Adaptive Neural Mechanism for Listing's Law Revealed in Patients with Skew Deviation Caused by Brainstem or Cerebellar Lesion

Maryam Fesharaki,[1] *Peter Karagiannis,*[2] *Douglas Tweed,*[1,3] *James A. Sharpe,*[2,3] *and Agnes M. F. Wong*[2,3]

Purpose. Skew deviation is a vertical strabismus caused by damage to the otolithic–ocular reflex pathway and is associated with abnormal ocular torsion. This study was conducted to determine whether patients with skew deviation show the normal pattern of three-dimensional eye control called Listing's law, which specifies the eye's torsional angle as a function of its horizontal and vertical position.

Methods. Ten patients with skew deviation caused by brain stem or cerebellar lesions and nine normal control subjects were studied. Patients with diplopia and neurologic symptoms less than 1 month in duration were designated as acute ($n = 4$) and those with longer duration were classified as chronic ($n = 10$). Serial recordings were made in the four patients with acute skew deviation. With the head immobile, subjects made saccades to a target that moved between straight ahead and eight eccentric positions, while wearing search coils. At each target position, fixation was maintained for 3 seconds before the next saccade. From the eye position data, the plane of best fit, referred to as Listing's plane, was fitted. Violations of Listing's law were quantified by computing the "thickness" of this plane, defined as the SD of the distances to the plane from the data points.

Results. Both the hypertropic and hypotropic eyes in patients with acute skew deviation violated Listing's and Donders' laws—that is, the eyes did not show one consistent angle of torsion in any given gaze direction, but rather an abnormally wide range of torsional angles. In contrast, each eye in patients with chronic skew deviation obeyed the laws. However, in chronic skew deviation, Listing's planes in both eyes had abnormal orientations.

Conclusions. Patients with acute skew deviation violated Listing's law, whereas those with chronic skew deviation obeyed it, indicating that despite brain lesions, neural adaptation can restore Listing's law so that the neural linkage between horizontal, vertical, and torsional eye position remains intact. Violation of Listing's and Donders' laws during fixation arises primarily from torsional drifts, indicating that patients with acute skew deviation have unstable torsional gaze holding that is independent of their horizontal–vertical eye positions. (*Invest Ophthalmol Vis Sci.* 2008;49:204–214) DOI:10.1167/iovs.07-0292

During fixation, saccades, and smooth pursuit, the eye rotates freely in the horizontal and vertical dimensions, with torsion being constrained.[1–4] Helmholtz[5] described this restriction on ocular torsion and expressed it as Donders' and Listing's laws. Donders' law states that there is only one torsional eye position for each combination of horizontal and vertical eye positions.[2,5] Listing's law is a special case of Donders' law and quantitatively specifies the torsional angle for each gaze direction. It states that, with the head fixed, there is an eye position called primary position, with the property that all other eye orientations that the eye actually assumes can be reached from primary position by a single rotation about an axis in a plane called Listing's plane.[5] This plane, furthermore, is orthogonal to the gaze line when the eye is in primary position.

Skew deviation is a vertical strabismus caused by supranuclear lesions and has been attributed to asymmetric disruption of projections from otolithic receptors to the oculomotor and trochlear nuclei.[6–8] It is typically caused by damage to the brain stem tegmentum or cerebellum.[6,9–13] Skew deviation can also be caused by vestibular afferent asymmetry. It is often associated with ocular torsion and head tilt, constituting the ocular tilt reaction.[7,14,15] Although abnormal *static* ocular torsion has been demonstrated by funduscopy in patients with skew deviation when they looked straight ahead,[12,16–21] it is unknown whether, or how, torsion is altered during *dynamic* eye movements or during different gaze directions and whether the relationship of ocular torsion with horizontal and vertical eye position is intact in skew deviation.

We investigated patients with skew deviation caused by brain stem or cerebellar lesions, to determine whether Listing's law is obeyed. We found that Listing's law was disrupted in the acute but not in the chronic stage of skew deviation, providing support for the notion that an adaptive neural mechanism is responsible for the implementation of Listing's law.

Methods

Ten patients with skew deviation caused by brain stem or cerebellar lesions were recruited from the Neuro-Ophthalmology Unit at the University Health Network. Detailed ophthalmic and neurologic examinations were performed. The age of onset, duration of diplopia, and associated neurologic symptoms and signs were recorded. The magnitude of vertical and horizontal strabismus was measured objectively by the prism cover test. Cyclotorsion in the straight-ahead position was measured subjectively using double Maddox rods. Appropriate tests were performed to rule out ocular motor nerve palsy, myasthenia

From the Departments of [1]Physiology and [2]Ophthalmology and Vision Science, and the [3]Division of Neurology, University Health Network, and the Hospital for Sick Children, University of Toronto, Toronto, Ontario, Canada.

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Corresponding author: Agnes M. F. Wong, Department of Ophthalmology and Vision Sciences, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario, Canada M5G 1X8; agnes.wong@utoronto.ca.

gravis, thyroid ophthalmopathy, or other orbital diseases. Axial and sagittal T_1- and T_2-weighted magnetic resonance (MR) images with gadolinium enhancement were obtained (slice thickness, 5 mm) in all patients. Skew deviation was diagnosed in patients who fulfilled the following clinical criteria: (1) a vertical misalignment (with or without head tilt or fundus torsion), the pattern of which is inconsistent with that found in a palsy of one or more cyclovertical muscles; (2) presence of associated neurologic symptoms and signs; and (3) presence of a lesion in the brain stem or cerebellum, as confirmed by (MR) imaging (Table 1). Patients with diplopia and neurologic symptoms of less than 4 weeks' duration were classified as having acute skew deviation. All others were classified as having chronic skew deviation. Patients with a history of diplopia or strabismus dating to infancy or early childhood or prior surgery for strabismus were excluded from the study.

Nine normal subjects served as the control (mean age, 39 ± 14 years; median age, 32 years; range, 20–60 years; three women). The research protocol was approved by the University Health Network Ethics Committee and adhered to the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects.

Visual Stimuli and Experimental Protocol

Eye position was measured with search coils while subjects fixated a red laser spot of 0.25° diameter, rear projected onto a vertical flat screen 1 m away from the nasion. The laser was programmed to appear in nine different target positions, arranged in a 3 × 3 square. The middle row of this array was at eye level, with the other two 10° above and below. In each row, the center target lay in the subject's midsagittal plane, the other two 10° to the right and left of it.

With the head immobilized and with one eye covered, subjects were instructed to follow the laser spot as it stepped among positions. At each position, the laser halted for 3 seconds. In the horizontal target sequence, the laser started in the center, stepped to the 10° right position, then back to center, then to the 10° left position—cycling through this pattern 20 times in each eye. The vertical sequence was the same but with the laser stepping center-up–center-down. The two diagonal sequences stepped along oblique lines, between opposite corners of the target array. Recordings were then made with the other eye fixating and the fellow eye occluded. Recordings were not made during binocular viewing. Breaks were provided approximately every 2 minutes for 1 to 3 minutes to avoid fatigue.

