Exp Brain Res (2000) 130:486–496
Digital Object Identifier (DOI) 10.1007/s002219900266

RESEARCH ARTICLE

Benjamin T. Crane · Jun-Ru Tian · Joseph L. Demer

Initial vestibulo-ocular reflex during transient angular and linear acceleration in human cerebellar dysfunction

Received: 13 July 1998 / Accepted: 30 September 1999 / Published online: 16 December 1999

Abstract During transient, high-acceleration rotation, performance of the normal vestibulo-ocular reflex (VOR) depends on viewing distance. With near targets, gain (eye velocity/head velocity) enhancement is manifest almost immediately after ocular rotation begins. Later in the response, VOR gain depends on both head rotation and translation; gain for near targets is decreased for rotation about axes anterior to the otoliths and augmented for rotation about axes posterior to the otoliths. We sought to determine whether subjects with cerebellar dysfunction have impaired modification of the VOR with target distance. Eleven subjects of average age 48±16 years (mean ± standard deviation, SD) with cerebellar dysfunction underwent transients of directionally unpredictable whole-body yaw rotation to a peak angular acceleration of 1000 or 2800°/s^2 while viewing a target either 15 cm or 500 cm distant. Immediately before onset of head rotation, the lights were extinguished and were relit only after the rotation was completed. The axis of head rotation was varied so that it was located 20 cm behind the eyes, 7 cm behind the eyes (centered between the otoliths), centered between the eyes, or 10 cm anterior to the eyes. Angular eye and head positions were measured with magnetic search coils. The VOR in subjects with cerebellar dysfunction was compared with the response from 12 normal subjects of mean age 25±4 years. In the period 35–45 ms after onset of 2800°/s^2 head rotation, gain was independent of rotational axis. In this period, subjects with cerebellar dysfunction had a mean VOR gain of 0.5±0.2, significantly lower than the normal range of 1.0±0.2. During a later period, 125–135 ms after head rotation about an otolith-centered axis, subjects with cerebellar dysfunction had a mean VOR gain of 0.67±0.46, significantly lower than the value of 1.06±0.14 in controls. Unlike normal subjects, those with cerebellar dysfunction did not show modification of VOR gain with target distance in the early response and only one subject showed a correct effect of target distance in the later response. The effect of target distance was quantitatively assessed by subtracting gain for a target 500 cm distant from gain for a target 15 cm distant. During the period 35–45 ms after the onset of 2800°/s^2 head motion, only two subjects with cerebellar loss demonstrated significant VOR gain enhancement with a near target, and both of these exhibited less than half of the mean enhancement for control subjects. During the later period 125–135 ms after the onset of head rotation, when VOR gain normally depended on both target location and otolith translation, only one subject with cerebellar dysfunction consistently demonstrated gain changes in the normal direction. These findings support a role for the cerebellum in gain modulation of both the canal and otolith VOR in response to changes in distance. The short latency of gain modification suggests that the cerebellum may normally participate in target distance-related modulation of direct VOR pathways in a manner similar to that found in plasticity induced by visual-vestibular mismatch.

Key words Eccentric rotation · Cerebellum · Otolith · Semicircular canals · Target distance · Vestibulo-ocular reflex · Human

Grant support: United States Public Health Service, grant DC-02952. B.T.C. was supported by an National Institutes of Health Medical Scientist Training Program grant. J.L.D. was a recipient of a Research to Prevent Blindness Lew R. Wasserman Merit Award and is Laraine and David Gerber Professor of Ophthalmology.

B.T. Crane · J.-R. Tian · J.L. Demer
Department of Ophthalmology, University of California, Los Angeles, CA 90095–7002, USA

B.T. Crane · J.-R. Tian · J.L. Demer
Department of Neurology, University of California, Los Angeles, CA 90095–7002, USA

J.L. Demer (✉)
Jules Stein Eye Institute, 100 Stein Plaza, UCLA, Los Angeles, CA 90095–7002, USA
e-mail: jld@ucla.edu
Tel: +1-310-8255931, Fax: +1-310-7947906

Introduction

The vestibulo-ocular reflex (VOR) stabilizes images on the retina during both rotational and translational head movement. Head rotation can be corrected by an equal and opposite rotation of the eye, but eye rotation must also be modified to compensate for head translation as appropriate for the distance to the target. Previous work has demonstrated that target distance modulates the VOR during pure linear motion in both humans (Bronstein and Gresty 1988; Paige 1989, 1991) and monkeys (Paige and Tomko 1991; Tomko and Paige 1992). During rotation about an axis eccentric from the labyrinths, these organs sense angular acceleration, as well as linear acceleration for which the ocular response must depend on target distance (Viirre et al. 1986; Gresty et al. 1987; Viirre and Demer 1996). Although target distance influences only the translational response of the VOR during sinusoidal head rotation (Crane et al. 1997), during transient high acceleration, target distance also modifies angular VOR gain (Snyder and King 1992; Crane and Demer 1998b). The estimate of target distance used by the VOR is influenced by multiple factors, including vergence (Paige 1991; Snyder et al. 1992), accommodation (Yue et al. 1995), and target size (Busettini et al. 1991). Both the short latency (Crane and Demer 1998b) of target distance modification and the behavior of vestibular nuclear neurons (Chen-Huang and McCrea 1999) suggest that target distance modifies properties of the disynaptic VOR pathway. The mechanism of this modification is not understood.

Two parallel channels normally modulate VOR gain (defined as the angular eye velocity divided by angular head velocity) in response to target distance. The first channel modulates the semi-circular canal response and increases VOR gain for near relative to far targets. Significant near-target gain enhancement occurred within 20 ms of head rotation at accelerations above 1600°/s^2 in humans (Crane and Demer 1998b) and with accelerations of 500°/s^2 in the monkey (Snyder and King 1992). This early enhancement was independent of the location of the rotational axis within the tested range of 10 cm anterior to 20 cm posterior to the eyes. Later in the response, VOR performance depends on both target distance and axis location via an otolith-mediated mechanism. This second channel was apparent 30–45 ms after head rotation in the monkey (Snyder and King 1992) and under optimal conditions can also be detected in humans within this interval (Crane and Demer 1998a). However, when the canal and otolith stimuli act in an antagonistic manner, as happens during rotation about an axis anterior to the eyes, the gain decrease expected with a near target due to otolith stimulation is not evident until 80–100 ms after onset of head rotation (Crane and Demer 1998a). Thus in normal humans and animals both linear and angular VOR are modified by target distance. Studying these target distance effects in patients with cerebellar dysfunction may help elucidate whether these mechanisms share a common target distance estimate.

Gain of the VOR is gradually modified under conditions of visual-vestibular mismatch. After prolonged wearing of magnifying spectacles, VOR gain changes can be manifest as early as 40 ms after the onset of head rotation in the human (Crane and Demer 2000), 19 ms in the monkey (Lisberger 1984; Lisberger and Pavelko 1988), 13 ms in the cat (Khater et al. 1993), and 18–20 ms in the goldfish (Pastor et al. 1994). This VOR adaptation requires the cerebellum, since plasticity can no longer be induced after cerebellectomy (Ito et al. 1974; Robinson 1976; Lisberger et al. 1984; Michnovicz and Bennett 1987), lesion of the climbing fiber pathway (Haddad et al. 1980), or inhibition of simple spike output by climbing fiber stimulation (Luebke and Robinson 1994). Modulation of VOR gain by target distance differs from magnification-induced plasticity in that gain modification by target distance does not require a period of training for expression. However, the latency of VOR plasticity in animals is similar to target distance-related VOR modification (Snyder and King 1992; Crane and Demer 1998b). By testing the effect of cerebellar dysfunction on VOR modification, we sought to determine whether the cerebellum has a common role in target distance determination and plastic modification of the VOR.

