Published in final edited form as:

Exp Brain Res. 2011 August ; 213(1): 141–152. doi:10.1007/s00221-011-2785-x.

Head position modulates optokinetic nystagmus

V. E. Pettorossi,

Department of Internal Medicine, Section of Human Physiology, Via del Giochetto, 06126 Perugia, Italy

A. Ferraresi,

Department of Internal Medicine, Section of Human Physiology, Via del Giochetto, 06126 Perugia, Italy

F. M. Botti,

Department of Internal Medicine, Section of Human Physiology, Via del Giochetto, 06126 Perugia, Italy

R. Panichi, and

Department of Internal Medicine, Section of Human Physiology, Via del Giochetto, 06126 Perugia, Italy

N. H. Barmack

Department of Physiology and Pharmacology, Oregon Health and Science University, Portland, OR, USA

V. E. Pettorossi: vitopett@unipg.it

Abstract

Orientation and movement relies on both visual and vestibular information mapped in separate coordinate systems. Here, we examine how coordinate systems interact to guide eye movements of rabbits. We exposed rabbits to continuous horizontal optokinetic stimulation (HOKS) at 5°/s to evoke horizontal eye movements, while they were statically or dynamically roll-tilted about the longitudinal axis. During monocular or binocular HOKS, when the rabbit was roll-tilted 30° onto the side of the eye stimulated in the posterior → anterior (P → A) direction, slow phase eye velocity (SPEV) increased by 3.5–5°/s. When the rabbit was roll-tilted 30° onto the side of the eye stimulated in the A → P direction, SPEV decreased to ~2.5°/s. We also tested the effect of roll-tilt after prolonged optokinetic stimulation had induced a negative optokinetic afternystagmus (OKAN II). In this condition, the SPEV occurred in the dark, “open loop.” Modulation of SPEV of OKAN II depended on the direction of the nystagmus and was consistent with that observed during “closed loop” HOKS. Dynamic roll-tilt influenced SPEV evoked by HOKS in a similar way. The amplitude and the phase of SPEV depended on the frequency of vestibular oscillation and on HOKS velocity. We conclude that the change in the linear acceleration of the gravity vector with respect to the head during roll-tilt modulates the gain of SPEV depending on its direction. This modulation improves gaze stability at different image retinal slip velocities caused by head roll-tilt during centric or eccentric head movement.

Keywords

Optokinetic reflex; Gravity; Gaze stability; Head tilt

Introduction

Spatial orientation requires frequent revisions of spatial coordinate information to guide movement. An earth-centric coordinate system is imposed by the linear acceleration of gravity. A head-centric coordinate system is imposed by the anatomical configuration of our vestibular and visual systems. We must choose how to extract information from these coordinate systems that includes linear acceleration, angular acceleration, vision, and proprioceptive information to optimally guide movement.

Dynamic and static otolithic signals influence both eye movements and other postural responses. During head roll and pitch, the influence of the linear acceleration of gravity changes with respect to polarized otolithic hair cells (Fernandez et al. 1972; Loe et al. 1973). This otolithic signal combines with a signal generated by head angular acceleration, detected by semicircular canals. These combined signals induce both vertical and torsional vestibulo-ocular reflexes (Barmack 1981; Van der Steen and Collewyn 1984; Pettorossi et al. 1991, 1997; Angelaki and Hess 1994; Maruta et al. 2006, 2008; Yakushin et al. 2009).

In addition to guiding reflexive eye movements, the combined signals modulate centrally stored eye movements such as post-rotatory vestibular nystagmus (PRN; Guedry 1965; Benson 1974; Harris 1987; Harris and Barnes 1987; Minor and Goldberg 1990; Fetter et al. 1996; Merfeld et al. 1993; Angelaki and Hess 1995; Wearne et al. 1998; Clément 2003), positive optokinetic afternystagmus (OKAN I) (Raphan and Cohen 1988; Waespe and Henn 1978; Dai et al. 1991), and negative optokinetic afternystagmus (OKAN II) (Maioli 1988; Pettorossi et al. 1999). The rotational axes of OKN, PRN, OKAN I, and OKAN II change when the head changes its orientation with respect to gravity (Dai et al. 1991; Merfeld et al. 1993; Gizzi et al. 1994; Angelaki and Hess 1995; Wearne et al. 1998; Kitama et al. 2004). Functionally, this reorientation of nystagmus during sustained head deviations from an upright position prolongs horizontal eye movements in space (Solomon and Cohen 1992).

The space constancy of the reoriented eye movement is also accompanied by changes in slow phase eye velocity (SPEV) within the orbit. Besides the alignment of eye rotation axis with gravity, there is also a reduction in SPEV termed “velocity dumping.” The functional significance of “velocity dumping” is unclear. It may minimize the sensory conflict between semicircular canal and otolith signals during roll-tilt (Guedry 1965). Alternatively, it may be a consequence of nystagmus reorientation (Angelaki and Hess 1994). “Velocity dumping” can be altered without affecting nystagmus reorientation in nodulectomized rabbits (Barmack et al. 2002) and monkeys (Wearne et al. 1998). Consequently, spatiotemporal transformation may not require “velocity dumping,” at least for optokinetically evoked eye movements.

