominant factor in producing vertical eye position changes, especially when \(1 \text{g}\) of linear acceleration was imposed across the otoliths, whereas there was a contribution of quick phases of nystagmus that reduced the amplitude of roll eye position changes while increasing roll eye velocity in response to higher rates of rotation.

**PHASES.** At a rotation velocity of \(60/\text{s}\), there was no difference in the phases of the horizontal beating field or of the vertical and roll eye position or velocity components for OVAR at tilt angles of \(60^\circ\) (0.87 g) and \(90^\circ\) (1.0 g). Thus data from both angles were used for phase computations. Variability of data points in the phase plots in each monkey were generally \(<30^\circ\) for eye position and \(35^\circ\) for eye velocity. The phase of the maximum downward vertical positions (Fig. 6, E and G) occurred close to the nose-up position for both directions of rotation, whereas the maximum clockwise roll positions (Fig. 6, I and K) occurred close to left side down positions. Vertical and roll slow phase velocity led the position phases by \(78.2 \pm 23.9^\circ\) and \(86.9 \pm 4.6^\circ\) on average, respectively (Fig. 6, F and H and J and L). This difference of \(\sim 90^\circ\) between the phases of the vertical and roll eye position and the corresponding eye velocities and the fact that there was no bias component of eye velocity for vertical and roll suggests that the modulations in velocity were related to the first derivative of

![Figure 6](http://jn.physiology.org/DownloadedFrom/10.2308/jn.2002.02.02.07)

**FIG. 6.** Phases of the peak value of the modulations in horizontal beating field (A and C) and slow phase velocity (B and D), vertical position (E and G) and vertical velocity (F and H), and roll position (I and K) and roll velocity (J and L). The curved arrows show the direction of rotation. Note that horizontal oscillations were superimposed on a horizontal bias velocity, and therefore were different from vertical and roll phases, which oscillated approximately symmetrically about 0 position and velocity. Phases for horizontal beating field and slow phase velocity for rightward rotation were determined for head positions relative to the nose down (0°) position, where beating field and eye velocity to the left was at a maximum (positive peak). For rotations to the left, phases were determined as the position of the head relative to nose down (0°) where beating field and eye velocity to the right was a maximum (negative peak). Vertical and roll eye position and velocity phases were determined from the head position at which peak eye rotation and velocity occurred according to the positive direction of the head coordinate frame for both directions of rotations. That is, the head position at which peak downward position and velocity occurred determined the phases of vertical eye movements. The head position at which peak clockwise roll eye position and velocity occurred relative to the monkey determined the phases of roll eye movements. Because the eyes moved counter to the horizontal head rotation, phase was considered positive when measured opposite to the direction of rotation and negative if measured in the direction of rotation. Each circle represents the phase of a different trial for each of the monkeys tested.
the modulations in eye position. The position modulations were, in turn, orienting responses to head position with regard to gravity.

Modulations in the horizontal beating field were studied in five animals. (The modulations were too small to calculate a stable phase in 3 monkeys, although the vertical and roll phases could be calculated in all animals). The position phase of the beating field of the horizontal nystagmus occurred at approximately equal to −90°, when the head was close to a side down position (−79.4°, Fig. 6A; −89.7°, Fig. 6C). Thus on average the eyes moved away from the linear acceleration of gravity during the nystagmus, suggesting an orienting response of the horizontal system. There was a large scatter in the phases of horizontal eye velocity in the different monkeys, although there was a clustering that tended toward right-side-down (RD) position and left-side-down (LD) for rightward and leftward rotation respectively (Fig. 6, B and D). The average separation between the phases of the beating field and horizontal slow phase eye velocity was close to 180° (compare Fig. 6, A to B, and C to D). Thus the phase of modulation in the horizontal slow phase eye velocity was not a simple differentiation of the modulation in the position of the beating field. Consequently, oscillations in horizontal eye velocity had a more complicated relationship to orientation of gravito-inertial acceleration (GIA) relative to the head than did the oscillations in the vertical and roll slow phase eye velocities (see Modeling responses to OVAR).

**Vergence**

Previous studies have shown that the eyes converge in response to the low-frequency naso-occipital linear acceleration of OVAR (Dai et al. 1996; Hess and Dieringer 1990; Maruta et al. 2001). This finding raised the possibility that the large phase differences between the horizontal changes in beating field and horizontal slow phase velocity could be explained by the vergence elicited by OVAR. For this, estimates of the amplitude and phase of the vergence were obtained in two animals in which we had determined the separation between the phases of horizontal position and velocity. Vergence eye movements appeared with slow oscillations at the stimulus frequency when the monkeys were rotated about a horizontal yaw axis at 30° and 60°/s (Fig. 7). The amplitude of the vergence modulations and the sinusoidal modulations in the beating field were small. The mean amplitude of the modulation in the vergence angle was 1.1 ± 0.6° (n = 18), which was ≈26% of the beating field modulation of 4.3 ± 2.3° (n = 36). Moreover, modulation in the velocity of vergence was ≈0.6°/s, which was ≈17% of the modulation in the conjugate slow phase velocity (3.5°/s). Because the vergence angle is the difference in the position of both eyes, the relative contribution of each eye to the oscillation component would on average be less than the vergence estimate from both eyes. It is unlikely that these small modulations were responsible for the difference in phase of ≈180° between horizontal eye position and eye velocity in these monkeys.

