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The vestibulo-ocular reflex in fourth nerve palsy: deficits and adaptation

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Abstract

The effects of fourth nerve palsy on the vestibulo-ocular reflex (VOR) had not been systematically investigated. We used the magnetic scleral search coil technique to study the VOR in patients with unilateral fourth nerve palsy during sinusoidal head rotations in yaw, pitch and roll at different frequencies. In darkness, VOR gains are reduced during *incyclotorsion*, *depression* and *abduction* of the paretic eye, as anticipated from paresis of the superior oblique muscle. VOR gains during *excyclotorsion*, *elevation* and *adduction* of the paretic eye are also reduced, whereas gains in the non-paretic eye remain normal, indicating a selective adjustment of innervation to the paretic eye. In light, torsional visually enhanced VOR (VVOR) gains in the paretic eye remain reduced; however, visual input increases vertical and horizontal VVOR gains to normal in the paretic eye, without a conjugate increase in VVOR gains in the non-paretic eye, providing further evidence of selective adaptation in the paretic eye. Motions of the eyes after fourth nerve palsy exemplify monocular adaptation of the VOR, in response to peripheral neuromuscular deficits.

Keywords: VOR; Adaptation; Palsy; Oculomotility; Strabismus

1. Introduction

Clinical testing of ocular motor nerve palsies emphasizes examination of static deviations of the eyes. The effects of fourth nerve palsy on the vestibulo-ocular reflex (VOR) have not been systematically investigated. The VOR stabilizes retinal images by generating compensatory smooth eye movements that are nearly equal in amplitude and opposite in direction to head rotations. Adaptive changes in the VOR occur in response to different visual stimuli (Cannon, Leigh, Zee, & Abel, 1985; Gauthier & Robinson, 1975; Gonshor & Jones, 1976a,b; Yagi, Shimizu, Sekine, & Kamio, 1981). When normal subjects wear reversing prisms for two days, a large reduction of VOR gains is observed (Gonshor & Jones, 1976a). After three to four weeks of vision reversal, VOR gains and phase actually reverse; head rotations cause eye movements in the *same* direction, so that retinal images are once again stabilized (Gonshor & Jones, 1976a). Disconjugate VOR adaptation has also been elicited in response to anisometropic prisms (Oohira & Zee, 1992) and experimental weakening of the horizontal recti muscles in monkeys (Snow, Hore, & Vilis, 1985; Virre, Werner, & Vilis, 1988).

Since the primary action of the superior oblique is incyclotorsion (Simpson & Graf, 1980; von Noorden, 1996), one might predict a decreased gain during incyclotorsion of the paretic eye in fourth nerve palsy. Similarly, one might also anticipate decreased gains of the paretic eye during depression, its secondary action (Simpson & Graf, 1980; von Noorden, 1996), and during abduction, its tertiary action (Simpson & Graf, 1980; von Noorden, 1996). In this study, we investigated patients with unilateral fourth nerve palsy to examine their VOR and its adaptation, if any, in three dimensions. We identified changes in VOR gains in the paretic eye that provide evidence of monocular neural adaptation to paralytic strabismus.

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2. Methods

2.1. Clinical assessment and imaging studies

Thirteen patients with unilateral fourth nerve palsy were recruited from the Neuro-ophthalmology Unit at the University Health Network. A complete history was taken, and detailed ophthalmic and neurologic examinations were performed. The age of onset, the presence or absence of risk factors for ischemia (diabetes mellitus and hypertension), and duration of diplopia were recorded. Superior oblique palsy was diagnosed using the following clinical criteria (Ellis & Helveston, 1976; Flanders & Draper, 1990; Parks, 1958): Deficient depression of the hypertropic eye in adduction; incomitant hypertropia which increased with adduction of the hypertropic eye, and with head tilt towards the hypertropic eye; and presence of subjective excyclotorsion. Patients with a history of head tilt, diplopia or strabismus dating to infancy or early childhood, or prior strabismus surgery were excluded from this study.

The magnitude of strabismus was measured objectively using the prism and cover test, and subjectively using the Maddox rod and prism test. When indicated, appropriate tests were performed to rule out myasthenia gravis, thyroid ophthalmopathy, other orbital diseases, or intracranial lesions.

In this investigation, magnetic resonance (MR) or computerized tomography (CT) imaging were performed on all patients with fourth nerve palsy, although imaging study is not our standard practice for all such patients. Serial axial and sagittal T1- and T2-weighted MR images with gadolinium enhancement were obtained (slice thickness = 5 mm) for all patients under 50 years of age. CT images of the head with contrast were obtained in all patients with ischemic risk factors and for patients over 50 years of age. Those with an abnormal CT were further investigated with MR imaging.

2.2. Eye movement recordings

2.2.1. Experimental protocol

With one eye occluded, subjects viewed a red laser spot of 0.25° in diameter, rear-projected onto a uniformly gray vertical flat screen 1 m away from the nasion. Subjects made active sinusoidal ±10° head on body rotations in yaw to elicit the horizontal VOR, and in pitch to elicit the vertical VOR, at approximately 0.5 and 2 Hz. Torsional VOR was elicited by head rotation in roll at approximately 0.5, 1 and 2 Hz. Head movements were paced by a periodic tone. The maintenance of desired amplitude and frequency of head movements was encouraged by placement of the examiners hands on each parietal area of the subject's skull. The procedure was performed in light to elicit visually enhanced VOR (VVOR), and repeated with the other eye fixating and the fellow eye occluded. The VOR was then recorded in complete darkness while subjects were instructed to fixate on an imaginary earth-fixed target.

To measure the static torsional VOR, patients fixated on the center target with one eye occluded as we measured their ocular responses to static, passive head rolls of about 30° toward each shoulder, as measured with a search coil. The procedure was then repeated with the other eye fixating and the fellow eye occluded, and also in total darkness.

2.2.2. Recordings of eye movement and calibration

Positions of each eye were simultaneously measured by a three-dimensional magnetic search coil technique. The field system consists of a 6 ft (183 cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, Washington), with two orthogonal magnetic fields. In each eye, the patient wore a dual-lead scleral coil annulus designed to detect horizontal, vertical, and torsional gaze positions (Skalar Instrumentation, Delft, Netherlands). Head position was recorded by another coil taped to the subjects forehead. Each subject's head was centered in the field coils. Horizontal, vertical and torsional movements were calibrated by attaching the scleral coil to a rotating protractor before each experiment. The coil was first calibrated for ±30° torsionally in the straight ahead position. The protractor was then rotated 30° right, and the signal was measured again as the mounted coil was rotated ±30° torsionally. The same procedure was performed with the protractor rotated 30° up. Phase detectors employing amplitude modulation as described by Robinson (1963) provided signals of torsional gaze position within the linear range. There was minimal crosstalk; horizontal and vertical movements produced deflections in the torsional channel of <4% of the amplitude of the horizontal and vertical movement. The difference in torsional deflections between straight ahead and 30° right (or up) positions was <4%. Torsional precision was about ±0.2°.

