Cerebellar Disease Alters the Axis of the High-Acceleration Vestibuloocular Reflex

Mark F. Walker1,2 and David S. Zee1,2,3,4
1Departments of Neurology, 2Ophthalmology, 3Otolaryngology-Head and Neck Surgery, and 4Neuroscience, The Johns Hopkins University School of Medicine, Baltimore, Maryland

Submitted 13 April 2005; accepted in final form 15 July 2005

Walker, Mark F. and David S. Zee. Cerebellar disease alters the axis of the high-acceleration vestibuloocular reflex. J Neurophysiol 94: 3417–3429, 2005. First published July 20, 2005; doi:10.1152/jn.00375.2005. L. W. Schultheis and D. A. Robinson showed that the axis of the rotational vestibuloocular reflex (RVOR) cannot be altered by visual-vestibular mismatch (“cross-axis adaptation”) when the vestibulocerebellum is lesioned. This suggests that the cerebellum may calibrate the axis of eye velocity of the RVOR under natural conditions. Thus we asked whether patients with cerebellar disease have alterations in the RVOR axis and, if so, what might be the mechanism. We used three-axis scleral coils to record head and eye movements during yaw, pitch, and roll head impulses in 18 patients with cerebellar disease and in a comparison group of eight subjects without neurologic disease. We found distinct shifts of the eye-velocity axis in patients. The characteristic finding was a disconjugate upward eye velocity during yaw. Measured at 70 ms after the onset of head rotation, the median upward gaze velocity was 15% of yaw head velocity for patients and <1% for normal subjects (P < 0.001). Upward eye velocity was greater in the contralateral (abducing) eye during yaw and in the ipsilateral eye during roll. Patients had a higher gain (eye speed/head speed) for downward than for upward pitch (median ratio of downward to upward gain: 1.3). In patients, upward gaze velocities during both yaw and roll correlated with the difference in anterior (AC) and posterior canal excitations, scaled by the respective pitch gains. Our findings support the hypothesis that upward eye velocity during yaw results from AC excitation, which must normally be suppressed by the intact cerebellum.

INTRODUCTION

The purpose of the rotational vestibuloocular reflex (RVOR) is to stabilize the eyes in space during angular motion of the head. Commonly, this is considered in a single-axis (one-dimensional) sense. For example, the “horizontal” RVOR is said to compensate for yaw head rotations by generating a horizontal eye velocity that is equal and opposite to head velocity. However, the head has 3 degrees of rotational freedom, and most natural head rotations contain components about the yaw, pitch, and roll axes. This requires that the RVOR be a three-dimensional reflex.

Each head rotation results in a unique pattern of semicircular canal (SCC) activation that depends on the orientations of the individual canals relative to the axis of head velocity. The orientations of the human SCCs were first described mathematically by Blanks et al. (1975), who based their work on measurements in a series of dissected skulls. Their findings suggested that the canals are not mutually orthogonal and that there is substantial variability in canal orientations among individuals. Recent studies have suggested that the canals may be more nearly orthogonal anatomically (Della Santa et al. 2005) and in their physiologic responses (Haque et al. 2004; Rambold et al. 1984; Nagao and Kitazawa 2003; Rambold et al. 1981). The plasticity of RVOR gain has also been shown to require not only appropriately weighted direct connections (e.g., between the HCs and horizontal recti) but also cross-connections. These connections would need to be calibrated uniquely in each individual to account for particular idiosyncrasies, e.g., in the exact orientations of the SCCs and EOMs.

The vestibulocerebellum is a likely candidate for the calibration of the RVOR axis. This is supported by the experimental finding that animals with vestibulocerebellar lesions are no longer able to adapt the RVOR axis in response to a visual-vestibular mismatch that asks the eyes to rotate around an axis that is different from that of the head (Schultheis and Robinson 1981). The plasticity of RVOR gain has also been shown to require an intact vestibulocerebellum (Blazquez et al. 2003; Lisberger et al. 1984; Nagao and Kitazawa 2003; Rambold et al. 2002; Robinson 1976). Consequently, we hypothesized that in patients with cerebellar disease, the normal three-dimensional calibration might be lost, resulting not only in changes in gain but also in shifts of the eye velocity axis during head rotation. To test this hypothesis, we studied responses to high-acceleration manual head impulses in a series of patients with cerebellar degeneration. Some data from this study have been previously presented in preliminary form (Walker and Zee 1999; Walker et al. 1999).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
TABLE 1. List of patients