**Horizontal deviations during roll tilt**

The finding that the amplitude of the modulation in the horizontal beating field was constant across velocities during rotation about a horizontal axis (Fig. 5A) indicated that the horizontal deviation in the beating field was a function of head position with regard to gravity, not of the velocity of rotation. To test for static positional effects, two monkeys were tilted at a low constant velocity (0.5°/s) in the roll plane, and eye position over each second was averaged and plotted as a function of the gravitational acceleration projected onto the interaural axis (Fig. 8). This speed of rotation is below the velocity threshold of the canals for producing nystagmus, which is ≈1°/s (Henn et al. 1980). Average eye positions consistently shifted away from the direction of gravitational acceleration, being rightward when the animals were right-side-down and leftward when they were left-side-down. Thus the eyes deviated on average in the same direction as the beating field during OVAR (Figs. 4A). The data were approximated with a sinusoid that was a linear function of gravity. The sensitivity during tilt was ∼6.9°/g, which was close to the average sensitivity of the modulation in the beating field during OVAR (Fig. 4A; 6.4°/g). These similarities support the hypothesis that the horizontal modulation of the beating field during OVAR is an orienting response to linear acceleration along the interaural axis.

**OKAN response in various static head orientation in space**

As shown in Fig. 3, the bias velocity during OVAR is dependent on the dominant time constant of the aVOR, and striking changes in the bias velocity can be produced by altering the time constant of the aVOR. Because the yaw axis time constant of velocity storage changes substantially according to head orientation in space (Dai et al. 1991; Gizzi et al. 1994; Raphan and Cohen 1988, 1996; Raphan and Sturm 1991; Wearn et al. 1998, 1999), we questioned whether changes in the yaw-axis time constant of velocity storage could have been responsible for the changes in the gain and phase of the horizontal components during the sequential changes in head orientation that occur during OVAR. Additionally, we asked...
whether these changes could be responsible for the \( \sim 180^\circ \) phase difference and the variations in phase between horizontal position of the beating field and horizontal slow phase velocity.

OKAN is a direct expression of the velocity storage integrator (Cohen et al. 1977; Raphan et al. 1979) and can be used to study effects of head position on the time constant of velocity storage (Dai et al. 1991; Raphan and Cohen 1988; Raphan and Sturm 1991). OKAN time constants were measured in three animals while they were statically placed at 30\(^\circ\) increments around an axis tilted 90\(^\circ\) from the vertical. There was a three- to fourfold change in the time constants of OKAN as head orientation in space was altered around a spatial horizontal axis (Fig. 9). The pattern of change of the OKAN time constants varied among animals. In M9865, the time constants tended to be longest in the nose-up position, whereas they were shortest in this position in M9860 and M9866. The changes were approximately sinusoidal for both right and left OKAN in M9865 (Fig. 9, C and D) and for right OKAN in M9866 (Fig. 9E), but there was no well-defined peak in M9860 for right or left OKAN (Fig. 9, A and B) and in M9866 for left OKAN (Fig. 9F). Thus while time constant variations in velocity storage undoubtedly play a role in modulating eye velocity during OVAR, the exact nature of the modulation can only be inferred from comparing the modulations with those predicted from a model.

**Modeling the responses to OVAR**

A model-based approach was used to elucidate the relative contribution of the compensatory IVOR to the yaw component and to determine how time-constant variations would affect the modulation of horizontal slow phase velocity. The model for driving eye movements in three dimensions during OVAR, shown in Fig. 10, was derived by combining the model that generates the aVOR-IVOR interaction (Raphan and Cohen 1996, 2002; Raphan et al. 1996; Wearne et al. 1999) with the model that generates the bias component of eye velocity during OVAR (Fanelli et al. 1990; Raphan and Schnabolk 1988).

![Figure 8](http://jn.physiology.org/)

**Fig. 8.** A: variation in horizontal eye position during constant velocity (0.5\(^\circ\)/s) tilt about a roll axis (ordinate) from left-side-down position to right-side-down position (insets below abscissa) as a function of the gravitational acceleration projected onto the interaural axis (abscissa). Each point is an average of eye position during 4 1-s periods in a particular head position. ○, data from monkey M9865; ●, data from M9866. The average eye position shifted toward the right when the animals were right side down and toward the left when left side down. A least-squares straight line was fit to each monkey’s data to compute the sensitivity of horizontal eye deviation as a function of interaural acceleration. B: model simulation of horizontal eye position as a function of interaural linear acceleration. ○, represent tilt to the right; ●, tilting to the left.

