Kinematics of the Rotational Vestibuloocular Reflex: Role of the Cerebellum

Mark F. Walker, Jing Tian, and David S. Zee

Departments of Neurology, Ophthalmology, Otolaryngology-Head and Neck Surgery, and Neuroscience; The Johns Hopkins University School of Medicine, Baltimore, Maryland

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INTRODUCTION

The purpose of the rotational vestibuloocular reflex (RVOR) is to stabilize the eyes in space when the head rotates to maintain a stable retinal image. To accomplish this, the brain must extract from the semicircular canal inputs the speed and axis of head rotation and then generate the appropriate innervations to the extraocular muscles. Several decades of work by many investigators have elucidated much of the anatomy and physiology of the RVOR. The particular focus of our investigations has been on the role of the cerebellum in calibrating the three-dimensional (3-D) axis of the RVOR.

Considerable evidence indicates that the 3-D calibration of the RVOR requires an intact cerebellum. First, humans with cerebellar degeneration demonstrate abnormal RVOR axes; the eyes rotate in a direction different from that of the head movement (Walker and Zee 2005). Second, animals with vestibulocerebellar lesions are impaired in their ability to alter the axis (Schultheis and Robinson 1981) or amplitude (e.g., Blazquez et al. 2003; Lisberger et al. 1984; Nagao and Kitazawa 2003; Lisberger et al. 1984) or not (Smith and Crawford 1998). We hypothesized that the cerebellum might play a more specific role in the neural control of the kinematics of the RVOR given its various roles in the long-term calibration of eye movements, including the axis of the RVOR (Walker and Zee 2005). To test this hypothesis, we compared the orbital-position dependency of the RVOR in patients with cerebellar disease and normal subjects. Preliminary data from this study have been previously presented in abstract form (Walker et al. 2004a), and control data from chair rotations for normal subjects were included in a separate report (Tian et al. 2006).

METHODS

Subjects

We studied nine patients with cerebellar degeneration (ages: 29–79, 6 male) and seven normal subjects (ages: 30–60, 6 male). Most patients had sporadic cerebellar degeneration. Two had a genetically undefined familial ataxia. Seven patients were tested for chair rotations and all nine for head impulses.

Eye-movement recording

Eye movements were measured using the magnetic field search coil method. Each subject wore dual scleral coils in each eye (Skalar,

In the present study, we address another important question regarding the RVOR: does the cerebellum contribute to the relationship of the eye-velocity axis to the position of the eye in the orbit? For some eye movements, such as saccades (Ferman et al. 1987; Tweed and Vilis 1990), pursuit (Ferman et al. 1987; Haslwanter et al. 1991; Tweed et al. 1992), and the interaural translational VOR (TVOR) (Angelaki et al. 2003; Walker et al. 2004a), there is a torsional eye velocity that depends on orbital position, i.e., a tilt of the angular-velocity axis. This behavior is in accord with Listing’s Law (LL), which defines the relationship of ocular torsion to the horizontal and vertical positions of the eye during fixation. In contrast, the RVOR demonstrates much less eye-position-dependent torsion; LL is violated (Crawford and Vilis 1991; Misslisch et al. 1994). The fact that the RVOR is more head-fixed (less dependent on eye position) has the theoretical advantage of more nearly stabilizing the entire visual image on the retina when the head is rotating.

Prior studies indicate that mechanical factors, e.g., orbital pulleys, the connective tissue sleeves that determine the pulling directions of the extraocular muscles (Demer et al. 1995), and neural innervation work together to determine the kinematic behavior of different types of eye movements, whether LL is obeyed (Ghasia and Angelaki 2005; Klier et al. 2006; Quaia and Optican 2003) or not (Smith and Crawford 1998). We hypothesized that the cerebellum might play a more specific role in the neural control of the kinematics of the RVOR given its various roles in the long-term calibration of eye movements, including the axis of the RVOR (Walker and Zee 2005). To test this hypothesis, we compared the orbital-position dependency of the RVOR in patients with cerebellar disease and normal subjects. Preliminary data from this study have been previously presented in abstract form (Walker et al. 2004b), and control data from chair rotations for normal subjects were included in a separate report (Tian et al. 2006).

