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Temporal Dynamics of Ocular Position Dependence of the Initial Human Vestibulo-ocular Reflex

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Abstract

Purpose—While an ideal vestibulo-ocular reflex (VOR) generates ocular rotations compensatory for head motion, during visually guided movements, Listing's Law (LL) constrains the eye to rotational axes lying in Listing's Plane (LP). The present study was conducted to explore the recent proposal that the VOR's rotational axis is not collinear with the head's, but rather follows a time-dependent strategy intermediate between LL and an ideal VOR.

Methods—Binocular LPs were defined during visual fixation in eight normal humans. The VOR was evoked by a highly repeatable transient whole-body yaw rotation in darkness at a peak acceleration of 2800 deg/s². Immediately before rotation, subjects regarded targets 15 or 500 cm distant located at eye level, 20° up, or 20° down. Eye and head responses were compared with LL predictions in the position and velocity domains.

Results—LP orientation varied both among subjects and between individual subject's eyes, and rotated temporally with convergence by $5 \pm 5^\circ$ ($\pm$ SEM). In the position domain, the eye compensated for head displacement even when the head rotated out of LP. Even within the first 20 ms from onset of head rotation, the ocular velocity axis tilted relative to the head axis by $30\% \pm 8\%$ of vertical gaze position. Saccades increased this tilt. Regardless of vertical gaze position, the ocular rotation axis tilted backward 4° farther in abduction than in adduction. There was also a binocular vertical eye velocity transient and lateral tilt of the ocular axis.

Conclusions—These disconjugate, short-latency axis perturbations appear intrinsic to the VOR and may have neural or mechanical origins.

Ocular rotation to foveate a visual target requires only a two-dimensional (2-D) specification of eye orientation: horizontal and vertical. Only this 2-D specification is evident in premotor saccadic commands in the superior colliculus.¹ Nevertheless, the eye is a three dimensional (3-D) rotating object, and so its orientation has three degrees of freedom (DF). When the head is upright and stationary, gaze positions to distant targets achieved during visual fixation, pursuit, or saccades are consistent with Listing's Law (LL) constraining ocular torsion.^{2,3}

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Three-dimensional (3-D) angular orientation can be specified in Euler angle formulation by an axis and a magnitude of rotation about that axis. The familiar Euler angle formulation of LL states that any eye position can be reached from a primary position by rotation about a single axis lying in a plane, Listing's Plane (LP). Consequently, a series of visually guided eye positions conforming to LL can be expressed mathematically as quaternions that lie in a plane.⁴ A second, equivalent formulation of LL is expressed in the velocity domain.⁵ Unlike 1-D velocity, which is merely a time derivative of position, 3-D eye velocity is a function both of eye position and its derivative. In the velocity domain, LL requires that the ocular velocity axis change by half the angle of eye position change relative to the head.⁶

Before the anatomy of the orbital connective tissues was known, it seemed certain that LL was implemented entirely in premotor circuits as an intrinsic component of central ocular motor control.^{7,8} Miller and Demer⁹ first proposed that the pulleys constraining rectus extraocular muscle (EOM) paths could make their directions dependent on eye position. It has subsequently emerged that the rectus EOMs have connective tissue soft pulleys.¹⁰ These pulleys receive insertions from the orbital layer of each rectus EOM, the force in which is controlled so that the pulley moves in coordination with the globe, thus mechanically causing the EOM pulling direction to change by half the change in eye position.^{1–13} Because 3-D eye velocity is imparted by the direction of EOM force, the mechanical arrangement and coordinated linear motion of the rectus EOM pulleys appears to account for some features of LL without explicit central computation of eye torsion.^{14–16} However, physiologic violations of LL have continued to suggest central neural control of 3-D ocular kinematics.¹⁷ For example, during convergence, both eyes extort,¹⁸ and LP for each eye rotates temporally.^{19–21} The ocular extorsion in central gaze is associated with torsional repositioning of the rectus EOM pulley array by the oblique EOMs, but the temporal rotation of LP appears to require that this effect be neurally modulated as a function of vertical gaze position.¹⁶

Another conspicuous physiologic violation of LL is the vestibulo-ocular reflex (VOR), which rotates the eyes during head rotation so that images of fixed objects are stabilized on the retina. During ambulation, head rotation is significant in all 3 DF.²² If head motion were not compensated, image motion on the retina would significantly degrade visual acuity.^{23,24} Unlike the 2-D retinal signals that provide input for pursuit and saccades, the angular VOR originates in the semicircular canals of the inner ear that detect head rotation in 3 DF. Specifically, the three pairs of orthogonally oriented canals detect three orthogonal time derivatives of the angular components rotational head position. Ideal VOR performance would perfectly stabilize images on the retina and is achieved when the eye rotates about an axis parallel to that of head rotation.²⁵ This would not be problematic if head position was confined to LP, but no such constraint exists on natural head motion. It is not uncommon for purely torsional head rotation to occur about an axis perpendicular to LP, and the evoked torsional VOR violates LL utterly. An ideal VOR would not be influenced by LL, since constrained conformity would destabilize images on the peripheral retina during head rotation. Some investigators have reported that the monkey and human VOR closely follow some axes of head rotation as would be optimal for image stabilization,²⁵ particularly when torsional VOR gain is high,²⁶ or in monkey viewing a structured visual environment.²⁷

Even though conformity of the VOR's axis to the axis of head rotation would be visually optimal, in several studies, it has been reported that the human angular VOR compromises between LL and the axis of head rotation.^{21,28–31} These studies have tested for experimental convenience the half angle velocity formulation of LL. In the velocity domain, an ideal VOR would follow an axis independent of eye position in the orbit, and thus be said to follow a "zero-angle rule" with respect to eye position. The general finding has been that regardless of the orientation of the head rotational axis relative to LP, the VOR velocity axis is influenced by eye position in the orbit. The change in VOR velocity axis is less than half the change in

ocular angle dictated by LL, motivating description of the VOR as observing a “half-Listing’s strategy” or “quarter-angle rule.”^{21,28–31} The quarter-angle velocity formulation implies obligatory violation of LL by the VOR, regardless of the relationship of the axis of head rotation to LP. Obligatory quarter-angle VOR behavior would be difficult to reconcile with the presence of rectus EOM pulleys as sole determinants of ocular kinematics.