<table>
<thead>
<tr>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>SPV of DBN</th>
<th>Yaw VGV (Head Velocity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1</td>
<td>71</td>
<td>M</td>
<td>−1.41</td>
<td>−40.5 (220)</td>
</tr>
<tr>
<td>P2</td>
<td>60</td>
<td>M</td>
<td>−0.11</td>
<td>−7.9 (101)</td>
</tr>
<tr>
<td>P3</td>
<td>51</td>
<td>F</td>
<td>−0.53</td>
<td>−35.2 (179)</td>
</tr>
<tr>
<td>P4</td>
<td>42</td>
<td>F</td>
<td>−0.85</td>
<td>−9.6 (210)</td>
</tr>
<tr>
<td>P5</td>
<td>64</td>
<td>M</td>
<td>−0.30</td>
<td>−8.5 (210)</td>
</tr>
<tr>
<td>P6</td>
<td>44</td>
<td>F</td>
<td>−6.01</td>
<td>−39.6 (173)</td>
</tr>
<tr>
<td>P7</td>
<td>75</td>
<td>F</td>
<td>−4.56</td>
<td>−21.8 (142)</td>
</tr>
<tr>
<td>P8</td>
<td>68</td>
<td>M</td>
<td>−0.61</td>
<td>−3.9 (190)</td>
</tr>
<tr>
<td>P9</td>
<td>33</td>
<td>F</td>
<td>−1.75</td>
<td>−60.3 (174)</td>
</tr>
<tr>
<td>P10</td>
<td>66</td>
<td>F</td>
<td>−1.77</td>
<td>−3.1 (113)</td>
</tr>
<tr>
<td>P11</td>
<td>50</td>
<td>F</td>
<td>−2.17</td>
<td>−18.5 (121)</td>
</tr>
<tr>
<td>P12</td>
<td>24</td>
<td>F</td>
<td>−4.07</td>
<td>−48.4 (125)</td>
</tr>
<tr>
<td>P13</td>
<td>56</td>
<td>F</td>
<td>−2.52</td>
<td>−17.1 (130)</td>
</tr>
<tr>
<td>P14</td>
<td>75</td>
<td>F</td>
<td>−0.33</td>
<td>−11.5 (301)</td>
</tr>
<tr>
<td>P15</td>
<td>49</td>
<td>M</td>
<td>−3.92</td>
<td>−1.4 (316)</td>
</tr>
<tr>
<td>P16</td>
<td>55</td>
<td>M</td>
<td>−2.54</td>
<td>−47 (190)</td>
</tr>
<tr>
<td>P17</td>
<td>32</td>
<td>F</td>
<td>−0.30</td>
<td>−6.9 (151)</td>
</tr>
<tr>
<td>P18</td>
<td>73</td>
<td>M</td>
<td>−1.6</td>
<td>−18.1 (134)</td>
</tr>
</tbody>
</table>

Age, sex, and diagnosis (if known) of patients studied; slow-phase velocity (SPV) of downbeat nystagmus (DBN), while looking straight ahead and maintaining fixation of a continuously illuminated light-emitting target; and vertical gaze velocity (VGV) during yaw impulses (70 ms after head impulse onset) in the abducting eye (average of both directions, unless only 1 eye was recorded).

METHODS

Subjects

Eighteen patients with clinically pure cerebellar disorders (Table 1) and a comparison group of eight normal subjects were studied. All patients had symptoms and signs commonly attributed to dysfunction of the vestibulocerebellum, including downbeat and gaze-evoked nystagmus, impaired smooth pursuit, and impaired cancellation of the VOR with visual fixation. Patients were excluded from the study if there were clinical signs of brain stem or any other neurological disorder (e.g., extrapyramidal systems and if there was evidence of prominent peripheral vestibular dysfunction (absent head impulse responses). For most patients, an underlying cause of the cerebellar disease was not identified. One patient had familial episodic ataxia, most consistent clinically with EA-2 (not genetically defined). Two patients had genetically confirmed spinocerebellar ataxia type 6 (SCA6). One patient was thought to have an arrested paraneoplastic familial syndrome related to a small cell carcinoma of the lung. The ages of the patients ranged from 24 to 73. Normal subjects (6 male, 2 female) ranged in age from 20 to 65.

TABLE 2. Peak velocities and accelerations of head impulses (median and range)

<table>
<thead>
<tr>
<th>Normal Subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Peak Velocity, °/s</td>
</tr>
<tr>
<td>Rightward yaw</td>
<td>208 (144–235)</td>
</tr>
<tr>
<td>Leftward yaw</td>
<td>194 (133–295)</td>
</tr>
<tr>
<td>CW roll</td>
<td>111 (71–145)</td>
</tr>
<tr>
<td>CCW roll</td>
<td>98 (72–115)</td>
</tr>
<tr>
<td>Upward pitch</td>
<td>88 (58–138)</td>
</tr>
<tr>
<td>Downward pitch</td>
<td>113 (77–140)</td>
</tr>
</tbody>
</table>

Stimulus dynamics for head impulses about yaw, pitch, and roll axes for normal subjects and patients. For each subject, the mean peak head velocity and acceleration about the primary axis were calculated. Each value in the table gives the median (of these means) for all subjects in a group followed by the range. There was no consistent difference between normal subjects and patients (see text). CW, clockwise; CCW, counterclockwise.
activation of the vertical semicircular canals (see following text). This was done to investigate the relationship between the degree of stimulation of the contralateral AC and the vertical eye velocity during yaw rotation. The procedure was to rotate the head about an earth-vertical axis while it was in different pitch positions (nose-down or nose-up). In a head-fixed coordinate system, this corresponds to a combination of yaw and roll. Instantaneous head position feedback allowed us to maintain the desired head rotation axis (although this was not essential, as analysis was done using the actual measured head velocity axis). The target position was moved up or down according to pitch position, so that the eyes always started in the center of the orbits. For example, if the head was pitched 20° forward, then the target was moved 20° down from the center.

Analysis

Rotation vectors representing head and eye position were derived from the coil signals using a standard method that has been previously described (e.g., Bergamin et al. 2001). The reference eye and head positions were taken with the head upright and centered and gaze directed at the center LED target. Details of angular velocity calculation, coordinate transformations, and projection of head velocity onto the SCCs are given in the APPENDIX.

Individual head impulses were selected for analysis using an interactive program. Trials were excluded from analysis if the subject was not fixating the target at the onset of head rotation or if the initial slow phase was interrupted by a blink or saccade. The onset of the head impulse was determined using a velocity criterion, namely when the magnitude of head velocity (around the principal axis) exceeded 5°/s.

