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Smooth pursuit eye movements and otolith–ocular responses are differently impaired in cerebellar ataxia

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Summary

Horizontal and vertical smooth pursuit was compared with otolith–ocular responses in 11 patients with cerebellar ataxia and 21 normal subjects using three-dimensional magnetic search coil eye movement recordings. Otolith–ocular responses were investigated during off-vertical axis rotation. This stimulus induces nystagmus consisting of the exponentially decaying canalicular response, and an eye-velocity modulation and offset which arise from the excitation of the otoliths by the gravity vector, which lasts as long as the rotation continues. Otolith–ocular reflexes are intimately interrelated with visual tracking when real targets are viewed during linear motion. The responses of both the translational vestibulo-ocular reflex and the pursuit system have been shown to be linearly dependent on the inverse of the viewing distance, so that a common central pathway for the two systems has been suggested, probably travelling through the cerebellum. Thus, the aim of the study was to evaluate to what extent these reflexes are disturbed in cerebellar disease. The results confirm the earlier notion that in normal subjects pursuit performance is better for horizontal than for vertical tracking, and that it is better for upward than for downward tracking. This pattern is also found in patients. In addition, smooth pursuit performance is clearly degraded in patients, but the modulation of eye-velocity during off-vertical axis rotation is enhanced. Since the amount of this enhancement does not correlate with the amount of pursuit impairment, degradation of smooth pursuit and pathological enhancement of otolith–ocular responses seem to be independent effects of cerebellar degeneration. Thus, the increase in the otolith–ocular response in patients cannot be attributed to adaptational mechanisms trying to overcome the smooth pursuit deficiency; it is more likely to represent pathological disinhibition of otolith derived responses. The absence of compensatory eye-velocity offset during off-vertical axis rotation may reflect the fact that in patients the otolith signals are not utilized in computations thought to be important for spatial orientation mechanisms arising from the interaction of vestibular, visual and somatosensory signals.

Keywords: cerebellar ataxia; otolith–canal interaction; smooth pursuit; off-vertical axis rotation; three-dimensional eye movements

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; ANOVA = analysis of variance; EOCA= early onset cerebellar ataxia; IDCA = idiopathic late onset ataxia; IDCA-C = cerebellar IDCA; MSA-C = cerebellar type of multiple system atrophy; SCA = spinocerebellar ataxia; VOR = vestibulo-ocular reflex

Introduction

Cerebellar dysfunction can result in specific abnormalities of ocular motor control (see Leigh and Zee, 1991). Disturbances of ocular following reflexes, of gaze holding and saccadic pulse-step mismatch can be produced by lesions of the flocculus and parafloccullus, while lesions of the dorsal vermis and the underlying fastigial nuclei cause mainly saccadic dysmetria. The nodulus and uvula appear to control the time constant of the vestibulo-ocular reflex (VOR) and seem to be involved in otolith mediated responses. Furthermore, long-term adaptive functions have been attributed to the cerebellum, which help to keep eye movements appropriate to the visual stimuli.

There are several lines of evidence that cerebellar dysfunction can afflict otolith mediated responses. Downbeat, upbeat and positional nystagmus of central origin have been frequently associated with cerebellar disease. Their

dependency on head position in the gravitational field implies the possibility of abnormal otolith function in cerebellar disease (Halmagyi *et al.*, 1983). Although there are major quantitative differences in otolith-derived ocular responses between monkey and man (Darlot *et al.*, 1988; Fetter *et al.*, 1996), some further evidence for a cerebellar involvement in otolith–ocular reflexes comes from primate experiments. Lesions of cerebellar nodulus and ventral uvula in primates produce oscillatory vestibular responses (periodic alternating nystagmus), abolish the capability of 'dumping' post-rotatory vestibular nystagmus by reorientation of the head relative to gravity (Waespe *et al.*, 1985), and abolish the ability of the otolith system to generate steady-state nystagmus during off-vertical axis rotation (Angelaki and Hess, 1995*a*). It was assumed that the periodic alternating nystagmus reflects disinhibition of otolith-controlled inhibitory effects on central vestibular processes, and that these structures may comprise part of the neural substrate involved in the computation of head angular velocity from rotation of a linear acceleration vector. This function is thought to be related to the central velocity storage mechanism (Cohen *et al.*, 1983; Angelaki and Hess, 1995*b*), which prolongs the time constant of the peripheral vestibular signal and generates optokinetic after-nystagmus following a period of optokinetic stimulation.

While the angular VOR, which serves to stabilize gaze during rotational head movements, has been extensively described in patients with cerebellar dysfunction (Zee *et al.*, 1976; Thurston *et al.*, 1987; Fetter *et al.*, 1994; Moschner *et al.*, 1994), there is only limited information on the otolith–ocular reflexes in cerebellar patients (Baloh *et al.*, 1995).