Recordings of Eye Movement and Calibration

Eye positions were measured by a three-dimensional (3-D) magnetic search coil technique, using a 6-ft (183-cm) diameter coil field arranged in a cube (CNC Engineering, Seattle, WA). In each eye, the subject wore a dual-lead scleral coil annulus (Skalar Instrumentation, Delft, The Netherlands). 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° to the 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 using amplitude modulation as described by Robinson[22] 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 less than 4% of the amplitude of the horizontal and vertical movements. The difference in torsional deflections between the straight-ahead and 30° right (or up) positions was less than 4%. Torsional precision was approximately ±0.2°.

To measure the offset of the coil signal, during the gimbal calibration, the coil was rotated through 360° to measure its maximum and minimum readings for each of the three fields (a total of six numbers). If there were no offsets for a particular field, the two corresponding readings would 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 the scleral coils were inserted 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 insertion of the coils provided evidence that the gimbal calibrations were valid. Because torsional eye position depended on the same magnetic field as vertical eye position, the accuracy of vertical calibration before and after insertion of the coils provided further evidence that the torsional calibration was also accurate.

The reference position, relative to which all eye positions were expressed, was defined by measuring the coil readings while the subject fixated a target straight ahead. To assess torsional coil slippage, throughout the experiment, the subject was required to fixate the same straight-ahead target repeatedly. Any discrepancy in voltage readings associated with reference position was corrected for by resetting the torsional position to the setting measured at the beginning of a trial during each straight-ahead fixation.

Eye position data were filtered with a bandwidth of 0 to 90 Hz and were digitized at 500 Hz. They were recorded on disc for off-line analysis.

Data Analyses and Statistical Methods

Eye position and angular velocity were computed from coil signals.[23,24] For Listing's and Donders' laws analysis, fixations were defined as periods within 100 ms before the next saccades when eye velocity was less than 3 deg/s. Eye movements were classified as saccades when eye velocity exceeded 50 deg/s. Coil signals were converted into eye-position quaternions, by a method described previously.[24] Quaternions represent each eye position as a fixed-axis rotation from a reference position. This reference position was defined as the eye position when subjects looked straight ahead at the center target. Listing's law predicts that during fixation and saccades, the quaternion vectors of eye positions lie in a plane. This plane is not necessarily Listing' plane, unless the reference position happens to be the primary position, but by computing the orientation of the plane with respect to the gaze direction at reference position, one can determine the primary position and the orientation of Listing's plane.[24] Listing's primary position is not the primary position commonly used clinically, which refers to the straight-ahead gaze position and roughly corresponds to the center of the oculomotor range. In this study, all plots of eye position were in Listing's coordinate so that the origin of the coordinate system (the zero position) was the Listing's primary position.

Figure 1 shows the 3-D eye position data of the left eye in a normal subject fixating nine target positions. Listing's plane is the best-fit plane through the data cloud of eye positions. To assess the scatter in the data, we measured the distance of each eye position from the plane of best fit. WE called the standard deviation of these distances the thickness of the plane. The smaller the thickness, the better the data fit Listing's law. For a distant target, Listing's plane is approximately parallel to the frontal plane of the head. During near viewing, however, the Listing's planes of the two eyes rotate temporally in normal subjects.[25–27] This rotation is also illustrated in Figure 1B, when the left eye of a normal subject viewed a target 1 m away from the nasion. This temporal rotation of Listing's plane means that the eye undergoes excyclotorsion during downgaze and incyclotorsion during upgaze. Thus, during vergence in normal subjects, eye positions remain restricted to a plane and therefore obey Listing's law, although the planes are turned.

We defined the direction of torsion from the subject's point of view. Rotation of the upper pole of the iris toward the subject's right shoulder was designated clockwise (CW), whereas rotation of the upper pole of the iris toward the subject's left shoulder was designated counterclockwise (CCW).

Donders' law implies that the eye position data lie in some two-dimensional surface, which is not necessarily a plane. To assess

TABLE 1. Characteristics of Patients with Skew Deviation

Patient	Age/Sex	Duration	Cyclotorsion in Straight-Ahead Position	Side of Hypertropia	Visual Acuity	Retractive Errors	MRI Findings	Clinical Features (In Addition to Skew Deviation)
1	36/M	3 wk (acute) 9 mo (chronic)	No torsion OD & OS No torsion OD & OS	LHT LHT	20/20 OD 20/20 OS	−1.25 OD −1.25 OS	Left rostral pontine demyelinating lesions	Ataxia
2	61/M	10 mo	Suppress OD; 3 deg ex OS	RHT	20/25 OD 20/20 OS	−2.00 + 0.50 × 180 OD −1.50 + 1.00 × 180 OS	Left cerebellar cavernous hemangioma	Ataxia
3	61/F	6 mo	4 deg ex OD; no torsion OS	LHT	20/25 OD 20/25 OS	+2.25 + 0.50 × 180 OD +2.25 + 0.50 × 180 OS	Left cerebellar hemorrage from arteriovenous malformation	Gaze-evoked nystagmus square wave jerks, ataxia
4	59/M	3 wk (acute) 6 mo (chronic)	No torsion OD; 7 deg ex OS No torsion OD; 6 deg ex OS	RHT RHT	20/30 OD 20/25 OS	Plano OD Plano OS	Left caudal pontine infarct	Left hemiplegia, right facial paresis
5	53/M	4 mo	10 deg ex OD; 8 deg in OS	LHT	20/25 OD 20/25 OS	−1.00 OD −0.50 OS	Bilateral pontine infarct	Dysarthria, left hemiparesis, ataxia
6	19/M	30 mo	2 deg in OD; 7 deg ex OS	Alternating skew	20/25 OD 20/25 OS	Plano OD Plano OS	Suprasellar and pineal germinoma in the midbrain	Mild vertical gaze palsy, light-near dissociation of pupils
7	22/F	10 mo	5 deg ex OD; no torsion OS	LHT	20/25 OD 20/25 OS	Plano OD Plano OS	Clival chordoma with mass effect on the pons	Increased tone with spasticity and limb weakness on right side, hyperreflexia
8	52/F	24 mo	10 deg ex OD; no torsion OS	LHT	20/30 OD 20/20 OS	Plano OD Plano OS	Right dorsal midbrain hemorrhage from a closed-head injury	Dysarthria, mild vertical gaze palsy, cognitive deficits
9	66/M	3 d (acute) 2 mo (chronic)	No torsion OD & OS No torsion OD & OS	LHT LHT	20/20 OD 20/40 OS	−3.00 OD −3.00 OS	Periventricular demyelinating lesions	Ataxia
10	59/M	4 d (acute) 2 mo (chronic)	No torsion OD & OS No torsion OD & OS	RHT RHT	20/20 OD 20/25 OS	Plano OD Plano OS	Right medial thalamus and rostral midbrain infarct	Slow vertical saccades, increased rigidity

Ex, excyclotorsion; in, incyclotorsion.