Post-rotatory nystagmus (PRN) and optokinetic afternystagmus (OKAN) are remarkably influenced by gravity independently of reorientation. SPEV is attenuated when the head assumes a different position in space with respect to a previously learned reference position (Pettorossi et al. 1999). For example, a long-lasting OKAN is induced by optokinetic stimulation, OKAN II, during which SPEV occurs in the opposite direction of the optokinetic stimulus used to evoke it (Pettorossi et al. 1999). OKAN II attains maximal velocity when the head is maintained in the position it held during horizontal optokinetic stimulation (HOKS). When the head is subsequently roll-tilted from this primary position, the velocity of OKAN II is attenuated. These data indicate that the head position at which maximal velocity OKAN II occurs is essentially learned. Similar effects have been observed in humans and monkeys during head roll-tilt following eccentric rotation-induced decreases in post-rotatory nystagmus and optokinetic afternystagmus (Schrader et al. 1985; Wearne et al. 1999; Curthoys et al. 1992; Holly et al. 2008).

Space constancy and SPEV may be differentially influenced by conditions of visual feedback. Consequently, it is important to compare the orientation of eye movements evoked under closed and open loop conditions. Theoretically, eye movements evoked by HOKS could adapt to changes in head position and thereby minimize changes in SPEV. However, it is also possible that vestibularly induced changes in SPEV persist even during closed loop HOKS (Dai et al. 1991; Gizzi et al. 1994; Kitama et al. 2004). Here, we analyze the effects of roll-tilt on eye movements evoked by HOKS under both closed and open loop conditions. Closed loop conditions were created when eye movements were driven directly by HOKS. Open loop conditions prevailed when eye movements occurred during OKAN II after HOKS was stopped and the rabbit was placed in the dark.

Methods

Subjects and surgical preparation

Experiments were carried out in 10 intact, experimentally naive pigmented rabbits weighing 2.5–3.5 kg. The procedures were in accordance with the regulations of the Italian Animal Welfare Act and were approved by Bioethic Committee of the University of Perugia. The animals were prepared initially under general anesthesia (tiletamine/zolazepam combination, 20 mg/kg). A small dental acrylic socket was fixed to the skull so that when the socket was coupled to a restraining apparatus, the head was positioned with the nose pointed down at an angle of 12°. This angle aligned the horizontal canals with the horizon and corresponds approximately to the natural head angle maintained by rabbits (Barmack and Nelson 1987; Soodak and Simpson 1988).

Eye movement recording

Eye movements were measured in 2D by an infrared light projection technique (Barmack and Nelson 1987). A miniature suction cup (diameter 5 mm, weight = 135 mg) bearing an infrared light-emitting diode (LED) was attached to the right eye after the eye was topically anesthetized with oxybuprocaine 0.4%. The axis of the light emitted from the LED was aligned with the visual axis (Fig. 1a). The narrow beam of infrared light was detected by a photosensitive x–y position detector (SC-50, United Detector Technology, Hawthorne, CA, USA) fixed relative to the head. The circular photosensitive x–y position detector had a diameter of 50 mm and gave a continuous x–y voltage proportional to the position of the incident centroid of infrared light. The system had a sensitivity of 0.2 min of arc and was linear to within 5% for eye deviations of $\pm 15^\circ$ and to 8% for deviations of $\pm 30^\circ$. Data were digitized with a sampling frequency of 100 Hz and stored on a hard disk for subsequent analysis.

In three rabbits, eye movements were recorded with the photosensitive x–y position detector to evaluate torsional as well as horizontal and vertical eye movements (Fig. 1b). For 3D recording, we mounted two LEDs on a single suction contact lens. We determined eye torsion by trigonometrically computing the relative angle of the two centroids of light alternately projected by the LEDs onto the photo-detector. 3D recordings were expressed as rotation vectors and afterwards decomposed in an orthogonal coordinate system. Since torsional components of eye movements were negligible (less than 0.2° for 10° of horizontal displacement), we concentrated on the x–y components of the eye movements. These could be conveniently recorded with only a single LED.

The eye movement recording system was calibrated by moving the LEDs on a model of the rabbit eye through a known angular displacement. The accuracy of the measurement was the same as that reported for vertical and horizontal eye movements above (Barmack et al. 2002).

Since the infrared light projection technique occludes the recorded eye, in three experiments, we used an IR video camera (MC1302, Mikrotron, Unterschleissheim, Germany) during binocular HOKS (Maruta et al. 2006; Fig. 1c). The camera was fixed in space above the rabbit. A small plastic stalk (1 mm diameter; length, 5 mm) was glued perpendicular to the topically anesthetized corneal limbus (Histoacryl[®], Aesculap AG, Tuttlingen, Germany; oxibuprocaine 0.4%). The tip of the stalk reflected the infrared light projected by an IR LED, concentric with the camera lens. We used customized image acquisition software (LabView, National Instruments, Austin, TX, USA) to measure horizontal eye rotation. Image resolution was 320×240 pixels, and images were sampled at 200 frames/s. This technique allowed us to measure only horizontal eye movements that remained horizontal in space during dynamic head tilt. The movement of the reflecting tip accurately reproduced the horizontal eye displacement and moved in circle on the camera sensor. This circular movement in degrees of displacement was corrected trigonometrically to obtain the correct horizontal angle of the eye in space. When eye movements were recorded in static head roll-tilt, vertical gaze compensation had a gain less than 1. In this case, the video camera was tilted to maintain the plane of the tip movement parallel to the surface of the video camera sensor. This video recording method was validated by using a model of rabbit eye and calibrated by known angular displacement.