Otolithic-ocular reflexes have been studied in normal human subjects by applying translations along the interaural axis (Niven *et al.*, 1966; Buizza *et al.*, 1980; Baloh *et al.*, 1988*a*, *b*) and by using constant speed rotations around an axis tilted relative to the vertical (off-vertical axis rotation: Guedry, 1965; Benson and Bodin, 1966; Harris and Barnes, 1987; Darlot *et al.*, 1988). In the study presented here we used the latter stimulus, off-vertical axis rotation, to investigate the otolith–ocular responses in patients with cerebellar ataxia. Off-vertical axis rotation in darkness induces nystagmus consisting of the exponentially decaying canalicular response and a component arising from the stimulation of the otoliths by the continuously changing orientation with respect to gravity, which lasts as long as the rotation continues. Otolith–ocular reflexes interact synergistically with the angular VOR during combined canal-otolithic stimulation in the horizontal plane (Anastasopoulos *et al.*, 1996). Furthermore, they are intimately interrelated with visual tracking when real targets are viewed during linear motion (Baloh *et al.*, 1988*a*, *b*; Shelhamer and Young, 1994; Gianna *et al.*, 1997). The responses of both the translational VOR and the pursuit system have been shown to be linearly dependent on the inverse of the viewing distance, so that a common central pathway for the two systems has been suggested, probably travelling through the cerebellum (Schwarz *et al.*, 1989; Baloh *et al.*, 1995).

The aim of the present study was to evaluate both the otolith–ocular reflex and smooth pursuit in cerebellar disease, thereby testing the earlier assumption that the enhancement of angular VOR gain in cerebellar disease reflects an adaptive mechanism to compensate for an impaired smooth pursuit (Robinson, 1976). If this is the case for the otolith-derived VOR, it should be expected that the increased retinal image slip due to pursuit impairment would lead to a parallel enhancement of otolith–ocular reflexes.

Methods

Patients and controls

Eleven patients with cerebellar ataxia, predominantly presenting with cerebellar symptoms, and 21 normal subjects gave their informed consent to the study according to a protocol of the University of Tübingen ethics committee. Table 1 shows the main clinical features of our patients. Severity of cerebellar dysfunction was assessed by using the rating scale developed by Massaquoi and Hallett (Wessel *et al.*, 1995). In all cases the ataxia was progressive, and possible symptomatic causes (toxic, malignancy, hypothyroidism, vitamin deficiency, inflammatory or vascular aetiology) were excluded. The diagnosis of autosomal dominant cerebellar ataxia (ADCA) was made if the family history was positive. A distinction was made between ADCA-I (one patient), when additional non-cerebellar symptoms were present, and ADCA-III (almost pure cerebellar ataxia; one patient). With molecular genetic testing, an expansion of the CAG repeat at the spinocerebellar ataxia (SCA1) locus could be demonstrated in the patient with ADCA-I. Patients with idiopathic late onset ataxia (IDCA, after the age of 25 years) were similarly classified according to the presence of a cerebellar type of multiple system atrophy (MSA-C; one patient) or absence of additional non-cerebellar signs (IDCA-C; three patients). The remainder of patients were classified as early onset cerebellar ataxia (EOCA, onset before the age of 20 years; five patients). The latter patients did not show the characteristic clinical and radiographic features of Friedreich's ataxia (Klockgether *et al.*, 1993, 1996). Pursuit performance of the patients was compared with that of 11 age-matched control subjects (39.2 $\pm$ 10.2 and 33.3 $\pm$ 8 years, respectively; means $\pm$ SD). The mean age for the 11 normal subjects who underwent the off-vertical axis rotations was 26 years (range 21–39 years). One of them participated in both tests. None of the subjects was taking medications known to influence ocular motility at the time of the measurements.

Apparatus and stimuli

Subjects were seated inside an opaque spherical cabin (1.95 m in diameter) and were firmly secured to the chair with seat belts. The cabin was supported by the inner ring of a four-axis gimbal system which had been specially designed for

Table 1 *Clinical and MRI data of patients with cerebellar degeneration*

Patient	Age (years)	Duration (years)	Diagnosis	Clinical rating score									Additional extracerebellar findings	MRI	
				Balance	Gait	Upper limb ataxia	Lower limb ataxia	Tone	Tremor	Dysarthria	Oculo	Total*		Cerebellar atrophy†	Brainstem atrophy‡
1	39	3	SCA1	1	1	0	0	0	0	0	2	4	–	++	+
2	43	18	ADCA-III	1	1	1	1	0	0	3	1	8	–	++	–
3	57	3	IDCA-C	2	2	1	2	0	0	1	3	11	–	+	–
4	45	13	IDCA-C	1	2	1	2	0	0	1	2	10	–	+++	–
5	41	14	IDCA-C	3	3	3	3	0	1	2	2	17	–	+++	–
6	51	4	MSA-C	3	3	2	3	0	1	4	2	18	Orthostasis	+++	+
7	20	9	EOCA	3	3	3	3	0	1	1	3	17	Polyneuropathy	+++	+
8	31	11	EOCA	3	3	2	2	0	2	2	3	17	–	+++	–
9	33	14	EOCA	3	3	2	3	2	1	2	3	19	Saccade slowing, Optic atrophy	++	+
10	31	17	EOCA	2	2	2	2	0	0	2	1	11	–	+++	+
11	41	25	EOCA	4	4	3	3	0	2	3	3	22	Pyramidal polyneuropathy	+++	–