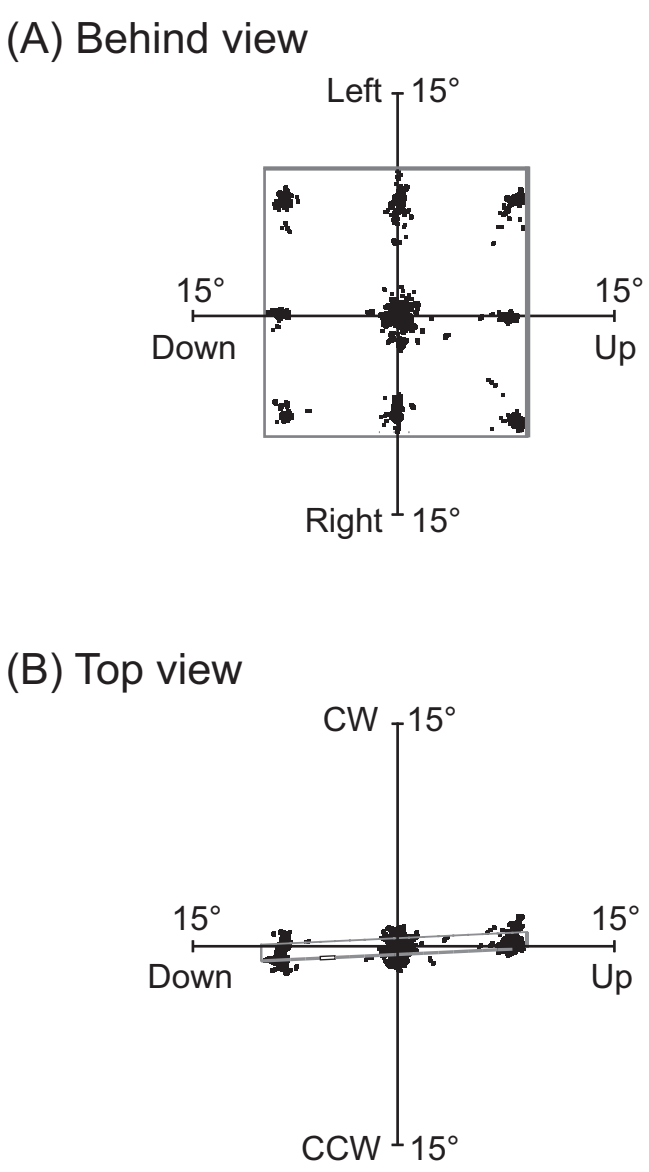


FIGURE 1. Plots of eye positions of the left eye in Listing's coordinate in a normal subject, during fixation at nine target positions, 1 m away from the nasion. (**A**) Listing's plane is the best-fit plane through the data cloud of eye positions. The central cloud among the nine small clouds of eye positions represents Listing's primary position and is centered at the 0 position of the coordinate system (intersection of left–right and up–down axes). (**B**) A small temporal rotation of Listing's plane is demonstrated in the left eye. CW-CCW axis denotes rotation about the line of sight, clockwise (CW) or counterclockwise (CCW) from the subject's point of view. The up–down axis denotes rotation around the interaural axis.

whether Donders' law was obeyed when Listing's law was violated, we also computed the second- and third-order surfaces of best fit, by a method described previously (see the Appendix). The thickness of the fitted curved surface was then compared in patients and normal subjects. The thickness and orientation of the fitted planes or surfaces during fixation and saccades were analyzed separately using 3 (between) × 4 (within) nested, repeated-measures ANOVAs. The between-subjects factor was the stage of skew deviation (acute, chronic, and control) and the within-subjects factor was the hypertropic and hypotropic eyes during monocular viewing with either eye. For the four patients who had serial recordings in both the acute and chronic stages, the effects of the stage of the skew deviation were analyzed by crossed-design, repeated-measures ANOVAs. The specific effects of each factor were analyzed further with post hoc Tukey tests, with significance set at $P < 0.05$.

RESULTS

General Characteristics of Patients

The characteristics of our 10 patients with skew deviation are shown in the Table. Four patients had lesions affecting the pons (patients 1, 4, 5, and 7), three had a midbrain lesion (patients 6, 8, and 10), and two had a cerebellar lesion (patients 2 and 3). In a 10th patient (patient 9), no lesion was identified in the posterior fossa, but multiple periventricular cerebral demyelinating lesions typical of MS were evident on MR imaging. All 10 patients had neurologic symptoms and signs consistent with a lesion in the brain stem or cerebellum. No patients had any spontaneous nystagmus in straight ahead position. Gaze-evoked nystagmus was present in a single patient with chronic recording only (patient 3). Four patients (patient 1, 4, 9, and 10) were tested acutely—that is, within 1 month of symptom onset. Serial eye movement recordings were performed on these four patients with acute skew deviation at presentation and at 2 to 9 months after symptom onset (i.e., chronic stage). The mean duration of diplopia and neurologic symptoms (at the time of eye movement recording) in acute skew deviation ($n = 4$) was 12 ± 10 days, whereas the mean duration in chronic skew deviation ($n = 10$) was 10 ± 9 months ($P < 0.01$). The mean age in acute skew deviation ($n = 4$) was 55 ± 13 years, whereas the mean age in chronic skew deviation ($n = 10$) was 49 ± 17 years (P = NS).

Figure 2 shows the vertical and horizontal alignment data of each of the four subjects with serial recordings in both acute and chronic stages, and Figure 3 shows the same data of each of the six subjects with chronic recordings only. Cyclotorsional data of all patients are shown in Table 1. No clinically significant differences in vertical, horizontal, or torsional alignment were found between acute and chronic stages in all four patients with serial measurements.

Violation of Listing's Law during the Acute Stage of Skew Deviation

Figure 4 (top) shows the 3-D eye position data and the fitted Listing's planes of patient 4 in the acute stage, while viewing with the hypertropic right eye during fixation. The fitted planes were abnormally thick—2.8° in the hypertropic eye and 2.2° in the hypotropic eye, compared with 0.8 ± 0.4° in the normal control (95% CI, 0.5°–1.2°). Similarly, each of four patients with recordings in the acute stage had abnormally thick planes. Figures 5 and 6 show the plane thickness data in acute skew deviation ($n = 4$) during fixation and saccades. Listing's planes in both the hypertropic and hypotropic eyes had increased thickness, independent of which eye was used for viewing ($P < 0.001$).