Quarter-angle behavior of the VOR does not have the same lawful consistency as does LL for visually guided eye movements, however. The eye-position dependence of the VOR rotational axis has been found to vary considerably. The dependence was initially described for the VOR in eccentric vertical gaze positions during sinusoidal yaw rotation, with the VOR conforming to LL in central gaze.^{28,32} Investigations of the temporal dynamics of the fractional angle behavior have yielded confusing findings. During manually delivered transient yaw head rotation, the human VOR reportedly matches the rotational axis of the head for the first 47 ms after the onset of head rotation, and thereafter in upward and central gaze to tend toward LL behavior.³⁰ However, in downward gaze and during self-generated yaw rotation, the human VOR axis remains aligned with that of the head.³⁰ Others have found that the human VOR in response to manually imposed yaw transients follows a partial LL strategy only at lower head velocities, while aligning with the head at higher velocities.²⁹ One study found the VOR axis to be time-dependent, most closely approaching quarter-angle behavior 40 ms after manual delivery of a transient yaw head rotation.²¹ These findings have motivated a suggestion that rectus pulley shifts contribute a time dependence to the axis of the human VOR.³⁰

Inconsistent findings regarding conformity of the VOR to LL might be the results of methodological differences. The method of delivering the head motion stimulus is potentially important. In the Walker et al.³¹ and Misslisch et al.²⁸ studies, subjects underwent sinusoidal, whole-body rotations about an earth-vertical axis at relatively low frequencies (0.2–0.7 Hz) and velocities (37.5 deg/s). Although the axis of head rotation can be well controlled during whole-body rotation at low velocity, quick phases interrupt the slow-phase VOR, and only the steady state response can be analyzed. Gaze position also cannot be well controlled in darkness during the long periods required for study of low frequency sinusoidal stimulation. Analysis of the VOR in the face of such factors required elaborate modeling²⁸ or selection of only brief time periods.³¹ Manually delivered head thrusts avoid the problem of quick phases, but the stimulus cannot be identically reproduced during multiple trials, and the axis of head rotation cannot be precisely controlled, with the inevitable introduction by neck mechanics of significant time-dependent head torsion leading to a time-dependent shift in the head’s rotational axis,²⁹ and a likelihood of otolith stimulation. The common practice of measurement of head position using sensors on the skin surface may be confounded by skin slippage over the skull at high acceleration. Possible differences in the rotational axes of the two eyes have not been evaluated.

To resolve the inconsistencies of previous studies, in the current re-examination, we evaluated the human VOR during highly repeatable, mechanically delivered, transient whole-body yaw transients having dynamics similar to manually delivered head thrusts.²² Whole-body rotation has the advantage of a well-controlled axis not confounded by neck mechanics and has the potential to place that axis so as to minimize stimulation of the otoliths.²² In the present study, skull rotation was measured at the rigidly fixed upper teeth to reflect faithfully the stimulus actually delivered to the VOR. Because target distance has been shown to have an effect on both the gain of the initial VOR^{22,33} and the orientation of LP,^{19,21,34} responses with both near and distant targets were examined. The orientation of LP was determined for each eye, permitting direct comparison of the VOR with both the Euler angle formulation of LL and the velocity axis formulation in unambiguous Listing’s coordinates.

Methods

Subjects

Eight normal paid volunteers gave written consent to participate in these experiments according to a protocol approved by the University of California, Los Angeles Human Subjects Protection Committee in conformity with the tenets of the Declaration of Helsinki. The subjects consisted of seven women and one man of average age 25 ± 4 years (mean $\pm$ SD; range, 20–30). All subjects underwent ophthalmic examination to verify that they were free of ocular disease and would be able to converge and focus targets clearly without the aid of corrective lenses. Subjects were monitored during experiments via infrared closed-circuit television and with a duplex intercom.

Apparatus

Binocular eye and head angular positions were measured with dual winding scleral magnetic search coils (Skalar Medical, Delft, The Netherlands),³⁵ as used by other investigators³⁶ and in the current laboratory.²² Reference magnetic fields were generated by three pairs of solenoid coils, each 2 m in diameter and arranged to form the sides of a cube (C-N-C Engineering, Seattle, WA). This configuration placed the center of the cube near eye level. The two vertically oriented coil pairs were driven by 60-kHz sinusoidal currents in phase quadrature.³⁵ The horizontally oriented coil pair was driven by a 120-kHz sinusoidal current.³⁷ Dual-winding scleral magnetic search coil annuli were placed on both eyes of each subject under topical anesthesia with proparacaine 0.5%. Angular head position was measured via dual search coils mounted on a bite bar, custom molded to the upper teeth of each subject so that they were rigidly coupled to skull motion. Preliminary experiments indicated that search coils affixed to a headband register head velocity with a significant delay compared with those affixed to a dental appliance, and so only the latter were regarded as accurate. Search coils were connected to external detectors (C-N-C Engineering) incorporating single-pole, low-pass filters with a cutoff frequency of 167 Hz. Horizontal angular positions were demodulated by a phase angle method that is linear over a range of $\pm 100^\circ$.

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

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

Subjects were rotated by a 500 N-m stepper motor (Compumotor, Rohnert Park, CA) with a dedicated driver and position feedback digital controller, as previously described.²² The motor had a resolution of 425,984 steps per revolution and could reliably reproduce the desired head motion. Because the motor's step resolution was 0.05 min arc, the steps were well below the noise level of the search coil system, making the steps indistinguishable from continuous rotation. The presence of the motor did not have a detectable effect on search coil measurements.