![Figure 9](http://jn.physiology.org/)

**Fig. 9.** Effect of head orientation with regard to gravity (abscissa) on the time constant of horizontal optokinetic after-nystagmus (OKAN; ordinate) induced by the drum rotation to the right (A, C, and E) and left (B, D, and F) at 30\(^\circ\)/s about the animals’ yaw axis. Animals included M9860 (A and B), M9865 (C and D), and M9866 (E and F). Animals were tested in static positions >360\(^\circ\) in increments of 30\(^\circ\); representative positions at each 90\(^\circ\) are shown in the insets below E and F. Each point represents the time constant derived from a single test.
Because there was no rotation about the pitch or roll axes of the head, pitch and roll ocular responses to OVAR were considered consistent with a direct otolithic drive on the oculomotor system to orient the eyes (Fig. 10, A–E). When upright, the yaw axes of the eyes are aligned with the acceleration of gravity, i.e., the spatial vertical (Fig. 10A, upward black arrow, GIA). When the head is oriented back toward the supine position, the yaw axis of the eyes orient downward in pitch relative to the head (Fig. 10B), and when the head is oriented toward prone, the yaw axes of the eyes are oriented up in pitch relative to the head (Fig. 10C). When the head is RD or LD, the eyes tort counterclockwise and clockwise, respectively, from the animal’s point of view (Fig. 10, D and E). We also modeled the changes in the beating field of nystagmus that shifted average eye position as a function of head position re gravity as a direct otolith drive on the oculomotor system. The average yaw eye position shifts away from the acceleration of gravity in the side-down positions (Fig. 10, D and E, eye yaw toward gravity). In the model, these changes in eye position are represented as direct activation of the orienting lVOR system, which orients the eyes directly through the matrix, $D_0$ (Fig. 10F) and orients the velocity storage system matrix, $H$, through the nodulus/uvula.

The output of the orienting lVOR system for pitch and roll, $y_{opr}$, was modeled as a cross-product between a unit vector along the head yaw, $a_z$, and one along the net GIA, $a_{GIA}$, all given in head coordinates as

$$ y_{opr} = a_z \wedge a_{GIA} \quad (1) $$

where $\wedge$ denotes the vector cross-product. The unit vector $a_{GIA}$ is along the direction of the vector sum of the acceleration of gravity in head coordinates, $A_g$, and the linear accelerations of the head in head coordinates, $A_l$. The vector $A_g$ is fixed in space (A, and is transformed to the head frame, depending on the motion of the head (Fig. 10, SPACE-HEAD TRANSFORM). During OVAR, utilized in this study, the only linear acceleration is that due to gravity.

The vector $y_{opr}$ has a direction along the axis about which the first vector must rotate to be aligned with the second vector and is orthogonal to the two unit vectors, $a_z$ and $a_{GIA}$. Because $a_z$ is along the head yaw axis, the orientation vector, $y_{opr}$, must lie in the pitch-roll plane of the head. In addition, the cross-product between two vectors codes the sine of the angle between them, which is the orienting response found across a wide range of species (Benjamins 1918; Cohen et al. 2001; Maruta et al. 2001; Raphan and Cohen 2002).

A vector that encodes the yaw component of the orientation was postulated to be a cross-product between a unit vector along the naso-occipital axis and the GIA, which is then projected along the head yaw axis. This yaw axis orientation command is given by

$$ y_{oyaw} = -(a_z \wedge a_{GIA}) a_x \quad (2) $$

where $\wedge$ denotes the vector cross-product and $\langle, \rangle$ denotes the inner product of two vectors. Equation 2 gives $y_{oyaw}$ as a vector projection of the orientation vector of the naso-occipital relative to the GIA onto the body vertical. The incorporation of such a component is postulated based on the idea that orientation of the GIA relative to head yaw only gives pitch-roll...
orientation of the eyes and cannot give complete three-dimensional orientation. The forward pointing naso-occipital axis could be another important direction on which the central vestibular system could code its orientation coding with regard to the GIA in three dimensions. This three-dimensional encoding of orientation is evident in the change in yaw eye position away from the GIA during OVAR and when the head is rolled relative to gravity (Fig. 8A).

