Disorders of binocular control of eye movements in patients with cerebellar dysfunction

Maurizio Versino,² Orest Hurko¹ and David S. Zee¹

¹Department of Neurology, Johns Hopkins Hospital, Baltimore, USA and the ²Department of Neurology, University of Pavia, Italy

Correspondence to: David S. Zee, MD, Department of Neurology, Pathology 2-210, Johns Hopkins Hospital, Baltimore, MD 21287-6921 USA

Summary
Recent research has implicated the cerebellum in conjugate ocular motor control, including steady gaze-holding and accuracy of pursuit and saccades. Whether the cerebellum also has a role in the control of the alignment of the eyes during fixation and of the yoking of the eyes during movement is less certain. We have studied binocular (disconjugate) ocular motor control in nine patients with cerebellar dysfunction and compared the results with those of normal subjects. Eye alignment during fixation and the yoking of the eyes during and immediately after saccades were quantified by recording the movements of both eyes using scleral search coils. Patients had disturbances of ocular alignment. All had an esophoria during monocular viewing and many an esotropia during binocular viewing, implying an increase in convergence tone. Most had a vertical misalignment that varied with horizontal eye position ('alternating skew deviation'). Patients showed conjugate dysmetria (saccade under- or overshoot and postsaccade drift) and disconjugate dysmetria (the eyes were poorly yoked during and immediately after saccades). Both the conjugate and disconjugate abnormalities were incomitant, i.e. they varied with orbital eye position. Correlations amongst the various abnormalities suggested that one part of the cerebellum, perhaps the dorsal vermis and the underlying posterior fastigial nucleus, controls the conjugate size of saccades and that another part of the cerebellum, perhaps the flocculus/paraflocculus, controls the yoking of the eyes during saccades and both the disconjugate and conjugate components of postsaccade drift.

Keywords: saccades; eye movements; cerebellum; disconjugate dysmetria; strabismus

Abbreviations: LED = light-emitting diode; VOR = vestibulo-ocular reflex

Introduction
The past few decades of clinical and basic ocular motor research have produced a relatively simple scheme relating specific parts of the cerebellum to the control of eye movements in normal subjects (Keller, 1989; Lewis and Zee, 1993). The flocculus and paraflocculus help to stabilize images on the retina during tracking of moving targets (smooth pursuit and cancellation of the vestibulo-ocular reflex (VOR) during combined eye-head tracking) and during attempted steady fixation. The nodulus modulates the low-frequency component of the VOR (as reflected in the gain and phase of the VOR at low frequencies of sinusoidal stimulation and in the time constant of the VOR in response to an impulse of acceleration). The dorsal vermis and the posterior fastigial nucleus help to control saccade amplitude and also pursuit tracking. This framework has led to hypotheses about the pathophysiology and topical localization of many of the eye movement disorders shown by patients with cerebellar lesions (Zee et al., 1976; Waespe, 1992; Lewis and Zee, 1993; Gaymard et al., 1994; Kanayama et al., 1994; Moschner et al., 1994; Straube and Büttner, 1994; Büttner and Straube, 1995; Vahedi et al., 1995; Waespe and Müller-Meisser, 1996).

Dysmetria of saccades is a particularly prominent cerebellar eye sign. To interpret the various patterns of saccade dysmetria it has been helpful to use the simplifying concept that saccades are generated by a pulse–step neuronal signal (Leigh and Zee, 1991). The pulse, a velocity command, provides the high-frequency phasic discharge that moves the eyes rapidly from one position to another. The step, a position command, provides the steady tonic discharge after the saccade that holds the eye still in its new position. The step signal is created from the pulse signal by the ocular motor gaze-holding network, or neural integrator. For saccades to be accurate, the pulse must be of the correct size. For the
eyes to be held still after the saccade, the step signal must be correctly matched to that of the pulse, and be sustained for the duration of the fixation.

Using this scheme, two components of saccade dysmetria have been identified: pulse (amplitude) dysmetria (causing saccade overshoot or undershoot) and pulse–step mismatch dysmetria (causing a brief period of post-saccade drift of several hundred milliseconds duration). Pulse dysmetria has been attributed to lesions of the dorsal cerebellar vermis/posterior fastigial nucleus (Optican and Robinson, 1980; Vilis et al., 1983; Büttner and Straube, 1995; Takagi et al., 1996; Waespe and Müller-Meissner, 1996); pulse–step match dysmetria has been attributed to flocculus/paraflocculus lesions (Zee et al., 1981; Optican et al., 1986). When the step signal is not sustained, the eyes will drift back to the primary position in the same way as the slow phase of gaze evoked nystagmus.

Most of the findings relating the cerebellum to ocular motor control have dealt with conjugate eye movements; little is known about the role of the cerebellum in disconjugate ocular motor control, either of the static alignment of the eyes during fixation, or of the dynamic yoking of the eyes during movement. There has been some evidence, however, implicating the cerebellum in several aspects of binocular motor control, even as far back as the classical studies of Gordon Holmes who reported that patients with cerebellar damage may show a skew deviation, i.e. a vertical misalignment of the eyes that can not be attributed to a peripheral oculomotor or trochlear nerve palsy (Holmes, 1922). An alternating skew deviation (a vertical misalignment of the eyes that changes with horizontal eye position) has also been reported in some patients with various lesions in the posterior fossa (Goldstein and Cogan, 1961; Keane, 1985; Moster et al., 1988; Hamed et al., 1993; Zee, 1996). Patients with cerebellar abnormalities have also been reported to have an esotropia (convergent squint) (Williams and Hoyt, 1989; Hoyt and Good, 1995) which is sometimes attributed to a divergence paralysis (Akman et al., 1995; Lewis et al., 1996) or to a divergence-beating nystagmus (convergent slow phases with divergent quick phases) (Yee et al., 1979). These types of abnormalities hint at an excess of convergence tone with cerebellar lesions.