Severity score after the scale of Massaquoi and Hallett (Wessel *et al.*, 1995). *Total score of 1–10 = mild; 11–20 = moderate; 21–32 = severe cerebellar ataxia. †Cerebellar atrophy: + = mild; ++ = moderate; +++ = severe. ‡Brainstem atrophy: + = visible: – = no visible atrophy.

three-dimensional investigations of the VOR (Koenig *et al.*, 1996). The subjects were positioned such that the middle of the interaural line was at the centre of the rotations during off-vertical axis rotation. Deflatable vacuum cushions which could be adjusted to the shape of the body were used to stabilize the subject. The head was in a comfortable position, which corresponded to Reid's line being ~7° nose up. In this orientation the horizontal semicircular canals are pitched, nose up, by ~30°. Measurement of this angle allowed standardization of head position relative to the rotation axis. Head movements were minimized by a helmet. Audio contact was maintained with the subject through an intercom system throughout the testing. After a set of calibration data were recorded with the subject in the upright position, two different paradigms were tested: first visual tracking of a spot target to assess the performance of the smooth-pursuit system, and then rotations about an axis tilted away from the earth vertical by 30°.

During smooth pursuit the subject was instructed to attempt to maintain fixation on a moving laser spot. The target had a visual angle of 0.2° and was projected onto the inside of the sphere by a mirror galvanometer mounted over the subject's head. It moved sinusoidally with a maximum amplitude of 22.5°, first in the horizontal and thereafter in the vertical mid-sagittal plane. The frequency was initially 0.07 Hz and increased linearly, over 20 s, to 0.42 Hz, which corresponds to a maximum target velocity of 108°/s (Fig. 1). Recordings were done twice for each plane.

For off-vertical axis rotation testing the subject was pitched 30° nose up (i.e. in a slightly supine position, see inset in Fig. 2), and then accelerated in darkness around the body longitudinal axis to the right, with 100°/s^2 up to a constant velocity of 100°/s. Subjects were instructed to keep their eyes open and look straight ahead at an imaginary horizon. The direction of the axis of rotation was kept constant throughout the 90 s constant velocity rotation. During the angular velocity step both the horizontal canals and the otolith organs are stimulated. The canal response decays with

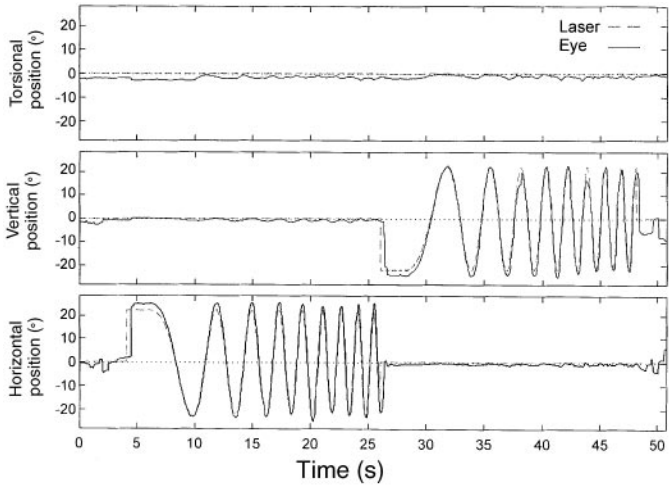

Fig. 1 Torsional, vertical and horizontal eye position (solid line) of a normal subject during smooth pursuit of a spot-target (dashed line) oscillating in the horizontal or vertical plane. The target (laser) moved sinusoidally with a maximum amplitude of 22.5°, first in the horizontal and then in the mid-sagittal (vertical) plane. It started eccentrically, with a frequency of 0.07 Hz, and increased its frequency linearly, over 20 s, to 0.42 Hz. This yielded a maximum target velocity of 108°/s.

a time constant of ~15 s, so that the otolithic response can be studied in isolation around the end of the 90 s stimulation time. While the force exerted by gravity along the body longitudinal axis is constant during off-vertical axis rotation, the gravitational force component in the body-horizontal plane (spanned by the naso-occipital and the interaural body axes) rotates continuously, and stimulates the otolith maculae sequentially. This is indicated in Fig. 2 (insert), where the component of gravity in the body-horizontal plane (dashed line) pulls in different directions depending on the orientation of the subject in space. The magnitude of this rotating-force component is proportional to the sine of the tilt angle. After 90 s of constant velocity rotation, the subject was decelerated with a matching deceleration such that he/she ended up in