The orientation vector in three dimensions is given by the sum of the vectors given in Eqs. 1 and 2 as

\[ \mathbf{y} = \mathbf{y}_{\text{eye}} + \mathbf{y}_{\text{yaw}} = \mathbf{a} \wedge \mathbf{a}_{\text{GIA}} - (\mathbf{a} \wedge \mathbf{a}_{\text{GIA}}) \mathbf{a} \mathbf{a} \]  

(3)

Thus the orienting vector \( \mathbf{y} \), given in terms of cross-products and projection operators provide separable bilinear mechanisms, operating on axes associated with the head coordinate frame and the GIA, for implementing the roll, pitch, and yaw components of the orienting IVOR. These operators can be implemented as a large-scale matrix transformation, affording the possibility of implementation as a neural network of weighted sums of neural activity over a wide range of polarization directions. The dynamic information is provided in the XYZ components of the otolith afferents, which are fixed in the head and respond with a wide range of dynamics to the net acceleration field relative to the head. The parameters of the orienting IVOR subsystem also determine the dynamics of the orienting response (Raphan and Cohen 1996, 2002). The orientation vector is assumed to affect eye position changes by a direct pathway determined by the matrix \( D_0 \) (Fig. 10).

The bias velocity component of the response was generated through the velocity storage integrator by combining two factors. The first was the drive on velocity storage through the otolith-velocity estimator (Fig. 10F, otolith velocity estimator). This estimator processes activity originating in regular, irregular, and intermediate hair cells in the otoliths to produce a signal proportional to head velocity (Fanelli et al. 1990; Raphan and Schnabolk 1988). The second factor was continuous modification of the yaw-axis velocity storage time constant due to the spatial orientation characteristics of velocity storage that are controlled by the nodulus/uvula (Fanelli et al. 1990, 1996). The output from the velocity storage integrator was also combined with the compensatory IVOR command through a system \( K(\mathbf{y}_{\text{eye}}, \gamma, \gamma_{\text{yaw}}) \) that generated the eye velocity command \( \mathbf{y} \). The yaw component of \( \mathbf{y} \), \( \gamma_{\text{yaw}} \), has a modulatory affect on the eye velocity command, increasing it when the eye velocity is on the quick phase side and decreasing it when the eye is on the slow phase side. The following equation was implemented for yaw component of \( \mathbf{y} \), \( \gamma_{\text{yaw}} \)

\[ \gamma_{\text{yaw}} = (k_1 \gamma_{\text{yaw}} + k_2 \gamma_{\text{yaw}}) (1 - k_3 \gamma_{\text{yaw}} (k_1 \gamma_{\text{yaw}} + k_2 \gamma_{\text{yaw}})) \]  

(4)

This nonlinear modulation was necessary to explain the dominant phase behavior of the oscillatory component of eye velocity during OVAR, which generated the peak eye velocity in the side down position, 180° out of phase with the peak beating field modulation. This modulation in the eye-velocity command is different from the Alexander’s law effect, which causes increments and decrements in eye velocity as the eyes move to the quick phase or slow phase side respectively. Alexander’s law is related to the velocity-position integrator and comes into play for large eye deviations or when lesions shorten the time constant of the velocity-position integrator (Robinson et al. 1984). In addition to these orientation affects, there is activation of the saccadic system by the orientation signal, which is a prominent feature of pitch eye orientation during OVAR. This was not considered in this modeling approach.

The velocity command, \( \gamma_{\text{eye}} \), is processed through the velocity-position integrator and combined with the direct vector of the orientation command derived through matrix \( D_0 \) that drives the motoneurons, \( m_0 \) that in turn, drive the eyes (Fig. 10F). For simplicity, it was assumed that the elements of the \( K \) matrix transforming the pitch and roll components of orientation were constant and were only affected by the direct orientation matrix, \( D_0 \). This assumption was warranted by the close relationship of the phase of the pitch eye position to the nose down position and of the phase of roll eye position to the side down position (Fig. 6, vertical: \( E \) and \( G \); roll: \( I \) and \( K \)).

Model simulations

Eye position and velocity were simulated to gain an understanding of how the compensatory and orienting components contributed to the OVAR response. We considered the contributing factors to the oscillatory component of the horizontal eye velocity by examining the model predictions of the compensatory IVOR, the direct orientation effects, the contribution from time constant variations of velocity storage as head position is changed with regard to gravity, and the proposed modulation of eye velocity as a function of head orientation relative to gravity to the total response. The compensatory IVOR parameters were obtained from simulations of the dynamics of the IVOR in previous studies (Raphan et al. 1996). For OVAR to the left, the model predicted a peak eye velocity modulation due to the compensatory IVOR component between right side down (RD) and nose-up position (NU) (Fig. 11A), and the gain of the response was negligible, producing eye-velocity modulations of only 0.05°/s. This was not consistent with the data of Figs. 1D, 4D, 5B, and 6B and D, which had a peak velocity for left side down and amplitudes of \( \sim 10^5 \)°/s.