Experimentally, too, there is evidence that cerebellar lesions can lead to abnormalities of disconjugate eye movement control. Westheimer and Blair, in the pioneering work in which they described the ocular motor syndrome of the cerebellectomized monkey (1973), noted poor convergence in acutely lesioned animals. Burde et al. (1975) reported alternating skew deviations in monkeys with cerebellar lesions. Vilis et al. (1983) found that cooling of the midline deep cerebellar nuclei in monkeys produced dysmetria of saccades that had both a disconjugate and a conjugate component.

Because of the scant information about the role of the cerebellum in the binocular coordination of eye movements, we studied a group of patients with cerebellar lesions and, by recording the movements of both eyes, systematically investigated both the static alignment of the eyes during fixation and the yoking of the eyes during and immediately after saccades. We show here that patients with cerebellar lesions have a considerable disturbance of binocular ocular motor control, and suggest that the cerebellum plays an important role in the binocular coordination of eye movements.

**Methods**

**Target stimuli**

An array of nine red light-emitting diodes (LEDs), each ~1 mm in diameter, were positioned on a vertical flat surface, 124 cm in front of the subject and arranged in a 3×3 matrix. The middle row was at the eye level of the subject, and the other two rows were 15° above and 15° below. In each row, the central LED was positioned along the midsagittal plane of the subject and the two lateral LEDs were left and right 15° with respect to the centre LED.

**Eye movement recording**

The movements of both eyes were measured with scleral annuli using the magnetic field technique. The horizontal and vertical eye position signals were filtered (0–90 Hz bandpass), sampled at 500 Hz with 12 bit precision and then stored to disk for later off-line analysis, by a digital computer. System noise limited the angular resolution to about 0.05°. The subject’s head was stabilized with a chin rest. Calibration of each eye was performed during monocular viewing.

**Experimental paradigms**

In the first paradigm, 15° vertical or horizontal saccades were elicited by illuminating one LED for 1 s and then an adjacent LED for 1 s. Seven to ten trials of each saccade type were obtained. This paradigm was performed during monocular and binocular viewing. Both static alignment data and metrics of saccades were obtained from this paradigm. Independent calibrations were obtained for saccades along each row and each column of three LEDs using the monocular viewing data.

In the second paradigm, the centre, 0° LED was illuminated for 1 s. Then, when it was turned off, either the 15° left or the 15° right LED was flashed for 500 ms. After 2 s of darkness the eccentric LED was reilluminated for 500 ms before the 0° LED was turned on again. This sequence was repeated 10 times for each direction. The subjects were asked to make a saccade to the flashed LED and then to keep that eye position even in the dark. Gaze-evoked nystagmus was measured with this paradigm.
Table 1  Clinical characteristics of patients

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Age (years)</th>
<th>Diagnosis</th>
<th>Non-cerebellar signs</th>
<th>Non-ocular cerebellar motor signs</th>
<th>CT or MRI scan</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>45</td>
<td>Arnold–Chiari type I degeneration</td>
<td>Gait ataxia</td>
<td>Tonsilar herniation</td>
<td></td>
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<tr>
<td>2</td>
<td>34</td>
<td>Arnold–Chiari type I degeneration</td>
<td>Brisk reflexes, downgoing toes</td>
<td>Cerebellar tonsils at C2</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>38</td>
<td>Spino-cerebellar degeneration</td>
<td>Brisk reflexes, downgoing toes</td>
<td>Gait ataxia and appendicular dysmetria</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>Progressive cerebellar degeneration</td>
<td>Gait ataxia and appendicular dysmetria</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>17</td>
<td>Arnold–Chiari type I degeneration</td>
<td>None</td>
<td>Cerebellar atrophy, more marked in the vermis</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>Progressive cerebellar degeneration</td>
<td>Gait ataxia, appendicular dysmetria, intentional tremor and dysarthric speech</td>
<td>Cerebellar tonsils at C2</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>68</td>
<td>Progressive cerebellar degeneration</td>
<td>Gait ataxia, appendicular dysmetria, intentional tremor and dysarthric speech</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Spino-cerebellar degeneration</td>
<td>Brisk reflexes, upgoing toes</td>
<td>Normal</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>47</td>
<td>Spino-cerebellar degeneration</td>
<td>Brisk reflexes, upgoing toes</td>
<td>Gait ataxia</td>
<td></td>
</tr>
</tbody>
</table>

Data analysis

In the first paradigm (saccades and fixation), each individual trial was marked by using a computer algorithm to identify the beginning of a saccade, ‘I’, when eye velocity reached 25°/s, and the end of a saccade, ‘P’, when eye velocity dropped below 25°/s. Measures of static alignment were based upon the position of the ‘I’ mark, the position of the eyes just before the saccade to the next target location. The difference between ‘I’ and ‘P’ determined the pulse portion of the saccade. The peak velocity of the saccade was also identified (‘V’). Two other marks (‘D’ and ‘S’) were positioned 80 and 160 ms, respectively, after the end of the pulse (at ‘P’). The difference between the positions of ‘D’ and ‘P’ determined the immediate postsaccade drift. The investigator verified the correct location of the marks and, if necessary, repositioned them. In addition, trials in which the subject did not look steadily at the target or made a saccade in the wrong direction were eliminated. For the analysis of alignment all trials were used including both monocular and binocular viewing data. Saccade metrics were based upon the binocular viewing data, using only those trials that began or ended at the centre LED (0,0).

In the second paradigm (gaze-evoked nystagmus), all responses were marked twice. The first set of marks were the same as described as above and were used to compute postsaccade drift (comparing positions ‘D’ and ‘P’). With the second marking, the investigator repositioned the ‘D’ and the ‘S’, so that they were separated by 200 ms and placed later, in the dark period when the eyes were drifting in the slow phase of gaze-evoked nystagmus. The velocity of the slow-phase drift (which appeared roughly linear) was taken as the average eye velocity in the ‘D’ to ‘S’ interval. A time constant was inferred from the ratio of the amplitude of eccentric gaze and the velocity of the slow phases of gaze-evoked nystagmus.