When we fit the data with curved surfaces rather than planes, the thickness scarcely diminished. During fixation, it averaged 2.7 ± 0.8° in the hypertropic and 1.8 ± 0.4° in the hypotropic eye when the surface was second order and 2.6 ± 0.4° in the hypertropic and 1.6 ± 0.7° in the hypotropic eye when the surface was third order, compared with 0.7 ± 0.3° (second and third order) in normal control eyes ($P < 0.01$). During saccades, the surface averaged 2.6 ± 0.5° in the hypertropic and 1.8 ± 0.5° in the hypotropic eye when it was second order and 2.3 ± 0.4° in the hypertropic and 1.6 ± 0.5° in the hypotropic eye when the surface was third order, compared with 0.7 ± 0.3° (second and third order) in normal control eyes ($P < 0.01$). Because fixations were defined as periods within 100 ms before the next saccades when eye velocity was less than 3 deg/s, these findings indicate that the

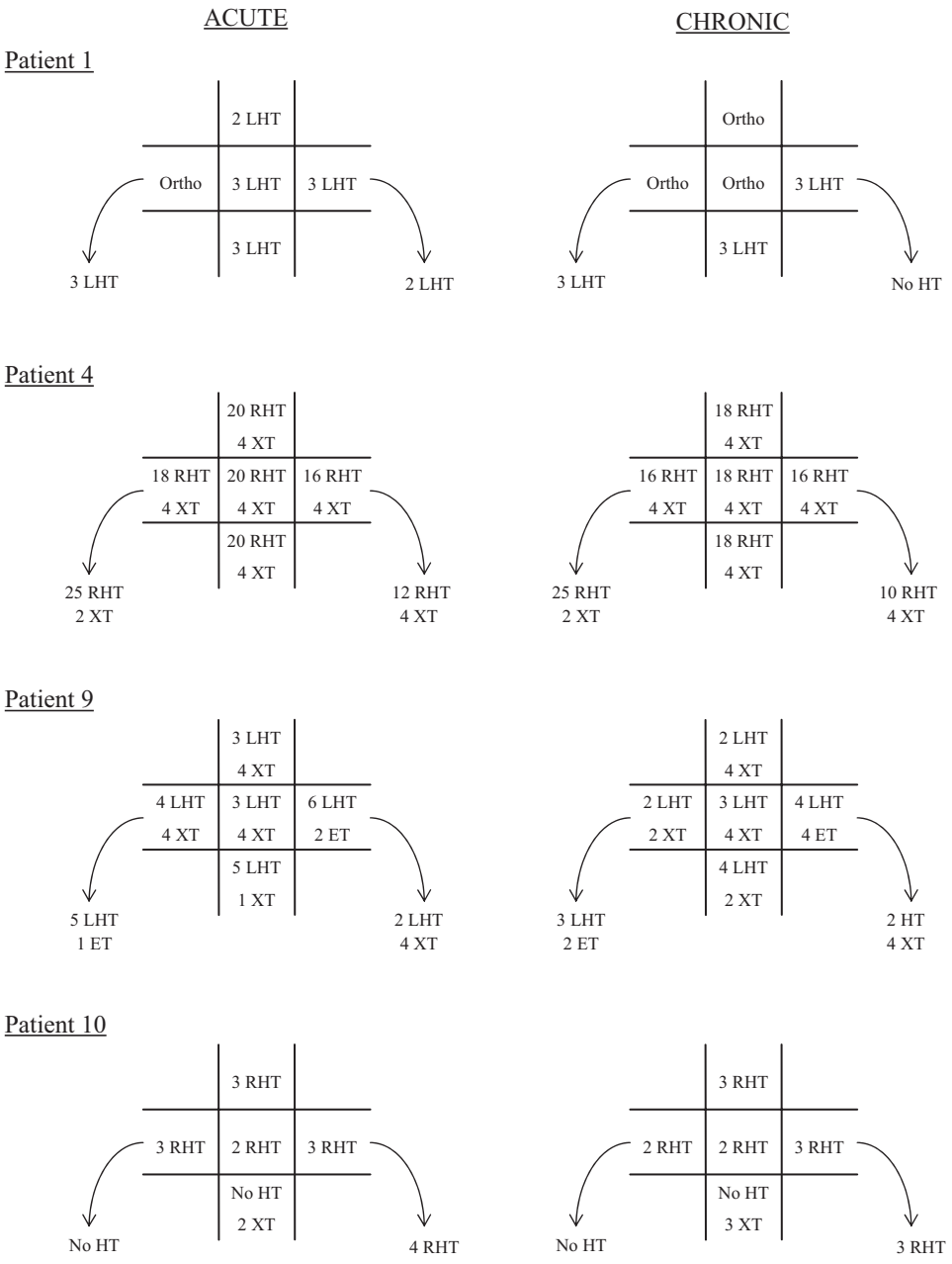


FIGURE 2. Prism cover test results (in prism diopters) in five diagnostic positions of gaze and during static lateral head tilt in four patients with acute and chronic eye movement recordings, as viewed by the examiner. *Counterclockwise arrows*: amount of deviation during right head tilt; *clockwise arrows*: amount of deviation during left head tilt. No clinically significant difference was evident between the acute and chronic stages. LHT, left hypertropia; RHT, right hypertropia; XT, exotropia; Ortho, orthophoria.

violation of Donders' law was a sustained phenomenon, rather than a transient deviation caused by a pulse-step mismatch during and immediately after each saccade. These findings suggest that, in acute skew deviation, not only was Listing's law violated but also Donders' law—that is, the eyes did not show one consistent angle of torsion in any given gaze direction, but rather an abnormally wide range of torsional angles.

The abnormally wide range of torsional angles we observed in patients with acute skew deviation during fixation arose primarily from instability of torsional gaze holding. During fixation in the straight-ahead and eccentric gaze positions, the mean change in torsional position was 2.3 ± 0.5° and the mean torsional velocity of drift was 0.82 ± 0.47 deg/s. These torsional drifts were idiosyncratic with no discernible pattern, both within an individual patient and across all four patients. In addition, because none of the four acute patients had any nystagmus, the torsional drifts were independent of the horizontal–vertical eye positions.

Listing's Law during the Chronic Stage of Skew Deviation

Figure 4 (bottom) shows the 3-D eye position data and the fitted Listing's plane of the same patient (patient 4) during fixation in the chronic stage. The thickness of Listing's plane returned to normal when recorded 6 months after symptom onset. Similarly, in each of four acute skew deviations tested serially, the thickness of Listing's plane became normal within 2 to 9 months of symptom onset, despite persisting ocular signs (i.e., there was no difference in the magnitude of vertical strabismus and cyclotorsion in the straight-ahead position between acute and chronic stages in all four patients) and neurologic symptoms. The thickness of Listing's plane was also normal in each of six other patients who had recordings in the chronic stage only. As shown in Figures 5 and 6, the mean thickness of Listing's plane in chronic skew deviation ($n = 10$) was comparable to that in the normal control eyes (P = NS).