Measurement Conditions

During each trial, the subject sat with the head comfortably upright in a hardwood chair fabricated with nonmetallic fasteners as previously described.²² The chair was fit with dense foam cushions. Lap and chest belts, as well as padded clamps, secured each subject over the knees and feet to prevent decoupled body motion. The head was held firmly within a nonmetallic head holder that provided adjustable pressure support via Confor-foam (Oregon Aero, Inc., Scappoose, OR)-padded clamps to the forehead, vertex, occiput, malar eminences, and mental promontory of the subject's head. Every rotational trial was preceded by a 2-second calibration recording in which the stationary subject looked directly at centered target 500 cm away.

In 60-second recordings, LP was defined for each eye for near viewing as subjects tracked the quasirandom movements of a projected laser target on a tangent screen 15 cm from the center of the eyes. For far viewing, LP was defined for each eye as the subject tracked the quasirandom motion of a laser target projected on the laboratory walls, floor, and ceiling at distances of 4 to 10 m, all of which adequately approximate optical infinity.

The angular VOR was tested during 50-second trials that included 20 directionally unpredictable transient yaw rotations (10 in each direction). During each trial, subjects were asked to regard a target located at eye level, approximately 20° up, or approximately 20° down. Each target consisted of a black cross against a white background, as previously described.²² Onset of rotations varied randomly by ≤ 250 ms, to avoid predictive effects. The laboratory was illuminated between rotations, to enable subjects to maintain an accurate memory of the target. The fluorescent room lights were extinguished at random times 50 to 70 ms before the onset of each head rotation and remained off until after the chair returned to center ~400 ms later. Subjects were instructed to maintain gaze on the target, even when the lights were extinguished. Far targets were 500 cm distant, centered between the eyes. Near targets were 15 cm anterior to the centers of the eyes and in separate trials were both centered horizontally between the two eyes and centered before the right eye.

Head position was adjusted so that the axis of rotation was located between the external auditory canals, which were approximately 7 cm posterior to the eyes. This axis was chosen to minimize the translational stimulus to the otoliths. Rotational stimulus had a peak acceleration of 2800 deg/s² to a velocity of 190 deg/s, which rotated the head 40° in 250 ms, which was the time at which the peak velocity was reached. At 300 ms the velocity averaged 150 deg/s. The head moved to its maximal offset of 55° after 550 ms.

Data Analysis

Data were analyzed automatically with custom software (LabView 7.1; National Instruments, Austin TX; Macintosh G4 and G5 computers; Apple Computer). For each subject, rotational transients were grouped based on target distance, direction of rotation, and direction of gaze. Transient rotations in which eye position varied by more than 0.2° in the 80 ms before rotation were discarded as failures of fixation. For study of the early slow-phase VOR, events were also discarded when there were saccades or blink artifact within 70 ms of the onset of head rotation. Less than 10% of trials had to be removed due to such artifacts, and most trials of all eight subjects were included in the analysis during this early period. Five of the eight subjects typically introduced a saccade 100 to 200 ms after rotation onset. The remaining three subjects only rarely introduced saccades before 300 ms, and so this subgroup was used to analyze the later period of the slow-phase VOR for events when no saccades were present.

Sampled search coil voltages were corrected for misalignment of the sine nonlinearity in the pitch axis of the search coil system. These Fick angles were converted to rotation matrices as

previously described.^{4,38} Data from LP definition and VOR trials were first corrected for presumed imperfect alignment of the coils on the eye in central gaze during the immediately preceding reference trial. This was done using the following equations where H and E represent the rotation matrices of head and eye positions, respectively, collected from the search coil signals after correction of the sine nonlinearity. H' and E' represent the inverses of the head and eye position matrices measured during the reference trial, and H_c and E_c represent corrected head and eye positions:

$$H_c = H' H,$$

$$E_c = E' E.$$

The position of the eye in the head, E_H , was calculated using the inverse of the corrected head position, H'_c :

$$E_H = H'_c E_c.$$

LP was determined by converting the eye position rotation matrices, E_H , to quaternions.⁴ Data collected during LP definition trials were decimated from 1.2 to 120 Hz to speed computation. Data were best fit with a single-value decomposition algorithm.^{30,39} The unit vector normal to LP determined its orientation. Eye position could then be rotated and expressed in Listing's coordinates.⁵

Torsional scleral coil slippage was identified by comparing measured ocular torsion with that predicted by LL during the period of visual target fixation immediately before each head rotation. Ideal torsion (ψ_{ideal}) was calculated from the yaw (θ) and pitch (ϕ) eye positions in a Fick sequence coordinate system as given below:

$$\psi_{\text{ideal}} = \arctan \left(\frac{\sin \theta \sin \phi}{\cos \theta + \cos \phi} \right).$$

During visual fixations between rotational transients, at roughly 3-second intervals, ideal and measured torsion were compared, to detect coil slippage. Because LL prevails during these visual fixations, discrepancies between ideal and measured torsion were considered to reflect torsional slippage of the search coil annulus around the limbus, which was corrected using a new reference matrix before analysis of the next VOR response to the transient yaw stimulus. Correction was performed during each fixation before VOR initiation, even though the eye position was often the same as in the previous trial within the noise of the system. After any necessary corrections of this kind, data from each rotational transient was temporally aligned and averaged as previously described.²² Eye-in-head position was then calculated as described for LP definition trials.

The orientations of eye and head rotations relative to LP were determined for each trial for each eye and viewing condition in the position domain. Head and eye positions during VOR initiation were also converted to quaternions in Listing's coordinates.