Multiple forms of human cerebellar dysfunction occur. These include a group of usually autosomal dominant cerebellar ataxias known collectively as olivopontocerebellar atrophy (OPCA), involving cerebellar cortical degeneration and atrophy of the inferior olivary nuclei (Brown 1994). In the spectrum of OPCA is a group of spinocerebellar ataxias (SCA) with well-characterized genotypes. Several SCA mutations have been identified and each mutation can produce a wide range of phenotypes (Dürr et al. 1996; Geschwind et al. 1997a, 1997b). All SCAs feature saccadic hypermetria, impaired smooth pursuit and optokinetic nystagmus, and rebound and downbeat nystagmus (Buttner et al. 1998). However, Buttner et al. have found that VOR performance depends on the specific mutation involved. In SCA III, VOR gain was significantly subnormal in four of seven subjects, and low normal in two others, while VOR gain was normal in all five subjects with SCA VI (Buttner et al. 1998). However, none of the subjects with SCA VI could lower VOR gain into the normal range during VOR suppression by visual fixation of a target moving with the head (cancellation). Based on these results, Buttner et al. conclude that SCA VI impaired cerebellar function only, while SCA III also impaired vestibular function. In contrast to OPCA, Friedreich's ataxia is usually autosomal recessive and involves degeneration of the spinocerebellar tracts and peripheral nerves, with variable cerebellar involvement and relative sparing of brainstem function (Brown 1994).

Previous data collected during sinusoidal head translation have demonstrated that humans with cerebellar lesions have low linear VOR gain not modifiable by target distance (Baloh et al. 1995). One interpretation of this finding is that the cerebellum is necessary for establish-

ing the target distance estimate used by the linear VOR. For near targets, the normal linear VOR gain is higher than for far target viewing. The observed small VOR response to pure linear motion in subjects with cerebellar dysfunction could be explained by default of the central target distance estimate to a fixed value similar to that of a distant target. Another interpretation of low linear VOR gain in subjects with cerebellar dysfunction might be that normal cerebellar function is essential for integration of otolith afferent signals into the VOR. The current investigation aimed to differentiate between these two interpretations. More proximal targets also tend to enhance VOR gain during transient, high angular head acceleration. The possible finding of a deficit in target distance modification of both the angular and linear VOR during eccentric rotations would support a cerebellar role in global target distance determination. Another aim of the current investigation was to determine whether the effects of target distance and head translation on the VOR occurred at a similar latency in subjects with cerebellar dysfunction as compared to previously published norms (Crane and Demer 1998b).

Materials and methods

Subjects

Eleven subjects with cerebellar dysfunction of mean (±SD) age 48±16 years gave written consent to participate in this study according to a protocol approved by the Human Subject Protection Committee in conformity with the tenets of the Declaration of Helsinki (Table 1). The diagnosis was based on history, clinical findings, and brain imaging by magnetic resonance (MRI) or computed radiographic tomography (CT). Molecular genetic testing for known causes of cerebellar dysfunction was performed in each subject when a genetic cause was suspected. Using techniques previously described (Geschwind et al. 1997a, 1997b; Zhuchenko et al. 1997), four subjects were identified with mutations for spinocerebellar ataxia (SCA) III and two had the mutation for SCA VI. All subjects with cerebellar dysfunction had impaired visual pursuit. All but two (subjects 7 and 9) of these had normal binocular alignment for the 500-cm distant target as tested by alternate cover, but only six had normal convergence for the target 15 cm distant. Convergence insufficiency is a common finding in cerebellar dysfunction (Rabiah et al. 1997) and may affect the ability to converge sufficiently for near targets.

Subject 1 was a 53-year-old man with Friedreich's ataxia who exhibited slowly progressive limb ataxia, intention tremor, dysarthria, square-wave jerks with occasional saccadic hypermetria, but no saccadic slowing or other brainstem signs. MRI showed that the brain was normal. There was a family history of similar disease in two brothers, one sister, and a maternal cousin.

Subject 2 was a 48-year-old woman who had suffered episodic dizziness and mild, slowly progressive gait and limb ataxia since she was 19 years old. Her daughter (subject 5) was similarly affected. The subject had bilateral horizontal gaze-evoked nystagmus, rebound nystagmus, and upbeat nystagmus in central gaze. Brain CT demonstrated atrophy of the superior cerebellar vermis. The near-point of convergence was remote.

Subject 3 was a 55-year-old woman with the SCA III genotype who had gait ataxia and postural instability with eyes closed in the Romberg position. She had gaze-evoked, downbeat, and rebound nystagmus. Brief episodes of paroxysmal positional nystagmus, predominantly torsional in one eye and vertical in the other, were induced by the head-hanging to the right and left. There was a static, direction-changing positional nystagmus beating to the right in the right and right lateral position, and to the left in the left and left lateral position. The static positional nystagmus was inhibited by fixation. Caloric vestibular testing and MR images of the brain showed no abnormalities.

Subject 4 was a 48-year-old man with the SCA III genotype who developed gradually progressive ataxia at age 36 years. He had horizontal gaze-evoked and rebound nystagmus with impairment of fixation-suppression of the VOR. MRI of the brain revealed no abnormalities except for focal widening of the subarachnoid space near the left temporal lobe.

Subject 5 was a 22-year-old woman first noted to have gait ataxia at age 1 year. Her mother (subject 2) and older sister were similarly affected. She had postural instability in the Romberg position. Upbeat nystagmus was present in central gaze, increasing in elevation and diminishing in depression. There was rebound nystagmus and impairment of suppression of the VOR by visual fixation.

Subject 6 was a 33-year-old woman with the SCA III genotype with rapidly progressive ataxia since onset of symptoms at age 24 years. She had finger-to-nose dysmetria, Babinski's sign, and could not walk. Gaze-evoked nystagmus and rebound nystagmus

Table 1 Subjects with cerebellar dysfunction. Summary of clinical findings in the 11 subjects with cerebellar dysfunction. Sinusoidal VOR was normal unless otherwise noted. The nearpoint of convergence was considered normal if it was 8 cm or closer. All subjects had gaze-paretic nystagmus in lateral gaze (see Materials and methods) and impaired visual pursuit (*CCD* congenital cerebellar dysgenesis, nonprogressive, *SCA* spinocerebellar ataxia, *OPCA* olivo-ponto-cerebellar atrophy)

Subject	Age at testing (years)	Age at diagnosis (years)	Sex	Diagnosis	Convergence	Nystagmus in primary position	Notes
1	53	25	M	Friedreich's ataxia	Normal	Mild horizontal	a
2	48	19	F	CCD	Remote near point	None	b
3	55	40	F	SCA III	Normal	None	d
4	48	36	M	SCA III	Remote near point	None	b–d
5	22	1	F	CCD	Normal	Up	b, d
6	33	24	F	SCA III	Remote near point	None	b,c
7	57	40	M	SCA III	Esotropia	Right	b–d
8	44	27	F	OPCA	Normal	None	d, c, e
9	25	1	M	Friedreich's ataxia	Unknown	None	c,e
10	66	46	M	SCA VI	Normal	None	
11	77	69	M	SCA VI	Normal	Down	e

[a] Pursuit only mildly impaired
[b] Low gain or qualitatively weak nystagmus response during steady state rotational VOR testing
[c] Dysmetric saccades
[d] Increased phase lead during steady state rotational VOR testing
[e] Tested negative for SCA I, II, III, and VI

Table 2 Sinusoidal VOR in subjects with cerebellar dysfunction. Quantitative electro-oculographic data for seven subjects with cerebellar dysfunction who underwent sinusoidal rotations. Values exceeding ±1 SD from normal are denoted by an *upward arrow* or *downward arrow* to indicate value relative to normal controls. Due to uncertainties in calibration arising from pathologic nystagmus, subjects not listed underwent qualitative data analysis only, with unusual performance noted in Table 1

Subject	VOR gain			Phase (deg)			Fixation suppression gain
	0.05 Hz	0.8 Hz	1.25 Hz	0.05 Hz	0.8 Hz	1.25 Hz	0.05 Hz
1	0.45	0.97	n.d.	↑27	–2	n.d.	↑0.12
2	↓0.11	0.72	↓0.59	↑32	↑6	↓–10	0.05
3	0.62	↓0.38	0.94	11	↓–12	↓–17	n.d.
4	↓0.31	↓0.10	↓0.11	↑31	↓–81	↑32	n.d.
5	↓0.11	↓0.30	↓0.53	↑25	–2	↑13	0.05
8	0.45	↓0.58	n.d.	13	–4	n.d.	↑0.09
9	0.54	0.82	n.d.	↑33	–4	n.d.	↑0.77
Normal ± SD	0.50±0.15	0.81±0.19	0.95±0.16	10±4	0±4	0±4	0.03±0.02

were present. The patient also had fixation instability (square-wave jerks) and limited gaze elevation. MR images showed that the brain was normal. Autopsy of the patient's similarly affected sister showed degeneration only in the substantia nigra.