Optokinetic stimulation

Recording sessions began 1 week after the preparatory surgical operation. Each session lasted 30–60 min. The body of the rabbit was restrained, and the head was secured to a rigid restraining bar at the center of a servo-controlled rate table placed inside a servo-controlled optokinetic drum (diameter, 1.2 m; height, 1.2 m). The interior wall of the drum was painted with a contour-rich pattern. Rabbits were exposed to HOKS over a range of constant velocities, 0.5–12.5°/s, in the Postero-Anterior (P → A) or Antero-Posterior (A → P) directions with respect to the left eye.

Combined vestibular and HOKS

During HOKS, rabbits were roll-tilted about the longitudinal axis over a range of $\pm 30^\circ$, in steps of 10° (static roll-tilt) or sinusoidally oscillated about the longitudinal axis ($\pm 20^\circ$, 0.02–0.10 Hz) (dynamic roll-tilt).

The possible contribution of retinal optic flow to changes in eye position with respect to the visual field was tested in three rabbits. They were maintained in a static, prone position while the optokinetic drum was rotated. The same animals were also roll-tilted while the optokinetic drum was roll-tilted an equal amount, thereby maintaining a constant distance between the viewing eye and drum wall.

Induction of optokinetic afternystagmus (OKAN II)

A subgroup of four rabbits received binocular HOKS at 5°/s for 24–48 h, evoking a type II optokinetic afternystagmus (OKAN II; Barmack and Nelson 1987). During HOKS, the head of the rabbit was fixed to the restrainer by a spring-loaded flexible coupling. This device prevented lateral head displacement and permitted only small sagittal movements, so that the imposed head position was maintained during HOKS. The rabbits were able to maintain their normal posture with all four paws in contact with the support surface. EKG and respiratory rate were monitored and remained within the normal range. Every 8 h, rabbits were removed from the apparatus for 30 min and given food and water. This feeding regimen was sufficient to maintain body weight. Rabbits easily adapted to the restraint and showed no reluctance to resubmit to restraint after the brief feeding intervals. When HOKS was stopped, the rabbits were placed in the dark and the spatial orientation of the OKAN II was studied during roll-tilt at different static angles ($0 \pm 60^\circ$) about the longitudinal axis.

Data analysis

Space constancy for HOKS- and vestibularly evoked eye movements was established using a two LED technique for recording horizontal, vertical, and torsional eye movements. Eye position was expressed as a rotation vector $E = \tan(\rho/2) u$ (u = unity vector and ρ = angle of rotation about u) (Haustein 1989) in a standard head-fixed reference system. 2D recordings were used to evaluate the influence of head position on nystagmus velocity, since the torsional velocity component was, in fact, negligible.

The 0° position of head in the pitch and roll planes was achieved when both horizontal semicircular canals were aligned with the horizontal plane (head pitched 12° nose down). The components of eye position measurements were linearized and differentiated using Savitzky and Golay smoothing method (Savitzky and Golay 1964) to obtain coordinate velocity. Eye velocity was defined as horizontal angular velocity in head coordinate system. Angular eye velocity vector Ω was calculated ($\Omega = 2/(dE/dt + ExdE/dt)/(1 + |E|^2)$). The derivative was taken by averaging the slopes of two adjacent position data points (100 points/s) of the horizontal and vertical components. Average horizontal and vertical slow phase eye velocities were computed from multiple inter-saccadic samples taken at 10-ms intervals. Slow phase eye movements were isolated from quick phases by removing quick phases and substituting an interpolated mean slow phase.

SPEV was measured during static and dynamic roll-tilt. During dynamic roll-tilt, the phase of SPEV modulation with respect to the table movement was calculated and fitted by a sine function or a double-peak Gaussian function or an exponential decay.

Statistical evaluation

The responses were statistically treated with a “mixed model” analysis in which changes in amplitude and phase of slow phase eye velocity (SPEV) are dependent variables. *Post hoc* analyses were performed using the Tukey test to compare single different experimental conditions. The level of significance was established at a $P \leq 0.05$. Goodness of fit was established by χ^2 for a sine function, double-peak Gaussian function, and by a correlation coefficient (R) for exponential decay. The fit was obtained by minimizing the mean square error (Levenberg–Marquardt algorithm).

Results

SPEV during HOKS depends on static roll-tilt

In ten rabbits, monocular HOKS (5°/s) was delivered in the P → A direction with respect to the left eye. Eye movements were recorded from right eye. Mean SPEV was $3.4 \pm 0.4^\circ/\text{s}$ when the rabbit was maintained in a prone position. The velocity increased to $5 \pm 0.6^\circ/\text{s}$ when the head was statically roll-tilted 30° onto the left side and decreased to $2.5 \pm 0.7^\circ/\text{s}$ when the rabbit was roll-tilted 30° onto the right side ($P < 0.05$, two tailed, Tukey test) (Figs. 2, 3a). Simultaneous recording of vertical eye movements showed normal vertical compensation during static roll-tilt. Vertical gain ranged from 0.75 to 1. In three animals, we measured torsional eye movements during HOKS. Torsional displacement was less than 0.2° for each 10° of horizontal eye displacement over a range of $\pm 30^\circ$ of static roll-tilts. The torsional component was also minimal with respect to the relatively high gain of the vertical vestibulo-ocular reflex during roll-tilt.