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Delft, the Netherlands). A similar custom-made dual coil was attached tightly to a bite bar made of dental impression material that was fit to each subject and was held firmly between the teeth during the experiment. For the chair rotations, the bite bar served to hold the head fixed in the same position relative to the axis of rotation. For head impulses, this coil was used to record three-axis head rotation while the head was free. Raw coil signals were filtered in hardware (90-Hz low-pass Butterworth), digitized (1,000 Hz), and saved on computer for later analysis.

**Experimental paradigms**

**CHAIR ROTATIONS.** The subject sat in a motor-driven vestibular chair with the head upright and held steady by the bite bar. Each trial pair began with fixation of a laser target that was back-projected on a tangent screen (distance: 124 cm) in an otherwise nearly dark room. Target position on the screen was controlled by the computer through a pair of mirror galvanometers. The target was centered horizontally and was at one of three vertical positions: 0° (straight-ahead), 15° up, or 15° down. The chair accelerated (−200°/s²) randomly to the left or right to a plateau velocity of 40°/s. The rotation was continued for an additional ~300 ms and then decelerated until it stopped. The total amplitude of each rotation was ~20°. After the chair stopped, the target was moved in the direction of prior chair motion to re-center the eyes in the orbits horizontally, and a second trial brought the chair back to the center position. Approximately 10 trial pairs were performed for each initial rotation direction and each vertical eye position. For approximately half of the trials (randomly determined), the target was extinguished when the chair started to move and the rotation continued in darkness. For the other trials, the target remained on throughout the trial. Neither the presence nor absence of the target nor the predictability of the direction of rotation affected the kinematics of the response. Therefore all trials in the same direction and with the same vertical eye position were combined in the analysis.

**HEAD IMPULSES.** Yaw head impulses were performed by one of the authors (M. Walker) while standing behind the subject. The subject's head was free to move, and the head coil was held firmly in the mouth by its attached bite bar. At the beginning of each trial, the head was centered in the fields by the examiner, using an on-line feedback monitor that displayed the instantaneous three-axis position of the head. The subject was instructed to look at an LED target that was back-projected on a tangent screen (distance: 124 cm) in an otherwise nearly dark room. The slopes of these regressions are the tilt angle slope as a function of time by aligning the trials at 0.5°/s. The onset of head impulses was defined as the time at which the horizontal component of angular head velocity exceeded 5°/s.

For each data point, we determined the angular velocity axis for each eye in the sagittal (torsional-horizontal) plane. The instantaneous tilt angle was calculated as the arctangent of the ratio of the torsional to the horizontal component of eye velocity. A least-squares linear regression of this tilt angle to the instantaneous vertical position of the eye in the orbit yielded the tilt angle slope, which is a measure of the variation of the eye velocity axis with vertical eye position. To perform the regressions, data were separated into bins of 10-ms width, starting 50 ms from the onset of the trial and continuing for an additional 350 ms.

Rotation vectors can be expressed in a coordinate system that is aligned with the Listing primary position, i.e., in “Listing coordinates,” when calculating the tilt angle slope. To do this, an accurate measurement of Listing's primary position is required. In some human subjects, however, it is difficult to determine primary positions precisely, due to the possibility of static torsional slip of the eye coils (Bergamin et al. 2004). In other experiments in our laboratory, we have addressed this problem using fixation paradigms in which frequent reference positions are taken (e.g., Steffen et al. 2000). Time constraints did not allow us to do this in the present study. Nonetheless, to investigate the possibility that not calculating the tilt angle slope in Listing’s coordinates influenced our results, we calculated primary positions using the best available data (a square fixation paradigm with 20° target positions but without repeated reference positions throughout the collection period). The effect on the tilt angle slope and the difference between groups was negligible. Thus we left our data in standard head-fixed coordinates for the calculation of the tilt angle slope.