All head and eye positions and velocities are specified according to the right-hand rule: positive positions and velocities are clockwise, down, and to the left (from the subject’s perspective). For proper comparison, both head and eye velocities were determined relative to a head-fixed coordinate system (see APPENDIX).

Statistics

Gains and gaze velocities for an individual subject were calculated as the mean values for the series of similar head impulses. To compare the groups, however, we used medians and nonparametric statistics because the heterogeneity of the patient group makes it unlikely that data from this group are normally distributed. Unless otherwise stated, all statistical comparisons used the Wilcoxon rank-sum test.

RESULTS

Yaw impulses

Yaw, pitch, and roll gains for normal subjects and patients are given in Table 3. There was a wider range of responses in patients, with gains ranging from lower to higher than normal. The main finding of the study is illustrated in the yaw impulse responses of Fig. 1. In the normal subject, horizontal eye position compensates appropriately for head rotation, and there is little vertical movement of the head or eye. In the patient, however, the evoked slow phase has both horizontal and vertical components. First, there is a leftward eye rotation but with a gain >1.0 (i.e., overcompensatory). At the same time, the eye moves up by almost 5°. This leads to a gaze position error: when the head stops, the eye is above and to the left of the target, triggering a corrective saccade down and to the right. Note that the upward eye movement is tied closely to the head rotation, and there is little upward drift (e.g., from downbeat nystagmus) when the head is not moving.

Figure 2 shows head-in-space and eye-in-head velocity axes during rightward yaw in two dimensional plots (vertical vs. horizontal).

### Table 3. RVOR Gains at 70 ms (median and range)

<table>
<thead>
<tr>
<th></th>
<th>Normal Subjects</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yaw</td>
<td>0.93 (0.78–1.06)</td>
<td>0.87 (0.56–1.81)</td>
</tr>
<tr>
<td>Roll</td>
<td>0.65 (0.59–0.81)</td>
<td>0.52 (0.29–0.97)</td>
</tr>
<tr>
<td>Upward pitch</td>
<td>0.92 (0.70–0.97)</td>
<td>0.72 (0.46–1.64)</td>
</tr>
<tr>
<td>Downward pitch</td>
<td>0.94 (0.91–0.97)</td>
<td>0.91 (0.57–2.18)</td>
</tr>
</tbody>
</table>

Rotational vestibuloocular reflex (RVOR) gains for each rotational axis. The gain (measured at 70 ms from the onset of head rotation) was calculated for each head impulse as the ratio of instantaneous eye-in-head speed to head speed along the primary axis. A mean was determined for the series of trials in each subject. The table shows the median value and range for these sets of mean gains for each subject group. For yaw and roll, data from both directions were combined. Pitch data were not combined, due to the difference in gains for upward and downward pitch in patients.
horizontal) for one normal subject and three patients. For this figure, we show the mean and 95% confidence interval of the first 70 ms of the response in a series of similar trials. In the normal subject, the velocity axes of both eyes were matched closely to that of the head. In patients, the response was very different. The axis of eye velocity deviated substantially from head velocity in a similar pattern: in each case, there was an upward (negative vertical) eye velocity that was larger in the eye contralateral to the direction of head rotation (the abducting eye). There were some differences in the exact response dynamics over time, among subjects, between abducting and adducting eyes, and between horizontal and vertical eye velocity. However, the overall axis shift is apparent throughout most of the response in each case.

Because the upward eye velocities seen in patients did not compensate for a downward head velocity, there was a substantial vertical gaze velocity (i.e., retinal slip of the target). Such upward gaze velocities were seen in most patients (Table 1, Fig. 3A). When normalized to yaw head velocity, the median gaze velocity (measured at 70 ms) was 0.0039 for normal subjects and 0.15 for patients (i.e., in patients, the median upward gaze velocity was 15% of yaw head velocity). This difference was highly significant ($P < 0.001$, rank-sum). 

In three patients, we extended our experiments, using a series of combined yaw-roll head impulses to test the effect of altering the axis of head rotation on vertical gaze velocity (see METHODS). For these data, we projected head velocity onto the axes of the SCCs, using the canal orientations of Della Santina et al. (2005) as described in METHODS. For each impulse, we then compared the vertical eye-in-head velocity of the contralateral eye to head velocity in the plane of the contralateral AC (Fig. 4B). In all 3 patients, the vertical eye velocity was minimal when AC excitation was expected to be small, and it increased with increasing AC velocity. This relationship is also evident in the two example impulses shown in Fig. 4A. For the first impulse (left), leftward yaw and a small downward pitch

![Graphs showing head and eye-in-head velocities](http://jn.physiology.org/)

**FIG. 2.** Two-dimensional plots of head and eye-in-head velocities during the first 70 ms of rightward head impulses in 1 normal subject and 3 patients. Solid lines show the mean velocities and shaded areas the 95% confidence intervals for a series of similar impulses (8–14 impulses for each subject). Head velocities are inverted for comparison. Head velocity is shown in green, left (abducting) eye in blue, and right (adducting) eye in red. Patients had a shift of the axis of eye velocity, greater in the abducting eye, with a negative (upward) vertical component. For comparison, axes are equivalent for all plots, and horizontal and vertical axis scales are equal.
combine to excite the right AC more than the right PC. For this impulse, there is a large upward velocity in the contralateral (right) eye. In contrast, the axis of the second impulse (right) is expected to produce a much greater stimulation of the PC than the AC. Correspondingly, there is little upward velocity in the right eye, and the left eye has a downward velocity, most likely due to activation of the left inferior rectus muscle from right PC excitation. There is also a large counterclockwise torsional eye velocity that is slightly larger in the ipsilateral (adducting) eye. For rightward impulses, the direction of torsion was reversed, becoming clockwise. Note also that for all three patients, there was no clear correlation between vertical eye velocity and HC velocity (data not shown).