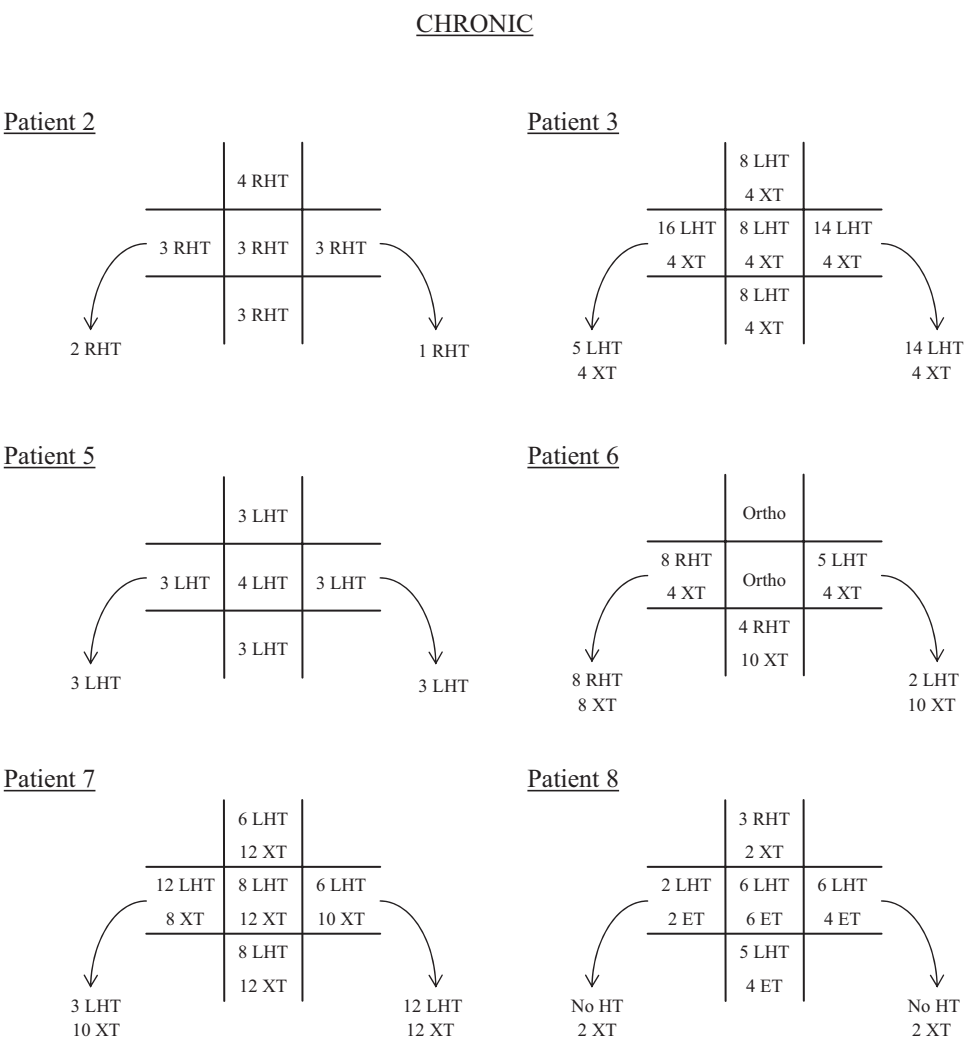


FIGURE 3. Prism cover test results (in prism diopters) in five diagnostic positions of gaze and during static lateral head tilt in six patients with chronic eye movement recordings only, as viewed by the examiner. *Counterclockwise arrows*: amount of deviation during right head tilt; *clockwise arrows*: amount of deviation during left head tilt. LHT, left hypertropia; RHT, right hypertropia; XT, exotropia; Ortho, orthophoria.

Although Listing's planes in chronic skew deviation had normal thickness, they were abnormally rotated horizontally. This rotation is also illustrated in Figure 4 (bottom) for patient 4. Listing's plane was rotated 15.1° nasally in the hypertropic eye, and 28.0° temporally in the hypotropic eye, compared with 1.7 ± 1.4° in both eyes of normal control subjects (95% CI 0.8°–2.6° temporally). Figure 7 shows the orientation of Listing's planes in all 10 chronic patients. Whereas there was a slight rotation of Listing's planes temporally in normal control eyes (as expected from the use of a near target at 1 m), we found a wide variation of plane rotation, without any consistent pattern, in both the hypertropic and hypotropic eyes in chronic skew deviation (Fig. 7). In other words, Listing's law was obeyed in chronic skew deviation with normal plane thickness, but the planes were abnormally rotated.

We also measured the *vertical* (up-down) rotation of Listing's planes, but no difference was found between patients and normal control subjects. We also found no correlations between the magnitude of torsional offset in the straight-ahead position and the degree of plane rotation, both horizontally and vertically.

DISCUSSION

A principal finding in this investigation is that during the acute stage of skew deviation, torsional control was abnormal, violating both Donders' and Listing's laws. Listing's plane in acute skew deviation was approximately two to three times thicker than that in normal subjects, with patients' eye position vectors widely scattered about their plane of best fit, indicating a failure of Listing's law. The scatter of the eye position vectors was also abnormally large when we fit them to second- and third-order surfaces rather than planes, indicating a further failure of Donders' law. Yet, in the chronic stage of the disease, both Donders' and Listing's laws were restored. These results are consistent with our previous findings in patients with acute and chronic trochlear or abducens nerve palsy,[28,29] where Listing's law was restored despite a palsied muscle or a disrupted muscle pulley system.[28,29] Although artificially induced superior oblique palsy in two monkeys produced quite different effects on Listing's law,[30] our current findings provide further evidence that, in humans, the neural circuitry underlying Listing's law is adaptive after certain *central* brain lesions, even when the more basic Donders' law is disrupted in the acute stage.

Neural and Mechanical Aspects of Listing's Law

For the past decade, there has been an ongoing debate as to whether 3-D eye movements are implemented neurally by brain stem circuits,[23] or mechanically by the positioning of orbital pulleys.[31–34] For example, during saccades and smooth pursuit, when eye movements are made from an eccentric