Patients and normal subjects

Table 1 shows the main features of our patients. For the nine normal subjects (six males and three females) the mean age was 34.4 years (range 19–53 years). For the patients the mean age was 43.5 years (range 17–68 years). No subjects were taking medications known to influence ocular motility. Clinical diagnoses in the patients are presumptive except for the patients with the Arnold–Chiari malformations and Patient 6 who is a member of a family with known pure cerebellar cortical degeneration (Zee et al., 1976; Zee, 1982a). Patients 8 and 9 are brother and sister. All recordings were made without subjects wearing any corrective lenses. Consent was obtained from all subjects and patients according to the Declaration of Helsinki.

Results

Disorders of static ocular alignment

Horizontal misalignment

All patients showed a disorder of either horizontal or vertical alignment or both. Figure 1 shows the phoria (misalignment with one eye viewing) and the tropia (misalignment with binocular viewing) for horizontal fixation in the straight ahead position of gaze. For the phoria all patients had an esodeviation and in five out of nine patients the value was greater than that of any of the normal subjects. For the tropia, six out of nine patients had a deviation that was greater than that of any of the normal subjects. In these six patients, five had an esodeviation that ranged from 1.8 to 10.2°. Figure 1 also shows that in most patients the tropia was considerably less than the phoria, implying a relatively preserved ability to use disparity cues to drive motor fusion.

Figure 2A shows the mean horizontal tropia values for the nine different positions in which alignment was measured.
Horizontal Deviation In Primary Position

For normal subjects, as expected, the values of the tropia were quite small (<1.0°). For the patients the horizontal tropia values were larger, especially in the diagonal, most eccentric positions of gaze (upper left, upper right, lower left, lower right). The horizontal misalignment tended to be incomitant; it varied with orbital position. Furthermore, the change in ocular alignment relative to orbital position was nonlinear, i.e. it did not change by a constant amount for a given change in eye position. Using the largest difference between two individual horizontal tropia values from any of the nine positions of fixation, patients showed a significant degree of incomitancy (nearly three times that of normal subjects; median 2.9° in patients versus 1.1° in normal subjects, \( P = 0.04\), Mann–Whitney).

We also looked for changes in the degree of horizontal misalignment with vertical eye position. This type of incomitancy is often reflected in so-called ‘A’ patterns (greater esodeviation on up gaze or greater exodeviation on down gaze) and ‘V’ patterns (greater esodeviation on down gaze or greater exodeviation on up gaze). Comparing the values for the horizontal phoria (average of right eye and left eye viewing data) in up and down gaze for targets on the midline, none of the normal subjects and only three of the patients had a difference in horizontal phoria of >1.1°. Two patients had small ‘A’ patterns (Patient 2, 2.3° difference and Patient 4, 4.4° difference) and one patient (no. 3) had a small ‘V’ pattern (2.8° difference).

Vertical misalignment

Patients also showed a vertical misalignment of the eyes. As was the case for the horizontal deviations, the degree of vertical misalignment was smallest in the straight ahead and in the straight down positions of gaze (Fig. 2B). The vertical misalignment tended to be incomitant, and the change in ocular alignment relative to orbital position was nonlinear. Looking at the largest difference between two individual tropia values at any of the nine positions of fixation, the median value was 2.6° in patients versus 0.5° in normal subjects (\( P = 0.003\), Mann–Whitney).

There was also a distinctive pattern of change of vertical alignment on lateral gaze (Fig. 3). Patients showed an ‘alternating skew’ such that there was a considerable difference in the vertical deviation depending upon right or left gaze (median for patients, 1.22°; for normal subjects, 0.11°). In six out of nine patients the right (abducting) eye was higher on right gaze, and in six out of nine the left (abducting) eye was higher on left gaze. In 10 out of 12 of these measures the hyperdeviation increased in down gaze. In five out of nine patients, but in no normal subjects, the
Binocular eye movements in cerebellar disease

1937

Horizontal Tropia

(A)

Horizontal Position

Vsttls J Tropta

1

LC CC RC

LU CU RU LO CD RO

Orbital Position

Fig. 2 Horizontal (A) and vertical (B) misalignment as a function of the position of gaze. Mean values (+SD) for the absolute values of the tropia at each position are shown, both for the normal subjects (light columns) and patients (dark columns). Position codes are given by the horizontal and vertical coordinates (using L = 15° left; R = 15° right; U = 15° up; D = 15° down; C = centre). Horizontal and vertical eccentricities are all 15°. For example, LC = 15° left and 0° vertical; CU = 0° horizontal and 15° up, etc. Note that for the patients the tropias tended to be greater in the diagonal, most eccentric positions of gaze.

Disorders of dynamic ocular alignment
Conjugate saccade dysmetria: abnormalities of the saccade pulse

We measured the conjugate component of the saccade pulse (average of right eye and left eye pulses), to look for conjugate pulse dysmetria. Typical raw records for saccades made by normal subjects and patients are shown in Figs 4

Fig. 3 Direction of vertical misalignment as a function of horizontal eye position ('alternating skew') in the nine individual patients. Vertical tropias at 0° elevation and at left 15° and right 15° eccentricity are shown. Note the considerable difference in vertical tropia as a function of lateral gaze with the abducting eye usually being higher.

(horizontal) and 5 (vertical). Data for individual subjects are shown in Figs 6 and 7. The group means and standard deviations for the patients and the normal subjects are summarized in Table 2. The following are the main findings. Most patients showed a conjugate pulse dysmetria that could be present for either horizontal or vertical saccades or for both (Table 2, Dysmetria). Both hypo- and hypermetria were observed; hypermetria was typically greatest for downward, centripetal saccades. For both horizontal and vertical saccades, six out of nine patients had dysmetria that was >2 SD from the mean value in the normal subjects; mean absolute values of the dysmetria (either undershoot or overshoot) in degrees plus 2 SD were 2.3° horizontally and 2.4° vertically. Using this criterion, only two patients (nos 2 and 3) had no pulse dysmetria for either horizontal or vertical saccades. The differences between the normal subjects and patients were significant (P < 0.01 for horizontal and vertical saccades, Mann–Whitney). Overall, in a given patient, there was no consistent relationship between the degree of horizontal and vertical saccade dysmetria.