We next determined the contribution of the direct orientation component (Fig. 11B). The orientation parameters were set to give a slope of 7.2°/g, which corresponded to the changes in horizontal eye orientation during slow tilts about a head roll axis (Fig. 8A). The model accurately predicted the trend in horizontal eye deviation as a function of head orientation relative to gravity (Fig. 8B). The small elliptical shape in the trajectory of the simulated response as the head was rolled from LD to RD and back to LD (Fig. 8B), represent a kinematic effect of roll eye orientation on horizontal eye rotation as the head is tilted from side to side (Raphan 1997). The kinematic effect was masked in the data of Fig. 8A by the saccades that occurred during the slow tilts about a roll axis. The same parameters predicted a peak eye velocity of the oscillating component at the nose down position, corresponding to a peak eye position at RD (Fig. 11B). This direct eye-orientation component of the response dominated the small response due to the compensatory IVOR (Fig. 11B) and fit the data in one monkey (Fig. 6D, circle in nose-down position) but not the other monkeys, which had a peak eye velocity at side down,
The phase of the peak eye velocity could also be modulated by the head position at which the time constant of velocity storage was a maximum (Fig. 11D). Time constant data from OKAN, which represents velocity storage (Cohen et al. 1977; Raphan et al. 1979), vary with head position, peaking at different orientations for different monkeys (right OKAN, M9866; Fig. 8). A vector was established in the head coordinate frame that defined the direction of the maximal horizontal time constant and was incorporated into the model. Simulations were then run for no time constant variations and for peak time constants occurring in LD, ND, RD, and NU. The bias component was generated by assuming that there was a constant input to velocity storage from sequential activation of otolith afferents by the rotating gravitational field (Raphan and Schnabolk 1988).

When the direct orientation pathway, $D_O$, was set to zero and there was no modulation of time constant of velocity storage, the phase of the peak eye velocity was at the LD position (Fig. 11Da, No TC Mod). Choosing the position of maximum time constant at nose down (Fig. 11Db, Max TC-ND), right side down (Fig. 11Dc, Max TC-RD), nose up (Fig. 11Dd, Max TC-NU), or left side down (Fig. 11De) had negligible effects on the phase of the eye velocity modulation, given the presence of velocity modulation due to orientation. The amplitude of the modulation, however, was affected. When the maximum time constant occurred at nose down (Fig. 11Db, Max TC) the amplitude of the modulation was smaller than during no time constant modulation (Fig. 11A, No TC Mod). Similarly, modulation amplitude increased when maximum time constant occurred at the nose-up position (Fig. 11Dd, Max TC – NU).

By appropriately weighting these orientation factors, the data from a wide range of monkeys could be simulated. For example, the model output overlay the data for leftward OVAR in monkey M9866 (Fig. 12, A–C), using parameters for $D_o$ obtained in Fig. 8. The model also predicted the data of monkey M9860, whose peak velocity occurred at the ND position, if the effects of velocity modulation ($K_{\text{orient}}$) were reduced and the orientation effects ($D_o$) dominated (Fig. 12, D–F). This indicates that orientation effects, which modulate horizontal eye velocity, horizontal beating field, and change the time constant of velocity storage are the key factors in modulating horizontal eye velocity during OVAR. As predicted, the compensatory IVOR has very little effect. However, if the gain of the compensatory IVOR were to be increased, such as with close viewing distance, we would predict that the phase could be shifted toward the NU position. Also, time constant variations could shift phase toward the NU position.

The model also predicted the pitch (vertical) and roll modulations using the orientation mechanism due to the cross-product (Fig. 12, B, C, E, and F). An interesting finding was obtained by differentiating the vertical eye position signal, removing the saccades and integrating the resultant vertical eye velocity signal. This extrapolated vertical position without saccades was accurately predicted by the pitch component of the model simulation, although the actual modulation of pitch eye position was larger due to saccades. This simulation indicates that while there is a direct orientation drive to control pitch, the gain is low. The orientating IVOR, therefore probably activates the saccadic system to generate improved gain of vertical orientation.

FIG. 11. Model simulation of the components contributing to the modulation in the horizontal beating field (position) and slow phase velocity during OVAR. Rotation to the left (positive) generated a negative eye velocity to the right. Simulations were done for OVAR at 30°/s about an axis tilted 90° from earth vertical. A: the contribution of the compensatory IVOR (C-IVOR) was simulated by setting contributions from all other components to 0, including the bias velocity. The phase of the C-IVOR component lead the nose up position with a small gain. Therefore it contributed little to the response. B: simulation of the horizontal eye position and velocity due to the C-IVOR and the direct orientation component. This summated component had a peak horizontal position deviation to the right in the right-side-down position (RD) and a peak rightward eye velocity at the nose down position (ND). C: addition of the velocity modulation ($K_{\text{orient}}$) shifted the peak eye velocity closer to the right-side-down position (LD). D: a–e: effects of C-IVOR + velocity modulation ($K_{\text{orient}}$) and the variation in time constant of velocity storage (if any) on the phase of eye velocity. There was no direct orientation ($D_o = 0$) in this simulation. With no modulations in velocity storage time constant (a), the phase of eye velocity occurred when left side down (LD). When the maximum time constant occurred at the nose-down (b) or nose up (d) positions, the modulation amplitude was affected, but not the phase. Time constant peaks at right-side-down (c) and left-side-down (e) positions, shifted the phase slightly toward leading and lagging the left-side-down head position, respectively.