To measure the offset of coil signal, during the gimbal calibration, the coil was rotated through 360° to measure its maximum and minimum readings. If there were no offset, these two readings should be equal and opposite. If they were not, the mean of the two readings was the offset, which was then subtracted from all coil recordings.

After insertion of the scleral coils onto the subject's eyes, horizontal and vertical eye movements were calibrated with saccades from the straight ahead reference position to steps of a laser target. Consistency of calibrated positions before and after coils insertion provided evidence that the gimbal calibrations were valid. As torsional eye position depended on the same magnetic field as vertical eye position, the accuracy of vertical calibration before and after coils insertion provided further evidence that the torsional calibration was also

accurate. Any coil slippage was assessed by requiring subjects to repeatedly refixate at the straight ahead reference position after each eye movement. Consistency of calibrated torsional coil signals after each eye movement provided evidence that the coil did not slip on the eye. Eye position data were filtered with a bandwidth of 0–90 Hz and cutoff frequency of −3 dB, and digitized at 200 Hz. They were recorded on disc for off-line analysis. Analog data were also displayed in real time by a rectilinear thermal array recorder (Model TA 2000, Gould Inc., Ohio).

2.2.3. Data analyses

In one dimension, the input (head velocity) and output (eye velocity) of the VOR are regarded as scalar quantities (i.e. real number), and the reflex is characterized by its gain, which is the ratio of eye velocity to head velocity. In most natural head rotation, however, the input and output of the VOR are not scalars but three-component vectors (the angular velocity vectors of the head and eye), having not only magnitudes but also directions. Thus, a more complete characterization of the VOR requires a description, not only of the relative sizes of eye and head velocities, but also of their relative directions; that is, the axes about which the eye and the head rotates.

The VOR, however, can be treated as one dimensional if head rotation occurs around only one axis. For example, during pure horizontal head rotation (that is, around the earth-vertical axis), the vertical and torsional components of the three-component rotation vector become zero. In this situation, the velocity of rotation can be derived by differentiation of position data. In this study, whereas horizontal, vertical and torsional *head* positions were measured simultaneously, *gaze* position data was measured in one dimension. That is, horizontal gaze positions were recorded during horizontal head motion, vertical gaze positions during vertical head motion and torsional gaze positions during head roll. Pure head rotation around one axis was approximated by analyzing only data where the other two axes showed $<1°$ variation from baseline (Fig. 1A).

Eye position was derived by subtracting head position from gaze position signals. Fast phases of vestibular nystagmus were identified by a computer program using velocity and acceleration criteria (Ranalli & Sharpe, 1988). Results of fast-phase identification were edited on a video monitor, allowing the operator to verify cursor placement for fast-phase removal. Eye positions between 80 ms before and after the identified fast phases were removed and the gaps were replaced with quadratic fits. Their average slopes were used to calculate the contribution of the ongoing slow phase during the fast phase. The offset due to the fast phase was then removed and the ongoing slow phase was interpolated to yield a cumulative trace of eye position.

Using position data, each cycle of rotation was identified by marking adjacent peaks with opposite direction,

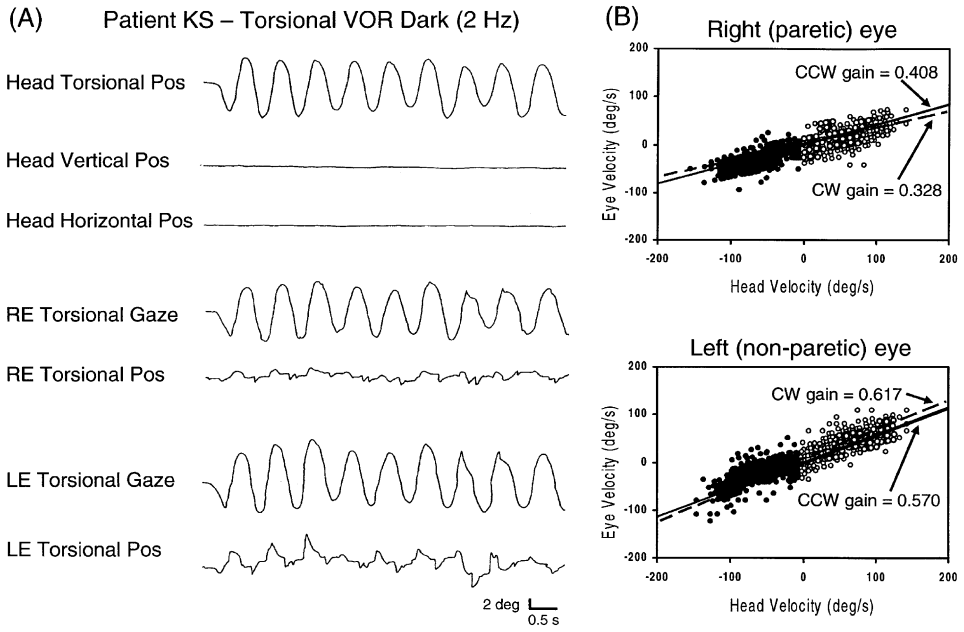

Fig. 1. (A) Recordings of a patient (KS) with right fourth nerve palsy during dynamic head roll at 2 Hz in darkness. (B) Plots of head velocity versus eye velocity of the paretic right eye (top graph) and the non-paretic left eye (bottom graph) of the same patient. VOR gains, defined as the slopes of the lines of best fit, were reduced in the paretic right eye in both directions (top graph), whereas gains were normal in the non-paretic left eye in both directions (bottom graph). (○) Data during clockwise movements; (- - -) line of best fit for data during clockwise movements; (●) data during counterclockwise movements; (—) line of best fit for data during counterclockwise movements.

and the frequency was computed. Using a least square sinusoidal fit (Sokolnikoff & Sokolnikoff, 1941), eye and head positions were fitted with one cycle, and the phase and amplitude were computed. The ratio of the amplitude of the eye and the amplitude of the head was the gain, and the difference between the phase of the eye and the phase of the head was the phase shift.

To calculate the gain in each direction, eye and head position data from each half cycle was used and reflected to form a full cycle. Each cycle was then fitted using a least square sinusoidal fit (Sokolnikoff & Sokolnikoff, 1941), and the gain was computed for each direction. In addition, we plotted head velocity against eye velocity, and performed a linear regression for each direction. The slopes of the fitted lines were the gains, and the results were comparable to those computed by the least square sinusoidal fit technique (Fig. 1B).

Subjects wore spectacles glasses, if habitually worn, during VOR testing. To account for the prismatic effect or rotational magnification induced by spectacle adaptation (Cannon et al., 1985; Rubin, 1993), horizontal and vertical VOR gains were adjusted by using the formula:

$$M_{\text{pred}} = 40/(40 - D) \quad (1)$$

where D is the lens power in diopters and M_{pred} is the predicted magnification (Cannon et al., 1985; Rubin, 1993). The lens power, D, was measured by us. For example, a hyperope who habitually wears a $+10D$ spherical lenses has an $M_{\text{pred}} = 40/(40 - 10) = 1.3$. This means that while wearing $+10D$, a VOR gain of 1.3, instead of 1.0, is required to prevent the visual scene from moving on the retina during head rotations.