The pulse dysmetria was usually greater in one direction than in the other. (Table 2, Directional asymmetry). The pulse dysmetria also commonly varied with orbital position. Comparing patients and normal subjects, the mean of the differences between the amplitude of saccades for centripetal and centrifugal saccades was statistically significant for horizontal, but not for vertical saccades (Table 2, Incomitancy). The pattern of incomitancy for horizontal saccades was variable; either centripetal or centrifugal saccades could be larger. Although there was no statistically significant difference in incomitancy for vertical saccades between patients and normal subjects, when the difference was large, it involved centripetal saccades being larger (e.g. downward saccades in Patient 8). This pattern was also present, to a lesser extent, in normal subjects.
Conjugate saccade dysmetria: abnormalities of the saccade pulse–step match

In patients the conjugate component of postsaccade drift was increased (average of right eye and left eye postsaccade drift at 80 ms, illustrated in Figs 4 and 5, and quantified in Conjugate saccade dysmetria: abnormalities of the saccade pulse–step match

In patients the conjugate component of postsaccade drift was increased (average of right eye and left eye postsaccade drift at 80 ms, illustrated in Figs 4 and 5, and quantified in Fig. 7 and in Table 2). For horizontal saccades, six out of nine patients and for vertical saccades, seven out of nine patients had conjugate postsaccade drift that was >2 SD from the mean value in the normal subjects (i.e. >0.3° horizontally and >0.4° vertically). Using this criterion only one patient (no. 6) had no increase in conjugate postsaccade...
Binocular eye movements in cerebellar disease

Drift for either horizontal or vertical saccades. The differences between the normal subjects and the patients were significant ($P < 0.05$ for horizontal saccades and $P < 0.01$ for vertical saccades, Mann–Whitney).

The data in Fig. 7 show that there was no consistent relationship between the absolute degree of pulse dysmetria and of postsaccade drift. The direction of any conjugate postsaccade drift was usually the same (onward) as the pulse portion of the saccade in both patients and normal subjects, both for horizontal saccades (72% of cases for patients and 95% for normal subjects) and for vertical saccades (78% of cases for patients and 84% for normal subjects), regardless of whether the pulse was too big (overshoot) or too small (undershoot). In other words, at least for the circumstances in which the conjugate pulse was too big, the ensuing postsaccade drift did not appear to be corrective for the conjugate pulse dysmetria.

Disconjugate saccade dysmetria: abnormal yoking of saccades

We measured the disconjugate component of saccades next (difference between right eye and left eye pulses) using both the right eye pulse to left eye pulse ratio and the left/right pulse difference corrected for the size (conjugate pulse) of the saccade. Raw records from an individual patient are shown in Figs 4 and 5 and data for individual subjects and
Fig. 6 Conjugate saccade pulse dysmetria (A, horizontal; B, vertical). Absolute values of the pulse component in movements to and from the primary position are shown. For horizontal saccades (A) there is considerable variability in the influence of movement direction and orbital position on the pattern of dysmetria among patients. For vertical saccades (B) downward overshoot is a more consistent finding. Nls = normal subjects (mean+SD).

Individual trial types are depicted in Fig. 8 and quantitatively summarized in Fig. 9. The group means and standard deviations for the patients and for the normal subjects are summarized in Table 3. All patients showed some degree of disconjugate pulse dysmetria that could be present for either horizontal or vertical saccades or for both (see Table 3, Dysmetria). For horizontal and vertical saccades (two different sets of) five out of nine patients and one normal subject had disconjugate pulse dysmetria that was >2 SD from the mean value in the normal subjects. There tended to be a relative divergence during horizontal saccades for both normal subjects (80% of cases) and patients (73% of cases).

We found no consistent relationship between the degrees of horizontal and vertical disconjugate saccade dysmetria.
Binocular eye movements in cerebellar disease

There were also no statistically significant differences in the pulse dysmetria as a function of saccade direction (right or left, up or down; see Table 3, Directional asymmetry). Comparing patients with the normal subjects, the mean of the differences between the amplitude of the pulse disconjugacy for centripetal and for centrifugal saccades was statistically significant for horizontal, but not for vertical saccades (Table 3, Incomitancy). Even so, for vertical saccades the mean value was considerably larger for the patient group. Finally, there was a consistent relationship between the degree of disconjugate pulse dysmetria and the degree of conjugate postsaccade drift for horizontal (linear regression, $r = 0.84$) but not for vertical saccades.

**Disconjugate saccade dysmetria: disconjugate postsaccade drift**

The disconjugate component of postsaccade drift was larger in patients (difference between right eye and left eye postsaccade

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**Fig. 7** Conjugate saccade pulse dysmetria and conjugate postsaccade drift dysmetria (A, horizontal; B, vertical). Absolute values of pooled data from the four saccade types, made to and from the primary position; for pulse dysmetria, values represent the average of absolute differences from $15^\circ$ (size of target step) and for postsaccade drift dysmetria actual values are shown. Nls = normal subjects (mean $\pm$ SD).
50% of the time in normal subjects and 57% of the time in patients. For vertical saccades, neither in normal subjects (convergent) was opposite to the intrasaccade drift in 84% of cases. In normal subjects, the direction of horizontal postsaccade disconjugate drift (convergent versus divergent) was opposite to the intrasaccade drift in 84% of cases. For patients, the drift was opposite in 73% of cases. For vertical saccades, neither in normal subjects nor in patients was there a consistent relationship between the directions of the intrasaccade pulse drift and the subsequent postsaccade disconjugate drift (being opposite 50% of the time in normal subjects and 57% of the time in patients). In other words, the disconjugate postsaccade drift did not appear to be corrective for the difference between the saccade pulses of each eye.