180° out of phase with the beating field modulation (Fig. 6, B and D).

To explain the phase behavior of the other monkeys, we next considered the contribution of the mechanism that modulates eye velocity due to eye orientation ($D_o$) through the nonlinear feedback ($K_{\text{orient}}$, Eq. 4). Simulations were done with 30°/s head rotation at 90° tilt (Fig. 11C). Quick phases were generated by a resetting horizontal eye position when that component reached a threshold of 40°. The peak negative eye velocity occurred between left side down and nose down positions (Fig. 11C). This simulation indicates that for each monkey, modulation of horizontal eye velocity ($K_{\text{orient}}$) and the direct orientation pathway ($D_o$) are weighted to shift the phase between LD and ND.
orient) and the yaw component of direct orientation gain matrix ($K_{D}$, upward arrow). By adjusting the relative contributions of velocity modulation and Bodin 1966; Cohen et al. 1983; Correia and Guedry studied (Angelaki and Hess 1996a; Angelaki et al. 2000; Ben-

FIG. 12. Model fits of the data from monkeys M9866 (A–C) and M9860 (D–F) for OVAR at 30°/s about an axis tilted 90° from earth vertical. These animals were chosen because they had different orientation properties. The desaccaded vertical and roll eye position responses of both monkeys (B and C and E and F–shaded traces) had approximately the same characteristics and were well fit by the model (B and C and E and F–solid traces). The desaccaded horizontal slow phase velocities of the 2 monkeys had different phase characteristics, however. In M9866 (A), peak velocity was close to left-side-down (A, upward arrow), while M9860 (D) had a peak velocity close to nose down (D, upward arrow). By adjusting the relative contributions of velocity modulation ($K_{\text{orient}}$) and the yaw component of direct orientation gain matrix ($D_{y}$), the model closely fit both sets of data.

**D I S C U S S I O N**

This study shows that the ocular response to OVAR is composed of eye rotations in three dimensions that are generated by compensatory and orienting mechanisms of the VOR. The major compensatory component is a horizontal bias velocity, which is related to tilt of the rotation axis and the yaw axis rotation velocity. The bias velocity is linked to velocity storage in the vestibular system (Cohen et al. 1977; Raphan et al. 1979, 1981), providing a mechanism whereby input from the otoliths can combine with information from the visual system, the somatosensory system and the semicircular canals to help generate a signal related to head and body velocity in space. We have also identified orienting mechanisms, which when combined with velocity storage, characterized, and predicted the bias and oscillation components of eye position and velocity during OVAR in three dimensions.

While the compensatory bias component had been widely studied (Angelaki and Hess 1996a; Angelaki et al. 2000; Benson and Bodin 1966; Cohen et al. 1983; Correia and Guedry 1966; Dai et al. 1996; Guedry 1965; Raphan et al. 1981), it was further shown that the storage capabilities determined from the time constant of postrotatory nystagmus due to canal activation are closely related to the bias velocity produced by otolith activation of velocity storage. Differences between the normalized velocity of nystagmus to the right and left were related to the difference in the time constants of velocity storage to the two sides (Fig. 2D), and administration of a GABAergic drug, baclofen, which simultaneously shortens the time constants of OKAN and the aVOR (Cohen et al. 1987), caused a concomitant decline in the time constant of the aVOR and the bias velocity (Fig. 3). Thus when velocity storage is affected, all systems that couple to it are impacted. This supports the conclusion that velocity storage is a common link for otolith, visual, and canal activation to maintain gaze in space (Raphan and Cohen 1996, 2002).

Consistent with previous studies (Young and Henn 1975), the bias velocity for a given velocity of rotation increased monotonically with axis tilts up to ~15° (0.25 g). This implies that OVAR could be used to produce invariant compensatory eye velocities along the GIA if there were misalignments of the axis of rotation with the GIA. Such small axis tilts occur transiently during natural locomotion, producing perturbations in the GIA relative to the head yaw axis (Imai et al. 2001). The sensitivity to small tilts of the head at low frequencies of rotation is another striking aspect of the orientation properties of velocity storage, which produces compensatory horizontal eye velocity through coupling from the otoliths. While the neural mechanism for generating the response to small tilts of the axis of rotation is not known, it may be an inherent property of the neural network that estimates rotational velocity from sequential activation of otolith afferents, which then activates velocity storage (Fanelli et al. 1990; Raphan and Schnabolk 1988; Schnabolk and Raphan 1992). This orientation effect on the compensatory response is separate from the previously demonstrated orientation properties of velocity storage that tend to align eye velocity toward the spatial vertical and to modify the time constant of the velocity storage integrator (Dai et al. 1991; Raphan and Sturm 1991; Raphan et al. 1992).