**RESULTS**

**Chair rotations**

Figure 1 shows responses of a representative normal subject and patient during head-fixed chair rotations. In the initial portion of the response, the response was close to head-fixed (there was very little torsion, regardless of vertical eye position). As the rotation proceeded, however, a torsional eye velocity appeared that was dependent on the vertical position: it was least for down gaze and greatest for up gaze. A similar behavior was seen in the patient, but the torsional velocities were larger.

Figure 2 shows 3-D eye velocity axes in two plots for one patient during leftward head rotation. At the very onset of rotation, there was little torsional eye velocity at any of the three vertical eye positions (left). When the horizontal eye velocity reached ~10°/s, the traces began to diverge (eye-position-dependent torsion and tilt angle slope started to increase). There was also an upward vertical component (upward velocities are negative) to the response, but this did not change with vertical eye position (right). Right eye data are shown, as our prior study (Walker and Zee 2005) showed that vertical eye velocities during yaw are greater in the abducting eye.

As in our prior report (Tian et al. 2006), we determined the tilt angle slope as a function of time by aligning the trials at their onsets and dividing the data points into bins of 10-ms width. All data in each bin were subjected to a least-squares linear regression of tilt angle to vertical eye position. Representative results for a single interval (270–280 ms) are shown in Fig. 3A. The slopes of these regressions are the tilt angle slopes. Note that the slope for the patient (0.63) is much greater.
than that of the normal subject (0.24). This difference was true
for the groups as a whole (Fig. 3B).

For each 10 ms interval, the tilt angle slopes from all
subjects in each group were averaged. The results are shown in
Fig. 4A. In normal subjects, the tilt angle slope was initially
very low but increased to a maximum of ∼0.3, near the time
when the chair velocity reached steady state. Patients also
began with a relatively low tilt angle slope. However, it
increased more rapidly with time and reached a higher maxi-
mum (∼0.5). Figure 4B shows that the difference in slopes
between the two groups was highly significant throughout most
of the response.

**Head impulses**

Representative responses to yaw head impulses are shown
in Fig. 5 for one normal subject and one patient. For both
subjects, the axis of eye velocity varied as a function of the
vertical position of the eyes in the orbits. When the eyes
were looking up, the head and eye velocities were most
closely aligned. When the eyes were looking down, there was a greater torsional eye velocity (the axis shifted downward), even though the axis of head velocity did not change. As for the head-fixed chair rotations, this shift of the eye velocity axis was much larger in the patient than in the normal subject.

FIG. 3. Determination of tilt angle slope. A: representative linear regressions are shown for 1 normal subject and 1 patient for chair rotation data during the interval 270–280 ms after stimulus onset (during the period of constant chair velocity). Each individual point represents the instantaneous tilt angle (arctangent of the ratio of torsional to horizontal eye velocity) at 1 time point during that interval. Data from all trials were pooled for the analysis. - - -, results of least-squares linear regressions of these data. B: regression lines depicting the tilt angle slopes for each subject during this same time interval. Each line represents 1 subject and 1 rotational direction (average slope from both eyes). The intercepts have been subtracted off.

FIG. 4. A: tilt angle slopes as a function of time for chair rotations. For each time interval, tilt angle slopes were calculated for each subject and direction of rotation, using least-squares linear regression, averaging values from the 2 eyes. The across-subject means of these values are plotted for each subject group along with the corresponding 95% confidence intervals. Tilt angle slopes could not be reliably calculated before 50 ms after rotation onset and thus are not shown. B: p values for each interval based on a Wilcoxon rank-sum test, comparing tilt angle slopes in patients and normal subjects. Note that the difference between the groups is highly significant, except for the initial interval where the difference was small.
Tilt angle slopes for head impulses were determined using eye velocity data from the interval 80–90 ms from head impulse onset, which was near the time of peak head velocity. As for chair rotations, tilt angle slopes were higher in the patient group than in the control subjects (Fig. 6). This difference in slopes between groups was highly significant (P < 0.005, Wilcoxon rank sum). The absolute magnitude of the slopes, however, was smaller in both groups of subjects than for the chair rotations.