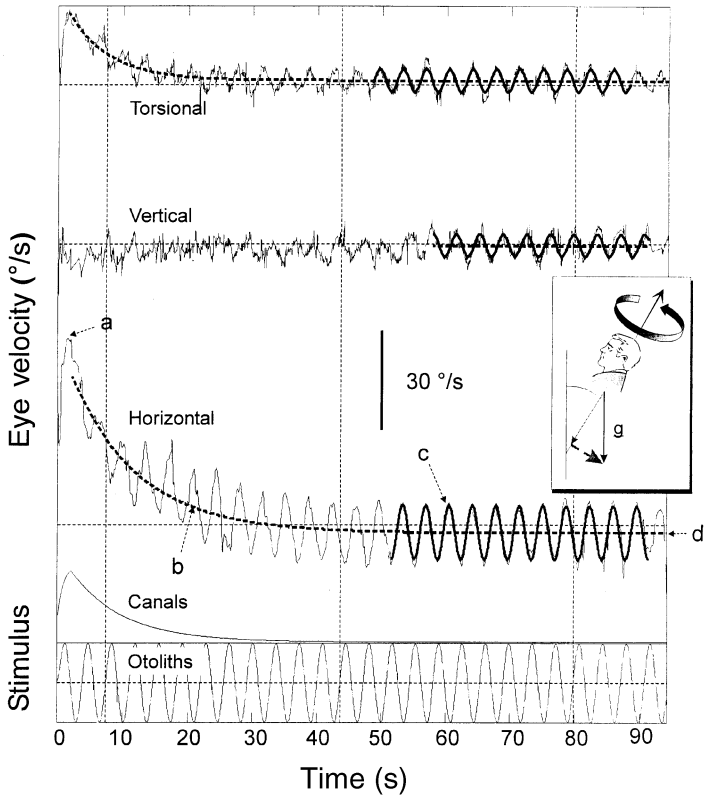

Fig. 2 Torsional, vertical and horizontal desaccaded eye-velocity components during off-vertical axis rotation with 100°/s about an axis tilted by 30° with respect to gravity. The dashed lines indicate the fits for the exponential decay of the offset velocity, and the solid lines the fitted sine functions. At the bottom, the stimulus to the semicircular canals and the otoliths is displayed schematically: the curve for the otoliths is the sine of the actual body yaw angle in space. For the data analysis, we determined the maximum eye velocity (a) and the time constant of its exponential decay (b, dashed line), allowing for a possible offset (d) at the end of the 90 s constant velocity stimulation. We also determined amplitude and phase (c) of the sinusoidal modulation of the eye velocity during off-vertical axis rotation (solid line). Insert: while the direction of gravity (g) stays constant in space, the component of this force in the body-horizontal plane (thick dashed arrow) is modulated with respect to the subject by the continuously changing orientation of the body in space.

the starting position. After the post-rotatory nystagmus had ceased, a short break was given during which the cabin was illuminated. The rotation was then repeated in the opposite direction, around the same axis as before. The subject was positioned upright after the end of the off-vertical axis rotation testing, and another set of calibration data were recorded.

Data acquisition and analysis

The three-dimensional position of the left eye was recorded with the dual search coil technique. Subjects wore a Skalar annulus containing two orthogonal coils (Skalar, Delft, Netherlands). The magnetic field was produced by three orthogonal pairs of coils, mounted on the outer surface of the cabin. The head of the subject was exactly in the centre of the magnetic fields. Signals from all three fields were recorded, and the system was automatically calibrated at the beginning of each experiment. The magnetic fields were stabilized at preset amplitude and phase values by means of an analogue circuit. A digital microprocessor automatically calibrated the analysis unit. With this system it is not necessary to switch on the magnetic field coils long before starting an experiment to ensure a constant temperature in the electronic circuits, nor is it necessary to adjust the amplitudes of the fields (Bechert and Koenig, 1996). Calibrations showed that eye positions measured with this system were accurate to within 5% of total eye eccentricity in three dimensions, and that there was no cross-talk between the horizontal, vertical and torsional channels.

The eye position at the beginning or at the end of the recordings, when the subject was instructed to look straight ahead, was taken as reference position. Data were sampled at 100 Hz, and the corresponding eye movements were expressed in head co-ordinates. From the eye position and its time derivative, determined with a Savitzky–Golay filter (Savitzky and Golay, 1964; Press *et al.*, 1992), three-dimensional angular eye velocity was calculated (Tweed *et al.*, 1990). It was expressed according to the right hand rule, i.e. leftward, downward and clockwise eye velocities were positive.