Velocity vectors (ω) for eye and head were computed from quaternion positions (q) and derivatives ($\dot{q}$) as previously described.^{4,31,40,41}

$$\omega = 2 \frac{\dot{q}}{q}.$$

Eye and head rotations were also examined in the velocity domain. The tilt angle of the velocity vector out of LP, ϕ (in the approximately sagittal plane perpendicular to LP), was determined with the horizontal (h) and torsional (t) components of velocity as previously described.³¹

$$\phi = \tan^{-1} (t / h)$$

Linear regression was used to calculate the tilt of the velocity axis in the sagittal plane, ϕ , relative to vertical ocular displacement. Linear regression was performed on data sets obtained from three similar trials when the eye was in central, up, and down gaze, respectively. Each regression was repeated every 800 μ s from 40 ms before the onset of head motion to 400 ms after the onset of head rotation. After a preliminary fit, data points lying farther than two standard deviations (SDs) from the initial fit were discarded. This process was then repeated once to determine the final slope and regression coefficient for the linear regression. On average, the process retained 92% of data points, with the range for individual subjects at 87% to 95%.

Gain of the VOR was determined in the velocity domain. Eye velocity was divided by head velocity during the first 80 ms of head rotation. Gain was only calculated when head velocity exceeded 20 deg/s, to avoid inaccurate gains due to poor signal-to-noise ratio during the initial milliseconds of rotation when head velocity was minimal. Because the axis of rotation was always earth vertical, head velocity components in pitch and torsion axes were typically so small as to preclude reliable computation of gains for pitch and torsion.

Results

Listing's Plane

It was possible to calculate LP reliably in all subjects under all viewing conditions, since all subjects had minimal scleral search coil slippage. A typical LP for a both eyes in a single trial is shown in Figure 1. The orientation of LP was variable, depending on target distance, subject, and right or left eye. Mean thickness of LP as measured by the SD of torsion in Listing's coordinates was 0.014 ± 0.006 (mean $\pm$ SD). There was no significant difference in the thickness of LP between the two eyes or target distances ($P > 0.1$ for both, Student's t -test).

There was considerable variation in orientation of LP among subjects, and between eyes of individual subjects. There was a significant difference in the orientation of LP between the two eyes relative to field coordinates in both the horizontal and vertical directions ($P < 0.01$ for both, Student's t -test). For the right eye, LP was oriented $10 \pm 6^\circ$ (mean $\pm$ SD) nasal, and $8 \pm 5^\circ$ upward. For the left eye, LP was oriented $8 \pm 10^\circ$ nasal, and $3 \pm 9^\circ$ downward. The LP orientation was highly variable but not significantly different in pitch ($P > 0.05$). All subjects achieved geometrically appropriate convergence during near target viewing. When the LP orientations of individual eyes were pooled, there was no significant effect of the near and far viewing condition on in either pitch or yaw orientation of LP for either eye ($P = 0.1$ to 0.8 , Student's t -test). However, comparison within individual subjects of the horizontal orientation of the right eye LP relative to the left eye LP showed a significant temporal tilt of LP during convergence of $5 \pm 5^\circ$ (mean $\pm$ SD, $P < 0.01$). The temporal tilting of LP with convergence was observed in five of the eight subjects, as shown in Figure 2. Since the near LP was defined during viewing of a tangent screen, both the geometrically required and observed vergence angles varied slightly with gaze eccentricity, with a vergence diminishing for more eccentric viewing positions. Mean vergence averaged $0.1 \pm 0.3^\circ$ for remote targets, and $17 \pm 3^\circ$ for the 15-cm viewing condition.

Yaw VOR

Each subject underwent 10 transients of whole-body rotation to the left randomly interleaved with 10 transients to the right, at both near and far viewing distances, repeated for three vertical gaze positions. Being imposed by a servomotor, there was negligible variation in the velocity and acceleration of the head rotational stimulus across conditions. Eye movement was similarly consistent for each subject except for less than 10% of trials in which there occurred artifacts such as distraction from target fixation at the start of the trial, an early saccade, or an eye blink in the initial 70 ms. Trials with such artifacts were excluded from further analysis. The VOR was analyzed in the coordinate system defined by the LP for the appropriate eye and target distance (Fig. 3). Although the axis of chair rotation and the coordinates of the magnetic search coil system were aligned to earth vertical, significant projection of the rotational stimulus was introduced into the LP pitch and torsion coordinate axes when LP was significantly misaligned from earth vertical. Gain in the LP yaw axis averaged 0.98 ± 0.01 (mean $\pm$ SE) for the 15 cm target, which was significantly higher ($P < 0.01$, *t*-test) than 0.87 ± 0.01 (mean $\pm$ SE) for the 500-cm target. Target proximity alone is known to increase yaw VOR gain even when rotation is about the axis used here midway between the otoliths that minimizes their net tangential stimulation.²² Such a gain increase may be compensatory for the small amount of eye translation that occurs. Yaw VOR gain was not significantly influenced by direction of motion ($P > 0.1$), left or right eye ($P > 0.1$), or vertical gaze direction ($P > 0.1$).

Eye and Head Rotation in the Position Domain

Eye and head positions were determined in each eye for both viewing conditions relative to LP during the first 80 ms of the response, an interval free of saccades or other artifacts in all subjects. Because the orientations of LP often differed significantly between the two eyes, it was sometimes the case that head position was in LP for one eye yet out of LP for the other eye, even though in an earth-fixed coordinate system the axis of head rotation was the same for both eyes (Fig. 4). The 3-D eye position roughly paralleled that of the head (subject to gaze position-dependent deviations described later), so that in some cases, one eye obeyed LL in the position domain while the contralateral eye violated it (Fig. 4). The relationship between the horizontal and the torsional quaternion components of both eye and head position remained linear functions throughout the initial 250 ms of the response in subjects who did not make saccades (Fig. 4). These linear fits were good, with the deviation of the head position accounted for 78% to 85% of the variability in the variation of the eye position. The mean SE of the linear regression to eye and head positions was 2×10^{-6} for the eye and 1×10^{-6} for the head, demonstrating excellent linear fits that did not depend on target distance. This indicates that once eye or head motion began, the rotations continued without regard to the *orientation* of LP.