### Saccade velocities

We analysed saccade peak velocity data using horizontal and vertical centrifugal saccades starting from the primary position. For each subject and for each type of saccade we plotted the mean values of saccade amplitude and peak velocity. In spite of some differences due to different values for the mean amplitude of the saccade pulse in patients, the normal subject and patient data did not cluster separately. It was always possible to compute a linear regression with no absolute value residual greater than three standard deviations from the regression. Moreover, the sign of the residuals was never in the direction that would indicate that the saccades made by the patients were slower. Finally, we never found an outlier on the basis of Cook’s coefficient (an index of the influence of an individual point on the regression statistic). Overall, there were no significant differences between normal subjects and patients in peak saccade velocities.

### Table 2 Pattern of conjugate saccade dysmetria

<table>
<thead>
<tr>
<th>Conjugate parameters (%, mean±SD)</th>
<th>Horizontal</th>
<th>Vertical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Pulse dysmetria</td>
<td>7.4±3.8</td>
<td>18.8±7.3**</td>
</tr>
<tr>
<td>Directional pulse asymmetry</td>
<td>4.3±3.0</td>
<td>15.6±17.7</td>
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<tr>
<td>Pulse incomitancy</td>
<td>4.9±3.0</td>
<td>19.7±9.8**</td>
</tr>
<tr>
<td>Postsaccade drift</td>
<td>1.8±0.8</td>
<td>3.9±2.2</td>
</tr>
</tbody>
</table>

All values are given as percentages (i.e. 100 × each of the following ratios) and represent group means±SD. Dysmetria = average of absolute values (15–pulse/15) of averages for each saccade type in each patient. Directional asymmetry (right/left or up/down) = absolute value of the difference between average absolute value of right (or up) saccades and average absolute value of left (or down saccades)/average absolute value of averages for each saccade type in each patient. Incomitancy (orbital-position dependency) = absolute value of the larger difference between centripetal (cp) and centrifugal (cf) saccades in the same direction (e.g. right versus left, up versus down)/average value of the cp and cf saccades. Postsaccade drift = absolute value of the conjugate component of saccade drift/amplitude of conjugate pulse. **P ≤ 0.01 and *P ≤ 0.05 (Mann-Whitney), significant difference between normal and patient groups.

### Table 3 Pattern of disconjugate saccade dysmetria

<table>
<thead>
<tr>
<th>Disconjugate parameters (%, mean±SD)</th>
<th>Horizontal</th>
<th>Vertical</th>
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<tr>
<td></td>
<td>Controls</td>
<td>Patients</td>
</tr>
<tr>
<td>Pulse dysmetria</td>
<td>3.4±2.2</td>
<td>6.0±2.8*</td>
</tr>
<tr>
<td>Directional pulse asymmetry</td>
<td>3.1±4.2</td>
<td>3.7±3.0</td>
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<tr>
<td>Pulse incomitancy</td>
<td>4.0±6.0</td>
<td>7.3±3.9*</td>
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<tr>
<td>Postsaccade drift</td>
<td>1.8±0.7</td>
<td>3.7±1.9*</td>
</tr>
</tbody>
</table>

All values are given as percentages (i.e. 100 × each of the following ratios) and represent group means±SD. Dysmetria = average of pulse-pulse difference/conjugate saccade size for horizontal (or vertical) saccades; Directional asymmetry (right/left or up/down) = absolute value of the difference between average absolute values of the pulse-pulse difference (corrected for conjugate pulse size) for right (or up) saccades and for left (or down saccades). Incomitancy (orbital-position dependency) = absolute value of the larger difference between the pulse-pulse differences (corrected for conjugate pulse size) for centripetal and centrifugal saccades for right (or up) versus left (or down) saccades. Postsaccade drift = absolute value of the conjugate component of postsaccade drift/amplitude of conjugate pulse. *P ≤ 0.05 (Mann-Whitney), significant difference between normal and patient groups.

Drift at 80 ms; Figs 4, 5 and 9; Table 3, Disconjugate drift. For horizontal saccades, six out of nine patients and for vertical saccades, five out of nine patients had disconjugate postsaccade drift that was >2 SD from the mean value in the normal subjects. The differences between the normal subjects and patients were significant for horizontal saccades (P < 0.05, Mann-Whitney) but not for vertical saccades.

The data in Fig. 9 also show that in patients there was a consistent relationship between the absolute degree of disconjugate pulse dysmetria and of disconjugate postsaccade drift (linear regression of mean values for each patient; r = 0.82 for horizontal saccades and r = 0.73 for vertical saccades). Looking at the relative directions of the disconjugate component of the saccade pulse and of the postsaccade drift, for normal subjects the direction of horizontal postsaccade disconjugate drift (convergent versus divergent) was opposite to the intrasaccade drift in 84% of cases. For patients, the drift was opposite in 73% of cases. For vertical saccades, neither in normal subjects nor in patients was there a consistent relationship between the directions of the intrasaccade pulse drift and the subsequent postsaccade disconjugate drift (being opposite 50% of the time in normal subjects and 57% of the time in patients). In other words, the disconjugate postsaccade drift did not appear to be corrective for the difference between the saccade pulses of each eye.
**Gaze-evoked nystagmus**

Patients 2, 4 and 6 had downbeat nystagmus at right and left 15° eccentric fixation. Slow-phase velocities ranged between 2 and 13°/s. Most patients showed a horizontal gaze-evoked nystagmus. Six of nine patients had an inferred time constant of the horizontal neural integrator of <15 s (range 1.1–14.2 s), while only one normal subject had a time constant <15 s (7.4 s). The slow-phase drifts of gaze-evoked nystagmus were disconjugate (Fig. 10). Figure 11 shows the difference in slow-phase velocities between the two eyes following saccades to right and left (15° eccentricity). The disconjugacy was also incomitant, with most subjects showing a considerable difference in the degree of disconjugacy when comparing drift from right and from left gaze. Even when...
Fig. 9 Comparison of the disconjugate components of the saccade pulse (PPdiffer) and postsaccade drift (Disconjdrift) (A, horizontal; B, vertical). Absolute values of pooled data from four saccade types, made to and from the primary position. Values are normalized to the size of the conjugate pulse. Nls = normal subjects (mean ± SD).

corrected for the degree of conjugate drift (dividing disconjugate drift velocity by conjugate drift velocity), the degree of disconjugacy of gaze evoked nystagmus was incomitant. Finally, the degree of disconjugacy of the slow phases of gaze-evoked nystagmus and the degree of disconjugacy of the immediate horizontal postsaccade drift were significantly correlated (linear regression, r = 0.57).