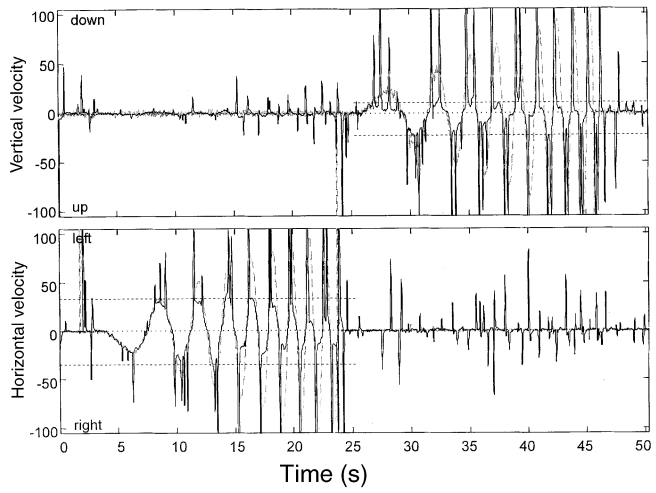

Fig. 3 Vertical and horizontal eye velocity (°/s) (solid line) of a patient during smooth pursuit of a spot-target (dashed line) oscillating in the horizontal or vertical plane. Horizontal dotted lines indicate the speed limits for horizontal and vertical pursuit.

Smooth pursuit

Horizontal and vertical eye-velocity components were plotted on the screen, and peak pursuit eye velocity was determined manually with a cross-hair for upward, downward, leftward and rightward eye-movements (Fig. 3). As the testing was done twice, pursuit performance in a particular direction was characterized by the average of the highest velocity of smooth pursuit attained during each of the two runs.

Off-vertical axis rotation

Fast phases of the nystagmus were removed with an algorithm developed by Holden *et al*. (1992). Visual inspection of the data was performed to ensure proper desaccading and smoothing. When necessary, fast phase eye-movements were further removed by interpolating a straight line between the manually determined beginning and end of the saccades. The graph in Fig. 2 shows the torsional, vertical and horizontal components of the desaccaded eye velocity signal. From the desaccaded values, the maximum eye velocity (V_{max}, labelled 'a' in Fig. 2) for the horizontal component and the time constant (τ, labelled 'b') of its exponential decay were determined by fitting an exponentially decaying function, allowing for a possible offset (labelled 'd') at the end of the 90 s constant velocity stimulation: velocity, V = offset + $V_{max} \times \exp(-t/\tau)$. For the vertical and torsional velocity data, which in most cases showed no exponential decay, the velocity offset was determined by averaging over a hand-selected interval towards the end of the recording. The figure graphically indicates these parameters.

The amplitude and the phase (labelled 'c') of the sinusoidal modulation of the eye velocity during off-vertical axis rotation were determined by fitting the $V = \text{amp} \times \sin(\omega t + \Delta\phi)$ to a hand-selected data interval of the eye velocity traces, after the exponential decay and the offset had been subtracted. $\Delta\phi$ is the phase difference between eye velocity and the sinusoidal modulation of the component of the gravity vector along the y (interaural) stereotactic axis. $\Delta\phi = 0$ is given when the modulation is zero with the subject in the nose-up starting position. Post-rotational maximum eye velocity and the time constant of the exponential eye velocity decay in the horizontal plane were calculated from data obtained during a 90 s recording period after the deceleration.

Statistical analysis

Unless stated otherwise, the significance of the findings was tested by analysis of variance (ANOVA), where Direction (left versus right and upward versus downward for smooth pursuit, and left versus right for off-vertical axis rotation) and Plane of eye movement rotation during off-vertical axis rotation (horizontal, vertical and torsional) were used as the within-subject repeated measures factors, with Group (patients versus normal subjects) as the between-groups factor.

The design applied when comparing each of the various parameters between patients and controls is explicitly indicated in the appropriate parts of the results.

Results

Smooth pursuit

At lower target frequencies, the eye followed the target smoothly up to a maximum target velocity. Then the maximum eye velocity stayed approximately constant, while the target frequency (and thus velocity) increased further (Fig. 3). In the horizontal plane normal subjects were on average able to generate smooth eye movements of up to 80°/s. Averaging the values for pursuit left and right within each subject, a maximum pursuit velocity of 78.0 ± 9.9°/s (means ± SD) was obtained for normal subjects. The upper speed limits of vertical pursuit were clearly higher for upward than downward tracking (57.7 ± 19.4°/s versus 44.9 ± 19.8°/s, Table 2), although the data demonstrate a larger interindividual variation in performance in the vertical plane.