Velocity Domain Eye- and Head Rotation Axes

The velocity axes of the eyes were calculated relative to the head during the initial 70 ms of rotation. After this period, many subjects introduced saccades or quick phases that confounded analysis of the axis. Preliminary analysis indicated that the vertical direction of gaze had a significant effect on the ocular axis as well as the direction of eye rotation (abduction versus adduction). Left or right eye and near or far target distance had no significant effect on the axis of rotation ($P > 0.05$) during the period under consideration. Thus, data from both target distances and both eyes were pooled for further analysis.

During the initial 70 ms, the axis of the abducting eye shifted back relative to that of the adducting eye for both up and central gaze viewing (Figs. 5A, 5B, respectively). This difference was not significant during down gaze (Fig. 5C). In central and up gaze the shift in the ocular axis became statistically significant by no later than 20 ms. After 70 ms, the duction-dependent effect on VOR axis reversed, so that the axis of the adducting eye shifted back relative to that

of the abducting eye. There was no significant late difference between the axes of the ab- and adducting eyes in up and central gaze (Figs. 5A, 5B). In down gaze, the axis of the adducting eye shifted further back than did that of the abducting eye (Fig. 5C), reversing the earlier effect observed in up and central gaze. The period after 100 ms had the potential to be problematic due to the tendency of many subjects to introduce quick phases. To determine whether these late effects might be influenced by quick phases, the analysis was repeated in the subset of three subjects in whom a significant number of trials could be selected that were free of quick phases for the initial 300 ms. In these selected trials, the result was similar to those of the larger dataset: The axis of eye rotation was tilted significantly farther back during abduction in the first 70 ms for up and center gaze and significantly farther forward during abduction after 70 ms in down gaze.

The axis of ocular rotation also exhibited a significant dependence on vertical gaze position. In up gaze, the VOR axis shifted backward (up) relative to central gaze, and in down gaze the axis shifted forward (down) relative to central gaze (Fig. 6). These effects became statistically significant 10 to 30 ms after the onset of head motion, and were similar during ad- and abduction.

Compliance with LL could be determined by calculating the tilt angle ratio (TAR), the ratio of tilt of the ocular velocity axis divided by the change in vertical gaze, for various vertical gaze positions. One measure of the TAR was taken to be the slope of a plot of VOR axis tilt against vertical eye position, as illustrated in Figure 6. The maximum change in vertical gaze was 40° , whereas the corresponding change in VOR velocity axis was 8° to 12° . Thus, the TAR was near a quarter the change in eye position. The data shown in Figure 6 are average values, with results varying among subjects and trials.

As an alternative method to determine the TAR in individual subjects and testing conditions, linear regression was performed on the tilt of the ocular axis in the sagittal plane versus vertical eye position (Fig. 7). This regression analysis was repeated for each eye of each subject at every time point (sampled at $800\ \mu\text{s}$ intervals) after onset of head rotation, exploiting the variability at each time point arising from variations in gaze positions in multiple trials. Although this could be done at any time in the response, the regression became more reliable with the passage of time as head and eye velocity increased. Because the earliest saccades in any subject were observed slightly more than 70 ms from head rotation onset, regressions 70 ms after the onset of head rotation were considered the most robust measure of VOR axis behavior. Because LP orientation varies among subjects, eyes, and target distances, linear regressions were performed separately for these conditions, and for each regression the correlation coefficient (R) was noted. Measured 70 ms after head rotation onset, the TAR averaged over all eight subjects was 0.30 ± 0.08 (mean $\pm$ SD), ranging 0.15 to 0.40 among individual subjects (Table 1). Correlation coefficients varied from 0.23 to 0.75. Unlike the raw eye velocity axis, the TAR did not vary significantly with ab- versus adduction, target distance, right versus left eye, or stimulus direction ($P > 0.1$ for all).

The time course of the vertical TAR was determined by calculating instantaneous linear regressions such as the one demonstrated at 70 ms in Figure 7, for each sampled time point from 50 ms before to 250 ms after onset of head rotation (Fig. 8A). Within the initial 30 ms after head rotation onset, eye and head velocity axes could not be accurately defined due to low signal-to-noise ratios. This indeterminacy was reflected in low correlation coefficients of the regressions before 30 ms. After this initial indeterminate period, the correlation coefficient exceeded 0.3 (Fig. 8B). The regression slope was initially near 0.25 but rose to near 0.5 by 100 ms after head rotation onset (Fig. 8B). This behavior is consistent with the suggested initial quarter-angle behavior, followed by a shift to half angle (LL) behavior at ~ 100 ms.

The possibility was considered that the apparent shift in VOR axis behavior might be due to the presence of saccades. Five of the eight subjects exhibited a saccade or a quick phase during the period from 80 to 300 ms after the onset of head rotation in most of their rotational transients. In the remaining three subjects (subjects 1, 3, and 6 in Table 1), saccades and quick phases only rarely occurred in this period. Trials in which these saccades occurred were manually removed from further analysis (Fig. 9). In the remaining trials that did not contain saccades, the TAR remained close to 0.25 and the correlation coefficient approached 0.8, consistent with the idea that the apparent late increase in TAR in the larger data set was due to the presence of saccades biasing the TAR toward half-angle kinematics.