Discussion

Our patients showed oculomotor signs that are typical of cerebellar disease including saccade under and overshoot, postsaccade drift and gaze-evoked and down-beat nystagmus. In spite of the heterogeneity of the underlying pathology in our patients none showed any ocular motor abnormalities that could not be attributed to cerebellar dysfunction (Lewis and Zee, 1993; Moschner et al., 1994). Our patients showed no slowing of horizontal or vertical saccades; thus, involvement of the abducens or oculomotor nuclei, or the portions of the paramedian pontine and mesencephalic reticular formation that contain premotor saccade burst neurons can be excluded.

The main new finding of this study is that patients with cerebellar disturbances show prominent disturbances of binocular eye movement control. The disorders of static eye alignment during fixation included horizontal esodeviations, suggesting a bias toward convergence, and vertical (skew) deviations, which changed with horizontal eye position such that the abducting eye was usually higher. Disorders of dynamic alignment associated with saccades were also prominent, with both intrasaccade and postsaccade disconjugacy. Patients also showed disconjugacy of gaze-holding so that on lateral gaze, the centripetal drift of gaze-evoked nystagmus was different in the two eyes. We will discuss and compare these abnormalities in turn, and then develop ideas about the role of the cerebellum in the control of eye movements, and how cerebellar lesions might lead to disorders of the control of eye alignment and eye movement conjugacy.

Fig. 10 Gaze-evoked nystagmus at 15° eccentricity. Right and left eye (RE and LE) horizontal position traces and difference trace (RE minus LE) from normal Subject 7 (A) and Patient 2 (B).
Binocular eye movements in cerebellar disease

Disturbances of saccade accuracy: conjugate control
Conjugate saccade pulse dysmetria, either undershoot or overshoot, is a classical sign in patients with cerebellar disease (Goldstein and Cogan, 1961; Zee et al., 1976; Zee, 1982b; Bötzel et al., 1993; Büttner and Straube, 1995; Takagi et al., 1996). Even though the brainstem is sometimes involved in cerebellar dysfunction in patients, autopsy studies have confirmed that abnormalities of eye movements including dysmetria of saccades can be present when the cerebellum alone is affected (Zee, 1982a). The disturbances of the conjugate control of saccades shown by our patients were similar to those described previously in cerebellar patients.

Evidence from experimental animals with lesions restricted to the cerebellum also establishes an essential role for the cerebellum in controlling saccade amplitude (Ritchie, 1976; Optican and Robinson, 1980; Vilis and Hore, 1981; Sato and Noda, 1992; Goldberg et al., 1993; Robinson et al., 1993). Results of single unit recordings and electrical stimulation in monkeys (Ohitsuka and Noda, 1992; Fuchs et al., 1993; Helmchen et al., 1994; Helmchen and Büttner, 1995; Ohitsuka and Noda, 1995) and of studies of eye movements (Vahedi et al., 1995; Waespe and Müller-Meissner, 1996) and transcranial magnetic stimulation in humans (Hashimoto and Ohtsuka, 1995) all point to the dorsal cerebellar vermis (lobules VI and VII) and the posterior 'ocular motor' portion of the fastigial nucleus as the critical structures within the cerebellum that participate in the control of saccade amplitude.

Our patients also showed brief drift of the eyes immediately following saccades. This post-saccadic drift is thought to reflect a mismatch between the neuronal pulse and step signals that generate saccades. The cerebellar flocculus and paraflocculus are critical structures for the correct matching of the saccade pulse and step (Zee et al., 1981; Optican et al., 1986). Post-saccadic drift was usually onward independent of whether the pulse was too big or too small. The emergence of this particular pattern of pulse–step mismatch suggests that the inherent, 'default' pattern of saccade control is for the step signal to be larger than the pulse signal.

Disturbances of eye alignment
A prominent finding in our patients was static horizontal misalignment. Patients frequently showed a bias towards convergence with esophorias being present in all patients, and esotropias in most. The absence of saccade slowing makes it unlikely that the brainstem and peripheral nerve and muscle are involved. These deviations were also incomitant, though the so-called 'A' and 'V' patterns, in which horizontal deviations vary in a characteristic way with vertical eye position, occurred in only a few patients and then were quite small. The degree of misalignment was greatest in diagonal, most eccentric positions of gaze, i.e. those least frequently held during natural fixation. This last finding is compatible with the idea that a function of the cerebellum is to correct for the nonlinear mechanical properties of orbital tissues which become more important when the eyes are moved to more eccentric orbital positions.

Why cerebellar lesions should lead to a bias toward convergence is not known. In rabbits the cerebellar flocculus has an inhibitory projection to the medial rectus but not to the lateral rectus muscles (Ito et al., 1977) so that a lesion in the flocculus could lead to a convergence bias. Hence, if there is a similar inherent bias towards divergence in the normal cerebellum of primates, cerebellar lesions could lead to excessive convergence. We did not measure the vergence capabilities of our patients directly. But the finding that their tropias were usually smaller than their phorias implies at least a relatively preserved ability to use disparity cues to drive vergence and motor fusion.
Although little studied, there is some electrophysiological evidence that the cerebellum could participate in the control of vergence and perhaps ocular alignment. The flocculus contains neurons that discharge with the angle of vergence (Miles et al., 1980) and stimulation in the cerebellar flocculus can lead to movements of one eye only (Balaban and Watanabe, 1984). The nucleus reticularis tegmenti pontis, which projects to the cerebellum, and the posterior nucleus interpositus (the globose and emboliform nuclei in humans) contain cells that discharge in relation to different aspects of the near response including vergence (Gamlin and Clarke, 1995; Gamlin et al., 1996).