For horizontal pursuit, patients achieved average maximum velocities of 27.3 ± 16.4°/s. For vertical pursuit, the maximum velocities upward and downward were 17.6 ± 11.7°/s and 9.5 ± 5.5°/s, respectively. Pursuit performance in the horizontal and vertical planes correlated with the severity score for cerebellar dysfunction (Pearson $\rho = -0.81$, $P = 0.0015$ for horizontal pursuit; $\rho = -0.61$, $P = 0.04$ for upward pursuit; $\rho = -0.68$, $P = 0.02$ for downward pursuit).

The maximum pursuit velocities attained by patients were compared with those of normal subjects, separately for the horizontal and vertical planes, by treating the data by 2 × 2 ANOVA with Direction (left versus right and upward versus downward, respectively) as the within-subject repeated measures factor and Group (patients versus normal subjects) as the between-groups factor. Pursuit performance was

Table 2 *Smooth pursuit performance (upper speed limits) and off-vertical axis rotation data*

	Normal subjects	Patients
Smooth pursuit (°/s)		
Horizontal	78.0 ± 9.9	27.3 ± 16.4
Upward	57.7 ± 19.4	17.6 ± 11.7
Downward	44.9 ± 17.8	9.5 ± 5.5
Off-vertical axis rotation		
Maximum velocity (°/s) after		
Acceleration	52.2 ± 9.4	61.6 ± 19.4
Deceleration	40.4 ± 5.5	65.6 ± 23.0
Modulation amplitude (°/s) in the		
Horizontal plane	3.8 ± 1.1	7.9 ± 1.7
Vertical plane	1.8 ± 0.7	2.9 ± 1.4
Torsional plane	1.9 ± 0.7	2.9 ± 1.5
Offset (°/s) in the horizontal plane during		
Rightward rotation	2.4 ± 3.2	–4.3 ± 6.1
Leftward rotation	–2.5 ± 2.9	2.9 ± 4.3
Offset (°/s) in the vertical plane	–0.9 ± 2.3	–1.3 ± 2.6
Offset (°/s) in the torsional plane	–0.2 ± 0.8	–1.7 ± 2.3

Values are shown as means ± SD.

significantly different between normal subjects and patients for both the horizontal plane ($F = 77.46$, $P < 0.0001$) and vertical plane ($F = 44.20$, $P < 0.0001$). In the vertical plane, both normal subjects and patients showed higher velocities during upward than downward pursuit ($F = 16.03$, $P = 0.0007$).

Off-vertical axis rotation

During off-vertical axis rotation the horizontal slow phase velocity consisted of three components: an exponentially decaying, mainly canalicular response (Fig. 2, a and b); a sinusoidal modulation showing a close phase relationship with the gravitational stimulus (Fig. 2, c); and a non-zero, offset, if the response did not decay to zero (Fig. 2, d).

Maximum velocity and time constant

Data for the horizontal plane were treated by a $2 \times 2 \times 2$ factorial ANOVA, with Stimulus (acceleration versus deceleration) and Direction of rotation (right versus left) as the within-subject repeated measures factors, and Group (patients versus normal subjects) as the between-groups factor. The maximum velocity was slightly higher in patients than in normal subjects (60.0 ± 20.4 versus 49.3 ± 10.8°/s; $F = 4.72$, $P < 0.05$; Table 2). The interaction of the factors Stimulus and Group reached statistical significance ($F = 5.44$, $P = 0.03$), reflecting the fact that, in contrast to normal subjects, maximum velocity in patients after deceleration was not smaller than after acceleration. The time-constants in patients (14.0 ± 5.1 s) were slightly, but not significantly, higher than those in normal subjects (12.1 ± 2.9 s).

Modulation

Modulation of eye velocity at the frequency of rotation started immediately during off-vertical axis rotation, with a mean steady state amplitude in normal subjects for the horizontal component of 3.8 ± 1.1°/s; for the vertical component it was 1.8 ± 0.7°/s, and for the torsional component 1.9 ± 0.7°/s. The modulation amplitudes of all three eye-velocity components in patients (7.9 ± 1.7°/s, 2.9 ± 1.4°/s and 2.9 ± 1.5°/s respectively, Table 2) were significantly increased compared with normal subjects ($F = 61.38$, $P = 0.0001$, $3 \times 2 \times 2$ ANOVA, with Plane of eye movement and Direction of rotation as the within-subject repeated measures factors and Group as the between-groups factor). On the whole, the amplitude in the horizontal plane was larger ($F = 35.90$, $P = 0.0001$), this tendency being more prominent in the patient group ($F = 6.40$, $P = 0.005$ for the interaction of the factors Plane and Group). In normal subjects, the modulation showed on average a small lag of –6.5 ± 22° for the horizontal component, i.e. its positive (leftward) maximum occurred approximately when the left ear was down, both for leftward and rightward rotations. An ANOVA comparison of the phases in normal subjects and in patients revealed a small but significant lead of the patients' responses of ~25° compared with normal subjects ($F = 6.35$, $P = 0.02$). The phase was quite variable for the torsional velocity modulation, and almost random for the vertical modulation in both normal subjects and patients. A statistical comparison was therefore not performed for these two components.