A consequence of horizontal gain variability and vertical gaze velocities is a worsening of gaze stability as shown in Fig. 5. In patients, the gaze position errors at the end of the impulse were greater, and gaze velocities during rotation were greater. The largest difference was in vertical position and velocity errors, which were minimal in normal subjects. Thus there was more retinal slip of the target in patients, and the fovea was displaced further from the original target, when the head was stopped. Note that for this comparison, we did not normalize to head velocity because we were interested in the visual consequences of the abnormal VOR and hence the actual gaze errors.

**Roll impulses**

During both clockwise (CW) and counterclockwise (CCW) roll, there was an inappropriate upward eye velocity. This was true in both normal subjects and patients, although the largest values were seen in patients (Fig. 6A). The disconjugacy was present only in patients. In contrast to yaw, during roll the vertical velocity in patients was greater in the eye ipsilateral to the rotation (e.g., the right eye for CW roll, Fig. 6B, \( P < 0.001 \), signed-rank pairing ipsilateral and contralateral eyes in each patient).

**Pitch impulses**

The main finding for pitch impulses was an asymmetry of gain in patients: responses to downward pitch were greater than those to upward pitch (Fig. 7A) (see also Walker and Zee 2005), i.e., there was an upward slow-phase bias. In patients, the ratio of pitch gains (downward/upward) ranged from 0.85 to 1.94 (median: 1.30). In contrast, normal subjects had overall more symmetric responses (gain ratio: 0.99–1.33, median: 1.01). These differences in gain ratios between groups were significant (\( P < 0.05 \)).

We asked whether this pitch asymmetry correlated with the upward eye velocity seen during yaw and roll in the same patients. For all 13 patients in whom the Reid angle was known, we projected head velocity onto the AC and PC (as for Fig. 4). We then multiplied AC velocity by the gain for downward pitch (measured in the same eye) and subtracted from this the PC velocity multiplied by upward pitch gain (see Fig. 7, legend). This net scaled vertical canal velocity correlated strongly with upward eye-in-head velocity across patients (Fig. 7B). Moreover, the relationship was similar for both yaw and roll in the subset of patients for whom data for both rotational axes were available and was consistent with the upward eye velocity seen during pitch (Fig. 7C).

Although there were gain asymmetries for pitch, we did not observe consistent axis shifts. During pitch impulses, there was a wider range of torsional and horizontal gaze errors in patients than in normal subjects. However, there was no difference in the median values (\( P > 0.2 \) for torsional and horizontal gaze velocity at 70 ms).
In this study, in agreement with our preliminary reports (Walker and Zee 1999), we have shown that patients with cerebellar disease have characteristic shifts of the axis of eye velocity during abrupt high-acceleration head rotations. The main finding was an upward eye velocity during yaw that was greater in the contralateral (abducting) eye. This upward velocity was found in most patients but not in normal subjects. There also was an upward velocity during roll, greater in the ipsilateral eye. This was found in both patients and normal subjects, although it was disconjugate only in patients. In extended experiments in three patients, using rotations with multiple yaw-roll axes, there was a high correlation between the measured upward eye velocity during yaw and the calculated excitation of the contralateral AC. Similarly, in the larger group of patients, responses could be explained by the expected AC and PC excitations, taking into account the differences in up- and downward pitch gains. These findings are all consistent with our hypothesis that inappropriate upward eye velocities result from a relative loss of inhibition of the AC input when it is excited during yaw or roll.

**Proposed mechanism for shifts of eye-velocity axis**

In a preliminary report (Walker and Zee 1999), we proposed that vertical eye velocity during yaw could result from contralateral AC excitation with a loss of the normal inhibition that prevents vertical eye velocity when there is no pitch head motion. Our current data further support this hypothesis.

As a first approximation, the sensitivity of a given semicircular canal to a particular head rotation can be estimated from the relationship of its anatomic orientation to the axis of head velocity. In this case, earth-vertical rotations at various pitch angles would be expected to have the canal sensitivities shown in Fig. 8 (recalculated after Curthoys et al. 1977; using the data of Della Santina 2005). In the normal head-upright position, yaw rotations excite the ipsilateral HC and the contralateral AC and PC. However, if the head is pitched forward, such that Reid’s line becomes earth horizontal, an earth-vertical axis rotation would be expected to produce very little AC stimulation. A pure roll rotation excites the ipsilateral AC and PC.

In normal subjects, a yaw rotation produces little vertical eye velocity even though the vertical canals receive a substantial stimulus. In our patients, however, there was typically an upward velocity during yaw in either direction. Based on our hypothesis, for this to occur, the gain of the contralateral AC input would need to be greater than that of the PC because, based on geometry, the AC and PC are expected to have a similar sensitivity to any yaw-roll axis (Fig. 8).

If AC gain is higher than PC gain, one would expect that this would be reflected in the responses to pitch: the gain for downward pitch (exciting the ACs) should be greater than the gain for upward pitch (exciting the PCs). This is, in fact, what
we found in these patients (Fig. 7A) (see also Walker and Zee 2005). Moreover, pitch gain asymmetries predicted well the vertical responses during yaw and roll (Fig. 7, B and C). Finally, in the three subjects tested with multiple rotational axes, minimizing the expected stimulation of the AC reduced the upward gaze velocity (Fig. 4). In contrast, there was no relationship of upward eye velocity to HC velocity, making it unlikely that the vertical eye velocity results from “misdirection” of HC inputs to vertical eye muscles. Thus our findings support the hypothesis that pitch gain asymmetries contribute to the cross-axis response.