Variation of the VOR axis was also examined in the coronal plane (Fig. 10). In all subjects there was a small downward eye velocity immediately after head motion onset. Despite stringent efforts to couple subjects' heads to the rotator, some decoupling nevertheless occurred in all 3 DF at the high yaw accelerations used. It was therefore important to exclude the possibility that the downward eye velocity might be an appropriate VOR response to inadvertently imposed upward head rotation, and that similar behavior might occur in roll. This possibility was evaluated by making the reasonable assumption that the small angle, transient VOR has gain near the ideal value of 1.0 in all 3 DF under the current conditions. If this were so, then gaze, the sum of each of the trigonometrically small-angle eye and head velocity components in space, should be zero. This approach, which is kinematically valid only for small angles typical of the rotational DF that were not intentionally stimulated, would null the visually appropriate VOR response to actual head rotation in each of the three dimensions, leaving only responses that were not due to gaze-stabilizing VOR action. Even after addition of the head velocity to eye velocity as in Figure 10, right, an initial vertical eye velocity was observed that was qualitatively the same, independent of starting gaze direction, direction of head rotation, eye, and target distance. The axis of ocular rotation was confounded in trials when subjects made a saccade or a quick phase, which was common in the period 80 to 300 ms after the onset of eye rotation. To eliminate this effect, a subset of three subjects who rarely made saccades and quick phases in the initial 300 ms of the response were chosen, and trials in which a saccade was made were removed. Even in the complete absence of saccades, there was a slight downward velocity in the first 70 ms of the VOR that was followed by an upward eye velocity that lasted beyond 200 ms (Fig. 10, center). This shift was equivalent to an extorsion of the ocular velocity axis (but not the eye itself) during adduction and an intorsion of the velocity axis during abduction.

Discussion

Listing's Law

In the currently study LP was defined for each eye of each subject during both near and far target viewing. For every subject, eye position conformed closely to LL during all visual target fixations. The thickness of LP determined in the present study was comparable to published values.^{25,28} Nevertheless, there was significant variation in the orientation of LP among subjects and between eyes, with binocular correspondence of LPs on average differing by $18 \pm 11^\circ$ (mean $\pm$ SD). Others have found similar idiosyncratic differences in LP orientation.¹⁹ Variation in LP orientation suggests implications for the relevance of LL to oculomotor physiology. If binocular correspondence of the peripheral retinas had critical visual importance, a predictable binocular relationship of the two LPs would be anticipated. Large and seemingly idiosyncratic interocular variations in LP assure lack of correspondence in the peripheral retina during eccentric gaze positions, making it doubtful that LL exists to facilitate retinal correspondence during distant viewing.

The present study generally supports a temporal tilt of LP with convergence. The magnitude of this effect varied considerably among subjects, with three of eight subjects demonstrating

virtually no temporal tilt (Fig. 2). Subjects had an average of 0.3° of temporal tilt in LP per deg of convergence. Other investigators have reported similar but variable ratios of temporal tilt in LP with convergence: 0.18 to 0.33,³⁴ 0.25,²⁰ 0.3,⁴² and 0.5.³ It has been argued that this temporal rotation of LP facilitates sensory alignment of corresponding retinal meridians during near viewing³ and improves stereopsis.⁴³ Some have proposed a neurally implemented, binocular extension of LL to explain temporal rotation of LP with convergence, invoking a central mechanism to maximize peripheral retinal correspondence,⁴⁴ but the phenomenon is so strongly dependent on visual sensory features that others regard it as a sensorimotor adjustment rather than a fundamental kinematic principle.¹⁹

The large observed interocular variation in LP also makes it unlikely that the brain encodes high-level binocular motor commands in Listing's coordinates. It is certainly implausible for premotor conjugate VOR commands to be encoded in Listing's coordinates, since in the present study the VOR in one eye can conform to LL, whereas that in the other eye violates it. It is difficult to reconcile this with the concept that LL is a premotor neural strategy explicitly computed in 3-D.^{7,45,46}

Several possible rationales for LL have been proposed. One advantage of LL is minimization of the ocular rotation required to achieve a gaze shift.²⁸ It has been pointed out that an oculomotor plant conforming to LL simplifies the requirements of neural control.⁴⁷ Although eye velocity is simply the derivative of eye position in 1-D, eye velocity in a head coordinate system is more complex for noncommutative 3-D rotations. Modeling suggests that if LL were implemented in the orbital mechanics, the oculomotor plant would appear commutative to the brain, and could then be commanded by signals corresponding to time derivatives of eye position without measurable errors in velocity position matching.^{14,47} Strong functional anatomic evidence from orbital magnetic resonance imaging (MRI) indicates that the rectus EOMs change their pulling directions by half the change in eye orientation across a broad range of secondary and tertiary gaze positions.^{48,49} This mechanical action intrinsically implements half-angle behavior that is also typical of the inferior⁵⁰ and superior oblique (SO) EOMs.¹⁶ The active pulley hypothesis proposes that half-angle kinematics of the rectus and inferior oblique (IO) EOMs is due to their path constraint by connective tissue rings comprising pulleys. These pulleys receive insertions from the orbital layers of their respective EOMs, permitting (for all pulleys except the trochlea of the SO) neurally commanded, active control of pulley position and hence the EOM pulling direction.^{13,48,49} Thus, although orbital layer EOM fibers could be driven by an apparently simple neural control rule to maintain a coordinated anteroposterior relationship between the pulleys and the globe, the 3-D aspects of LL can largely be explained as emergent properties of the gaze-dependence of rectus EOM paths. This structure in some respects simplifies the encoding of visually guided eye movements to drive the ocular motor plant. With such plant structure, visual fixation and pursuit can be commanded by low level 2-D signals,¹¹ leaving more complex 3-D sensorimotor transformations to higher central processing levels for the computation of target locations in space.⁴⁶

Notwithstanding LL, the orbits are configured to permit 3-D control of ocular orientation when the oblique EOMs participate. The orbital layers of the IO⁵⁰ and SO⁵¹ EOMs insert directly and indirectly on the rectus pulleys, so that oblique EOM activity can alter the torsional orientation of the rectus pulley array during convergence and during the ocular counterrolling.^{16,18} Such an arrangement would impose a torsional offset in the mechanically implemented LP, as is observed during static head tilts,^{52–54} for pursuit and saccades,^{25,55} and for both slow and quick phases during the dynamic VOR.⁵⁶ Consistent with the noncommutative demands of the VOR,⁵⁷ torsional repositioning of the rectus pulley array would be expected to influence the directional response of the rectus EOMs to subsequent activation by semicircular canal activity.