Mean peak velocities of nystagmus quick-phase during head rotation in three axes were quantified. Asymptotic velocities were derived by computer analysis of velocity–amplitude scatter plots using an exponential best fit curve: $\text{PV} = V(1 - \text{e}^{-A/C})$, where PV is peak velocity at any point on the curve, V is asymptotic velocity, A is saccade amplitude, and C is a constant.

For the measurement of static torsional VOR, head and gaze position signals were sampled for 6 s in each of 20 trials of 30° lateral tilt. The position of the eye in the head was derived from the difference between head and gaze position signals. Head and eye positions were computed off-line over each 6-s period after the eye had come to a torsional resting position (defined as having angular velocity $\leqslant 1$ deg/s). Responses containing blinks or rapid drifts were not analyzed. Change of torsional eye position was plotted as a function of static change of head position after roll, and a linear regression was performed. Static torsional VOR gain, defined as change in torsional eye position divided by change in head position in static roll, was calculated from the slope of the regression line.

Oculography was performed at one point in each patients course (Table 1). Thus, changes from normal, rather than serial intrasubject changes were available for analyses. Statistical analyses of VOR and VVOR gains and phase were performed using Student's t-tests, two-tailed, unequal variance. Values were defined as significant when $p < 0.05$.

The research protocol was approved by the University Health Network Ethics Committee and followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Table 1
Characteristics of patients with fourth nerve palsy

Patient		Age	Sex	Side of hypertropia	Duration (months)	Hypertropia in primary position (PD)	Imaging	Comments
1	KG	23	M	Right	48	4 RHT	Normal MRI & MRA	–
2	MA	75	F	Right	60	12 RHT	Normal MRI	–
3	ER	49	F	Right	42	3 RHT	Normal MRI	–
4	KS	39	F	Right	1 week	3 RHT	Normal MRI	Hypertension
5	SD	66	M	Right	3 weeks	2 RHT	Normal CT	Hypertension
6	GW	67	M	Left	39	7 LHT	Normal CT	Trauma
7	SF	59	M	Left	24	12 LHT	Normal MRI	Trauma
8	JG	53	F	Left	24	10 LHT	Normal CT	–
9	CG	59	M	Left	9	2 LHT	Normal MRI	–
10	HL	41	F	Left	19	3 LHT	Normal MRI	–
11	LA	55	F	Left	12	6 LHT	Normal CT	–
12	EB	81	F	Left	132	8 LHT	Normal MRI	–
13	SW	37	F	Left	40	4 LHT	Normal MRI and MRA	–

PD: prism diopter; RHT: right hypertropia; LHT: left hypertropia; MRA: MR angiogram.

3. Results

3.1. General characteristics of patients

The characteristics of the 13 patients with fourth nerve palsy are shown in Table 1. The mean age was 54 ± 16 years (median age: 55; age range: 23–81). There were eight women. Mean age of symptoms onset was 51 ± 15 years (median age: 54; age range: 19–70). The duration of symptoms ranged from one week to 132 months, with a mean duration of 35 months. Mean follow-up duration was 49 months (range: 13–165 months). No patients had any associated neurologic symptoms or signs. Nine patients had normal MR imaging and four had normal CT of the head.

Fifteen normal subjects served as controls (mean age: 52 ± 15 years; median age: 58; age range: 19–69; eight women).

3.2. Dynamic torsional VOR gain and phase

In darkness, torsional VOR gains of the paretic eye were reduced symmetrically during both incyclotorsion and excyclotorsion in each of 13 patients ($p < 0.01$), whereas gains of the non-paretic eye were normal (Fig. 2, top graph). In light, during either paretic or non-paretic eye viewing (Fig. 2, middle and bottom graphs), visually enhanced torsional VOR (VVOR) gains of the paretic eye were also low in both directions ($p < 0.05$), while those of the non-paretic eye remained normal. In light and in darkness, the mean phase differences between the eye and head positions approximated 180°, designated as zero phase shift.

Mean peak velocities of torsional nystagmus quick phase were asymmetric in the paretic eye, being reduced for incyclotorting and normal for excyclotorting quick phases. For a 2° torsional quick phase, mean peak

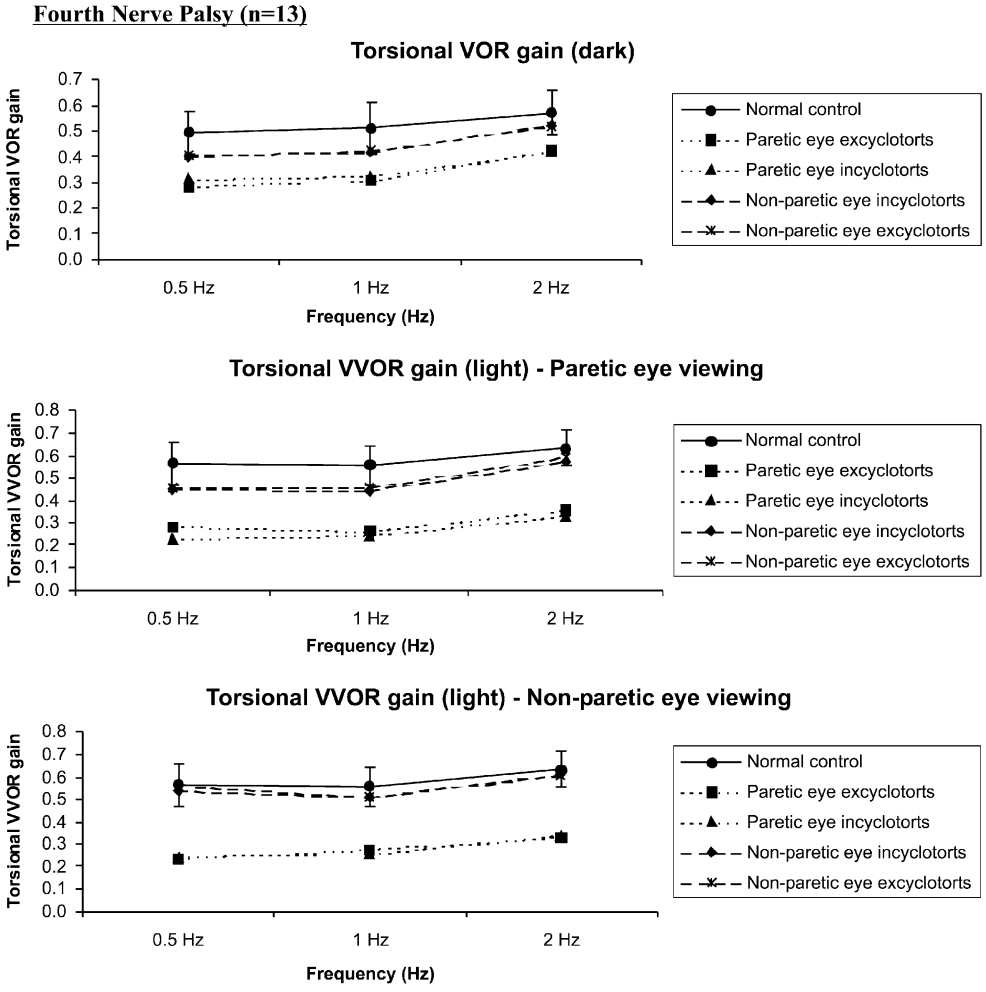

Fig. 2. Mean dynamic torsional VOR and VVOR gains in patients fourth nerve palsy. Error bars indicate one standard deviation.

velocity of the paretic eye during incyclotorsion was 27.2 ± 12.7 deg/s, compared with 40.3 ± 10.4 deg/s during excyclotorsion ($p < 0.05$), and 42.5 ± 13.5 deg/s in normal controls ($p < 0.05$). Mean peak velocities of torsional quick phase were normal and symmetric in the non-paretic eye.