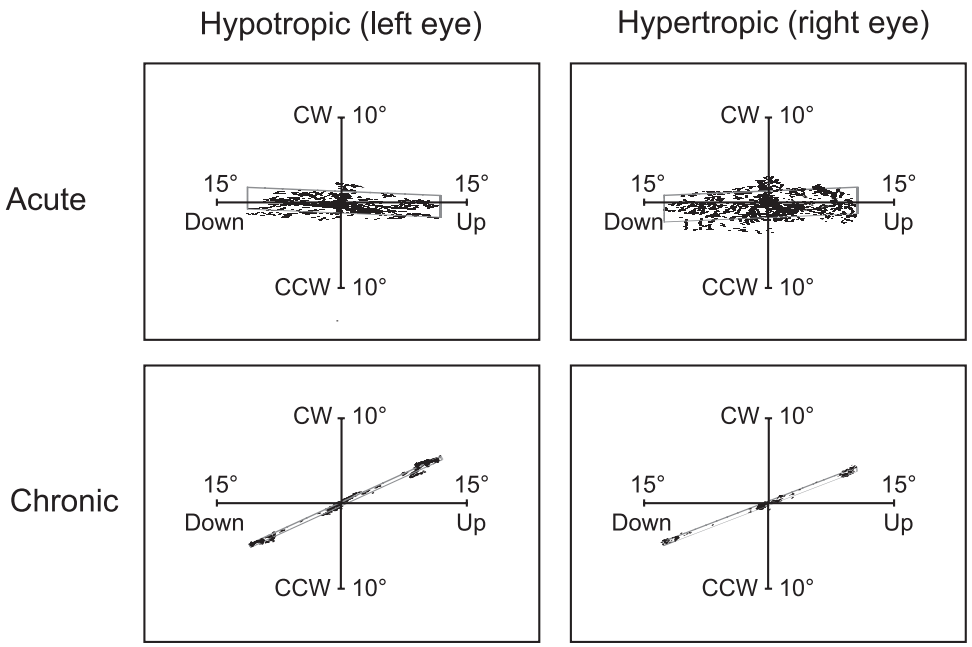


FIGURE 4. *Top row*: top view of eye position vectors and the fitted Listing's plane of patient 4 in the acute stage, while viewing with the hypertropic right eye during fixation. The thickness of the fitted planes of both the hypotropic and hypertropic eyes was two to three times that of normal subjects. *Bottom row*: Same plots during the chronic stage. The thickness of the fitted planes of both the hypotropic and hypertropic eyes became normal. However, the planes were abnormally oriented in the horizontal (nasal–temporal) dimension—that is, the plane was temporally rotated in the hypotropic left eye and nasally rotated in the hypertropic right eye. All plots are in Listing's coordinate.

initial eye position, the eye velocity vectors do not remain confined to Listing's plane, but deviate in the same direction as gaze by approximately half as much (Listing's half-angle rule).[2,23] By what mechanism are the eye velocity vectors confined to these different planes? Do the burst neurons send different phasic commands depending on the initial eye position, as suggested by Tweed and Vilis,[23] or do burst neurons send the *same* command regardless of initial eye position, and the eye rotates about different axes because of the mechanical properties of the eye muscles and other orbital tissues? This latter theory, called the *linear plant model*, was first proposed by Tweed et al.[35] Soon after, a more specific mechanism was proposed[34,36]: mobile, connective-tissue sleeves in the orbit, called "pulleys," influence the pulling directions of the extraocular muscles so that their pulling axes change when the eye moves. Refined over the years, this idea became known as the *active pulley hypothesis*,[34] which states that contraction of muscle fibers in the global layer of extraocular muscles rotates the eyeball, whereas contraction of fibers in the orbital layer moves the pulleys.

The key idea behind the linear plant model, and the more specific active pulley hypothesis, is that burst and motor neurons can send out the same phasic commands independent of initial eye position, because the eye, by its own mechanical properties, will automatically rotate about the axes required by the half-angle rule. In support of the general linear plant model, recent evidence in monkeys show no correlation between neuronal activity that drove the cyclovertical muscles and the torsional component of eye velocity during smooth pursuit.[37] In addition, the eye could rotate about different axes, depending on initial eye position, despite identical electrical stimulation of the abducens nerve in monkeys.[38] Using MR imaging in humans, horizontal rectus pulleys were inferred to move in the orbit, which may allow implementation of the half-angle rule.[39] Although the anatomic evidence for active pulleys is still controversial,[40–42] the more general functional point that the eye rotates differently in response to identical phasic commands, as predicted by the general linear plant model, is experimentally well supported.

Although the linear plant model is well supported, it does not absolve the brain from dealing with torsion altogether or from implementing Listing's law. For example, Listing's law holds during fixation, saccades, and smooth pursuit, but it fails during sleep and the rotational vestibulo-ocular reflex.[2,43] These failures of Listing's law show that extraocular muscles are fully capable of breaking the law, and maintain it only when they are activated by appropriate neural commands.[24] In addition, Listing's plane can rotate with no change in eye position. For example, during asymmetric convergence, rotation of Listing's plane of the eye that is aligned to the target depends on the position of the *other* eye and is independent of its own position.[44] Furthermore, Listing's plane can rotate in both the paretic and nonparetic fellow eyes in unilateral trochlear nerve palsy,[28] as well as in both the operated and the nonsurgical eye[45] after surgical correction of strabismus. Our present results in patients with skew deviation, which is caused by a brain lesion, without damage to any extraocular muscles or orbital structures, provide further support that neural coordination plays a critical role in implementing Listing's law that cannot be explained by pulleys alone.

Rotation of Listing's Plane in Chronic Skew Deviation

When healthy subjects look straight ahead, with zero convergence, Listing's planes of both eyes are roughly parallel to the frontal plane. However, during convergence, Listing's plane is rotated temporally and roughly symmetrically in each eye,[26,46–48] through about a quarter of the vergence angle (binocular extension of Listing's law). In addition, after prolonged viewing through vertical prisms which induce a vertical disparity, a vertical rotation of Listing's plane can be observed in normal subjects, indicating that Listing's law is mutable.[49] In our experiment, the target was 1 m away and required the eyes to converge by ~3°, which explains the slight temporal rotation of Listing's planes in our normal subjects. However, in our patients with chronic skew deviation, an abnormal horizontal rotation of Listing's plane was evident. In addition, there was a wide variation in the horizontal orientation of the planes, without any consistent pattern across patients. These findings may be due to the heterogeneous nature of the pathology and the location of the brain stem or cerebellar lesions in our patients. The abnormal orientation of Listing's plane may also reflect abnormal innervation to extraocular muscle pulleys or a

change in the position of the extraocular muscle pulleys because of altered torsion.

Despite the variation in the horizontal orientation of the Listing planes, a consistent finding that emerges from this study is that adaptive mechanisms in the brain were able to restore Listing's law, so that all eye position vectors lie on Listing's planes. This leads to an interesting question as to why the adaptive mechanism failed to restore the original normal orientation of the planes. Did the adaptive mechanism choose the plane closest to the distribution of eye positions soon after the lesion? Does this mean that the function of Listing's law has more to do with having some planar arrangement than with having the eye position vectors in some specific plane? All current theories of the function of Listing's law propose that the specific plane is important, and so the issue is puzzling.