During an extended range of roll-tilt ($\pm 30^\circ$), the rotation axis of eye movements evoked by HOKS remained aligned with the gravity vector. The change in SPEV was linearly related to roll-tilt by $\sim 0.04^\circ/\text{s}$ for each 1° of roll-tilt (Fig. 3a). The rise time of the horizontal eye movements at the onset of HOKS was 3.07 ± 0.49 s at a head roll-tilt angle = 0°. It

decreased to a value of 2.16 ± 0.51 s at 30° roll-tilt to the right and increased to 4.77 ± 0.37 s during roll-tilt to the left ($P < 0.05$, two tailed, Tukey test) (Fig. 2).

Monocular HOKS of the right eye in the $P \rightarrow A$ direction at $5^\circ/\text{s}$ evoked SPEV from the left eye that increased when the head was roll-tilted by 30° onto the right side ($4.9 \pm 0.3^\circ/\text{s}$) and decreased when the head was roll-tilted by 30° onto the left side ($2.1 \pm 0.6^\circ/\text{s}$; $P < 0.05$, two tailed, Tukey test; Fig. 3a).

Only lower stimulus velocities during monocular HOKS in the $A \rightarrow P$ direction were effective in evoking horizontal eye movements with gains comparable to those of monocular stimulation in the $P \rightarrow A$ direction (Erickson and Barmack 1980). Accordingly, we restricted the velocity of HOKS in the $A \rightarrow P$ direction to $0.5^\circ/\text{s}$ to induce a consistent optokinetic responses. During monocular HOKS of the left eye in the $A \rightarrow P$ direction, SPEV was modulated by the head roll-tilt. SPEV increased during roll-tilt onto the right side from $0.25 \pm 0.2^\circ/\text{s}$ to $0.35 \pm 0.3^\circ/\text{s}$. SPEV decreased during roll-tilt onto the left side to $0.10 \pm 0.08^\circ/\text{s}$ ($P < 0.05$, two tailed, Tukey test). In sum, roll-tilt modulation of SPEV was enhanced when the rabbit was roll-tilted onto the side in which the eye moved in the $P \rightarrow A$ direction.

Since our main observations concerning the effect of head roll-tilt on SPEV were obtained using a method of eye movement recording that obscures vision of the recorded eye, we examined whether unobscured binocular vision would lead to a different result. It did not. Binocular HOKS confirmed the results obtained with monocular HOKS. During HOKS in the $P \rightarrow A$ direction with respect to the left eye, SPEV increased during roll-tilt onto the left side and decreased during roll-tilt onto the right side. Modulation of SPEV was $\sim 0.04^\circ/\text{s}$ for each 1° of roll-tilt over the range of $\pm 30^\circ$ and was not significantly different from that observed during monocular HOKS (Fig. 3a).

Drum rotation axis tilt does not modulate horizontal SPEV evoked by HOKS

Change in optic flow caused by roll-tilt of the rabbit with respect to the walls of the optokinetic drum could possibly account for the modulated SPEV evoked by HOKS. Consequently, we examined the effect of tilting the optokinetic drum alone and together when the rabbit was roll-tilted during HOKS in three rabbits. When the rabbit's head remained in the prone position and only the drum was tilted, the velocity of SPEV did not change ($P > 0.05$, two tailed, Tukey test; Fig. 3b). When both head and drum were equally roll-tilted, SPEV modulation was comparable to that evoked by HOKS when the head alone was roll-tilted ($0.04^\circ/\text{s}$ for 1° of roll-tilt; $P > 0.05$, two tailed, Tukey test; Fig. 3b).

OKAN II during tonic head tilt

The experiments above tested the effects of static roll-tilt on SPEV evoked by HOKS in a closed loop paradigm. We also investigated the effects of static roll-tilt on SPEV that were induced initially by HOKS, but persisted in its absence, creating a constant velocity nystagmus that persisted in the dark under "open loop" conditions. We induced long-lasting negative optokinetic afternystagmus (OKAN II) by exposing rabbits to 24 h of binocular HOKS at $5^\circ/\text{s}$ in the $P \rightarrow A$ direction with respect to the left eye. When HOKS stopped, rabbits developed a steady-state nystagmus during which OKAN II developed with the SPEV of the left eye in the $A \rightarrow P$ direction. This OKAN II lasted several hours and SPEV reached velocities of $15\text{--}50^\circ/\text{s}$.