3.3. Vertical VOR gain and phase

In darkness (Fig. 3, top graph), vertical VOR gains of the paretic eye were reduced during both depression and elevation ($p < 0.05$), whereas gains of the non-paretic eye were normal; upward and downward gains did not differ. In light, during paretic eye and non-paretic eye viewing (Fig. 3, middle and bottom graphs), vertical VVOR gains of both the paretic and the non-paretic eyes were normal ($p < 0.05$). Neither eye showed any significant phase shift from zero in light or in darkness.

Mean peak velocities of vertical nystagmus quick phase were asymmetric in the paretic eye, being reduced for depression and normal for elevation. For a 5° vertical quick phase, mean peak velocity of the paretic eye during depression was 93.4 ± 24.7 deg/s, compared with 128.5 ± 22.9 deg/s during elevation ($p < 0.05$), and 139.1 ± 23.0 deg/s in normal controls ($p < 0.05$). Mean peak velocities of vertical quick phase were normal and symmetric in the non-paretic eye.

3.4. Horizontal VOR gain and phase

In darkness (Fig. 4, top graph), horizontal VOR gains of the paretic eye were reduced during both abduction and adduction ($p < 0.01$), whereas gains of the non-paretic eye were normal. Abducting and adducting gains were symmetric. In light, during paretic or non-paretic eye viewing (Fig. 4, middle and bottom graphs), horizontal VVOR gains of both the paretic and the non-

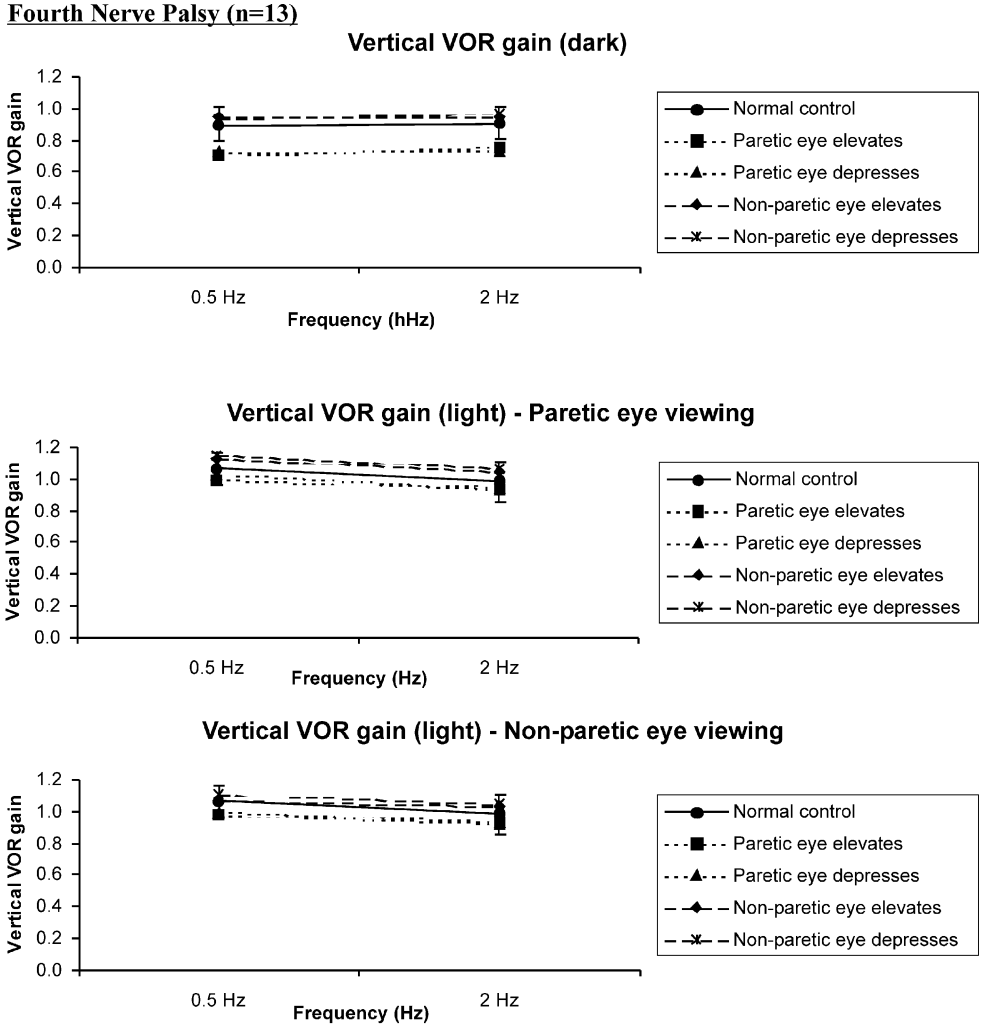

Fig. 3. Mean vertical VOR and VVOR gains in patients fourth nerve palsy. Error bars indicate one standard deviation.