Subject 7 was a 40-year-old man with the SCA III genotype and gait ataxia. There was bilateral horizontal gaze nystagmus but rightward beating nystagmus in primary gaze. Saccades were slow and dysmetric. There was an esotropia of 10–12° with horizontal diplopia.

Subject 8 was a 44-year-old woman with autosomal recessive OPCA who tested negative for SCA types I, II, III, and VI. She had gait ataxia, dysarthria, and impairment of VOR suppression by target fixation.

Subject 9 was a 25-year-old man with Friedreich's ataxia who exhibited tremor, dysarthria, and gait and limb ataxia. He exhibited gaze-evoked nystagmus, rebound nystagmus, delayed saccadic initiation, and saccadic dysmetria. A right esotropia was surgically corrected prior to the experiment. Brain CT demonstrated a Dandy-Walker malformation.

Subject 10 had the SCA VI genotype and had experienced slowly progressive limb and gait ataxia since age 46 years. He complained of episodic vertigo; speech was dysarthric. There was horizontal gaze-evoked nystagmus, as well as downbeating nystagmus evoked by lateral and downward gaze; there was impairment of VOR suppression by visual target fixation. MRI of the brain demonstrated midline cerebellar atrophy. Other family members were affected.

Subject 11 was a 77-year-old man with a sporadic SCA VI genotype who first noted ataxia, oscillopsia, and dizziness at age 70 years. There was spontaneous downbeating nystagmus in central gaze that increased in depression and with convergence, as well as impairment of VOR suppression by visual target fixation. Brain MRI showed mild to moderate atrophy of the cerebellar vermis.

Apparatus

Details of the apparatus and techniques of transient VOR testing were as previously described (Crane and Demer 1998b). In brief, angular eye and head positions were measured with magnetic search coils. Reference magnetic fields were generated by three pairs of solenoid coils, each 2 m in diameter, and arranged to form the sides of a cube (C-N-C Engineering, Seattle, Wash.). Single-winding scleral magnetic search coil annuli were placed on the right eye. Angular head position was measured with a search coil mounted on a bitebar, custom-molded to the upper teeth of each subject. The ocular coil was embedded in a suction annulus (Skalar Medical, Delft, Netherlands) that adhered to one eye under topical anesthesia (Collewijn et al. 1975). The suction seal of the annulus to the eye was monitored and examined after the experiment to verify that the coil remained in position. Horizontal angular positions were demodulated by a phase-angle method linear over a range of ±100°. Since a previous study employing binocular recording indicated uniformly ideal vergence for all targets under all conditions employed in these experiments (Crane and Demer 1998b), monocular recordings were employed here. All subjects were tested for convergence prior to rotational testing, and some subjects with cerebellar dysfunction were not able to converge to the 15-cm target. It is likely that these subjects had insufficient convergence during the experiment.

Experiment control and data acquisition were performed by a Macintosh Power PC-compatible computer running the MacEyeball software package (Regents of the University of California). Eye and head position data were displayed on a digital polygraph and low-pass filtered over a bandwidth (4-pole Butterworth) of 300 Hz before digital sampling with 16-bit precision at 1.2 kHz.

Stimuli were delivered by a 500-Nm rotator (Compumotor, Rohnert Park, Calif.) as previously described (Crane and Demer 1998b). Subjects were securely strapped in a cushioned nonmetallic chair affixed to the rotator (Crane and Demer 1998b). The head was strapped to a nonmetallic head-holder padded with stiff conforming foam.

In addition to transient rotation, some subjects with cerebellar dysfunction underwent caloric and steady state, sinusoidal yaw vestibular testing using electro-oculography (EOG) with a bandwidth of 0–40 Hz as previously described (Demer et al. 1987, 1989). Caloric testing was performed by measuring the maximum slow component of evoked nystagmus during 40-s irrigation of the external auditory canal with warm water at 44°C or cool water at 30°C. During sinusoidal testing, subjects were rotated in yaw in a motorized chair in complete darkness at 0.05 Hz, 0.8 Hz, and, in some subjects, 1.25 Hz (Demer et al. 1990). Responses were automatically analyzed for VOR gain and phase (Baloh et al. 1980). Fixation suppression of the VOR was tested by rotating the subject while viewing a target moving with the chair. Results of sinusoidal testing are summarized in Table 2. Due to uncertainties in calibration arising from pathologic nystagmus, the subjects not listed in Table 2 underwent qualitative data analysis only, although unusual performance is noted in Table 1.

Initial VOR measurement conditions

For testing of the initial transient VOR, each 50-s trial consisted of 20 directionally unpredictable transient rotations (10 in each direction) administered in random order as previously described (Crane and Demer 1998b). Targets were centered directly in front of the right eye at distances of 15 cm and 500 cm. Although the laboratory was illuminated between rotations to enable subjects to maintain an accurate memory of the target, the fluorescent room lights were extinguished at a random interval 50–70 ms before onset of each rotation. Subjects were instructed to maintain gaze on target even when the lights were extinguished.

Eccentricity of the head relative to the axis of rotation was varied by changing the location of the head-holder relative to the

chair and by sliding the chair on a track attached to the motor hub. Eccentricity of the rotational axis was defined relative to the midpoint of the line connecting the centers of the eyes; positions anterior to this are described as negative. Eccentricities of 20 cm and 7 cm (posterior to the eyes) were achieved with the chair centered over the motor axis while eccentricities of 0 cm (between the eyes) and –10 cm (anterior to the eyes) were achieved with the chair posterior to the motor axis. For eccentricities of 20 cm and 0 cm the head was moved forward by 13 cm or 10 cm, respectively, relative to the chair. The eccentricity of 7 cm, the mean distance between the eyes and otoliths (Crane et al. 1997), was designed as an otolith-centered rotation.

Subjects were rotated at two peak accelerations. The larger consisted of a 2800°/s^2 acceleration to a velocity of 190°/s, which rotated the head 40° in 250 ms. The smaller stimulus was an acceleration of 1000°/s^2 to a peak velocity of 70°/s, which rotated the head 14° in 250 ms.

Data analysis

Data were automatically analyzed using custom software written using the LabView package (National Instruments, Austin, Tex.). Events during which eye position varied by more than 0.2° in the 80 ms preceding head rotation were discarded as failures of fixation and not considered for further analysis. Events were also discarded when the response was not typical for an individual when compared with other trials within the same testing conditions. Such atypical events were often due to sporadic saccades. However, trials including saccades were analyzed if a subject consistently made saccades of the same latency and direction.

After differentiation, eye and head data were filtered using a third-order low-pass Butterworth filter (0–50 Hz). Most results were analyzed in terms of angular VOR gain, the ratio of compensatory eye velocity to head velocity. This approach normalizes the effect of small variation in the head stimulus due to decoupling of the head from the rotator. Gain was calculated instantaneously, but, for intersubject comparison, gains were also averaged over 10-ms intervals.