Our finding of asymmetric pitch gains in patients appears different from a recent report by Glasauer et al. (2004). That study found no difference in the mean gains for up- and downward pitch in a group of patients with downbeat nystagmus. Consistent with our findings, however, a number of the patients in their study had higher gains for downward pitch. The main difference was that there were two patients in their study who had much lower gains for downward pitch. In contrast, all but one of our patients had a higher gain for downward pitch. Moreover, an important finding in our patients is that the asymmetry of pitch in each subject was correlated with the upward eye velocity during yaw and roll: the greater the asymmetry, the larger the axis shift (Fig. 7). Based on this, we would predict that patients with a much higher gain for upward pitch would not demonstrate an upward eye velocity (but might have a downward eye velocity) during yaw.

Our hypothesis does not imply that pitch gain asymmetries in the absence of cerebellar disease would lead to similar RVOR cross-axis responses. For example, one of our normal subjects had a lower gain for upward pitch but had no vertical velocity during yaw. It may be that the normal cerebellum is able to take vertical canal gain asymmetries into account when calibrating the yaw RVOR, and that it is only when the cerebellum is diseased that yaw RVOR cross-coupling appears.

Why might AC pathway gains be high?

The implication of this hypothesis is that the AC is preferentially disinhibited by cerebellar disease. This is consistent with prior studies that suggest that the flocculus and ventral paraflocculus (FL/VPF) largely send their inhibitory output to flocculus target neurons in the anterior and HC pathways with less involvement of the PC pathways (Ito et al. 1977; Sato and Kawasaki 1990; Zhang et al. 1995). Perhaps loss of FL/VPF Purkinje cells removes this asymmetric inhibition, uncovering an underlying AC bias. Of course, we recognize that a simple disinhibition may not adequately account for the changes in gain but that other mechanisms, such as changes in synaptic plasticity, may also take place.

Our hypothesis is also consistent with the roll results (including the disconjugacy). In patients, CW roll was associated with an upward eye velocity greater in the right eye, and CCW roll was associated with an upward eye velocity greater in the left eye. Based on anatomic orientations, roll excites all three ipsilateral canals similarly (Fig. 8). Again, because the AC input has a higher gain than the PC in patients, one would expect an upward eye movement during roll, and this might be greater in the eye ipsilateral to the excited AC. Normal subjects had upward eye velocities during roll. It may be that, just as roll gains are normally less than compensatory, the axis of eye rotation is less precisely calibrated than for yaw or pitch, even in normal subjects.

Why is vertical eye velocity disconjugate?

Upward eye velocity during yaw was disconjugate: it was greater in the contralateral (abducting) eye. This “dynamic skew” resembles the static alternating skew deviation that is seen in many of these patients, in which there is usually a hypertropia of the abducting eye (Versino et al. 1996). There are two possible explanations for the dynamic skew, not necessarily mutually exclusive. The first is that this is simply the static skew superimposed on a conjugate (horizontal and
upward) vestibular response. Second, the dynamic disconjugacy could result from a difference in pulling directions of the muscle pair activated by excitation of one AC. For example, excitation of the right AC (e.g., during leftward yaw) is transmitted to the right superior rectus (SR) and left inferior oblique (IO) muscles. Given the orientation of the IO (Robinson 1975) and the effect of its pulley (Demer et al. 2003), one would expect that it would have a more torsional pulling direction than the SR. Thus during leftward yaw, one would expect a greater upward velocity in the right eye and a greater torsional velocity in the left eye. This is the pattern that we observed (Fig. 4A).

Vertical velocity during roll was also disconjugate in patients: as for yaw, it was greater in the eye ipsilateral to the excited AC (e.g., the right eye for CW rotations). Once again, this could be due to differences in the pulling directions of the SR and IO. Because for roll the head was tilted relative to gravity, a skew could also result from otolith mechanisms (i.e., the ocular tilt reaction, see following text), but this would not explain the findings during yaw. Thus a better explanation for both the yaw and roll disconjugacies is the difference in SR and IO pulling directions.

Could otolith mechanisms be responsible for cross-axis responses?

This is a question that is most relevant for interpretation of roll responses because roll impulses were performed with the head upright, leading to a tilting of the head relative to gravity. During yaw, there was no head tilt, but there might have been a translation of the labyrinths because the axis of rotation for head impulses is centered on the vertebral column rather than between the ears. This raises the question of whether an otolith-mediated mechanism could have contributed to the
vertical eye velocity during yaw and/or roll. Indeed, the otolith induced translational VOR has been shown to undergo cross axis plasticity (Wei and Angelaki 2001).

There are several reasons that otolith mechanisms are unlikely to explain most of our findings. First, in general, dynamic utricular responses tend to be reduced or absent in patients with cerebellar disease, at least when measured by the horizontal eye velocity during interaural translation (Balogh et al. 1995; Wiest et al. 2001; Zee et al. 2002). Second, vertical eye velocities correlated well with pitch gain asymmetries. Moreover, the relationship was similar for yaw and roll (Fig. 7C). Finally, when the axis of yaw-roll head velocity was varied, vertical eye velocity correlated strongly with calculated AC excitation (Fig. 4). Nonetheless, it remains possible that some part of the response, for example the disconjugate (skew) component during roll, might have been due to otolithic activation.