Vertical misalignment was also prominent in our patients. The deviations were incomitant and greatest in diagonal, most eccentric positions of gaze, as was the case for the horizontal misalignment. Our patients often showed a characteristic pattern of alternating skew deviation on right and left lateral gaze usually with the abducting eye higher. In most cases the deviation on lateral gaze was greater on down gaze giving a pattern of ‘inferior rectus skew’ (Moster et al., 1988). This particular pattern of eye misalignment has been described both in patients with brainstem disturbances and in patients with cerebellar disturbances (Keane, 1985; Zee, 1996). It will be discussed further below.

In view of the abnormalities of eye alignment shown by our patients one might ask why diplopia is not reported more commonly by patients with cerebellar disease. First, the tropias were less than the phorias so that in some cases the deviations with binocular viewing were not large enough to cause diplopia. Furthermore, our measures of tropias were made during fixation of a single small light emitting diode in an otherwise dark room. With a larger, more natural field of stimulation, disparity-driven vergence mechanisms would have been more likely to overcome the phorias completely. In addition, the deviations were least in the most naturally and frequently used positions of fixation (straight ahead and straight down). Finally, oscillopsia from any accompanying spontaneous nystagmus may have obscured the diplopia since nystagmus also tends to be more prominent in eccentric positions of gaze. Regardless of whether or not our patients reported diplopia, they showed a consistent and prominent disorder of ocular alignment which we attribute to their cerebellar disease.

Disturbances of saccade accuracy: disconjugate control

Our patients also showed a prominent abnormality of the yoking of the eyes during and immediately after saccades; the eyes did not travel together. All patients showed some abnormality of saccade pulse conjugacy, and just as for conjugate pulse dysmetria, the changes were often incomitant. Similarly, postsaccade drift was frequently disconjugate. For individual patients, the absolute degree of disconjugacy during saccades correlated well with the absolute degree (but not the direction) of disconjugate drift immediately after the saccade and, at least for horizontal saccades, with the absolute degree of conjugate postsaccade drift. Furthermore, the conjugate component of saccade pulse dysmetria did not correlate well with its disconjugate component, nor with the conjugate or disconjugate components of postsaccade drift.

A hypothesis which could explain these findings is that one part of the cerebellum, perhaps the dorsal vermis, participates in the control of the conjugate size of saccades, and another part of the cerebellum, perhaps the flocculus/paraflocculus, participates in the control of the yoking of the eyes during saccades and in the control of both the disconjugate and conjugate components of postsaccade drift.

Gaze-evoked nystagmus

Most of our patients showed horizontal gaze-evoked nystagmus, even at only 15° eccentricity. The drift of gaze-evoked nystagmus reflects the time constant of the neural integrator, the neural network that converts velocity commands to position commands, to create the step signal for steady gaze-holding. The rate of decay of the step, as reflected in its time constant, determines how well eccentric positions of gaze are held. The lower the time constant, the ‘leakier’ the integrator, and the higher the velocity of centripetal drift.

The slow phases of gaze-evoked nystagmus were disconjugate. This is not surprising since the horizontal ocular misalignment in our patients was incomitant. Accordingly, when the eyes drift toward a new position in which eye alignment changes, the eyes drift by different amounts. The disconjugacy of the slow phases of gaze-evoked nystagmus itself was incomitant, in accord with the fact that static ocular misalignment did not change linearly with orbital position. Finally, the degree of disconjugacy of the slow phases of gaze-evoked nystagmus correlated well with that of immediate postsaccade drift. This finding suggests that the control of the conjugacy of the amplitude and of the decay of the step output of the neural integrator have a common anatomical substrate within the cerebellum. The cerebellar flocculus/paraflocculus plays an important role in regulating the ocular motor integrator, and may also participate in its disconjugate control.
The cerebellum and ocular motor plasticity

Since many eye movement abnormalities appear immediately after a cerebellar insult [most convincingly shown experimentally during reversible block with cooling or with chemicals (Vilis and Hore, 1981; Sato and Noda, 1992; Kurzan et al., 1993; Robinson et al., 1993)] there is a unequivocal role for the cerebellum in the immediate, online control of eye movements. But there also appears to be an essential role for the cerebellum in the long-term adaptive mechanisms that monitor motor performance and keep brainstem circuits calibrated for optimal visuo-oculomotor behavior (Lewis and Zee, 1993; du Lac et al., 1995).

In the absence of such a ‘learning’ mechanism, not only would the ability to recover from the acute effects of a neurological lesion be limited, but additional eye movement abnormalities might emerge slowly as various ocular motor reflexes subserved by pathways that need not course through the cerebellum directly, gradually become uncalibrated. In other words, maintenance of ocular motor accuracy is a dynamic process, relying on a robust learning mechanism to monitor visuomotor performance continuously and to fine-tune ocular motor innervation in the face of the inevitable demands for recalibration that are incurred during natural development and ageing, and in response to disease and trauma. The cerebellum may be essential to this process.