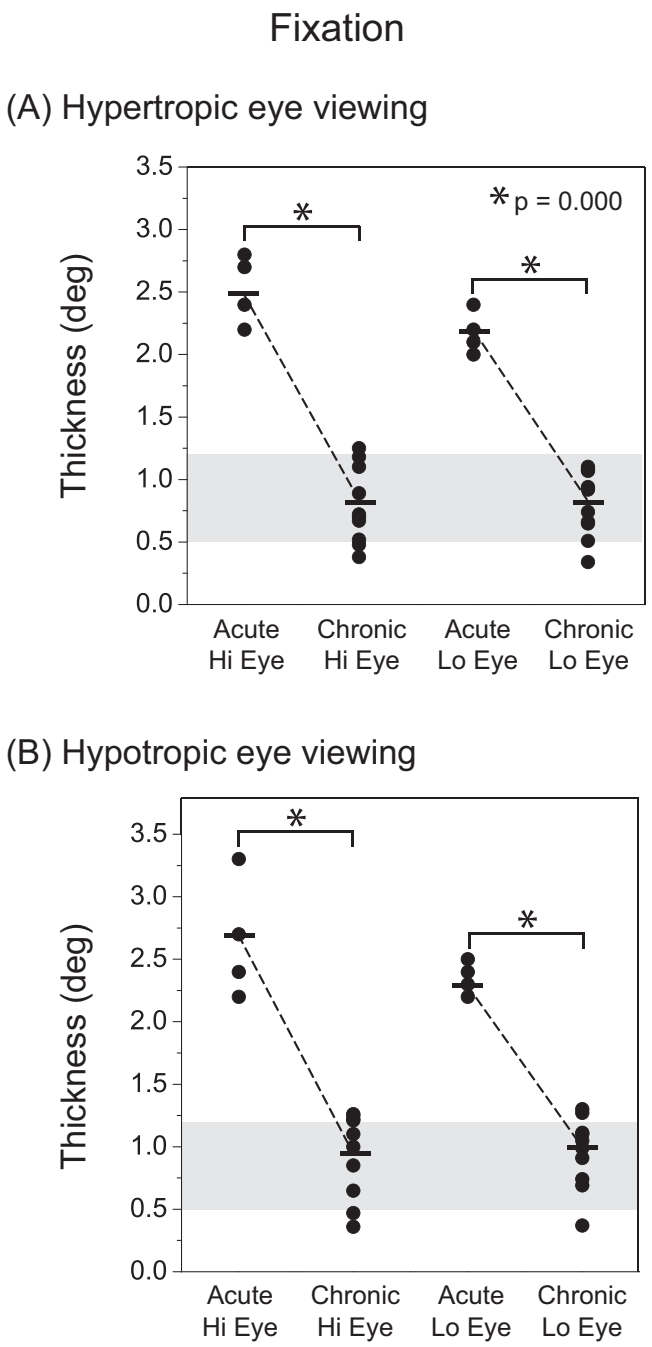


FIGURE 5. Thickness of Listing's plane in acute and chronic stage of skew deviation during monocular fixation with the (**A**) hypertropic and (**B**) hypotropic eye. The planes were abnormally thick during the acute stage of the disease, but they returned to normal thickness during the chronic stage. *Shaded area*: 95% CI in normal control eyes. (●) Individual data points for each patient. *Short horizontal dashed line*: mean thickness. *Dashed line*: change in mean thickness from acute to chronic stages. Hi Eye, hypertropic eye; Lo Eye, hypotropic eye.

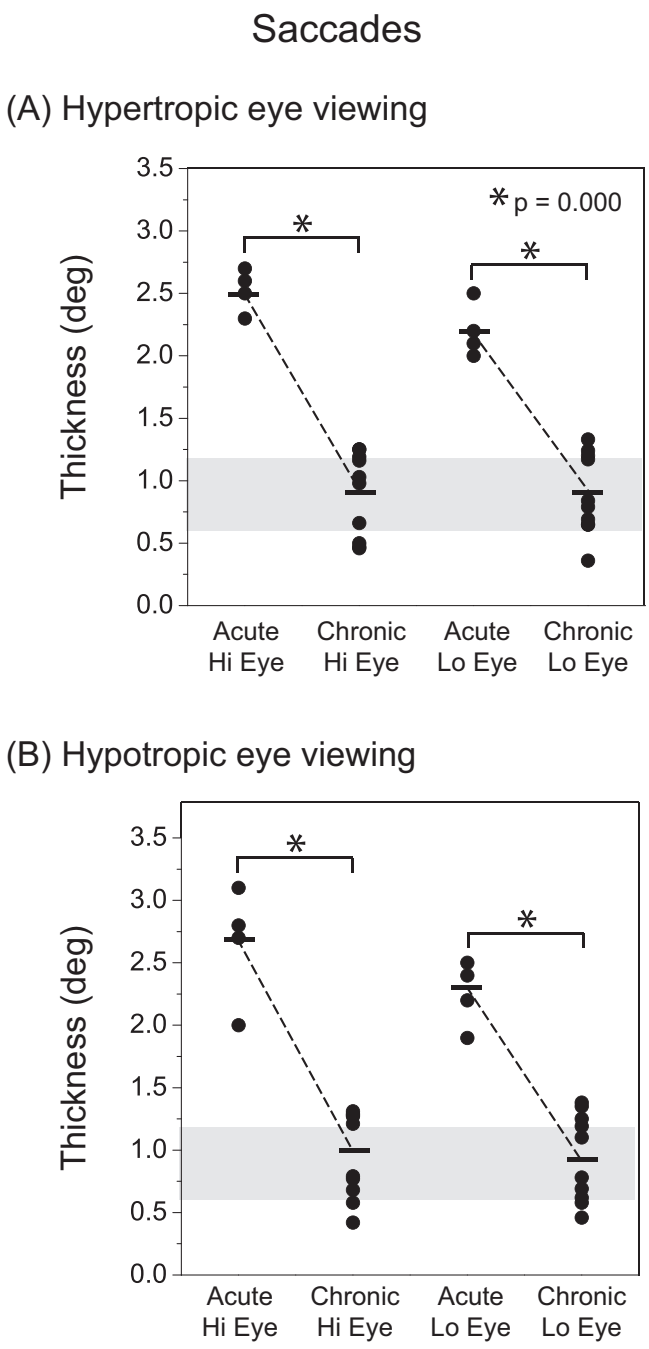
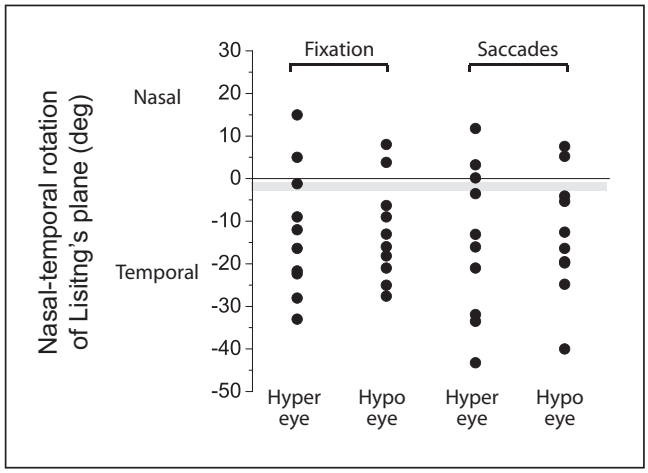


FIGURE 6. Thickness of Listing's plane in acute and chronic stage of skew deviation during (**A**) hypertropic and (**B**) hypotropic eye viewing during saccades. The planes were abnormally thick during the acute stage of the disease, but they returned to normal thickness during the chronic stage. *Shaded area*: 95% CI in normal eyes. (●) Individual data points for each patient. *Short horizontal dashed line*: mean thickness. *Dashed line*: change in mean thickness from acute to chronic stages. Hi Eye, hypertropic eye; Lo Eye, hypotropic eye.