**Response dynamics**

Among patients, there was some variability in the exact dynamics of their yaw responses. In patient P16, for example, vertical eye velocity increased more rapidly than horizontal eye velocity, leading to a slightly curved axis, most prominently in the abducting eye (Fig. 2). How could a miscalibration of primary RVOR pathways lead to responses with nonlinear dynamics? In basic models of the RVOR, it is generally assumed that the reflex is linear, such that instantaneous eye velocity is a scalar multiple of head velocity. However, this assumption is most valid for low-frequency and low-acceleration stimuli. Response dynamics for high-acceleration and -velocity stimuli may be different. For example, Minor et al. (1999) have shown in a series of experiments in squirrel monkeys that the high-frequency RVOR is nonlinear with a gain that appears to depend on head velocity. To some extent, this may be species-dependent: in one study, such nonlinearities were not observed in rhesus monkeys (Huterer and Cullen 2002), although a recent study showed gain increases at very high frequencies (Ramachandran and Lisberger 2005). To what extent the RVOR is nonlinear in humans has not yet been adequately investigated. However, even if high-acceleration responses are linear in humans, this does not necessarily imply that this would be the case in the setting of disease. One possibility, for example, would be that the cerebellum is normally involved in the “linearization” of the RVOR (this might be more efficient in rhesus monkeys than in squirrel monkeys, for example). In this case, cerebellar disease might not only lead to a miscalibrated RVOR axis but might also result in dynamic nonlinearities.

**Relation to published three-dimensional RVOR models**

Although many investigations of the RVOR have been limited to a one-dimensional analysis (e.g., the “horizontal VOR”), some early models focused on three-dimensional issues (e.g., Ostriker et al. 1985; Pellionisz and Llinas 1980; Robinson 1982). Robinson (1982) proposed an explicit model of the VOR in three dimensions based on a matrix of connections between semicircular canal inputs and the eye muscles. This was expanded to a binocular model by Vilis and Tweed (1988). Considering the six semicircular canals in three coplanar, “push-pull” pairs and the six extra-ocular muscles of each eye in agonist-antagonist pairs, Robinson showed that the eye velocity axis could be matched to any arbitrary head rotation, as long as the elements of the “brain stem matrix,” representing the weights of direct connections and cross-connections between semicircular canals and extraocular motor nuclei, were calibrated appropriately.

Our findings for head impulses have implications for the Robinson matrix model. First, the model pairs semicircular canals into a linear push-pull system. In such a system, vector opposite inputs must produce opposite outputs. Thus a change to the brain stem matrix that would produce an upward eye velocity during rightward yaw would result in a downward eye velocity during leftward yaw. However, our data show that the vertical eye velocity during both rightward and leftward impulses is upward. In a vector sense, this is nonlinear, and thus our findings cannot be explained by the original matrix model. Instead they suggest that, at least for these transient, high-acceleration rotations, the RVOR does not act in a push-pull fashion, with equivalent effects of excitation and inhibition. For example, during head-upright yaw, the contralateral vertical canals are excited and the ipsilateral vertical canals are inhibited. If excitation and inhibition were equivalent, then these would cancel (assuming anatomic symmetry), and there would be no net vertical velocity, even if the individual canal gains were high. However, the presence of substantial upward eye velocities during yaw in our patients suggests that inhibition of the ipsilateral AC does not cancel excitation of the contralateral AC. An excitation-inhibition asymmetry for head impulses is also supported by data in patients with unilateral labyrinthine lesions in whom responses to yaw impulses to...
ward the lesioned side have lower gains than those toward the intact side (e.g., Aw et al. 1996; Peng et al. 2004). This is true, even for velocities below those expected to cause inhibitory cutoff of vestibular afferents (i.e., Ewald’s Second Law).

What is the relationship of RVOR axis shifts to downbeat nystagmus?

Our patients had upward eye velocities during yaw and roll as well as asymmetric pitch gains, both of which reflect a sort of upward slow-phase “bias” of the RVOR. Could this be related to the spontaneous upward drift of these patients’ downbeat nystagmus (DBN)?

First, the DBN does not itself account for the RVOR axis shift; this was not simply the slow-phase velocity (SPV) of the DBN superimposed on a normal RVOR. Upward RVOR velocities were coupled strongly to head velocity (Figs. 1 and 2). Moreover, peak vertical velocities during yaw were many times greater than the DBN SPV (Table 1). For pitch, gains remain asymmetric even when the spontaneous drift is subtracted off (Walker and Zee 2005).

The second question is whether the RVOR axis shifts and DBN could have a common mechanism. For example, Böhmer and Straumann (1998) proposed that DBN could be due to an imbalance in tonic vertical SCC signals with a loss of normal cerebellar inhibition. However, this is unlikely, as further studies have found no direct correlation between DBN and the degree of pitch gain asymmetry (Glasauer et al. 2004; Walker and Zee 2005). Other mechanisms for DBN have been proposed, including asymmetries in the vertical neural integrator (Glasauer et al. 2003), asymmetries in vertical pursuit pathways (Marti et al. 2005; Zee et al. 1974), and otolith mechanisms (Halmagyi and Leigh 2004). It is thought that the projection of the FL/VPF to the vestibular nuclei includes a commissural pathway that is involved in the vertical velocity-to-position neural integrator (Fukushima and Kaneko 1995). Thus another possible mechanism for upward eye velocity during yaw could be an enhancement by head motion of an asymmetry in the vertical neural integrator (Glasauer et al. 2003). The tight relationship between vertical eye velocity and head (canal) velocity, however, is against this hypothesis. Lesions that disrupt the horizontal (Cannon and Robinson 1987) or vertical (Fukushima et al. 1992; Partsalis et al. 1994) neural integrator alter the time constant and phase of the corresponding RVOR. This suggests that one way to investigate further the effect of cerebellar disease on the vertical neural integrator might be to study the responses to low-frequency sinusoidal pitch rotation in these patients.