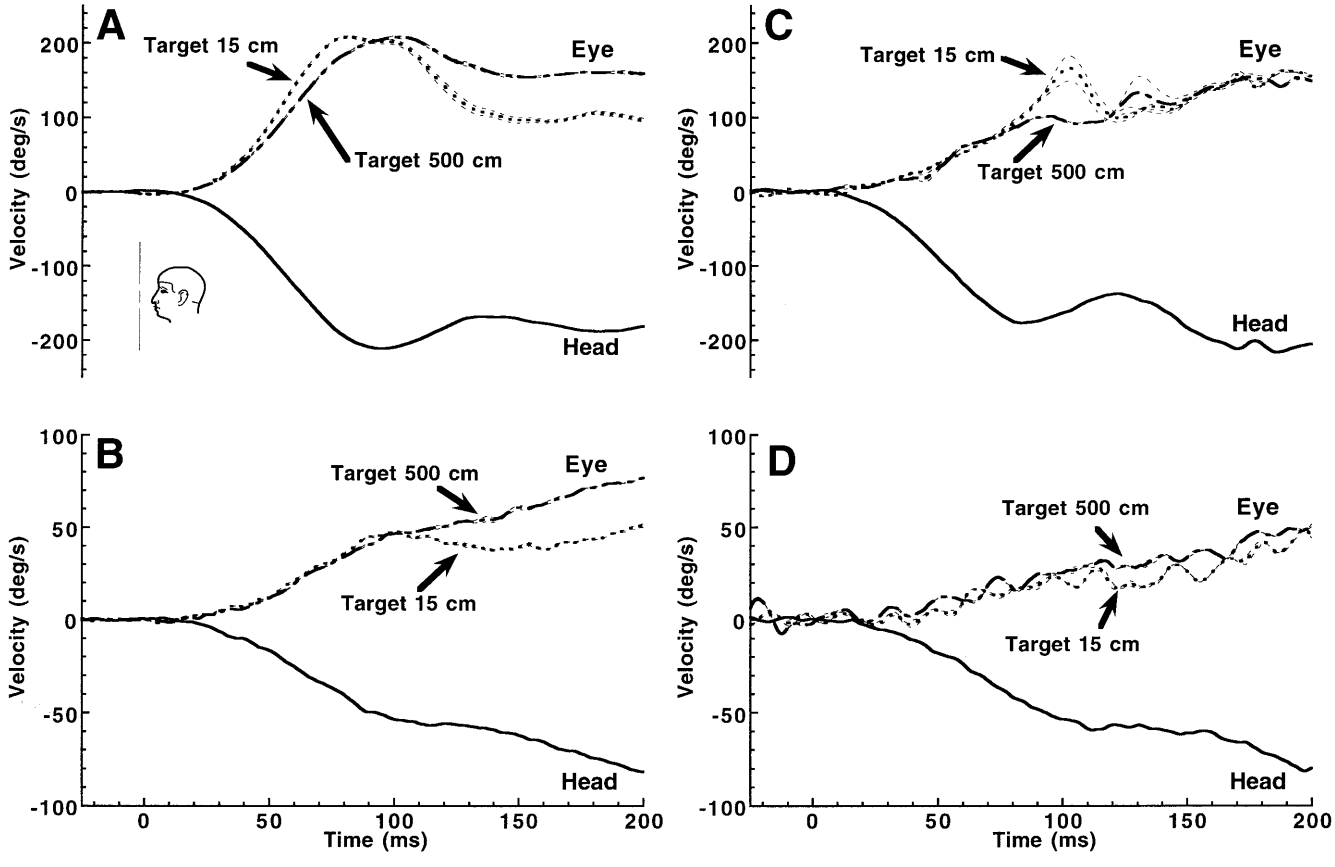
Differences in gains between conditions were considered significant when the standard error of the mean (SEM) did not overlap for the two conditions for a period of at least 30 ms (Crane and Demer 1998b). The onset of these gain differences was defined as the first time at which the SEMs no longer overlapped.

Results

Steady state angular VOR

Some subjects underwent steady state sinusoidal rotation to test the VOR and its suppression by visual fixation. Three of the seven subjects (2, 4, and 5) tested quantitatively had VOR gain at least one standard deviation below the normal mean (Baloh et al. 1984) over the range

Fig. 1A–D Initial VOR in normal subject (**A,B**) and representative subject 10 (**C,D**) with cerebellar dysfunction (spinocerebellar ataxia, SCA VI) during transient, whole-body rotation. Rotations were about an axis 10 cm anterior to the eyes. Mean eye responses for ten rotations are shown with *dashed lines* for two target distances. *Error bands* represent ±1 SE (often too close to the mean to be visible). **A** and **C** represent peak head acceleration of 2800°/s^2; **B** and **D** represent peak head acceleration of 1000°/s^2. In normal subjects, viewing the near target increased eye velocity early in the response for the 2800°/s^2 but not the 1000°/s^2 peak head acceleration. Later in the response for both peak acceleration stimuli, eye velocity with the near target was reduced as compared to the far target. In subjects with cerebellar dysfunction, these target distance effects were not observed