An important focus of this study was to determine the mechanisms by which the IVOR orients eye position and eye velocity in three dimensions during OVAR. The pitch and roll orienting movements are in agreement with those found by others (Angelaki and Hess 1996a), and the direction of the maximum phases of the vertical and roll positions of ocular counter-pitch and counter-roll induced during OVAR were similar to those of static or low-frequency otolith-ocular reflexes (Haslwanter et al. 1992; Telford et al. 1998). The roll and pitch oscillations could be modeled by driving these components with a simple cross-product of a unit vector along the head yaw with the net GIA in head coordinates, based on the postulate that they tended to align the yaw axis of the eyes (Fig. 11, $Z_{o}$) with the GIA. This simple mechanism, which is conceptually appealing, simulated the data, obviating the need to postulate complex internal models for the relative tilt of the GIA with estimates of the gravity vector (Angelaki et al. 2000; Merfeld 1995). Because the cross-product is directly related to the sine of the angle of tilt of the head relative to the GIA, it would be closely related to the activation of the utricles, which has been postulated as a major drive of the orienting IVOR response (Paige and Seidman 1999).
Another important orienting component was identified in this study, which moves the eyes about a yaw axis and tends to align the visual axis (Fig. 1I, X) with gravity. The presence of the yaw orientation mechanisms was inferred from the close relationship of the peak phase of the beating field modulation to the side down position and by the similar sensitivity of the changes in beating field to the static horizontal tilt response of the eyes in a similar position. Thus while the measured pitch and roll eye velocities are close to simple differentiations of the slow component pitch and roll positional changes, the same relationship did not hold for the phase relationship between the horizontal position changes of the beating field and horizontal slow phase velocity. Rather than being 90° phase advanced from the positional changes as for vertical and roll velocities, horizontal slow phase velocity had orienting properties with phases that were maximal in or close to side-down positions. Thus different mechanisms must be at work in generating these responses. In the model, this yaw-orienting mechanism was represented as a cross-product of the naso-occipital axis with the GIA, projected along the yaw axis of the head. In the upright position, the cross-product of the naso-occipital axis with the GIA is along the pitch direction and the projection along the yaw axis would be zero. During OVAR at 90° tilt, the cross-product of the naso-occipital axis with the GIA is along the yaw direction and would produce maximal horizontal orientation shifts. For tilts of the rotation axis other than 90°, the cross-product would have pitch as well as yaw components. The projection of the vector associated with the cross-product of the naso-occipital axis with the GIA onto the yaw axis ensures that this signal will only drive horizontal eye position. Such cross-product and projection operators are easily realized by a neural network using linear combinations of neural activity from units with the wide range of polarization vectors and could be realized in the vestibular nuclei (Raphan et al. 1996).

One interesting aspect of this horizontal orientation component is that it drives the eyes in the opposite direction to that of the yaw eye deviations produced by OVAR in rats (Hess and Dieringer 1990) and rabbits (Cohen et al. 2001; Maruta et al. 2001). This indicates that otolith-driven, horizontal eye orientation, which is an important part of the orienting IVOR, is implemented differently in lateral and frontal-eyed animals.

Together, the yaw and roll-pitch orientation mechanisms form a single three-dimensional orientation command for eye position (y_{0}). While the inclusion of this three-dimensional orienting command explained the amplitudes and phases of the roll, pitch, and beating field modulations during OVAR, it explained the dominant phase of the horizontal eye velocity modulations in only one monkey. To encompass the wider range of phase characteristics, it was necessary to postulate a velocity modulating mechanism that increased horizontal eye velocity when eye position was directed toward the quick phase side and reduced eye velocity when on the slow phase side. Although the behavior of this orientation-dependent velocity is similar to velocity behavior predicted by Alexander’s law, the two are not equivalent. Alexander’s law is primarily a consequence of large eye deviations or when the velocity position integrator becomes “leaky” (Robinson et al. 1984), which did not occur in this study. Interestingly, the simulated phase showed the peak eye velocity occurring at side down to nose down positions in every simulation that incorporated the effects of eye velocity modulation as a function of head positions (maximum at side down) and the orientation effects on beating field (maximum at nose down). By weighting these two components appropriately, the data of monkeys with wide variation in peak eye velocity could be simulated (Fig. 11). Thus this orienting component of the IVOR not only helps align the eyes so that gaze is directed along the visual horizon for pitch and roll tilts but also orientates the gaze direction (visual axis) about the yaw axis so that it tends to align with gravity and modulates the eye velocity command coming from velocity storage. The direct orientation mechanisms are consistent with the synaptic connections from the otoliths to vestibular neurons and oculomotor neurons, including the direct monosynaptic pathways to the motor nuclei (Kushiro et al. 2000; Uchino et al. 1997a,b, Uchino et al. 1999; Zakir et al. 2000).