Other prior studies in patients and animals

Viirre et al. (1987) studied the RVOR in monkeys when one eye was deprived of vision by prolonged patching. The patched eye was found to acquire a vertical eye velocity during yaw, moving up when adducting and down when adducting. This is somewhat similar to our head impulse results in which the eye contralateral to the direction of yaw rotation, i.e., the abducting eye, has a greater upward eye velocity. However, a difference in our data are that, in general, during impulses, both eyes moved upward during rotations in both directions, just by different amounts. Nonetheless, the finding of Viirre et al. suggests that the calibration of RVOR axis is an ongoing process that requires visual feedback, that can occur, at least to some extent, in each eye independently, and that requires calibration of axis as well as gain. Again, it is likely that the cerebellum plays a key role in this calibration.

Several other studies have investigated the RVOR in patients with cerebellar disease. Most comparable to our data is the study of Crane et al. (2000) that examined responses to high-acceleration chair rotations. Their analysis focused on gain modulation related to target distance and did not describe alterations in the VOR axis. Other studies (Thurston et al. 1987; Zee et al. 1976) have reported high yaw gains with low-frequency rotations but also did not describe axis shifts.

In monkeys, lesions to the nodulus and ventral uvula (Nod/VU) affect the RVOR axis somewhat differently, likely through a mechanism involving the velocity-storage system (Angelaki and Hess 1995; Wearne et al. 1996, 1998). These studies showed that the normal reorientation of the eye velocity axis to the gravito-inertial vector (such as during off-vertical axis rotation) is lost when the Nod/VU is lesioned. Again, these authors did not report an alteration of the baseline VOR axis (e.g., with earth vertical axis rotations) after these lesions. The effect of experimental lesions of the cerebellar flocculus and paraflocculus on the axis of eye rotation during head motion remains unknown.

Unanswered questions

Our data provide strong support for the hypothesis that cerebellar disease disrupts the three-dimensional calibration of the RVOR. At the same time, our findings have raised several important issues requiring additional study. First, our results identified nonlinearities in the dynamics of the responses in patients that could depend on which pairs of semicircular canals are excited. These findings point to the general question about the role of the cerebellum in linearizing VOR responses over a wide range of stimulus parameters. As a specific example, how does the brain compensate for nonlinearities that might arise due to the various manifestations of Ewald’s Second law (excitatory stimuli give rise to greater responses than inhibitory stimuli)? A related question is how shifts of the RVOR axis relate to the frequency and acceleration of the stimulus. Finally, our results raise issues about the cerebellar contribution to otolith-ocular reflexes, both dynamic and static. In particular, what might be the otolith contribution to the disconjugacies that are observed during roll rotations of the head?

To summarize, our findings point further to a critical role of the cerebellum in the control of the RVOR, calibrating not only the amplitude but also the direction and conjugacy of eye rotation. Indeed, taking these results together with prior studies of the nodulus and ventral uvula, it appears that all aspects of the three-dimensional ocular motor response to head rotation are under the influence of the cerebellum.

APPENDIX

Mathematical methods

Angular velocities of the head and of the eye relative to external space (eye-in-space or gaze velocity) were calculated directly from the rotation vectors, using the following equation (Hepp 1990)
Before this calculation, the rotation vector data were filtered digitally (50 Hz FIR filter) and differentiated with a simple two-point difference (data from all coils were filtered equivalently). The angular velocity of the eye relative to the head (eye-in-head velocity) was determined by first calculating the rotation vectors representing eye-in-head position using the following transformation

$$\vec{r}_{EH} = -\vec{r}_H + \vec{r}_E + \left( \vec{r}_H \times \vec{r}_E \right)$$

where $\vec{r}_{EH}$ is the rotation vector representing eye-in-head position, $\vec{r}_E$ is the rotation vector representing eye-in-space position, and $\vec{r}_H$ is the rotation vector representing head position in space. The angular velocity of eye-in-head was then calculated from equation (A1), substituting $\vec{r}_{EH}$ for $\vec{r}$. In addition, to compare eye velocity to head velocity, it is necessary that both be expressed relative to the same coordinate system. Thus we calculated head velocity relative to head velocity, it is necessary that both be expressed relative to the same coordinate system. Therefore, we calculated head velocity relative to the head velocity of the eye relative to the head (eye-in-head velocity) was determined the projection of the head velocity vector onto each of the SCC vectors, using the following equation

$$\vec{w}_{ih} = R^{-1} \cdot \vec{w}_{hi}$$

where $\vec{w}_{ih}$ is the angular velocity of the head relative to head position in standard coordinates, $\vec{w}_{hi}$ is the angular velocity of the head in Reid coordinates, and $\theta_r$ is the Reid angle (the angle of inclination of Reid’s line from the earth horizontal), which was measured during the experiment, while the subject was biting on the bite bar with the head in the standard upright position, using an inclinometer. Then, we determined the projection of the head velocity vector onto each of the SCC vectors, using the following equation

$$\vec{w}_{nc} = C \cdot \vec{w}_{hi}$$

where $C$ is the matrix of normal vectors to the semicircular canals of one labyrinth (either $C_{RSCC}$ or $C_{LSCC}$ in the preceding text), and $\vec{w}_{nc}$ is the computed vector of head velocity projections onto the semicircular canals. For convenience we refer to these projections as “canal velocities.” For example, the projection of the head velocity vector onto the right AC is considered to be the “right AC velocity.”