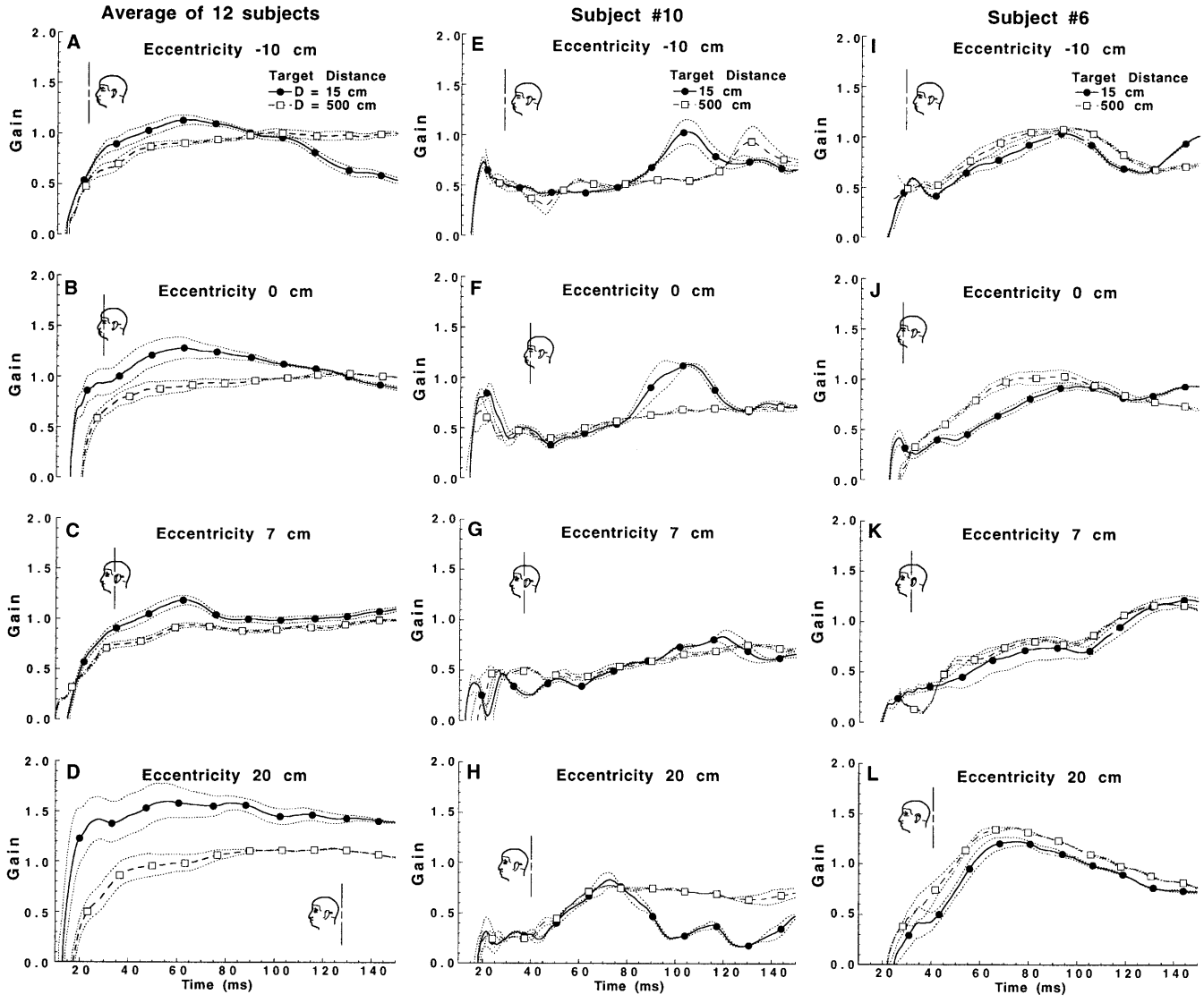


Fig. 2A–L Effect of target distance and rotational axis eccentricity on mean VOR gain in control subjects and subjects with cerebellar dysfunction. Ten repetitions of transient peak head accelerations of 2800°/s² were averaged. Data from Fig. 1 are shown in **A** and **E**. *Thin dashed lines* represent ±1 SE. Mean control response is on the *left* (**A–D**) as redrawn from Crane and Demer (1998b), and responses from two subjects with cerebellar dysfunction are shown in the *center panel* and *right panel* (**E–L**). The rotational axis of the head was located 10 cm anterior to the eyes (**A,E,I**), centered between the eyes (**B,F,J**), 7 cm behind the eyes and thus centered between the otoliths (**C,G,K**), or 20 cm behind the eyes (**D,H,L**). In normal subjects, near-target viewing increased gain early in the response independent of rotational axis. Later in the response, gain for the near target was lower for axes anterior to the labyrinths and remained high for axes posterior to the labyrinth. In subjects with cerebellar dysfunction, these target distance effects were not observed

of frequencies from 0.05 to 1.25 Hz (Table 2). Two additional subjects (6 and 7) had qualitatively subnormal VOR gain. All of these subjects with subnormal VOR gain had either congenital cerebellar dysgenesis of an unknown genetic cause or SCA III.

Transient angular VOR

The underlying pathology of cerebellar dysfunction varied among subjects. Given differences in pathology, variation in VOR performance was expected. Despite variability, the responses of all subjects showed common trends. In each subject, head rotation was followed by compensatory eye rotation in the appropriate direction (Fig. 1). Such results can also be expressed in terms of instantaneous VOR gain as shown in Fig. 2. Subjects with cerebellar dysfunction exhibited reduced VOR responses as assessed either as eye velocity (Fig. 1) or VOR gain (Fig. 2).

The pure angular VOR can be conveniently studied during rotation about an axis centered between the otoliths, so that these organs sense only small accelerations in equal and opposite directions. For this axis, angular VOR gain for the distant target was lower in subjects with cerebellar dysfunction than in control subjects during the initial period of head rotation (Fig. 3A; 35–45 ms after rotation onset). Subjects with cerebellar dysfunction also had lower VOR gain during the period 125 to 135 ms after the onset of head rotation (Fig. 3B).

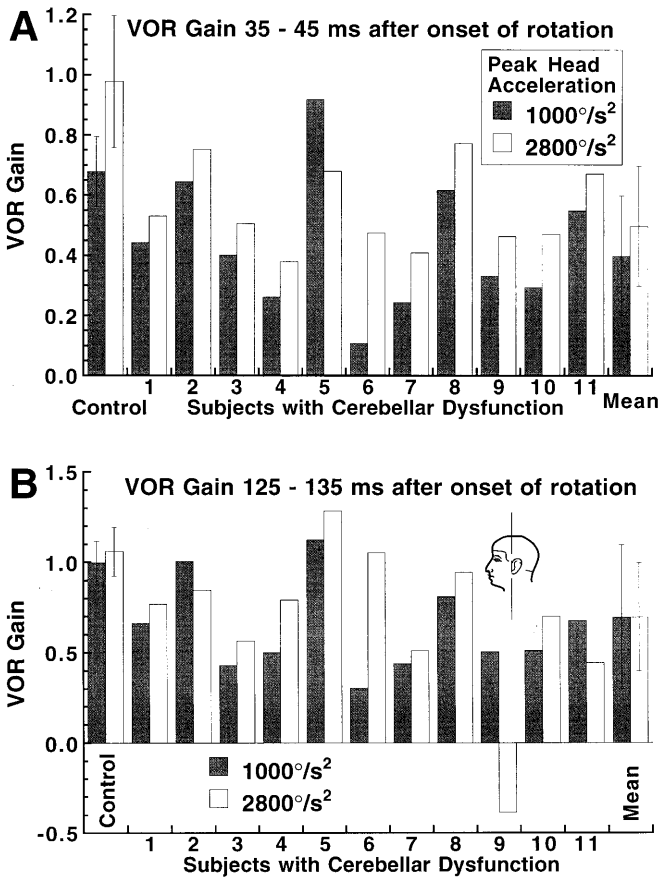


Fig. 3A,B Mean VOR gain during an early (35–45 ms; **A**) and late (125–135 ms; **B**) interval after onset of transient head rotation for a target 500 cm distant. Data shown in **A** are means of all rotation axes. **B** includes only the axis centered between the otoliths (eccentricity 7 cm). Mean values (± SD) of 12 control subjects are shown at *far left*. Subjects with cerebellar dysfunction typically had lower VOR gain than controls during both periods