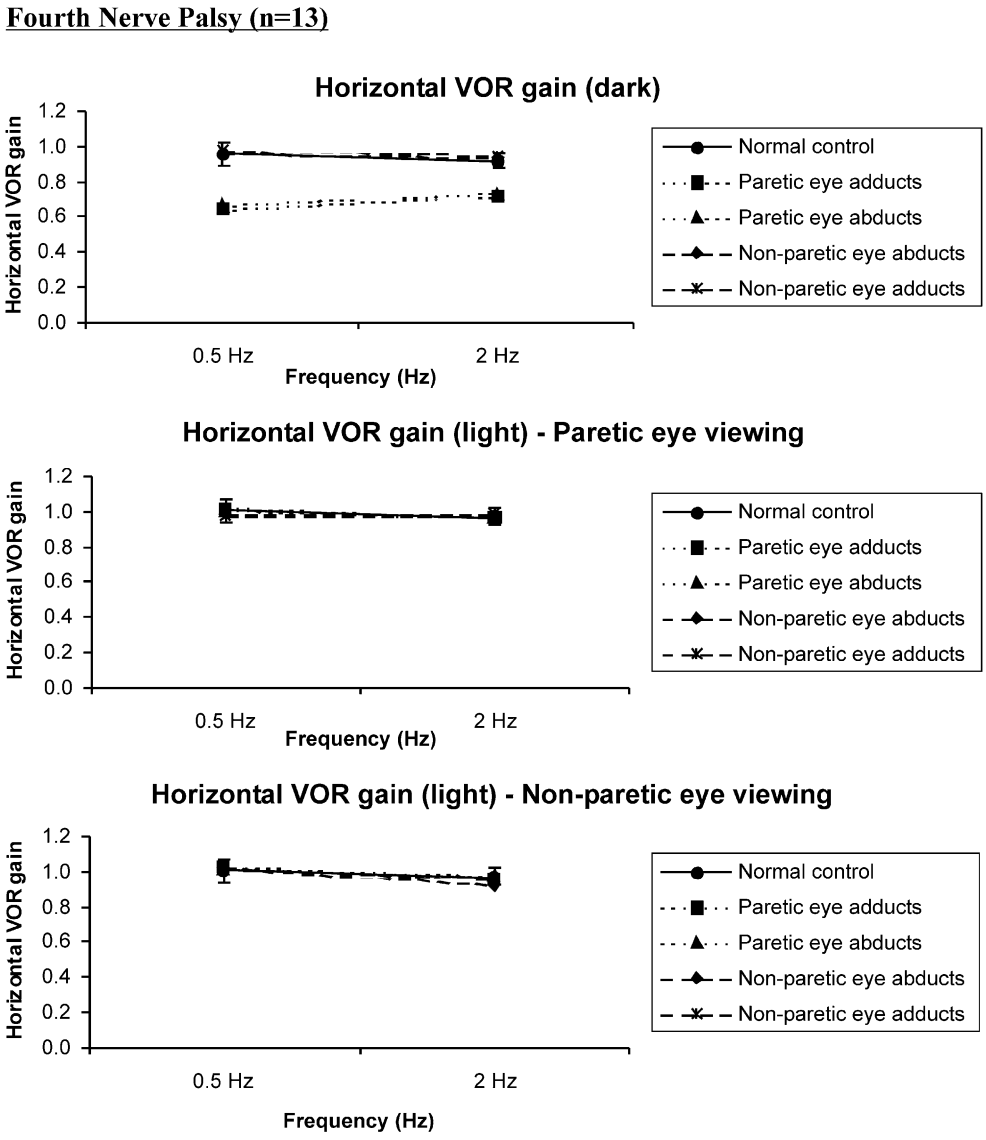

Fig. 4. Mean horizontal VOR and VVOR gains in patients fourth nerve palsy. Error bars indicate one standard deviation.

paretic eyes were normal ($p < 0.05$). Neither eye showed any significant phase shift from zero in light or in darkness.

Mean peak velocities of horizontal nystagmus quick phase were asymmetric in the paretic eye, being reduced for abduction and normal for adduction. For a 5° horizontal quick phase, mean peak velocity of the paretic eye during abduction was 123.3 ± 26.7 deg/s, compared with 178.6 ± 27.9 deg/s during adduction ($p < 0.05$), and 199.5 ± 41.5 deg/s in normal controls ($p < 0.05$). Mean peak velocities of horizontal quick phase were normal and symmetric in the non-paretic eye.

3.5. Static torsional VOR gain

Static torsional VOR gains did not differ between viewing with the paretic eye or non-paretic eye, they were therefore reported as the pooled mean, under both viewing conditions, in light and in darkness (Table 2). Static torsional VOR and VVOR gains of the paretic eye were reduced during incyclotorsion ($p < 0.05$); they were normal during excyclotorsion of the paretic eye. In the non-paretic eye, static torsional VOR and VVOR gains were normal.

4. Discussion

In this study, we investigated patients with unilateral fourth nerve palsy to examine their VOR. We found that torsional, vertical, and horizontal VOR gains in darkness are reduced during incyclotorsion, depression and abduction of the paretic eye, as anticipated from paresis of the superior oblique. However, VOR gains in darkness

Table 2
Static torsional VOR gain in patients with fourth nerve palsy

	Light				Dark			
	Paretic eye		Non-paretic eye		Paretic eye		Non-paretic eye	
	Incyclotort	Excyclotort	Excyclotort	Incyclotort	Incyclotort	Excyclotort	Excyclotort	Incyclotort
Normal ($n = 10$)	0.21 (0.10)	0.20 (0.11)	0.22 (0.09)	0.21 (0.11)	0.20 (0.14)	0.19 (0.15)	0.21 (0.13)	0.20 (0.13)
Patients ($n = 13$)	0.11 (0.07)*	0.17 (0.08)	0.22 (0.13)	0.19 (0.19)	0.12 (0.10)*	0.17 (0.10)	0.20 (0.13)	0.21 (0.22)

Values in parentheses are standard deviations.
*$p < 0.01$.

are also reduced during *excyclotorsion*, *elevation* and *adduction* of the paretic eye, while gains in the non-paretic eye remain normal in all directions.

Changes in the VOR in our patients, who were tested at one point in their courses, are expressed as changes from normal, rather than serial intrasubject changes. Recovery toward normal values was not determined. Abnormalities are interpreted as deficits as a result of the palsy, or adaptation to those deficits.

4.1. VOR gains during active head rotation in normal subjects

During passive whole-body rotation, horizontal VOR gains are less than unity, with typical values ranging from 0.7 at 0.5 Hz to 0.95 at 1 Hz (Sharpe, Goldberg, Lo, & Herishanu, 1981; White, Saint-Cyr, & Sharpe, 1983). In agreement with previous studies (Demer, Oas, & Baloh, 1993; Goebel, Hanson, Langhoffer, & Fishel, 1995; Kim & Sharpe, 2001; Tomlinson, Saunders, & Schwarz, 1980), higher VOR gains were observed in our normal subjects during active head rotation in darkness; horizontal gains were close to unity, while vertical gains were about 0.9.

Higher VOR gains during active head motions can be attributed to several mechanisms: (1) Modulation by the cervico-ocular reflex (Anastasopoulos & Mergner, 1982; Gdowski & McCrea, 1999; Hikosaka & Maeda, 1973). However, its contribution in normal humans is negligible (Bronstein & Hood, 1986; Jurgens & Mergner, 1989); (2) contribution from the translational VOR as a result of backward displacement of the rotational axis of the head relative to the vertebral column (Medendorp, Melis, Gielen, & Gisbergen, 1998; Virre, Tweed, Milner, & Vilis, 1986); and (3) modulation by preprogrammed eye movements (Kasai & Zee, 1978).

4.2. Overview of the vertical and torsional angular VOR pathway

Primary afferents of the vertical and torsional VOR pathway originate from the anterior and posterior canals. When one anterior (or posterior) canal is stimulated, the posterior (or anterior) canal in the opposite labyrinth is inhibited. One anterior canal excites the ipsilateral superior rectus muscle and the contralateral inferior oblique muscle (Carpenter & Cowie, 1985), resulting in dysconjugate elevation and contralateral torsion of the upper poles of both eyes (Fig. 5A); elevation of the ipsilateral eye is greater than that of the contralateral eye and torsion of the contralateral eye is greater than that of the ipsilateral eye (Cohen, Suzuki, & Bender, 1964). At the same time, the anterior canal sends reciprocal inhibitory signals to the antagonistic ipsilateral inferior rectus and contralateral superior oblique muscles (Graf & Ezure, 1986; Uchino & Suzuki, 1983) (Fig. 5B).