Vestibulo-ocular Reflex Kinematics

The present study is the first to examine temporal dynamics of the initial human VOR axis during transient, high acceleration of the whole body. Velocity domain analysis confirmed that the VOR has an axis dependence on eye position that is approximately quarter angle. In individual subjects, the VOR velocity axis shifted by 0.15 to 0.40 of the vertical gaze angle when measured 70 ms after the onset of motion (Table 1) with an average value of 0.30 ± 0.08 (mean $\pm$ SD) not significantly different from one quarter. However, the significant variation in this value among subjects suggests that precise quarter-angle behavior is not critical to the function of the VOR. Furthermore, the velocity axis shift did not depend on target distance. The time course of this quarter-angle behavior has been controversial. During manual head thrusts, quarter-angle behavior has been described only in the period 47 ms after head motion onset, with the VOR axis aligned with that of the head ear-lier.³⁰ Other laboratories have reported quarter-angle behavior at its maximum 40 ms after head rotation²¹ or only during lower acceleration head thrusts.²⁹ The current study is uniquely suited to studying the velocity axis of the early VOR. Using a mechanical stimulus to provide en bloc rotation of subjects, we avoided the variability and large amounts of torsion inherent in manually delivered head thrusts. Signal-to-noise ratio was also improved by averaging multiple similar trials. Using this technique we found that even 20 ms after the onset of head rotation, the earliest time at which the velocity axis could be accurately calculated (Figs. 8-9), the VOR had approximately quarter-angle behavior. For this stimulus used in the present study, there is no early period of the VOR in which the velocity axis follows a zero-angle rule. Others have suggested a zero-angle rule early in the response, which may be due to the higher acceleration of the manual head thrust stimulus.³⁰ The present study did not use accelerations above 2800 deg/s^2 , and it is possible that the zero-angle behavior described by others is specific to very high accelerations. In the present study, quarter-angle behavior applies from the earliest time the VOR can be analyzed, suggesting that the strategy is implemented by the same neural commands that initiate the VOR. As shown by examination of trials with (Fig. 8) and without (Fig. 9) saccades, saccades in the same plane as the VOR slow phase appear to shift quarter-angle VOR behavior toward the half-angle behavior of LL.

Some early studies have reported that the angular VOR axis matches the head rotational axis in the position domain. This was the case in monkeys during vertical axis rotation²⁵ and in humans during rotation about pitch and yaw axes.²⁶ These findings have been confirmed in the current experiments: Eye displacement mirrors head displacement independent of LP orientation. The eye-position error produced by this quarter-angle behavior is small, even in tertiary gaze positions: 0.75° in gaze 20° up and 10° lateral, or 0.47° in gaze was 20° down and 10° lateral. For secondary positions or central gaze, the error would be considerably less. Because the resultant eye position error is very small and only evident at large tertiary gaze positions, it is likely to be of minor influence on behavior. The effect on eye velocity may be more important.

The present study indicates that the VOR observes quarter-angle strategy even at very short latency, varying from this behavior only with the occurrence of saccades or quick phases that would be expected to conform to LL. A completely mechanical implementation of a partial LL strategy seems improbable, because it would require an anatomically unrealistically large rectus pulley shift and cannot explain some observed VOR axis behavior during roll.⁴⁵ The short latency of the quarter-angle VOR behavior observed here suggests that it is intrinsic to the neural processing of the angular VOR. As suggested by Misslisch and Tweed,⁴⁵ this neural processing must incorporate 3-D eye position to derive commands consistent with half LL behavior.

A novel finding is that the VOR velocity axis has a duction dependence. In addition to the gaze-position dependence (Fig. 6), the current results demonstrate a difference in VOR axis

dependent on ab- versus adduction (Fig. 5). There was an approximately 4° greater backward tilt in the velocity axis of the ab- than adducting eye in central and up gaze in the initial 70 ms after head rotation onset, with a reversal of this effect in down gaze after 70 ms. This tilt in the ocular axis depending on ab- versus adduction cannot be explained as a direction-dependent decoupling of the head. The head-velocity axis was of course identical for the two eyes and both directions of head rotation. This duction dependence is presumably due to some neural or orbital mechanical factor and lacks an obvious physiologic advantage. It may also be related to the velocity or acceleration profile of the stimulus used, which changed with time.

A small vertical eye velocity occurred during the initial VOR in most subjects under every viewing condition. There was an initial downward eye velocity peaking 50 ms after onset of head rotation, then reversing to become an upward eye velocity 20 ms later (Fig. 10). This effect cannot be explained as a physiologically appropriate VOR to a vertical component of head rotation, because when eye and head velocities were added (Fig. 10, panels on right), the vertical eye movement remained significant. During this sort of addition, a VOR response to vertical head rotation would have cancelled it, to produce a null gaze change. The coincidental vertical eye velocity corresponds to a rotation of the ocular velocity axis within LP. It is possible that this effect is neurally mediated, but this small transient perturbation is likely to be of no advantage and little visual consequence, since it occurred in the early period of the VOR when no visual feedback is available. It is also possible that the velocity aberration may be the result of an aborted blink, which occurred in a stereotyped manner across subjects, since blinking is associated with downward eye movement.⁵⁸

A possibility worth considering is that the duction dependence of the VOR velocity axis and the adventitious initial vertical velocity are consequences of orbital mechanical factors. It is not known what occurs during the initial milliseconds of transient eye rotation, but magnetic resonance imaging (MRI) evidence suggests that the globe moves medially during both sustained ab- and adduction.¹² Such a medial shift would be likely to decrease tension on the SO and IO EOMs. If globe translation reduced tension in both oblique EOMs equally, no ocular torsion would occur. However, the pulleys of the IO and inferior rectus muscles are tightly coupled, probably more so than the SO sheath is coupled to the superior rectus pulley.^{13,50} The trochlea of the SO muscle is rigidly attached to the orbital wall, whereas the IO pulley moves elastically under the influence of inferior rectus and IO tension. Thus, medial globe translation might result in a dynamic imbalance of the vertical and torsional effects of the oblique EOMs, and could perhaps be the cause of the apparently uncommanded vertical components observed in the initial VOR. Data on the temporal dynamics of the EOM pulleys are needed to evaluate this possibility.