The velocity modulating orienting mechanisms are more complex and may be related to otolith activation of the vestibular nuclei through vestibulocerebellar neurons in the nodulus and uvula (Ono et al. 2000).

Another orienting component that was considered in this study was the alignment of velocity storage to the spatial vertical by modifying the time constants of roll, pitch, and yaw storage in accordance with changes in position of the head (Dai et al. 1991; Raphan and Sturm 1991; Raphan et al. 1992). By systematically observing the time constant of the OKAN in different head orientations in the yaw plane, it was shown that there were three- to fourfold differences in time constant between the maximum and minimum. Because OKAN is a direct representation of the state of the velocity-storage integrator (Cohen et al. 1977; Raphan et al. 1979), we questioned whether the orientation properties obtained from OKAN could predict the phase of the oscillation component of horizontal eye velocity during OVAR. The simulations indicated that while time-constant variations could modulate the position at which the peak eye velocity occurred, they could not systematically explain the data across all monkeys because many had little or no modulation. Thus the model simulations indicate that while time constant variations do not determine the dominant phase of the modulations in eye velocity, they contribute to varying the phase of the peak eye velocity about the head position determined by IVOR orienting mechanisms. This does not negate the crucial role played by velocity storage in generating the bias velocity during OVAR and the associated orientation of eye velocity toward the spatial vertical at zero or very low frequencies. We also considered whether Vergence could have been responsible for the phase behavior of horizontal eye velocity during OVAR (Dai et al. 1996). Binocular recordings, however, showed that the amplitude of the modulation in vergence was too small to significantly affect the horizontal phases and vergence was not modeled.

When velocity estimation from otoliths activating velocity storage (Raphan and Schnabolk 1988), the compensatory IVOR (Raphan et al. 1996), and each of the orienting components was incorporated into the model, it was possible to simulate the experimental data from animals with very different oscillation characteristics and infer the relative importance of the neural mechanisms that govern orientation and compensation in three dimensions. It had previously been assumed that the horizontal modulations produced by OVAR were produced by the compensatory IVOR, similar to the compensatory horizontal eye movements generated by sinusoidal acceleration along the interaural axis on a linear sled (Angelaki and Hess 2001).
In experiments using sinusoidal oscillation on a linear sled, however, eye velocities were only generated at higher frequencies (>0.5 Hz) through the compensatory IVOR (Paige and Tomko 1991). Because this frequency limitation also applies to OVAR, the maximum horizontal velocity would appear close to or somewhat leading the nose-up position, i.e., 90° phase lagging the gravitational acceleration along the interaural axis, and the gains would be very small. The data were not consistent with this postulate, however. Peak eye velocity occurred close to left-side-down for leftward rotation and right-side-down for rightward rotation and the gains were larger. There was also a close-to-180° phase lag observed in the data between peak eye position (beating field) modulation and peak eye velocity that could not be explained by the compensatory IVOR. Simulations of the oscillation component of the horizontal eye velocity supported the contention that the compensatory IVOR makes little contribution to the overall response. Rather, the simulation showed that the wide range of ocular responses is related to the different weightings of the orienting components observed during OVAR were considered. As shown in Figs. 4 and 5, vertical eye orientation was augmented by saccades during OVAR. These saccades were recruited by the otolith system under dynamic conditions to produce changes in pitch eye position and were not reflected in slow phase eye velocity. Similar vertical position changes are not elicited during static tilt (Haslwanter et al. 2000; Maruta et al. 2001) and are probably related to the dynamics of head reorientation with respect to gravity. The central mechanism that couples the otoliths to the system producing vertical saccades is not known but is related to the velocity at which the gravity vector rotated about the head and was not due to the magnitude of the vector. Roll eye orientation was also augmented by backward saccades (nystagmus) and by forward saccades, but these rapid eye movements were not as prominent as for pitch. Thus the model will have to be extended to incorporate these effects when more is known about otolith control of the saccadic system.

In summary, we have shown that OVAR activates important orientation mechanisms associated with the IVOR. The orienting component of the IVOR, which is known to orient the eyes about pitch and roll axes, also has a yaw component in frontal-eyed primates. This horizontal eye orientation and its associated eye-velocity command modulations are critical factors in determining the phase of the oscillating component of horizontal eye velocity during OVAR. The data further show that there are orientation properties that determine the effects of small tilts on the bias velocity. These characteristics could also play a significant role in producing and modulating eye velocity during natural movements that entail slow angular rotations.

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EYE MOVEMENTS DURING OFF-VERTICAL AXIS ROTATION


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