One posterior canal excites the ipsilateral superior oblique muscle and the contralateral inferior rectus muscle (Uchino, Hirai, & Watanabe, 1978) (Fig. 5C). Thus, one posterior canal activates dysconjugate depression and contralateral torsion of the upper poles of both eyes; depression of the contralateral eye is greater than that of the ipsilateral eye and the torsion of the ipsilateral eye is greater than that of the contralateral eye (Cohen et al., 1964). Reciprocal inhibition is conveyed from the posterior canal to the antagonistic ipsilateral inferior oblique and contralateral superior rectus muscles (Tokumasu, Goto, & Cohen, 1969; Uchino & Suzuki, 1983) (Fig. 5D).

Stimulation of both anterior canals by downward head acceleration (nose down pitch) activates the upward angular VOR, whereas stimulation of both posterior canals by upward head acceleration (nose up pitch) activates the downward angular VOR. Stimulation of the anterior and posterior canals on one side during ipsilateral head roll activates the torsional angular VOR, so that the upper poles of the eyes roll toward the contralateral shoulder.

4.3. VOR in darkness in unilateral fourth nerve palsy

4.3.1. Torsional VOR in darkness

During head roll toward the right shoulder, the right eye incyclotorts, and the left eye excyclotorts. In right

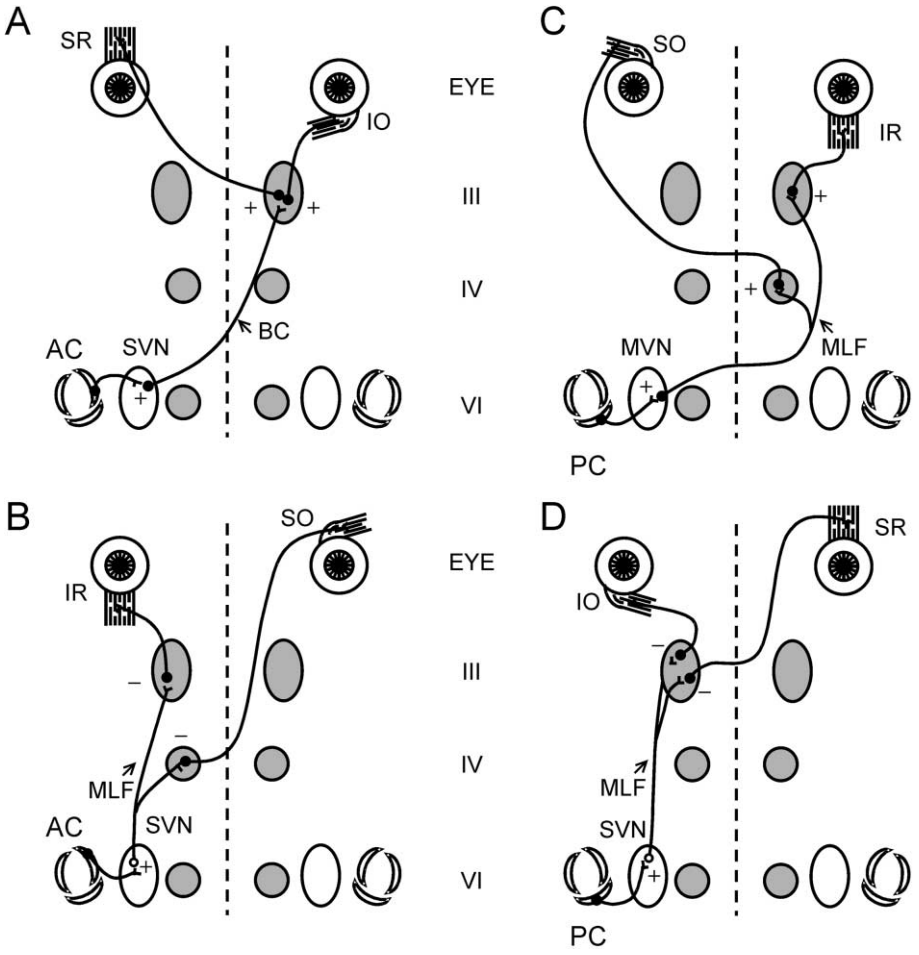

Fig. 5. Direct vertical vestibulo-ocular projections from the vertical semicircular canals. (A) Excitatory afferents from the anterior semicircular canals (AC) synapse in the superior vestibular nucleus (SVN), and their signals are relayed via the brachium conjunctivum (BC) to the contralateral oculomotor subnuclei that drive the ipsilateral superior rectus (SR) and contralateral inferior oblique (IO) muscles. (B) Inhibitory afferents from the anterior semicircular canals synapse in the SVN, and their signals are relayed via the medial longitudinal fasciculus (MLF) to the ipsilateral trochlear nucleus, which innervates the contralateral superior oblique (SO) muscle, and to the ipsilateral oculomotor subnucleus that innervates the ipsilateral inferior rectus (IR) muscle. (C) Excitatory afferents from the posterior semicircular canals (PC) synapse in the medial vestibular nucleus (MVN), and their signals are relayed via the MLF to the contralateral trochlear nucleus, which innervates the ipsilateral SO muscle, and to the contralateral oculomotor subnucleus that innervates the contralateral IR muscle. (D) Inhibitory afferents from the posterior semicircular canals synapse in the SVN, and their signals are relayed via the MLF to the ipsilateral oculomotor subnuclei that drive the ipsilateral IO and contralateral SR muscles (Ghelarducci, Highstein, & Ito, 1977). Note that excitatory neurons are represented by filled circles and inhibitory neurons by unfilled circles.

fourth nerve palsy, for example, weakness of the superior oblique muscle would decrease incyclotorting VOR gain of the paretic right eye during head roll to right shoulder. During head roll toward the left shoulder, the right eye excyclotorts, and the left eye incyclotorts. A right fourth nerve palsy might not be expected to affect excyclotorsion of the paretic right eye, so that excyclotorting VOR during head roll to left shoulder would be normal. We found that torsional VOR gains in darkness are reduced during *incyclotorsion* of the paretic eye in all patients, as anticipated from superior oblique palsy. However, VOR gains during *excyclotorsion* of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Fig. 2, top graph).

The unpredicted decreased VOR gains during excyclotorsion of the paretic eye, without any change in gains in the non-paretic eye, indicates a functional monocular adaptation to unilateral fourth nerve palsy. Without it, the VOR would be asymmetric in the paretic eye, weak in incyclotorsion but normal in excyclotorsion. The asymmetry would drive the paretic eye farther and farther into excyclotortion with each cycle of head rotation, resulting in increased torsional disparity between the two eyes and diplopia.