During OKAN II, SPEV was modulated by roll-tilt similarly to the SPEV evoked under closed loop conditions. It increased when the rabbit was roll-tilted onto the side in which the SPEV was in the $P \rightarrow A$ direction and decreased when the rabbit was roll-tilted onto the side in which the SPEV was in the $A \rightarrow P$ direction. In other words, the direction of roll-tilt that

increased SPEV depended on the direction of the SPEV rather than on the direction of long-term HOKS. The amplitude of SPEV modulation was similar to that observed during closed loop HOKS. The amplitude and phase of the modulated SPEV under open and close condition were similar ($P > 0.05$, two tailed, Tukey test). During open loop testing, it was possible to extend the range of roll-tilt investigated without the constraint of also tilting the optokinetic drum. Roll-tilt beyond 30° was ineffective in modulating SPEV (Fig. 3c). In sum, SPEV of OKAN II was enhanced when the rabbit was roll-tilted on the side in which the eye was moving in the $P \rightarrow A$ direction even if during the previous 48 h of long-term HOKS the eye had been moving in the $A \rightarrow P$ direction.

HOKS-evoked SPEV during dynamic roll-tilt

In separate experiments, we measured SPEV during binocular or monocular HOKS in ten rabbits in response to dynamic roll-tilt ($\pm 20^\circ$, 0.05 Hz). We measured SPEV with a light projection technique that partially obscured vision of the right eye while rabbits received monocular HOKS of $5^\circ/\text{s}$ in the $P \rightarrow A$ direction with respect to the left eye. During sinusoidal roll-tilt, the SPEV increased from a steady-state value of $3.2 \pm 0.3^\circ/\text{s}$ to a peak of $5.6 \pm 0.3^\circ/\text{s}$ when the rabbit was tilted onto its left side. When the rabbit was roll-tilted onto its right side, SPEV decreased to $1.4 \pm 0.2^\circ/\text{s}$. Both the increase and the decrease in SPEV reached at the peak of roll-tilt were significantly different compared with the baseline value ($P < 0.05$, two tailed, Tukey test; Fig. 4a, b). SPEV modulation in response to sinusoidal roll-tilt was symmetric in four rabbits and asymmetric in 6 rabbits. For rabbits with symmetric responses, the peaks of velocity increases and decreases led table position by $32 \pm 5^\circ$, while rabbits with asymmetric responses the peak of velocity increase led table position by $43 \pm 6^\circ$, and the peak of velocity decrease was $0 \pm 3^\circ$ (Fig. 4b).

In all rabbits, compensatory vertical eye movements had a gain (eye velocity/stimulus velocity) of 0.90 ± 0.05 . In three experiments, torsional eye movements were also recorded. We found no significant torsional eye responses during sinusoidal roll-tilt.

Horizontal SPEV was modulated by sinusoidal roll-tilt during monocular HOKS of the left eye in the $A \rightarrow P$ direction at $0.5^\circ/\text{s}$. SPEV increased from $2.5 \pm 0.2^\circ/\text{s}$ to $3.5 \pm 0.3^\circ/\text{s}$ during roll-tilt to the right and decreased to $1 \pm 0.2^\circ/\text{s}$ during tilt-roll to the left. Changes in SPEV were asymmetric. The phase lead for increasing SPEV was $5.00 \pm 9^\circ/\text{s}$. The phase lead for decreasing SPEV was $20.0 \pm 7^\circ/\text{s}$ (Fig. 4c).

Horizontal SPEV increased during binocular HOKS at $5^\circ/\text{s}$ in the $P \rightarrow A$ direction with respect to the left eye when the rabbit was roll-tilted sinusoidally onto its left side ($\pm 20^\circ$, 0.05 Hz) and decreased when roll-tilted onto its right side (Fig. 4d, e). The amplitude of SPEV modulation ranged from a peak of $5.4 \pm 0.6^\circ$ to a minimum of $1.7 \pm 0.3^\circ$. The phase leads of SPEV increases and decreases were symmetrical and had a value of $23 \pm 5^\circ$. Both amplitude and phase of SPEV modulations were variable. In fact, the phase lead of SPEV modulation in response to roll-tilt at 0.02 Hz increased during increases in HOKS velocity, ranging from $\sim 0^\circ$ for HOKS velocity of $5^\circ/\text{s}$ to a phase lag of $\sim 90^\circ$ for HOKS velocity of $12.5^\circ/\text{s}$ (Fig. 5). SPEV modulation increased from ~ 30 to $\sim 80\%$ ($\text{SPEV}_{\text{max}} - \text{SPEV}_{\text{min}} / \text{SPEV at } 0^\circ \text{ tilt} \times 100$) when the velocity of HOKS increased from 5 to $12.5^\circ/\text{s}$. Roll-tilt frequency also modulated the amplitude and phase of SPEV. At the lowest tested frequency (0.02 Hz), the phase of SPEV was $\sim 0^\circ$. At higher frequencies, the phase of the SPEV led the roll-tilt sinusoid by $\sim 60^\circ$ at 0.1 Hz. The modulation amplitude increased from ~ 35 to $\sim 60\%$ (Fig. 5).

Discussion

Compensatory eye responses are induced by mix of angular and linear accelerations that activate semicircular canal ampullae and otolith maculae. These vestibular stimuli interact with a retinal image slip signal to achieve gaze and postural stability. However, the after-effects of vestibular and visual stimulation, PRN and OKAN, show a significant change in SPEV in response to roll or tilt. This modulation of SPEV observed along the axis of stimulation has been attributed to spatial reorientation of afternystagmus (Angelaki and Hess 1995) or to sensory conflict during the post-stimulation period (Guedry 1965). It appears that SPEV remained almost aligned with the horizon during head roll-tilt.