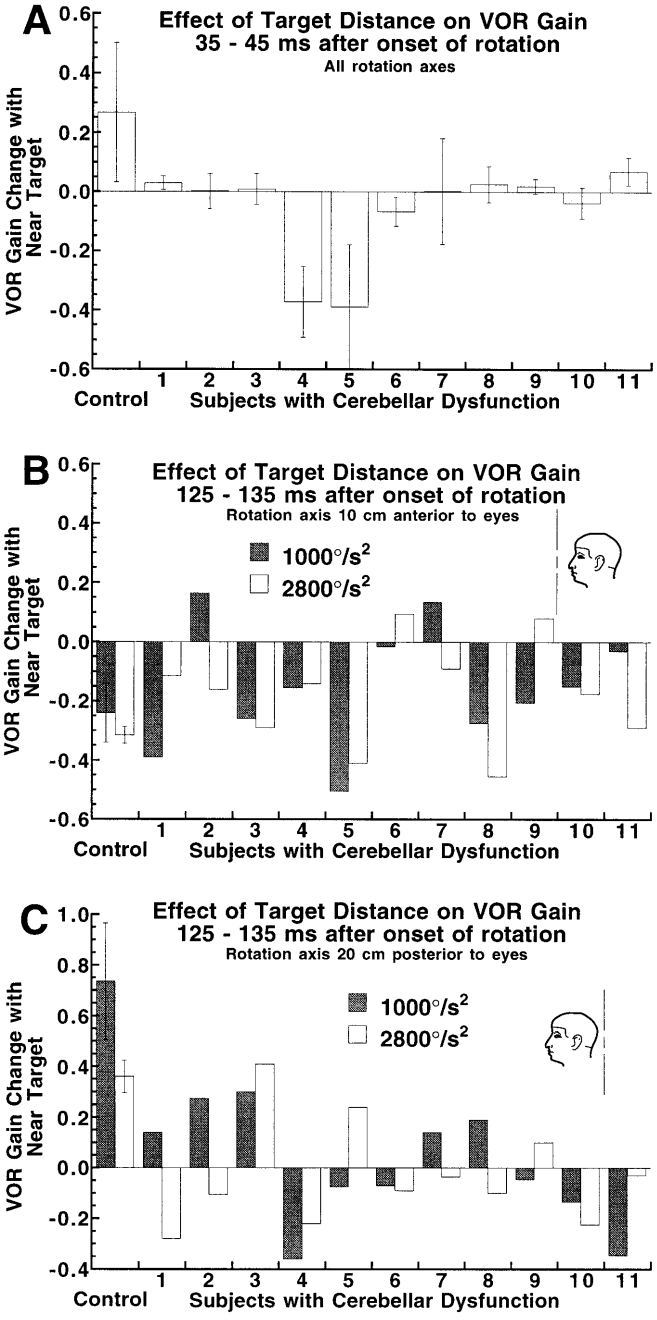


Fig. 4A–C VOR gain was not normally modified by target distance in subjects with cerebellar dysfunction. Values represent mean (±1 SD) difference in gain between that measured for the 15-cm target distance minus that with the 500-cm target distance. Control data from 12 normal subjects are presented at *left*. *Error bars* are only shown when the mean value was based on more than two rotations. **A** Target distance-related VOR gain difference 35–45 ms after the onset of head rotation. Mean of trials for all four axes during 2800°/s² peak head accelerations. All subjects with cerebellar dysfunction had less VOR gain enhancement with near targets than the mean control during this period. **B,C** Effect of target distance on VOR gain 125–135 ms after head rotation about an axis 10 cm anterior (**B**) and 20 cm posterior (**C**) to the eyes. In this period, with near targets, control subjects decreased VOR gain with the axis anterior to the labyrinth, and increased VOR gain with the axis posterior to the labyrinth. Only one subject with cerebellar dysfunction (subject 3) demonstrated the normal pattern at both head accelerations

In normal subjects, VOR gain in the period 35–45 ms from onset of head rotation was enhanced for near targets during 2800°/s² peak head acceleration regardless of rotational axis. To investigate target distance-related modification of the purely angular VOR, gain in this period was determined for rotation about a midotolithic axis. With the near target, VOR gain of control subjects was significantly ($P<0.01$) higher by 0.17±0.05 than gain for the distant target during 2800°/s² peak head acceleration, but gain did not depend significantly on target distance during 1000°/s² peak head rotation. In subjects with cerebellar dysfunction, gain in the period 35–45 ms from onset of head rotation was lower than in control subjects for both near and far targets, but not significantly influenced by target distance for either peak head acceleration.

The latency of the otolith-driven VOR usually exceeds 50 ms. Thus normal VOR gain during the 35- to 45-ms period was independent of axis location, although gain was higher with near targets (Fig. 2), as summarized in Fig. 4. For responses to the 2800°/s² peak head acceleration pooled over all rotational axes, subjects

with cerebellar dysfunction demonstrated early VOR responses to target distance smaller than those of control subjects. In only two subjects with cerebellar dysfunction (subject 1 with Friedreich's ataxia and 11 with vermian atrophy) did the early difference in gain with the near versus far target exceed zero by even 1 SD (Fig. 4A). Mean VOR gain over the period from 35 to 45 ms after the onset of 2800°/s^2 peak head acceleration for all subjects with cerebellar dysfunction did not significantly (P>0.01) differ with target distance, being 0.5±0.3 for the near and 0.6±0.2 for the far target. At the lower peak head acceleration of 1000°/s^2, VOR gain averaged 0.4±0.3 over this early period and did not depend on target distance in either the control group or the group with cerebellar dysfunction.

Otolith contribution to the VOR

Otolithic influence on the VOR can be assessed from the variation in VOR gain in response to changes in target distance during eccentric rotations producing significant otolith translation. Otolith effects were consistently evident only 50 ms or more following onset of head rotation in normal subjects. As shown in Fig. 2, during 2800°/s^2 peak head acceleration VOR gain was initially higher with the near than the far target regardless of the axis of rotation. Later, VOR gain with the near target was influenced by the axis of rotation. For axes anterior to the otoliths (Figs. 1A, 2A,B), the VOR gain of normal subjects with the near target declined with time to ultimately become less than VOR gain with the far target. For axes located between or posterior to the otoliths, the VOR gain of normal subjects for the near target persistently exceeded that for the far target. This was not the case for subjects with cerebellar dysfunction (Fig. 2E–L), where the effect of target distance was often subtle and difficult to distinguish from random variation. When a later effect of target distance was clearly present in a subject with cerebellar dysfunction, it was typically either a decrease in VOR gain for the near target independent of axis location (subjects 4, 10, and 11), or effects of target distance were only present at a single head acceleration or axis location. When the rotational axis was anterior to the eyes (Fig. 4B), 7 subjects with cerebellar dysfunction (subjects 1, 3, 4, 5, 8, 10, and 11) exhibited the normally expected decrease in VOR gain for the near target during the period 125–135 ms from onset of head rotation. However, when the axis was posterior to the otoliths (Fig. 4C), only subject 3 (SCA III) exhibited the normal increase in VOR gain for the near target. Thus, during the 125- to 135-ms period, only subject 3 consistently demonstrated the complete pattern of normal VOR gain modification with target distance. Two additional subjects (subjects 1 and 8) made gain modifications in the correct direction in response to the 1000°/s^2 peak head acceleration only. One additional subject (subject 5) was able to make gain modifications in the correct direction only with the 2800°/s^2 stimulus (Fig. 4B,C).

Discussion

In normal humans (Crane and Demer 1998b) and monkeys (Snyder and King 1992), VOR gain is modified by target distance within the first 10 ms of eye movement, and this early modification is independent of otolith stimulation. The timing of this phenomenon is consistent with target distance modification of the disynaptic angular VOR (Crane and Demer 1998b). The current data provide evidence that the cerebellum is important in human target distance-dependent modification of VOR gain. In most subjects with cerebellar dysfunction, target distance had no effect on VOR gain in response to 2800°/s^2 peak head acceleration. In the few subjects who did show significant VOR modification by target distance, the effect occurred late in the response and was often in a paradoxical, functionally inappropriate direction (Fig. 4).

The current study includes data from patients with several types of cerebellar dysfunction, many of whom are likely to have significant extracerebellar pathology. A previous study has suggested vestibular nerve or nuclei involvement in SCA III, although SCA VI appears to produce pathology limited to the cerebellum (Buttner et al. 1998). Even so, the one patient with SCA VI (subject 10, data shown in Fig. 2E–H) demonstrated a clear loss of target distance related modification of the VOR. Since all the subjects with cerebellar dysfunction also demonstrated either subnormal VOR gain or directionally inappropriate gain change with target distance, the cerebellum appears essential for normal VOR gain over a range of target distances.

Cerebellar role in effects of target distance

Earlier behavioral data indicate that target distance normally modifies both the translational and rotational VOR in normal subjects (Crane and Demer 1998b). The initial effect of target distance is observed only during high head acceleration and, since it occurs independent of translation, it must originate in the semicircular canals. A later effect modifies the translation-dependent otolith VOR pathway (Snyder and King 1992; Crane and Demer 1998b). The early effect was never observed in subjects with cerebellar dysfunction.

The short latency of target distance influence and the necessity of cerebellar function can be reconciled if the cerebellum modulates the responsiveness (i.e., sets the gain) of neurons within the disynaptic VOR pathway. Such a mechanism has been proposed to occur in VOR gain plasticity. After exposure to mismatching of visual and vestibular signals (i.e., as produced by wearing magnifying spectacles), VOR gain changes to minimize retinal image slip in humans (Istl-Lenz et al. 1985; Paige and Sargent 1991), monkeys (Lisberger and Miles 1980), goldfish (Pastor et al. 1994), and cats (Demer 1981; Khater et al. 1993). This plasticity cannot be induced after the cerebellum has been deactivated (Demer and

Robinson 1982; Luebke and Robinson 1994) or removed (Ito et al. 1974; Robinson 1976; Lisberger et al. 1984; Michnovicz and Bennett 1987), suggesting its key role in plasticity. In animals the latency at which a plastically modified VOR response can be discerned is within the first 10 ms of eye movement (Lisberger 1984; Khater et al. 1993; Pastor et al. 1994; Lasker et al. 1997). Due to this short latency and based on examination of the Purkinje cell activity, it has been suggested that synaptic modifications underlying VOR plasticity occur in the brainstem (Miles and Lisberger 1981; Lisberger 1984; Peterson et al. 1996).