The brain might adopt any one of four strategies to prevent this torsional disparity. First, it might increase its innervation to the superior oblique to increase VOR gain of the paretic eye, but this strategy is limited by the palsy itself. Second, the brain might generate incyclotorting

saccades in the paretic eye to correct for the low incyclotorting VOR gains. Incyclotorting saccades could be generated either by activating the superior oblique or the superior rectus muscles of the paretic eye. However, during activation of the superior oblique muscle, if common premotor signals are sent to trochlear motoneurons and to motoneurons in the inferior rectus subdivision of the oculomotor nucleus, unwanted downward and excyclotorting (primary and secondary actions of inferior rectus) saccades would appear conjugately in the non-paretic eye. Similarly, during activation of the superior rectus muscle, if common premotor signals are sent to the superior rectus and inferior oblique subdivisions of the oculomotor nucleus, unwanted excyclotorting and upward (primary and secondary actions of inferior oblique) saccades would appear conjugately in the non-paretic eye.

Third, the brain might attempt to prevent asymmetry of the torsional VOR by decreasing excyclotorting gains in the paretic eye. This could be achieved by either inhibiting the ipsilateral inferior oblique, via the inhibitory *posterior* canal pathway (see Fig. 5D), or by inhibiting the ipsilateral inferior rectus, via the inhibitory *anterior* canal pathway (see Fig. 5B). However, for the inhibitory posterior canal pathway, if common premotor signals are sent to motoneurons in both the inferior oblique and superior rectus subdivisions of the oculomotor nucleus (see Fig. 5D), the contralateral superior rectus would also be inhibited, decreasing the gains during elevation and incyclotorsion (primary and secondary actions of superior rectus), resulting in asymmetry of gains, and even upward and incyclotorting jerk nystagmus in the non-paretic eye. Similarly, for the inhibitory anterior canal pathway (see Fig. 5B), the superior oblique muscle in the non-paretic eye would also be inhibited conjugately, resulting in asymmetry of gains, and incyclotorting and downward jerk nystagmus in the non-paretic eye.

Fourth, the brain could selectively reduce VOR gains during excyclotorsion of the paretic eye by decreasing the innervation to the inferior oblique (but not to the contralateral superior rectus), or to the inferior rectus (but not to the contralateral superior oblique), or both. This is apparently the strategy that the brain uses in unilateral fourth nerve palsy to adapt to reduced gains of incyclotorsion.

4.3.2. Vertical VOR in darkness

During vertical head rotation about the interaural axis, an upward head acceleration (nose up pitch) stimulates depression of the eyes. In fourth nerve palsy, because the secondary action of superior oblique is depression (Simpson & Graf, 1980; von Noorden, 1996), a decrease in VOR gain during depression of the paretic eye may occur. A downward head acceleration (nose down pitch) stimulates binocular elevation, and this might be expected to remain normal in fourth nerve palsy. As anticipated, we found that vertical VOR gains in darkness are reduced during *depression* of the paretic eye in all patients. However, VOR gains during *elevation* of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Fig. 3, top graph). The decrease in VOR gain during elevation of the paretic eye, without any change in gains in the non-paretic eye, again indicates monocular adaptation in the paretic eye. Using the same rationale discussed for the torsional VOR, this adaptation in the paretic eye could be achieved by decreasing the innervation to the ipsilateral inferior oblique (but not to the contralateral superior rectus), or to the ipsilateral superior rectus (but not to the contralateral inferior oblique), or both, of the paretic eye.

4.3.3. Horizontal VOR in darkness

The tertiary action of the superior oblique is abduction (Simpson & Graf, 1980; von Noorden, 1996). We found that horizontal VOR gains in darkness are reduced during *abduction* of the paretic eye in all patients, as expected from superior oblique palsy. However, VOR gains during adduction of the paretic eye are also reduced, while gains remain normal in the non-paretic eye in both directions (see Fig. 4, top graph). The decrease in VOR gains during adduction of the paretic eye, without a conjugate decrease in VOR gains during abduction of the non-paretic eye, again indicates a central reduction of innervation selectively to the medial rectus, and possibly also to the vertical recti muscles of the paretic eye whose tertiary action is adduction (Simpson & Graf, 1980; von Noorden, 1996).

4.4. Visually enhanced VOR in unilateral fourth nerve palsy

In darkness, the VOR functions poorly with a gain below one during passive head rotation at frequencies below 1 Hz. Visual following mechanism enhances VOR gain to unity. In all patients, during head rotation in light, vertical and horizontal VVOR gains increased to normal values in the paretic eye. This visual enhancement of VOR in the paretic eye can be the result of contributions from the smooth pursuit or fixation system at the frequencies tested (Das et al., 1995; Johnston & Sharpe, 1994; Leigh, Huebner, & Gordon, 1994). Visual input enhances the response of the viewing paretic eye without inappropriately raising that of the occluded non-paretic eye, providing further evidence for monocular readjustment of innervation selectively to the paretic eye. In contrast to vertical and horizontal VVOR, during head roll in light, torsional VVOR gains of the paretic eye remain low during viewing with either eye. Vision does not increase torsional VVOR gains to normal in the paretic eye. The use of a small laser spot as

a fixation target against a uniformly gray background in our experiments is adequate to elicit a strong VVOR response during vertical and horizontal head rotations, but not during head roll.

4.5. Proprioception and VOR adaptation

A decrease in proprioceptive signals from extraocular muscles of the paretic eye might also contribute to the VOR changes in our patients. Extraocular muscle afferents leave the ocular motor nerves near the apex of the orbit or in the region of the cavernous sinus, travel via the ophthalmic branch of the trigeminal nerve (V1) and the Gasserian ganglion, to reach the spinal trigeminal nucleus (Baker, Precht, & Llinas, 1972; Cooper & Fillenz, 1955; Porter, 1986; Ruskell, 1999; Whitteridge, 1955; Winckler, 1937). There is disagreement as to whether some afferents also project centrally via the ocular motor nerves (Bortolami et al., 1991; Gentle & Ruskell, 1997; Manni et al., 1989; Porter & Donaldson, 1991; Ruskell, 1999; Spencer & Porter, 1988). Sectioning of V1 reduces horizontal VOR gains in rabbits (Kashii et al., 1989; Kimura, Takeda, & Maekawa, 1981, 1991) and pigeons (Hayman & Donaldson, 1995). Immediately after unilateral V1 sectioning in pigeons, horizontal VOR gains of the deafferented eye are dramatically reduced, while gains in the contralateral eye are little affected (Hayman & Donaldson, 1995). Proprioceptive deafferentation worsens saccade conjugacy (Lewis, Zee, Gaymard, & Guthrie, 1994) and results in disconjugate adaptation (Lewis, Zee, Goldstein, & Guthrie, 1999). In our patients, VOR gains of the paretic eye were reduced in all directions, while gains of the non-paretic eye remained normal. Our results might be explained by defective transmission of afferent signals from the paretic eye to the brainstem, as a result of a lesion in the trochlear nerve, which normally carries proprioceptive signals from extraocular muscles to the ophthalmic branch of the trigeminal nerve and the spinal trigeminal nucleus.