Offset

The offset of the horizontal component was small but compensatory in most normal subjects, i.e. the nystagmus slow phase was in the opposite direction to that of head rotation (2.4 ± 3.2°/s), while those of the vertical and torsional components were not significantly different from zero (Table 2). Offset of the horizontal component was mostly anticompensatory in patients. Comparison by a $3 \times 2 \times 2$ ANOVA (Plane of eye movement and Direction of rotation as the within-subject repeated measures factors and Group as the between-groups factor) revealed a highly significant interaction between them ($F = 13.59$, $P = 0.0001$); while the velocity offset of the horizontal component was positive during rotation to the right and negative during rotation to the left in normal subjects, it was in the opposite direction in patients for the same rotations to the right and the left. Neither the modulation-amplitude nor the offset-magnitude correlated with smooth pursuit performance, the severity score or the disease duration. Patients with a downbeat nystagmus showed a negative (upward) offset, while those with an upbeat nystagmus showed a positive one (three and two patients, respectively, range between –7.7 and 1.6°/s). This offset represents, approximately, the slow phase velocity of the vertical nystagmus. The modulation of the eye velocity of these patients was not different from that of the remaining ones.

Discussion

The main finding of this study is that the otolith–ocular responses are regularly enhanced in cerebellar degeneration. Despite this enhancement, the absence of compensatory offset during off-vertical axis rotation, thought to result from the otolith signals feeding into the central velocity storage mechanism, suggest that this pathway is hampered in patients with cerebellar ataxia. Experiments in rhesus monkeys suggest that this pathway involves the nodulus and ventral uvula (Angelaki and Hess, 1995*a*). As the enhancement of the otolith–ocular reflexes does not correlate with the pursuit deficit, it cannot be attributed to adaptational mechanisms, but may represent pathological disinhibition. In addition, pursuit performance was better for upward than for downward tracking, and better for horizontal than for vertical pursuit in patients, which is similar to the known pattern in normal subjects.

Smooth pursuit

Most previous studies have tested pursuit maintenance by using triangular or sinusoidal target motion of constant frequency, or a sum of multiple harmonics, and have expressed the performance in terms of gain (Demer, 1994). As the results of our study show, continuously increasing the velocity of target motion can push up the velocity of pursuit in normal subjects to high levels. As pursuit is related to optokinetic nystagmus, in both humans and primates, sharing part of the same transcortical neuronal network, our results for vertical pursuit are in agreement with reports showing directional asymmetries of optokinetic nystagmus in humans, with higher slow phases up than down (van den Berg and Collewijn, 1988; Howard and Simpson, 1989; Murasugi and Howard, 1989). Similar asymmetries have been found during optokinetic nystagmus in monkeys (Matsuo and Cohen, 1984). Our study also confirms earlier findings that pursuit can achieve larger velocities in the horizontal plane than in the vertical plane (Baloh *et al.*, 1988*a*, *b*; Rottach *et al.*, 1996).

This is the first study where precise search-coil measurements were made of horizontal and vertical smooth pursuit performance in patients with cerebellar ataxia. It is well known that patients with lesions in the cerebellum, including the flocculus and/or the dorsal vermis, have pursuit deficits (Leigh and Zee, 1991). We can add to this database by showing that although smooth pursuit performance was impaired in our patients, the performance patterns (better horizontal pursuit, and better pursuit for upward than for downward tracking) were similar to normal subjects. The vertical pursuit asymmetry in patients cannot be explained by the weak downbeat or upbeat nystagmus observed in some of them, as they were otherwise not different in their performance. None of our patients showed torsional nystagmus during vertical pursuit, a sign described in three patients presenting with cavernous angioma within the middle cerebellar peduncle (FitzGibbon *et al.*, 1996), suggesting that this feature can only be seen in asymmetric lesions.

Off-vertical axis rotation

Maximum velocity and time constant

The horizontal angular VOR has been described as normal, hyperactive or hypoactive in different progressive ataxia syndromes (Zee *et al.*, 1976; Thurston *et al.*, 1987; Fetter *et al.*, 1994; Moschner *et al.*, 1994). This is not surprising, as the underlying pathology is variable and sometimes includes degeneration of the VIIIth nerve as in Friedreich's ataxia or in SCA3. Most of our patients presented with pure cerebellar symptoms. Thus, our findings are in agreement with the study of Moschner *et al.* (1994), in which augmented VOR responses in patients with cerebello-olivary atrophy were reported. The normal VOR phase of patients in our study corresponds to our finding of a normal time constant, but it has to be pointed out that the latter parameter reflects the result of canal–otolith interaction. This may explain the fact that the time constant was found to be somewhat shorter than the canalicular time constant during rotations around an earth-vertical axis (Guedry, 1965; Benson and Bodin, 1966).