Despite the similarity between target distance-related changes in VOR gain and plastic changes induced by prolonged visual-vestibular mismatch, there are significant behavioral differences between these two mechanisms. The most notable difference is that plastic VOR gain changes are only evident after a significant training period, whereas the target distance-related change is observed for the very first transient rotation (Snyder et al. 1992). It is unclear how this difference might be implemented at the neuronal level. The neuronal mechanism of VOR plasticity is not well understood and several alternative or combined mechanisms are possible (Peterson et al. 1996).

In addition to the early canal-mediated target distance modification, the otolith VOR adjusts the response to translation as appropriate to target distance. This linear VOR can be detected at latencies as short as 25–60 ms in humans during eccentric rotation (Crane and Demer 1998b). Even though the otolith response has a longer latency during eccentric rotation, during pure translation a linear VOR has been observed as early as 16 ms in the monkey (Bush and Miles 1996). The influence of the otolith VOR is most obvious during eccentric rotation about an axis anterior to the otoliths (i.e., eccentricity of –10 cm). In this case a near target normally causes canal VOR gain to be higher early in the response, and the antagonistic otolith-mediated VOR overcomes this increase to reduce gain (as compared to a distant target) late in the response (Fig. 1A). These findings suggest that, although the otolith VOR may be detectable very early, its influence becomes important after that of the semicircular canals. The longer latency suggests that the otolith VOR is modulated outside the disynaptic VOR and might even be influenced by a different target distance estimate than that used by the canal VOR.

Findings in subjects with cerebellar dysfunction support the idea that the mechanism for target distance modulation of the VOR may be related but distinct for the canal and otolith pathways. The otolith pathway was correctly modulated by target distance for both anterior and posterior axes during both head accelerations in only one subject with cerebellar dysfunction (Fig. 4, subject 3), but was observed only during particular measurement conditions or head accelerations in others. The universal absence of target distance modification in the early canal VOR of subjects with cerebellar dysfunction, despite some preservation of target distance effects in the later response (as in subject 3), suggests preservation of target distance influence on the otolith VOR even after target distance effects on the canal VOR are lost.

Vergence angle is directly related to target distance when the target is bifoveated, and it has been suggested reasonably that vergence and the neural target distance estimate are related (Busettini et al. 1991; Paige 1991; Snyder et al. 1992). Although we did not measure vergence in subjects with cerebellar dysfunction, directed examination prior to the experiment indicated that all subjects except for 7 and 9 had appropriate binocular alignment for the distant target. All normal subjects and at least six of the subjects with cerebellar dysfunction (Table 1) had adequate convergence for the near target. Under these near and distant target conditions, binocular search coil recordings have demonstrated that normal subjects maintain vergence near the ideal level throughout the dynamic response to transient head rotations (Crane and Demer 1998b). This is probably because the visibility of the target until a few milliseconds prior to transient head rotation allows appropriate vergence to be established, and this established vergence is maintained throughout the relevant interval of rotation. None of the subjects with cerebellar dysfunction who had adequate convergence could make normal target distance-related modifications to VOR gain. This suggests that vergence can be dissociated from a neural target distance estimate. Consistent with the convergence insufficiency commonly associated with cerebellar dysfunction (Rabiah et al. 1997), subjects 2, 4, 6, 7, and 9 could not verge the near target, and none of these subjects demonstrated correct early or late VOR gain modification with target distance. This implies a possible common pathology affecting both vergence angle and the target distance estimate. However, the performance of the subjects who could not converge was similar to others with cerebellar dysfunction who could do so (Figs. 3, 4).

VOR in cerebellar dysfunction

Mean VOR gain was significantly lower in subjects with cerebellar dysfunction than in normal subjects. There are multiple explanations for this reduced gain. The mean age of the control subjects was 25±4 years (Crane and Demer 1998b), significantly younger than the mean (48±16 years) for those with cerebellar loss. Human VOR gain has been shown to decrease under some conditions with advanced age (Wall et al. 1984; Demer 1994). However, the reported decrease in VOR gain with age was largest and significant only during rotation at frequencies of 0.01 Hz and lower (Wall et al. 1984) and is therefore unlikely to have a major effect at higher frequencies. In 25-year-old subject 9, VOR gain was lower than the mean of those with cerebellar dysfunction (Fig. 3) over both time intervals despite his youth, implying that other factors are dominant. Some subjects with cerebellar dysfunction also may have had extracerebellar pathology affecting the VOR such as involvement

of the vestibular nucleus, as found with SCA III (Buttner et al. 1998), or vestibular nerve, in Friedreich's ataxia, either of which could reduce VOR gain.

In all 11 subjects with cerebellar dysfunction, early target distance-dependent VOR gain modification was absent, and late target distance and translation-dependent VOR gain modification was impaired. Based on these results, it can be concluded that the cerebellum is involved in target distance determination in both the angular and linear VOR.

It is impossible from behavioral data to distinguish a remote target distance estimate from loss of otolith function, since otolith input to the VOR is normally scaled by a factor roughly inversely proportional to target distance (Paige 1991; Crane et al. 1997). Furthermore, otolith input could be appropriately scaled to the correct target distance, yet cerebellar pathology might prevent the scaled signal from being integrated into the VOR. The late VOR response in subjects with cerebellar dysfunction suggests that target distance-specific responses to otolith translation are present in some individuals (i.e., subject 3) who lack an initial canal-mediated effect of target distance. Possibly, the target distance effect can be lost from the angular VOR but retained in the otolith VOR, via separate mechanisms. However, normal target distance modification of the canal VOR is a weaker effect than target distance modification of the otolith VOR, so a similar degree of pathology of both might make the former effect empirically undetectable in subjects with cerebellar dysfunction. Thus the evidence for dissociation of the two effects is inconclusive.

References

Baloh RW, Langhofer L, Honrubia V, Yee RD (1980) On-line analysis of eye movements using a digital computer. Aviat Space Environ Med 51:563–7

Baloh RW, Honrubia V, Yee RD, Hess K (1984) Changes in the human vestibulo-ocular reflex after loss of peripheral sensitivity. Ann Neurol 16:222–8

Baloh RW, Yue Q, Demer JL (1995) The linear vestibulo-ocular reflex in normal subjects and patients with vestibular and cerebellar lesions. J Vestib Res 5:349–61

Bronstein AM, Gresty MA (1988) Short latency compensatory eye movement responses to transient linear head acceleration: a specific function of the otolith-ocular reflex. Exp Brain Res 71:406–10

Brown RH (1994) Motor neuron disease and the progressive ataxias. In: Isselbacher KJ, Braunwald E, Wilson JD, Martin JB, Fauci AS, Kasper DL (eds) Harrison's principles of internal medicine. McGraw-Hill, New York, pp 2280–6

Busettini C, Miles FA, Schwarz U (1991) Ocular responses to translation and their dependence on viewing distance. II. Motion of the scene. J Neurophysiol 66:865–78

Bush GA, Miles FA (1996) Short-latency compensatory eye movements associated with a brief period of free fall. Exp Brain Res 108:337–40

Buttner N, Geshwind G, Jen JC, Perlman S, Pulst SM, Baloh RW (1998) Oculomotor phenotypes in autosomal dominant ataxias. Arch Neurol 55:1353–7

Chen-Huang C, McCrea RA (1999) Effects of viewing distance on the responses of vestibular neurons to combined angular and linear vestibular stimulation. J Neurophysiol 81:2538–2557