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FIGURE 1.

Quaternions representing binocular LP for one subject viewing at distance. The subject tracked a projected laser spot moving in quasirandom fashion to $\pm 30^\circ$ eccentricity for 60 seconds. Data are expressed in quaternions in earth-fixed magnetic field coordinates. *Left*: right eye; *right*: left eye. In this example the right eye LP was tilted 14° up and 9° left, and the left eye LP tilted 3° down and 22° right. Cartoons show the orientation of LP relative to the subject's head in each view. In this trial, the thickness of LP (SD of torsion in Listing's coordinates) was 0.010 for the right eye and 0.009 for the left eye.

FIGURE 2.

Temporal tilt of LP with convergence. Data represent the difference between the horizontal orientations of LP with near versus far target viewing. Positive data indicate an outward (temporal) tilt of LP with near target viewing (convergence); negative data indicate a relative inward tilt of LP with near target viewing.

FIGURE 3.

Initial VOR during viewing of a target 500 cm distant at eye level. *Top*: yaw; *middle*: pitch; *bottom*: torsion in Fick sequence coordinates oriented relative to Listing's primary position for each eye (shown in Fig. 1), so the coordinate axes differ between eyes. Data are the mean (dark lines) $\pm$ SEM for 10 repetitions of head rotation to the right. Error lines are often covered by the mean data, as there was minimal variation between trials. *Bottom*: theoretical torsional eye position predicted by Listing's Law.

FIGURE 4.

Quaternions in Listing coordinates depicting LP with superimposed eye (*blue*) and head (*red*) positions during the initial 225 ms of the VOR. Data for LP were defined by the trial shown in Figure 1, but here have been rotated into Listing's coordinates. Eye and head positions are those shown in Figure 3. Head rotation appears different in the differing Listing's coordinates for each eye. There was an upward tilt of the right eye LP relative to the axis of head rotation, and so the right eye and head did not remain in LP. The head and left eye remained closely aligned with the left eye LP.

FIGURE 5.

Duction dependence of the VOR velocity axis in the first 120 ms after onset of head rotation. Positive data indicate a backward (upward) tilt of the ocular velocity axis. Data are the average of all subjects, both right and left eyes, and near and far target distances and are plotted using *triangles* when the difference between ab- and adduction was significant at the 0.01 level. For clarity, *triangles* are only shown for every fourth significant data point. In downgaze there was no significant difference between ab- and adduction before 70 ms.

FIGURE 6.

Effect of vertical gaze position on the VOR velocity axis in the initial 120 ms after onset of head rotation. Positive data indicate backward tilt of the velocity axis. Data average all subjects, both eyes, and both target distances. Data are plotted with *triangles* when the difference between eccentric (up or down) and central gaze was significant at the 0.01 level. For clarity *triangles* are shown only every fourth data point.

FIGURE 7.

Effect of vertical eye position on backward tilt of the VOR velocity axis 70 ms after head rotation onset in right eye of a typical subject viewing a target 500 cm distant. Data include multiple trials with rotation in both directions and three vertical gaze positions.

FIGURE 8.

Time dependence of mean vertical TAR of both eyes of all eight subjects viewing at near and far target distances. (A) TAR. The Axis was definable starting approximately 25 ms after the head rotation onset. The TAR was initially near 0.25 (quarter-angle behavior) but increased to approach 0.5 at ~100 ms, the time when several subjects made quick phases and saccades. (B) Average correlation coefficient (R) for linear regressions used to derive TARs in (A). R increased with time between 0 and 100 ms from head rotation onset, reflecting improving the signal-to-noise ratio as eye velocity increased.

FIGURE 9.

Mean change of vertical tilt angle ratio (TAR) in three subjects who made no saccades or quick phases. Data average both eyes and near and far target distances. **(A)** TAR. Comparing with Figure 8A, note that TAR remains near one quarter in the absence of saccades. **(B)** Average correlation coefficient (R) for linear regressions used to derive TARs in **(A)**.

FIGURE 10.

Mean VOR data in velocity domain in trials of three subjects in whom no saccades occurred in the first 300 ms after onset of head rotation. Vertical gaze position, left or right eye, and target distance had no qualitative effect, and so results of trials in which these conditions were altered have been pooled. Trials with leftward head rotation (compensatory eye movement to the right) are shown in *blue*; data for rightward head rotation are shown in *red*. *Thin dashed line*: head velocity. In the *left* panels eye-in-head velocity is shown with a *dark solid line*. In the panels on the *right* side, eye velocity was added to head velocity; assuming VOR gain near unity, this approach would null the apparent response to actual head rotation in each of the three dimensions, leaving only responses not due to gaze-stabilizing VOR action. During the initial 70 ms of the response there was a downward eye velocity (*middle right*) that later reversed to become upward. Error bars are omitted because ± 1 SEM was less than 1 deg/s in every case.

TABLE 1

Vertical Tilt Angle Ratio of the VOR Velocity Axis 70 ms after Head Rotation Onset in Eight Subjects

Subject	Tilt Angle Ratio ($\pm$ SE)	Mean Correlation Coefficient (<i>R</i>)
1	0.24 $\pm$ 0.09	0.41
2	0.37 $\pm$ 0.07	0.68
3	0.32 $\pm$ 0.04	0.75
4	0.29 $\pm$ 0.11	0.51
5	0.32 $\pm$ 0.05	0.57
6	0.40 $\pm$ 0.05	0.73
7	0.15 $\pm$ 0.09	0.23
8	0.33 $\pm$ 0.12	0.26

Data average both eyes and both near and far target distances. TARs were obtained as slopes of linear regressions, with the correlation coefficients specified.