**ACKNOWLEDGMENTS**

A. G. Lasker and D. C. Roberts provided technical assistance.

**GRANTS**

This work was supported by the National Eye Institute Grants K23 EY-00400 and R01 EY-01849, by the Arnold Chiari Foundation, and by the Albert Pennick Fund. Dr. Walker is a Pollin Scholar.

**REFERENCES**


Specific patterns of neuronal
Huterer M and Cullen KE.

Directional coding of three-dimensional movements by the
Rabbitt RD.

On Listing’s Law.
Hepp K.

Potential contribution of the flocculus and ventral paraflocculus in monkeys cause linked
deficits in smooth pursuit eye movements and adaptive modification of the
Zee DS, Friendlich AR, and Robinson DA.

Neutralization of split visual field affect on horizontal vestibulo-ocular reflex evoked by high-acceleration rotations in the squirrel monkey.
Walker MF and Zee DS.

2004.

Asymmetric Unsigned to High-Acceleration Rotations of the Head on Body in Conscious Rhesus Monkeys.
Haque A, Angelaki DE, and Dickman JD.

vestibular semicircular canal afferents in rhesus monkeys.
Glasauer S, Hoshi M, Kempermann U, Eggert T, and Büttrich N. Three-dimensional eye position and slow phase velocity in humans with downbeat nystagmus.

vestibular responses to head impulses are symmetric in downbeat nystagmus.
Glasauer S, von Lindener H, Siebold C, and Büttrich N. Vertical vestibular responses to head impulses are symmetric in downbeat nystagmus.


Directional abnormalities of vestibular and optokinetic responses in cerebellar disease.
Walker MF, Zee DS. Directional cross-coupling of eye velocity in response to head impulses in patients with cerebellar disease.

Walker MF and Zee DS. Asymmetry of the pitch vestibulo-ocular reflex in patients with cerebellar disease.


Wiest G, Tian JR, Baloh RW, Crane BT, and Demer JL. Initiation of the linear vestibulo-ocular reflex in cerebellar dysfunction.

Zee DS, Friendlich AR, and Robinson DA. The mechanism of downbeat nystagmus.

Zee DS, Walker MF, and Ramat S. The cerebellar contribution to eye movements based upon lesions: binocular three-axis control and the translational vestibulo-ocular reflex.

Zee DS, Yee RD, Cogan DG, Robinson DA, and Engel WK. Ocular motor abnormalities in hereditary cerebellar ataxia.

Zhang Y, Partalis AM, and Highstein SM. Properties of superior vestibular nucleus flocculus target neurons in the squirrel monkey. I. General properties in comparison with flocculus projecting neurons.

property in comparison with flocculus projecting neurons.

vestibular semicircular canal afferents in rhesus monkeys.
Glasauer S, Miles FA, and Zee DS. Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus.

Pellionisz A and Llinas R. Tensorial approach to the geometry of brain function: cerebellar coordination via a metric tensor.

Peng GC, Zee DS, and Minor LB. Phase-plane analysis of gaze stabilization to high acceleration head thrusts: a continuum across normal subjects and patients with loss of vestibular function.

Rabbit RD. Directional coding of three-dimenional movements by the vestibular saccular canals.

Ramachandran R and Lisberger SG. Normal performance and expression of learning in the vestibulo-ocular reflex (VOR) at high frequencies.

Rambold H, Churchland A, Selig Y, Jasmin L, and Lisberger SG. Partial ablation of the flocculus and ventral paraflocculus in monkeys cause linked deficits in smooth pursuit eye movements and adaptive modification of the VOR.

Robinson DA. A quantitative analysis of extraocular muscle cooperation and squint.

Robinson DA. Adaptive gain control of vestibuloocular reflex by the cerebellum.

Robinson DA. The use of matrices in analyzing the three-dimensional behavior of the vestibulo-ocular reflex.

Sato Y and Kawasaki T. Operational unit responsible for plane-specific control of eye movement by cerebellar flocculus in cat.

Schemlhans I.W and Robinson DA. Directional plasticity of the vestibuloocular reflex in the cat.

Thurston SE, Leigh RJ, Abel LA, and Dell’Oso LF. Hyperactive vestibulo-ocular reflex in cerebellar degeneration: pathogenesis and treatment.

Versino M, Hurko O, and Zee DS. Disorders of binocular control of eye movements in patients with cerebellar dysfunction.

Vierre E, Cadera W, and Vilis T. The pattern of changes produced in the saccadic system and vestibuloocular reflex by visually patching one eye.

Vilis T and Tweed D. A matrix analysis for a conjugate vestibulo-ocular reflex.

Walker MF, Peng GCY, and Zee DS. Initiation of the linear vestibulo-ocular reflex by visually patching one eye.

Minor LB, Lasker DM, Backous DD, and Hullar TE. Horizontal vestibuloocular reflex evoked by high-accerelation rotations in the squirrel monkey.
I. Normal responses.

Nagao S and Kitazawa H. Effects of reversible shutdown of the monkey flocculus on the retention of adaptation of the horizontal vestibulo-ocular reflex.

I. Oculomotor activity is expressed in non-orthogonal natural coordinates.