Conversely, we found that the absolute value of SPEV was modulated by roll-tilt during HOKS. This suggests that SPEV is influenced by gravity as well as retinal image slip. In fact, the SPEV evoked by HOKS had higher gain, reaching a value of ~ 1.0 when the head was roll-tilted toward the side in which the nystagmus was in the $P \rightarrow A$ direction. The gain of the SPEV decreased during roll-tilt in the opposite direction. This effect on the velocity of SPEV was observed during both static and dynamic head tilt. It was accompanied by a reorientation of nystagmus since its rotational axis remained aligned with gravity within the range of tested roll-tilt angles.

The space constancy of SPEV could be partially attributed to the continuous HOKS and to velocity storage reorientation. Consequently, SPEV remained constantly aligned with the optokinetic stimulus. In spite of the presence of HOKS, that might override velocity dumping during roll-tilt, SPEV was modulated.

We attribute modulation of SPEV to the change in the orientation of the head with respect to the linear acceleration of gravity, not to a change in the retinal stimulation. Combined vestibulo-ocular and optokinetic reflexes assure vertical gaze stability during head roll without evoking quick phases. Optic flow changes are minimal. However, when the gain of the vertical reflex is <1 , optic flow to the retina varies.

Previous descriptions of coordinate systems that contribute to eye movement have emphasized the congruence of optokinetic signals conveyed from the accessory optic system, with vestibular signals conveyed from the semicircular canals (Simpson and Soodak 1984). These coordinate systems appear to align with the pulling angles of extraocular muscles (Simpson and Graaf 1981). Our data suggest that an otolithic signal takes precedence over a coordinate system based upon the orientation of the semicircular canals in regulating the gain and orientation of SPEV.

To exclude any possible influence of HOKS on modulation of SPEV, the vertical rotation axis of drum was tilted, both with and without head tilt. In both cases, the optic flow to the retina changed, but not sufficiently to change modulation of SPEV within the range of $\pm 30^\circ$ of roll-tilt. Slight changes in the relative angle of HOKS during roll-tilt did not modulate SPEV. We conclude that the modulation of SPEV during roll-tilt can be attributed exclusively to the influence of gravity.

The effect of gravity depends on direction of SPEV

SPEV modulation depended on the direction of the SPEV. Increased SPEV was always observed when the rabbit was roll-tilted onto the side in which the SPEV was in the $P \rightarrow A$ direction, even when HOKS was delivered in the $A \rightarrow P$ direction during long-term HOKS to evoke OKAN II under in open loop conditions.

Analysis of the effect on optokinetic reflexes during dynamic head tilt

Dynamic roll-tilt, monocular, and binocular HOKS, SPEV in the $P \rightarrow A$ direction of the recorded eye always increased during, and SPEV in the $A \rightarrow P$ direction always decreased. Binocular HOKS evoked almost symmetric responses during sinusoidal roll-tilt. During monocular HOKS the phase of SPEV became asymmetric. SPEV led the stimulus sinusoid when the eye moved in the $P \rightarrow A$ direction by more than it when the head roll-tilt sinusoid reduced the velocity of SPEV moving in the $A \rightarrow P$ direction. During binocular HOKS, the asymmetric phase differences evoked by $A \rightarrow P$ stimulation of one eye and $P \rightarrow A$ stimulation of the other, mutually cancelled. In general the amplitude of SPEV modulation during binocular or monocular HOKS was greater than 50% and the phase always led roll-tilt position.

Locus of vestibular influence on gain of HOKS-evoked SPEV

A subset of neurons in the vestibular complex may be the locus of the interaction. The medial, descending and lateral vestibular nuclei receive monosynaptic otolithic signals from the ipsilateral utricle (Kubo et al. 1977; Zhang et al. 2001). A subset of these neurons is also responsive to HOKS (Boyle et al. 1985).

Horizontal rotation evokes increased activity in semicircular canal afferents, excites secondary vestibular neurons and evokes $P \rightarrow A$ movement of the ipsilateral eye. Ipsilateral roll-tilt evokes increased activity in the predominantly medio-laterally polarized utricular hair cells and excites secondary vestibular neurons. This otolith-modulated signal is synergistic with the optokinetic signal to the same subset of vestibular neurons. Consequently it could increase the gain of the SPEV driven by these neurons. This vestibular-visual interaction may be complemented by cerebellar projections onto the vestibular complex. However, the interaction persists in cerebellectomized animals (Keller and Precht 1978).

Comparison of present finding with previous observations

Previous studies emphasized the orientation of gravito-inertial acceleration (GIA) in roll plane as an influence on vestibulo-ocular responses (Curthoys et al. 1992; Wearne et al. 1999). However, this view is not consistent with our findings. Eccentric rotation of humans evokes increased gain of the VOR when the humans face changes in motion orientation as opposed to when they reversed their orientation and faced away from the increased motion. This suggests that in forward eccentric movement, the external inclination of GIA would potentiate the vestibulo-ocular reflex (Curthoys et al. 1992). Given this observation, one would expect that during centric rotation, head tilting in the opposite direction should inhibit the VOR. However, this was contrary to what we observed in the rabbit. Conversely, in monkeys, a longer time constant of vestibular decay was observed during the back to motion condition (Wearne et al. 1999). This partially fits the direction of the effect of head tilt of rabbit in centric rotation, but the peak of velocity was observed in centered rotation. Instead, in rabbit there was a progressive change of optokinetic gain from one side to the other side of the roll-tilt. The difference of our results with those from both human and monkey studies may be due to the stimulus (eccentric and centric rotation) or differences in the examined reflexes (VOR and OKR).