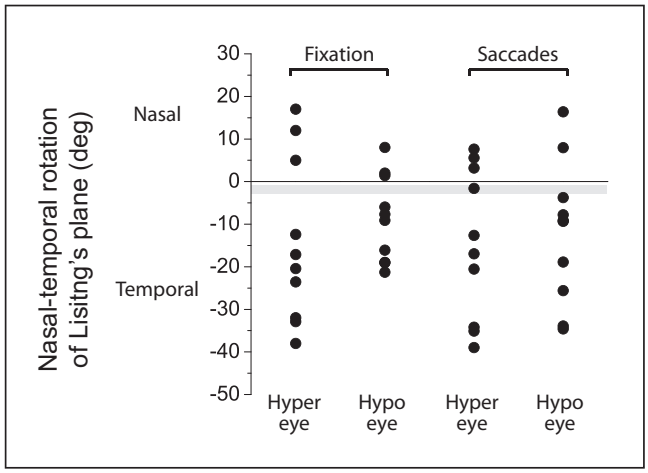


FIGURE 7. Abnormal horizontal (nasal–temporal) rotation of Listing's plane in chronic skew deviation during fixation and saccades. A wide variation of plane rotation was seen in both the hypertropic and hypotropic eyes during (**A**) hypertropic and (**B**) hypotropic eye viewing. Positive value indicates nasal rotation, whereas negative value indicates temporal rotation. (●) Individual data points for each patient. *Shaded area*: 95% CI in normal control eyes.

Violation of Donders' Law in Acute Skew Deviation

We asked whether the violation of Donders' law in acute skew deviation was a transient deviation, present only during and immediately after each saccade, or whether it was sustained. Donders' law might be violated if there was a mismatch of tonic (step) and phasic (pulse) components of motoneuron firing. Such a pulse–step mismatch would lead to transient violations of Donders' law during and after each saccade, but the violations should disappear in 0.6 to 0.8 seconds after the saccade was over.[28] However, we found that Donders' law remained violated more than 2.5 seconds after saccade offset, indicating that the violation of Donders' law was sustained.

Violation of Donders' law is a more drastic abnormality than the failure of Listing's law. Theoretically, almost any lesions in the oculomotor system could warp Listing's plane. That is, any lesion could disrupt the coordination that is required to keep eye-position vectors in a flat surface and limit the eyes to 2 degrees of freedom. But a failure of Donders' law means that the patients' eyes did not show one consistent angle of torsion in any given gaze direction; rather, they adopted an abnormally wide range of torsional angles. We found that the violation of Donders' law during straight-ahead and eccentric fixation arises primarily from torsional drifts, indicating that patients with acute skew deviation (without nystagmus) have unstable torsional gaze holding that is independent of their horizontal–vertical eye positions. Patients with cerebellar atrophy have been shown to exhibit torsional drifts, suggesting that the cerebellum is critically involved in maintaining the eyes in Listing's plane.[50] Failure of Donders' law during saccades suggests that, after an acute injury to the brain, eye position commands were altered such that the eyes' degrees of freedom expanded from 2 to 3. The mechanism for this expansion remains to be investigated.

Neural Pathway for the Implementation of Listing's Law

Our results indicate that an adaptive neural mechanism is responsible for the implementation of Listing's law. However, the brain circuits responsible for Listing's law have not been located. A major neural pathway underlying saccadic eye movements involves the superior colliculus,[51–53] which sends saccadic signals to the medium-lead burst neurons in the pontine paramedian reticular formation (PPRF) and the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF).[54,55] These burst neurons, in turn, project to the extraocular motoneurons, the final common pathway for all eye movements.[54,55] Electrical stimulation and three-dimensional recordings in alert monkeys have shown that the superior colliculus generates saccades that fit Listing's law.[56] Stimulation of the medium-lead burst neurons in the caudal PPRF and riMLF evokes abnormal saccades that violate Listing's law.[57] These findings suggest that the circuitry implementing Listing's law is downstream from the superior colliculus and upstream from the medium-lead burst neurons.

The caudal nucleus reticularis tegmenti pontis (cNRTP), which lies ventral to the rostral PPRF, receives inputs from the superior colliculus and projects to the dorsal vermis and caudal fastigial nucleus.[58,59] Inactivation of the cNRTP caused torsional errors, indicating that the cNRTP contributes to stabilization of Listing's plane against torsional errors of the saccadic system.[60] Torsional pulsion of vertical and horizontal saccades is observed in patients with lateral medullary infarction,[11] indicating that the lateral medulla participates in torsional control. Another center for 3-D eye control may be in the cerebellum[56]; the influence of NRTP on the 3-D control of eye movements may depend on its cerebellar projections.[61] In this study, we found that patients with acute skew deviation caused by disruption of the otolith–ocular reflex pathway violate Listing's law. This suggests that part of the otolith–ocular reflex pathway is an element of the neural circuit that enforces Listing's law. Based on our findings, we predict similar deficits in patients with skew deviation caused by peripheral vestibular lesions.

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APPENDIX

To quantify how well subjects obeyed Listing's law, we computed the best-fit function relating the eye's torsion, t, to its horizontal and vertical angles, h and v, in a three-parameter equation:

$$t = -hv/2 + a_1 + a_2 h \cdot a_3 v \quad (1)$$

We computed the parameters a_1 through a_3 that yielded the best fit to the data. Here, a_1 quantifies any torsional shift of primary position, and a_2 and a_3 quantify its vertical and horizontal rotations. This equation defined a surface of best fit to the eye position data. The SD of the separation of the data points from the surface was the Listing deviation.

To quantify adherence to Donders' law, we fitted a very flexible, curved surface to the same eye position data using a 15-parameter equation:

$$\begin{aligned} t = {} & a_1 + a_2 h + a_3 v + a_4 d_h + a_5 d_v + a_6 h^2 + a_7 hv \\ & + a_8 h d_h + a_9 h d_v + a_{10} v^2 + a_{11} v d_h \\ & + a_{12} v d_v + a_{13} {d_h}^2 + a_{14} d_h d_v + a_{15} {d_v}^2, \end{aligned} \quad (2)$$

where d_h is disconjugate horizontal eye position (i.e., the difference between the Helmholtz horizontal angles of the two eyes) and d_v is disconjugate vertical eye position. We called the standard deviation of the data points' separation from this surface the Donders' deviation, reasoning that, if the data could not be well fitted using a highly flexible surface with 15 parameters, they were likely not confined to any surface at all.