4.6. Orbital mechanics and VOR adaptation

Changes in normal orbital plant mechanics might contribute to the decreased VOR gains of the paretic eye in fourth nerve palsy. The relative contribution of agonist contraction and antagonist relaxation varies with orbital position (Collins, 1975), and it may be altered when one muscle of an agonist–antagonist pair is palsied. In superior oblique paresis, secondary changes such as "overaction" of the inferior oblique (Guyton & Weingarten, 1994) and "contracture" of the superior rectus muscle (Jampolsky, 1971), characterized by muscle shortening and stiffening as a result of decreased number of sarcomeres (Scott, 1994), are also observed. If the reduction of VOR gains in both directions of the three axes of rotation was due to changes in extraocular muscle mechanics, one would predict VOR gains to remain the same during rotation in darkness or in light, and that the peak velocities of nystagmus quick phases would be reduced in each direction. However, our results indicate that while vertical and horizontal VOR gains were decreased, they increased immediately to normal values in light during VVOR. In addition, although VOR gains were reduced in each direction, and incyclotorting, depressing and abducting peak velocities in the paretic eye were reduced, *excyclotorting*, *elevating* and *adducting* peak velocities in the paretic eye were normal. Our results provide evidence that decrease VOR gains in fourth nerve palsy is not the result of changes in mechanical properties of the orbital plant, but due to a functional adaptation to the palsy.

4.7. Monocular adaptation in unilateral fourth nerve palsy

Hering suggested that the brain circuitry controlling gaze consists of two systems, one for conjugate movements, the other for vergence (Hering, 1868). Conjugate control operates in the vestibulo-ocular, saccade, smooth pursuit and optokinetic systems. Premotor neurons encode common signals to both abducens motoneurons and internuclear neurons in the abducens nucleus (Henn & Cohen, 1973, 1976; Luschei & Fuchs, 1972). The abducens motoneurons innervate the ipsilateral lateral rectus, while the internuclear neurons innervate the medial rectus motoneurons in the contralateral oculomotor nucleus (Baker & Highstein, 1975; Carpenter & Batton, 1980; Highstein & Baker, 1978). For upward and torsional eye movements, common premotor signals are sent to the oculomotor subnuclei that drive the contralateral superior rectus and ipsilateral inferior oblique muscles (see Fig. 5A). For downward and torsional movements, common signals are relayed to the trochlear nucleus, which innervates the contralateral superior oblique muscle, and to the oculomotor subnucleus that innervates the ipsilateral inferior rectus muscle (see Fig. 5C).

Because the neuronal connectivity is suitable for conjugate motion, it might be presumed that only conjugate plasticity is possible. However, experiments on primates have shown that the ocular motor systems are capable of selective, monocular adaptation (Snow et al., 1985; Virre, Werner, & Vilis, 1987, 1988). For example, in monkeys, surgical weakening of the horizontal recti muscles of one eye causes an adaptation that selectively increases saccadic and VOR gains in the affected eye, while those of the unaffected eye remain normal (Snow et al., 1985; Virre et al., 1988). Disconjugate ocular motor adaptation has also been demonstrated in normal humans (Erkelens, Collewijn, & Steinman, 1989; Schor, Gleason, & Horner, 1990) and monkeys (Oohira & Zee, 1992) in response to optical devices such as

anisometropic spectacles and prisms. Disconjugate saccades and pursuit are generated to compensate for the disparate retinal errors produced by the optical device (Erkelens et al., 1989; Schor et al., 1990).

To our knowledge, this study is the first to demonstrate monocular adaptation of the VOR in humans with fourth nerve palsy. We found that VOR gains are reduced in darkness during excyclotorsion, elevation and adduction of the paretic eye, as well as in the directions of paretic duction. Moreover, in light, vertical and horizontal VVOR gains are selectively increased in the paretic eye, without a conjugate increase in gains of the non-paretic eye. These results exemplify monocular adaptation in humans with peripheral neuromuscular deficits. Retinal slip differences between the two eyes is the stimulus that drives the monocular adaptation that we have identified.

One possible site where changes in neural drive to each eye could occur independently is at the level of motoneurons. Selective adaptation might be achieved by changing the sensitivity of each motoneurons pool to innervation from premotor neurons. The cerebellum, which mediates ocular motor adaptation, may have direct projections to ocular motoneurons (Carpenter & Strominger, 1964). Using the Nauta method for tracing Wallerian degeneration, Carpenter and Strominger (1964) suggested that cerebello-oculomotor fibers from all parts of the dentate nucleus project to the inferior rectus subdivision of the contralateral oculomotor nucleus, whereas fibers from ventral portions of the dentate nucleus project to the superior rectus subdivision of the contralateral oculomotor nucleus (Carpenter & Strominger, 1964). However, more modern retrograde tracer technique identifies no afferents from the dentate nucleus to the oculomotor nucleus (Graybiel & Hartwieg, 1974; Steiger & Buttner-Ennever, 1979).

Supranuclear neural circuitry is another possible source of monocular drive to adaptation. For example, for saccades, different populations of burst neurons mediate a pulse of innervation to each eye. In monkeys (Zhou & King, 1998), 79% of premotor excitatory burst neurons in the caudal pontine paramedian reticular formation that were thought to encode conjugate velocity commands for saccades (Henn & Cohen, 1973, 1976; Luschei & Fuchs, 1972), actually encode monocular commands for either the ipsilateral or contralateral eye. Similarly, different populations of vestibular neurons provide innervation to the horizontal muscles of each eye (Uchino, Hirai, & Suzuki, 1982). Neurons in the feline medial vestibular nucleus (MVN) are activated antidromically only by local stimulation of the contralateral abducens nucleus (Uchino et al., 1982). Another group of MVN neurons are activated only by stimulation of the ipsilateral medial rectus motoneurons pool, but not by stimulation of contralateral abducens nucleus (Uchino et al., 1982).

The cerebellum plays important roles in adaptive control of saccades (Optican & Robinson, 1980; Optican, Zee, & Miles, 1986; Takagi, Zee, & Tamargo, 1998; Zee, Yamazaki, Butler, & Gucer, 1981) and the VOR, including disconjugate control (Cohen, Cohen, Raphan, & Waespe, 1992; Lisberger, Miles, & Zee, 1984; Schultheis & Robinson, 1981; Waespe, Cohen, & Raphan, 1983; Zee et al., 1981). Experimental inactivation of the deep cerebellar nuclei (including the fastigial nucleus) causes disconjugate saccadic dysmetria, such that both saccade magnitude and peak velocity differ in the two eyes (Vilis, Snow, & Hore, 1983). Patients with cerebellar dysfunction also show disconjugate dysmetria during and immediately after horizontal or vertical saccades (Versino, Hurko, & Zee, 1996). The flocculus regulates conjugate VOR responses, and unilateral lesions of the rabbit flocculus cause different VOR gain changes in the two eyes (Ito, Jastreboff, & Miyashita, 1982). Thus the cerebellum exerts selective, monocular control and may participate in the adaptation that we have identified.

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