Functional role of roll-tilt modulation of SPEV

Continuous modulation of SPEV during head roll-tilt observed in the rabbit seems to exclude that the effect of head tilt is just a curiosity of the otolithic and optokinetic responses. Rather it may indicate a functional role of the head tilt during rotation. Head tilt toward the side where the head is rotating is a common head postural attitude during

eccentric rotation. It depends on the velocity or acceleration of movement. During rotation, the head tilts toward the internal side to oppose centrifugal force. Centrifugal force reorients the gravity vector with respect to the polarization of otolithic hair cells in the utricular maculae externally to the curve, while head tilt shifts the gravity vector toward the centre of curvature. The net effect on the otolithic receptors is dominance of tilt over the centrifugal force (Fig. 6). When head tilt fully opposes centrifugal force, the gravito-inertial acceleration is orthogonal to the otolithic receptors, vestibular primary afferents will be not modulated, and the gain of the VOR will not be modulated. Conversely, if the effect on GIA of the centrifugal force is greater than the head tilt, the gain of the reflex will be reduced. The gain of the reflex will be enhanced if centrifugal force is less than the head tilt (Fig. 6).

The gain of the optokinetic reflex in the $P \rightarrow A$ direction could be differently modulated. It would be maximal in the $P \rightarrow A$ direction when the head tilts toward the rotation axis to reinforce the reflex. Conversely, the gain of the optokinetic reflex will decrease when the head is tilted less. These differential effects on OKN gain may induce gaze stability during head rotation. Compensatory vertical eye movements would be largely reduced. In this condition, the eye internal to the axis of rotation looks down toward the ground. Therefore, the optokinetic flow velocity on the internal side of the curvature increases and this would potentiate the optokinetic reflex. Interestingly, SPEV modulation in the present experiment was enhanced by increased HOKS and by increased head oscillation frequency. The finding supports the hypothesis that the modulation of SPEV by gravity is a function of the retinal slip. Indeed, rotation of the head at different velocities imposes different head tilt and different image movement of the visual field. Consequently, SPEV should be modulated accordingly.

Although we have demonstrated the influence of static changes in head position on SPEV evoked by HOKS, gravitational modulation of SPEV likely extends to higher frequency head movements as well. Slow residual retinal slip is not perfectly nulled. The vestibulo-ocular reflex is important even for short-lasting rotations, since the rise time of SPEV during OKS is quickly modulated by head tilt. This may suggest that the influence of head tilt on SPEV may not only apply to movements evoked by constant velocity HOKS, but also to higher order derivatives of eye position.

If a rabbit is rotating and the gravitational force exerted by head tilt detected by otoliths is less than centrifugal force acting on the otoliths, then the optokinetic reflex will be reduced. In this case, signal of optic flow will be greater and may be useful for detecting rotation. Facilitation and reduction of the reflex will then be important for gaze stability or for detecting movement, and this will depend on the degree of head inclination. In conclusion, the role of head position in the roll plane is important for controlling the velocity of the optokinetic response and depends on the orientation of GIA.

Acknowledgments

This research was supported in part by NIH DC006668, Fondazione Cassa di Risparmio di Perugia and Prin 2007 Ministero dell'Istruzione, dell'Università e della Ricerca.

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Fig. 1.

Schematic drawing of eye movement recording in rabbits. **a** Infra-red light projection technique records *horizontal* and *vertical* eye position using a small suction cup bearing an infrared light-emitting diode (LED) attached to the cornea. The LED projected a narrow beam of IR light onto a dual axis infrared x–y photodiode. Its output encoded both *horizontal* and *vertical* eye position. **b** Torsional eye position was recorded using two LEDs. The projected angle of these two LEDs was trigonometrically computed. **c** A digital video camera was used to record eye position. The camera was mounted above the rabbit. It detected IR reflection of the tip of a small plastic stalk glued to the limbus of the topically anesthetized as the eye moving in the *horizontal plane*, allowing unobstructed HOKS of the recorded eye

Fig. 2.

Static roll-tilt modulates the velocity of optokinetic nystagmus. **a** *Horizontal* eye movements were evoked by HOKS ($0-5^{\circ}/s$), while the head-body of the rabbit was roll-tilted statically ($\pm 20^{\circ}$) about the longitudinal axis. The *upper* trace indicates *right* eye *vertical* eye position (V). The second trace indicates *horizontal* eye position (H). The *lower* trace indicates *horizontal* eye velocity (Hv). The time constant (Tc) of the velocity increases induced by roll-tilt was determined by fitting the peak velocity with a single exponential (*dashed line*). **b** Static roll-tilt (30°) onto the side contralateral to the eye stimulated in the $P \rightarrow A$ direction ($5^{\circ}/s$) decreased SPEV. Roll-tilt (30°) onto the side ipsilateral to the eye stimulated in the $P \rightarrow A$ direction, increased SPEV

Fig. 3.