Collewijn H, Mark F van der, Jansen TC (1975) Precise recording of human eye movements. Vision Res 15:447–450

Crane BT, Demer JL (1998a) Gaze stabilization during dynamic posturography in normal and vestibulopathic humans. Exp Brain Res 122:235–46

Crane BT, Demer JL (1998b) Human horizontal vestibulo-ocular reflex initiation: effects of angular acceleration, linear acceleration, stimulus intensity, target distance, and unilateral deafferentation. J Neurophysiol 80:1151–66

Crane BT, Demer JL (2000) Effect of adaptation to telescopic spectacles on the initial human horizontal vestibulo-ocular reflex. J Neurophysiol (in press)

Crane BT, Viirre ES, Demer JL (1997) The human horizontal vestibulo-ocular reflex during combined linear and angular acceleration. Exp Brain Res 114:304–20

Demer J (1981) The variable gain element of the vestibulo-ocular reflex is common to the optokinetic system of the cat. Brain Res 229:1–13

Demer JL (1994) Effect of aging on vertical visual tracking and visual-vestibular interaction. J Vestib Res 4:355–70

Demer J, Robinson D (1982) Effects of reversible lesions and stimulation of olivocerebellar system on vestibuloocular reflex plasticity. J Neurophysiol 47:1084–107

Demer JL, Goldberg J, Jenkins HA, Porter FI (1987) Vestibulo-ocular reflex during magnified vision: adaptation to reduce visual-vestibular conflict. Aviat Space Environ Med 58:A175–9

Demer JL, Volkow ND, Ulrich I, Krajewski K, Davis CM, Porter FI (1989) Eye movements in cocaine abusers. Psychiatry Res 29:123–36

Demer JL, Holds JB, Hovis LA (1990) Ocular movements in essential blepharospasm. Am J Ophthalmol 110:674–82

Dürr A, Stevanin G, Cancel G, Duyckaerts C, Abbas N, Didierjean O, Chneiweiss H, Benomar A, Lyon-Caen O, Julien J, Serdaru M, Penet C, Agid Y, Brice A (1996) Spinocerebellar ataxia 3 and Machado-Joseph disease: clinical, molecular, and neuropathological features. Ann Neurol 39:490–9

Geschwind DH, Perlman S, Figueroa CP, Karrim J, Baloh RW, Pulst SM (1997a) Spinocerebellar ataxia type 6. Frequency of the mutation and genotype-phenotype correlations. Neurology 49:1247–51

Geschwind DH, Perlman S, Figueroa CP, Treiman LJ, Pulst SM (1997b) The prevalence and wide clinical spectrum of the spinocerebellar ataxia type 2 trinucleotide repeat in patients with autosomal dominant cerebellar ataxia. Am J Hum Genet 60:842–50

Gresty MA, Bronstein AM, Barratt H (1987) Eye movement responses to combined linear and angular head movement. Exp Brain Res 65:377–84

Haddad GM, Demer JL, Robinson DA (1980) The effect of lesions of the dorsal cap of the inferior olive on the vestibulo-ocular and optokinetic systems of the cat. Brain Res 185: 265–75

Istl-Lenz Y, Hyden D, Schwarz D (1985) Response of the human vestibulo-ocular reflex following long-term 2× magnified visual input. Exp Brain Res 57:448–55

Ito M, Shiida T, Yagi N, Yamamoto M (1974) Visual influence on rabbit horizontal vestibulo-ocular reflex presumably effected via the cerebellar flocculus. Brain Res 65:170–4

Khater TT, Quinn KJ, Pena J, Baker JF, Peterson BW (1993) The latency of the cat vestibulo-ocular reflex before and after short- and long-term adaptation. Exp Brain Res 94:16–32

Lasker DM, Backous DD, Minor LB (1997) Horizontal VOR dynamics following unilateral canal plugging and lens-induced adaption. Soc Neurosci Abstr 23:1293

Lisberger SG (1984) The latency of pathways containing the site of motor learning in the monkey vestibulo-ocular reflex. Science 225:74–6

Lisberger SG, Miles FA (1980) Role of primate medial vestibular nucleus in long-term adaptive plasticity of vestibuloocular reflex. J Neurophysiol 43:1725–45

Lisberger SG, Pavelko TA (1988) Brain stem neurons in modified pathways for motor learning in the primate vestibulo-ocular reflex. Science 242:771–3

Lisberger SG, Miles FA, Zee DS (1984) Signals used to compute errors in monkey vestibuloocular reflex: possible role of flocculus. J Neurophysiol 52:1140–53

Luebke AE, Robinson DA (1994) Gain changes of the cat's vestibulo-ocular reflex after flocculus deactivation. Exp Brain Res 98:379–90

Michnovicz JJ, Bennett MV (1987) Effects of rapid cerebellectomy on adaptive gain control of the vestibulo-ocular reflex in alert goldfish. Exp Brain Res 66:287–94

Miles FA, Lisberger SG (1981) Plasticity in the vestibulo-ocular reflex: a new hypothesis. Annu Rev Neurosci 4:273–99

Paige GD (1989) The influence of target distance on eye movement responses during vertical linear motion. Exp Brain Res 77:585–93

Paige GD (1991) Linear vestibulo-ocular reflex (LVOR) and modulation by vergence. Acta Otolaryngol [Suppl] 481:282–6

Paige GD, Sargent EW (1991) Visually induced adaptive plasticity in the human vestibulo-ocular reflex. Exp Brain Res 84:25–34

Paige GD, Tomko DL (1991) Eye movement responses to linear head motion in the squirrel monkey. I. Basic characteristics. J Neurophysiol 65:1170–82

Pastor AM, Cruz RR de la, Baker R (1994) Cerebellar role in adaptation of the goldfish vestibuloocular reflex. J Neurophysiol 72:1383–94

Peterson BW, Kinney GA, Quinn KJ, Slater NT (1996) Potential mechanisms of plastic adaptive changes in the vestibulo-ocular reflex. Ann NY Acad Sci 781:499–512

Rabiah PK, Bateman JB, Demer JL, Perlman S (1997) Ataxia: ophthalmologic findings. Am J Ophthalmol 123:108–17

Robinson DA (1976) Adaptive gain control of vestibulo-ocular by the cerebellum. J Neurophysiol 39:954–69

Snyder LH, King WM (1992) Effect of viewing distance and location of the axis of head rotation on the monkey's vestibuloocular reflex. I. Eye movement responses. J Neurophysiol 67: 861–74

Snyder LH, Lawrence DM, King WM (1992) Changes in vestibulo-ocular reflex (VOR) anticipate changes in vergence angle in monkey. Vision Res 32:569–75

Tomko DL, Paige GD (1992) Linear vestibuloocular reflex during motion along axes between naso-occipital and interaural. Ann NY Acad Sci 656:233–41

Viirre ES, Demer JL (1996) The human vertical vestibulo-ocular reflex during combined linear and angular acceleration with near target fixation. Exp Brain Res 112:313–24

Viirre E, Tweed D, Milner K, Vilis T (1986) A reexamination of the gain of the vestibuloocular reflex. J Neurophysiol 56: 439–50

Wall C, Black FO, Hunt AE (1984) Effects of age, sex and stimulus parameters upon vestibulo-ocular responses to sinusoidal rotation. Acta Otolaryngol (Stockh) 98:270–8

Yue Q, Demer JL, Baloh RW (1995) The effect of vergence and accommodation on the linear vestibulo-ocular reflex (LVOR). Soc Neurosci Abstr 21:136

Zhuchenko O, Bailey J, Bonnen P, Ashizawa T, Stockton DW, Amos C, Dobyns WB, Subramony SH, Zoghbi HY, Lee CC (1997) Autosomal dominant cerebellar ataxia (SCA6) associated with small polyglutamine expansions in the alpha 1A-voltage-dependent calcium channel. Nat Genet 15:62–9