**DISCUSSION**

Here we have shown that cerebellar disease has a major effect on the 3-D kinematics of eye velocity during rotation of the head around the yaw-axis. Compared with normal subjects, there is substantially more eye-position-dependent torsional velocity. This new finding supports a central role for the cerebellum in the control of 3-D eye position during the RVOR.

Two additional, and potentially related, aspects of eye-velocity kinematics did not require an intact cerebellum. First, in our cerebellar patients, as we have shown for normal subjects (Tian et al. 2006), the axis of eye velocity evolved over time during rotation of the head. Remarkably, at the onset of head rotation, eye velocity was nearly head-fixed, i.e., there was little eye-position-dependent torsion. Second, consistent with the combined results from prior studies (Misslisch and Tweed 2001; Palla et al. 1999; Thurtell et al. 1999; Tian et al. 2006; Walker et al. 2004a), the dynamics of the stimulus affected the kinematics of eye motion. In both patients and normal subjects, responses to head impulses were more head-fixed than responses to lower-acceleration chair rotations. We will discuss all these results in light of prior work regarding the kinematics of the RVOR, the possible relationship to LL, and the cerebellar contribution to control of the axis of eye rotation during head rotation.

**Torsion, the RVOR, and LL**

Misslisch et al. (1994) showed that the axis of the RVOR, in humans, depends on orbital position, but it does not obey LL. For low-frequency stimuli, the eye-velocity axis tilts ~25% of the orthogonal gaze angle; this is half of what LL predicts (Tweed and Vilis 1987). Misslisch et al. (1994) suggested that this represents a compromise between LL and the head-fixed axis of an ideal RVOR. Subsequent studies have suggested that many other variables, such as the frequency and/or acceleration of the stimulus, species, and the visual environment during head rotation, can influence the eye-velocity axis (e.g., Misslisch and Hess 2000; Palla et al. 1999; Thurtell et al. 1999; Tian et al. 2006; Walker et al. 2004a).

Here we focused on the temporal dependence of RVOR kinematics (Tian et al. 2006). Using transient stimuli, the RVOR axis evolved over time: the early response (from the point at which it could be reliably measured, ~50 ms from the onset of chair rotation) is nearly head-fixed; thereafter eye-position-dependent torsion increases with time, reaching a plateau at about the time that steady-state head velocity is reached. Temporal dependence of RVOR kinematics was reported by Thurtell et al. (1999) but not by Crane et al. (2006).
The results of our studies and those of Thurtell et al. (1999) support the hypothesis that the early RVOR is close to head-fixed, i.e., the response axis is not modulated by orbital position. We show here that this property of the initial RVOR does not require an intact cerebellum, suggesting that it is mediated by elementary RVOR pathways within the brain stem.

Origin of eye-position-dependent torsion

What implications do our findings in the RVOR have for an understanding of the control of ocular torsion by the brain? Over the last two decades, a general consensus has emerged that ocular kinematics are determined by a combination of neural innervation and the mechanical constraints of the orbital pulleys, the connective tissue sleeves that determine the pulling directions on the globe of the extraocular muscles (Angelaki 2003; Angelaki and Hess 2004; Crawford et al. 2003; Demer 2006; Demer et al. 1995; Klier et al. 2006; Misslisch and Hess 2000; Misslisch and Tweed 2001; Quaia and Optican 2003; Smith and Crawford 1998). Important questions remain, however, regarding the interaction between 3-D neural signals and orbital mechanics, including which brain areas are important for the calibration of the neural component. Our data here in cerebellar patients do not address directly the mechanisms responsible for LL as the RVOR does not follow LL. They do, however, provide new and important information regarding the neural control of RVOR kinematics, and they show that the cerebellum plays a critical role in this process, particularly just after the initial response to head rotation (see also: Cerebellum and the axis of eye rotation during the RVOR).