Conjugate dysmetria of saccades after cerebellar lesions

Considering this learning hypothesis, dysmetria of saccades may reflect both the immediate effects of cerebellar dysfunction and the loss of the normal learning mechanisms that maintain ocular motor accuracy in the long-term. For example, the cerebellum might be needed for the adjustments in innervation that must compensate for the inherent orbital mechanical factors that make muscle forces a nonlinear function of eye position. Centripetally directed saccades are often larger than centrifugally directed saccades in normal subjects and this inconstant pattern of dysmetria sometimes becomes exaggerated in patients or experimental animals with cerebellar lesions (e.g. Ritchie, 1976; Optican and Robinson, 1980; Vilis and Hore, 1981; Bötzl et al., 1993). As another example, the orientations of the eye muscles also depend upon the positions of the eyes in the orbit in the orthogonal direction (Miller and Demer, 1992); e.g. the actions of the oblique muscles and vertical recti vary with horizontal eye position. If not corrected for, this anisotropy could be another possible source of an inconstant dysmetria.

Adaptation of conjugate saccade properties has been tested both in patients and in monkeys with cerebellar lesions and found to be wanting. The cerebellar dorsal vermis and probably the underlying fastigial nuclei seem critical for correction of saccade amplitude dysmetria (Optican and Robinson, 1980; Waespe and Baumgartner, 1992; Goldberg et al., 1993; Waespe, 1995; Takagi et al., 1996; Waespe and Müller-Meisser, 1996) and the flocculus and paraflocculus for the correction of postsaccade drift (Optican et al., 1986).

Disconjugate dysmetria of saccades emerging with cerebellar lesions

Since each pair of yoke muscles consists of two anatomically different muscles (e.g. the lateral rectus of one eye and the medial rectus of the other) any corrections in orbital-position dependent nonlinearities would have to be tailored differently for each eye. Hence, in the absence of a mechanism to correct for potential sources of saccade dysmetria, both conjugate and disconjugate patterns of dysmetria might be expected to emerge during saccades. If the cerebellum makes both immediate, ‘on-line’ adjustments in saccade control and also participates in more long-term ocular motor learning, it follows that some variability in the pattern of dysmetria would be expected from patient to patient based on the individual subject’s inherent imperfections and prior ‘ocular motor history’. These factors may contribute to the variability in dysmetria of saccades amongst patients even from the same family (Zee et al., 1976).

Disturbances of eye alignment after cerebellar lesions

The hypothesis that the emergence of dysmetria after cerebellar lesions is due, at least in part, to loss of an adaptive mechanism might also apply to the maintenance of static eye alignment. When a normal subject wears a patch over one eye for a few days, to eliminate disparity cues, disorders of vertical alignment appear, often with the pattern of an alternating hyperdeviation (Liesch and Simonsz, 1993; Neikter, 1994). Vertical alignment has been shown to be under adaptive control with visual, ‘disparity’ inputs providing a potent error signal for change (Ygge and Zee, 1995; McCandless et al., 1996). Hence, if the cerebellum is involved in the maintenance of static eye alignment, and uses disparity cues as the error signal, patching of one eye could lead to the appearance of ‘cerebellar’-type oculomotor signs by virtue of depriving the cerebellum of the necessary error signal to monitor oculomotor performance in the same way as would a direct lesion in the cerebellum.

More direct tests of a role for the cerebellum in adaptation of eye alignment have given conflicting results. In human beings with cerebellar dysfunction, Milder and Reinecke (1983), but not Hain and Luebke (1990), found impaired short-term (hours) phoria adaptation (adaptation to a laterally displacing prism placed in front of one eye for minutes to hours). The differences in the results between these two studies may have depended upon whether or not the deep cerebellar nuclei, or extracerebellar structures were involved, as was possibly the case in the Milder and Reinecke study. Judge found a normal range of phoria adaptation in monkeys that had had their cerebellar flocculi and paraflocculi removed,
but no prelesion control data were available and only the ability to adjust to a comitant deviation was measured (Judge, 1987).

*Disturbances of binocular ocular motor control and the VOR*

The abnormalities of disconjugate ocular motor control that appear following cerebellar lesions may also relate to the needs of the vestibular system. With the eyes being separated laterally in their orbits, geometrical considerations dictate that when viewing near objects while the head is moving, the eyes must move disconjugately or even disjunctively (such as when moving forward or backward) for the VOR to ensure optimal stabilization of gaze (Vierle et al., 1986; Gresty et al., 1987; Snyder and King, 1992; Seidman et al., 1995). Hence a need for a disconjugate capability, and presumably a mechanism to keep it properly calibrated, already exists in the phylogenetically oldest types of eye movements, the slow and quick phases of vestibular nystagmus. It has been shown in the monkey that some cells in the flocculus discharge in relation to the angle of vergence (Miles et al., 1980). Whether these cells have some role in adjusting the VOR for viewing distance, or participate in some other aspect of disconjugate ocular motor control is not known.

*The VOR and skew deviation*

Vestibular stimuli may also elicit changes in static eye alignment. Consider that a skew deviation is a physiologically normal response to lateral head tilt in lateral-eyed animals. It may be that in pathological circumstances in frontal-eyed animals, such a phylogenetically old reflex pattern of skew deviation emerges and indeed this has been suggested as the mechanism for the frequent occurrence in human patients with brainstem lesions of the ocular tilt reaction, with its skew deviation, cyclorotation of the eyes and head tilt (Brandt et al., 1995). Analogously, an alternating skew deviation, as was frequently seen in our patients, can be interpreted as a vestibular abnormality deriving from the normal response of a lateral-eyed animal to fore and aft pitch with the eyes in different lateral positions in the orbit (Zee, 1996). Thus, one can envisage that cerebellar lesions lead to disorders of eye alignment on the basis of interference with the normal mechanisms that maintain conjugacy or disconjugacy of the vestibular response, as called for by the particular pattern of vestibular stimulation.

*Conclusion*

Our results implicate the cerebellum in a number of aspects of binocular (disconjugate) control of eye movements, including the maintenance of correct eye alignment during fixation and the correct yoking of the eyes during and immediately after saccades. Some of these abnormalities may be related to the hypothetical role for the cerebellum in ocular motor learning. While the exact loci within the cerebellum that control the yoking of the eyes are not known, it may be that the cerebellar flocculus/paraflocculus is important for disconjugate ocular motor control.

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