Sinusoidal modulation

The small modulation amplitudes of our normal subjects are similar to those of earlier studies (Harris and Barnes, 1987; Darlot *et al.*, 1988; Furman *et al.*, 1992), but varying experimental conditions make direct comparisons difficult. Also, the gain of the linear VOR has been found to be clearly larger at similar stimulus frequencies during sinusoidal acceleration along the interaural axis (~15°/s/*g*; Shelhamer and Young, 1994). It is known that target distance cues are able to modify the response considerably. Thus, the instruction to look at an imaginary horizon, i.e. to set target distance at infinity, may be responsible for the small modulation amplitudes.

Vergence is less important than the perceived target distance in modifying linear VOR sensitivity (Schwarz and Miles, 1991; Baloh *et al.*, 1995). As the vergence angle attains a constant idiosyncratic phoria within 1 s after human subjects are put into darkness (Anastasopoulos *et al.*, 1996), we did not control for vergence during off-vertical axis rotation.

In contrast to reports showing reduced linear VOR sensitivity in patients with cerebellar atrophy (Baloh *et al.*, 1995), the horizontal modulation amplitude during off-vertical axis rotation more than doubled in patients compared with normal subjects. The apparent discrepancy may be explained by the fact that the linear VOR sensitivity in the above study was evaluated by asking the subjects to visualize or to imagine an earth-fixed target during linear movement along the interaural axis on a parallel swing. During this procedure, the responses do not depend exclusively on the otolith–ocular reflexes; they also involve smooth pursuit and other signals controlled by voluntary mechanisms. A similar increase of the modulation amplitude has been reported in patients with periodic alternating nystagmus, an eye movement abnormality probably caused by lesions of the

cerebellar uvula and nodulus (Furman *et al.*, 1990). The enhancement of otolith signals in our study did not correlate with pursuit performance, indicating that it cannot be attributed to adaptational mechanisms as postulated by Robinson (1976). It may represent pathological disinhibition of otolith derived responses. Furthermore, we also found an increased amplitude of vertical and torsional eye-velocity modulation during off-vertical axis rotation. The latter finding would support the above assumption, as there is no torsional pursuit in cerebellar patients to be compensated for.

Offset

The steady-state horizontal eye-velocity offset, which is equivalent to the mean horizontal eye-velocity, was compensatory in normal subjects during constant velocity off-vertical axis rotation, but anticompensatory in patients. In other words, while in normal subjects the eyes moved in a direction opposite to the rotation of the body, a reflex which would in the light serve to stabilize the retinal image, they moved in the direction of the rotation in patients. Under normal conditions, this offset, which reconstructs a head velocity signal from the stimulation of otolithic receptors, is clearly smaller in humans than in primates (Benson and Bodin, 1966; Darlot *et al.*, 1988). Its physiological significance in humans is uncertain. The velocity-storage hypothesis proposes that the same neural mechanism is responsible for the prolongation of the time constant of the VOR and the compensatory offset of the horizontal eye velocity during off-vertical axis rotation. In a study investigating the effects of selective lesions of the nodulus and ventral uvula on the processing of otolith signals in rhesus monkeys, it was found that during yaw-off-vertical axis rotation the offset in the horizontal eye-velocity component is completely eliminated, compared with normal animals (Angelaki and Hess, 1995*a*). Does the anticompensatory offset found in the patients represent the same phenomenon? In spite of the major differences in otolith–ocular responses between humans and primates, there is some evidence from the evaluation of a small number of patients with episodic ataxia that the offset may also depend on the integrity of cerebellum in humans (Furman, 1997). The overshoot of the horizontal eye-velocity to the opposite direction, which follows the exponential decay, may reflect an augmentation of mechanisms involved in the generation of the secondary phase of the yaw angular VOR response in healthy subjects during rotation about an earth-vertical axis. This overshoot is interpreted on the basis of an adaptation during the application of the stimulus which leads to a response in the opposite direction when the stimulus is removed. This mechanism can even lead to oscillatory vestibular responses (periodic alternating nystagmus) to a velocity step, which has been observed in primates subjected to nodulectomy and partial uvulectomy (Waespe *et al.*, 1985), as well as during parabolic flight (Graybiel *et al.*, 1981). A related finding in cerebellar patients, suggesting involvement of the otolith pathway via the nodulus and ventral uvula, is the loss of the ability to ‘dump’ post-rotatory vestibular nystagmus (Hain *et al.*, 1988). The inability of the patients to reduce the VOR gain after deceleration may reflect a disturbance of the integration of conflicting somatosensory signals. This could be a contributing factor to the ataxia present with cerebellar lesions.

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