Eye velocity evoked by monocular and binocular OKS is modulated by static roll-tilt modulates. **a** Monocular and binocular HOKS evoked eye movements at different static head roll-tilt angles. When roll-tilt was toward the side of the eye stimulated in the $P \rightarrow A$ direction, SPEV increased. When the roll-tilt was toward the side stimulated in the $A \rightarrow P$ direction, SPEV decreased. *Left* (filled circles) and *right* (open circles) eyes received monocular HOKS in the $P \rightarrow A$ direction in separate experiments. Binocular HOKS was also performed in which the *left* eye was stimulated in the $P \rightarrow A$ direction (half filled circles). Data show mean and $\pm$ SD for 10 rabbits. **b** Roll-tilt modulation of SPEV is independent of angle of head tilt with respect to the optokinetic drum. The *left* eyes of three rabbits received HOKS in the $P \rightarrow A$ direction. The optokinetic drum was roll-tilted alone or in phase with the roll-tilt of the rabbit. When the optokinetic drum was roll-tilted and the rabbit remained upright, SPEV was not modulated (open squares). When the optokinetic drum and the rabbit were roll-tilted in phase (filled diamonds), eye velocity was modulated. Mean and $\pm$ SD for 3 rabbits. **c** Head roll-tilt modulates optokinetic afternystagmus (OKAN II). The *left* eyes of four rabbits were stimulated in the $P \rightarrow A$ or $A \rightarrow P$ direction with respect to the left eye for 24 h, inducing negative optokinetic nystagmus (OKAN II) when the HOKS was discontinued. During OKAN II, slow phase eye movements move opposite to the direction of the inducing OKS. The velocity of OKAN II was modulated by static roll-tilt depending on the direction of OKAN II. When the slow phase of OKAN II was in the $P \rightarrow A$ direction with respect to the *left* eye, SPEV increased during leftward roll-tilt (filled squares). When the slow phase of OKAN II was in the $A \rightarrow P$ direction with respect to the *left* eye, SPEV decreased during leftward roll-tilt (open squares). Modulation of SPEV is normalized with respect to the steady-state OKAN II velocity when the rabbit's head was not tilted. Data show mean and $\pm$ SD for four rabbits

Fig. 4.

Velocity of optokinetically evoked eye movements is modulated by sinusoidal roll-tilt. **a** Monocular HOKS at 5°/s in the P → A direction with respect to the *left* eye evoked *horizontal* eye movements with modulated SPEV over a range of sinusoidal roll-tilts ($\pm 20^\circ$, 0.05 Hz). SPEV increased when the rabbit was rotated onto its *left* side within the optokinetic drum. The first trace indicates *vertical* eye position. The second trace indicates *horizontal* eye position. The third trace indicates *horizontal* eye velocity. The *bottom* trace indicates the imposed roll-tilt sinusoidal stimulus. **b–e** HOKS in the P → A and A → P directions have opposite effects on eye velocity modulated by head roll-tilt. Modulation of SPEV is evoked by roll-tilt during monocular (**b, c**) and binocular (**d, e**) HOKS. **b** Ipsilateral head roll-tilt increased SPEV evoked by monocular HOKS of the *left* eye in the P → A direction. **c** Ipsilateral head roll-tilt decreased SPEV evoked by monocular HOKS of the *left* eye in the A → P direction. Note that monocular HOKS in the A → P direction evokes a lower gain optokinetic reflex than does P → A stimulation. The responses were asymmetric. **d** Ipsilateral head roll-tilt increased SPEV evoked by binocular HOKS (P → A with respect

to the *left* eye). **e** Ipsilateral head roll-tilt decreased SPEV evoked by binocular HOKS (A → P with respect to the *left* eye). The *dashed lines* in **b** and **c** represent Gaussian 2 peak fitting curve and sine wave fitting curve in **d** and **e**. The responses were symmetric. *Vertical dotted lines* indicate the phase of peak change in eye velocity re: head roll-tilt. Each *open symbol* indicates results from one of four cycles of oscillation

Fig. 5.

Effects of stimulus parameters on tilt modulation of SPEV induced by binocular HOKS. **a** and **b** Influence of HOKS velocity on the phase (retable position) and modulation of SPEV during 0.02 Hz sinusoidal roll-tilt. SPEV modulation is reported as percent change with respect to the baseline velocity recorded in static upright position. Phase lead and SPEV modulation increased as HOKS velocity increased. **c** and **d** Influence of sinusoidal head tilt frequency on SPEV evoked by HOKS at 5°/s. Phase lead and SPEV modulation increased as head tilt oscillation frequency increased. Data show mean $\pm$ SD for 10 rabbits

Fig. 6. Influence of centrifugal force during eccentric body rotation and head tilt on the gravity inertial acceleration (GIA). **a** No effect is induced when GIA stimulates otolith receptors orthogonally. **b** When the GIA stimulates otolith receptors toward the external side of the curve, the gain of the OKR is reduced. **c** When the GIA activates otolith receptors toward the internal side, the OKR gain is enhanced