The RVOR, unlike saccades and pursuit, is inherently 3-D (Tweed 1997). Semicircular canal afferents carry signals that encode 3-D angular head velocity. This alone, however, would not necessarily be sufficient to generate a head-fixed eye velocity. A recent study found that eye movements generated by direct abducens nerve stimulation follow the “half-angle rule,” i.e., they obey LL (Klier et al. 2006). This suggests that the ocular pulleys confer a default orbital-position dependence to the pulling directions of the eye muscles and hence an eye-position-dependent torsion. To compensate for this imposed eye-position-dependent torsion, the RVOR would need to incorporate eye-position information itself into the eye muscle innervations. An innervation that was eye-position invariant, even though 3-D, would not suffice.

An important question then is how such eye-position compensation might be achieved by the RVOR. Originally it was suggested that the pulleys might move posteriorly in the orbit during head rotation (Demer et al. 2000; Thurtell et al. 1999, 2000), but this was shown unlikely to be feasible and at odds with other experimental data (Angelaki 2003; Crane et al. 2005; Misslisch and Tweed 2001). Alternatively, there might be a neurally generated torsional signal, dependent on eye position, that is sent to the cyclovertical eye muscles to counteract the effects of pulleys. Such a signal, however, has not been found on primary motor neurons during eye movements (Ghasia and Angelaki 2005). It is conceivable, however, that the eye-position dependence of the 3-D neural signal might not be readily seen in the responses of individual neurons (Smith and Crawford 2005). Clearly more information is needed to resolve the seeming discrepancies between neural recordings.

**Fig. 6.** Tilt angle slopes for head impulses (80–90 ms from head rotation onset). A: example regressions for 1 normal subject and 1 patient (as in Fig. 3A). B: boxplot comparing tilt angle slopes in the 2 groups. The boxes indicate the median and include the 2 middle quartiles for each group. The whiskers encompass the full range of data values, except for a single outlier (+) in the patient group.
and the measured 3-D kinematics of eye movements during head rotation.

Cerebellum and the axis of eye rotation during the RVOR

A role for the cerebellum and its brain stem connections in the control of eye-position-dependent torsion (e.g., in the case of fixation, LL) is supported by several prior studies. The caudal nucleus reticularis tegmenti pontis (cNRTP), which projects to the cerebellum, is necessary for the correction of torsional errors that occur during saccades (Van Opstal et al. 1996). Moreover, spontaneous nystagmus in cerebellar disease violates LL (Glasauer et al. 2003; Straumann et al. 2000).

Our data indicate that the cerebellum also has a large effect on eye-position-dependent torsion in the RVOR, not on the initial eye-velocity axis but rather on its evolution over time. How might this happen? One possibility is that, similar to the role of the cNRTP for saccades, the brain monitors changes in torsional orientation of the eyes during the RVOR and imposes eye-position-dependent torsion to prevent the eyes from drifting too far from Listing's plane. The function of the cerebellum might then be to modulate this effect to achieve the compromise between the competing goals of keeping eye positions in LP (half-angle rule) and maintaining retinal stability of the visual image (head-fixed axis) (Misslisch et al. 1994). Without the cerebellum, there is no such compromise. Alternatively, the evolution of kinematics could reflect the activity of the velocity-to-position ocular motor neural integrator (Crawford 1994; Glasauer et al. 2003). Indeed the cerebellum and the flocculus and paraflocculus in particular play a key role in the function of the ocular motor integrator (Zee et al. 1981).

In conclusion, in spite of the uncertainty of neural mechanisms, our findings here strongly support the idea that the cerebellum is directly involved in the 3-D control of the RVOR in response to abrupt head rotations. Except perhaps for the very early portion of the response—the initial 50 ms or so, when the axis of eye rotation is close to head-fixed – the cerebellum controls the relationship of eye-velocity axis to the position of the eye in the orbit. This behavior complements the previously shown roles of the cerebellum in processing canal position of the eye in the orbit. This behavior complements the very early portion of the response—the initial 50 ms or so, controlling the axis of the RVOR in response to sustained, lower-frequency rotational stimuli (Angelaki and Zee 2005) and controlling the axis of the RVOR in response to the cerebellum controls the relationship of eye-velocity axis to the position of the head. J Neurophysiol 65: 407–423, 1991.


