Acute Superior Oblique Palsy in Monkeys: I. Changes in Static Eye Alignment

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PURPOSE. To investigate immediate and long-term changes in static ocular alignment with acute acquired superior oblique palsy (SOP) in monkeys.

METHODS. The trochlear nerve was severed intracranially in two rhesus monkeys. After the surgery, the paretic eye was patched for 6 to 9 days, and then binocular viewing was allowed. Three-axis eye movements (horizontal, vertical, and torsional) were measured with binocular, dual search coils. Eye movements were recorded over a ±20° horizontal and vertical range of fixations before the lesion and then, beginning the first day after surgery. Changes in alignment with ±30° head tilt were also studied.

RESULTS. The main findings were (1) misalignment (10–12° vertical in adduction, down; 10–12° torsional in abduction, down); (2) changes in vertical deviation (VD) with head tilt (Δ 2–6° with left versus right 30° tilt); and (3) changes in comitance and VD over time. During the early postlesion period, before binocular viewing was allowed, VD decreased and comitance improved. Once binocular viewing was allowed, VD increased and comitance worsened.

CONCLUSIONS. Rhesus monkeys with induced SOP show a characteristic pattern of misalignment that helps define the ocular motor signature of acute denervation of the superior oblique muscle. The animals also showed striking changes over time in the amount and comitance of the vertical misalignment that depended on whether viewing was monocular or binocular, suggesting a role for proprioception in adaptation to misalignment with habitual monococular viewing. (Invest Ophthalmol Vis Sci. 2007;48:2602–2611) DOI:10.1167/iovs.06-1316

In humans with strabismus, vertical misalignment of the eyes, which is greater when the higher eye is in adduction, is commonly attributed to a palsy of the superior oblique muscle (SOP). In many patients, however, it is difficult to determine the cause based on a clinical examination alone. First, imaging of the orbit suggests that many patients who are thought to have congenital SOP do not have trochlear nerve palsy but rather an anatomic abnormality in the orbit that mimics SOP. Examples include anomalies of the superior oblique tendon and anomalous locations (heterotopy) of the orbital pulleys. Second, in patients thought to have acquired SOP due to a trochlear nerve lesion, there is considerable variability in the degree and pattern of the static deviations, both with the head upright and tilted. How much of this variability is due to different degrees of paresis of the trochlear nerve, to inherent variation in the anatomic configuration of the superior oblique muscle and its tendon in the orbit, to secondary changes in the lengths and mechanical properties of the palsied muscle and its antagonists, and to central adaptive processes is not known. Finally, there is considerable controversy about how to differentiate acquired SOP from decompensated congenital SOP (i.e., vertical strabismus that becomes symptomatic in adulthood but is thought to have a congenital basis). Usually, the clinical criteria such as the absolute size of the deviation, the degree and pattern of incomitance, the range of vertical fusion, and facial asymmetries do not consistently separate congenital and acquired SOP.

To provide a frame of reference for analyzing the clinical presentation of SOP in humans in both the acute and chronic stages we sought to define the raw, ocular motor signature of acute, acquired complete SOP, before centrally mediated adaptive mechanisms or mechanical alterations in the periphery associated with sustained misalignment of the eyes could supervene. We also aimed to determine the factors, including the presence of disparity cues, that influence the changes in alignment that occur over time after the initial lesion. In this first paper, we discuss the effects of acute SOP on static alignment, in the second paper the effects on saccadic dynamics, and in the third paper the effects on the torsional orientation of the eye in the orbit relative to Listing’s Law.

METHODS

General Experimental Procedure

Two female juvenile rhesus monkeys (M1 and M2) weighing from 4 to 6 kg were studied. Three-dimensional (3-D) eye movements were measured with the magnetic field search coil method. The protocol was approved by the Institutional Animal Care and Use Committee (IACUC) of the Johns Hopkins University and adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research. During the experiments, the monkey was seated in a primate chair with its head fixed to the frame of the chair. The chair was placed in the center of a cubic frame that generated three orthogonal magnetic fields of different frequencies (55.5, 83.3, and 42.6 kHz). The output signal of the coil system was filtered with a bandwidth of 0 to 90 Hz, sampled at 1000 Hz, and saved on computer for later analysis. Coil signals were calibrated by first zeroing the signal offsets with a test coil in the center of a metallic tube and then determining the relative gains of signals from each of the three fields separately. Offsets from coil connectors were minimized by shielding the connectors with a magnetic shield (MuMetal; MuShield Co., Inc., Londonderry, NH).
Surgical Procedures

All surgeries were performed in monkeys under anesthesia, in strict aseptic surroundings.27,28 A head plate was fixed on the skull with dental acrylic and small screws. Two eye coils made from Teflon-coated stainless steel wire were implanted in each eye. A directional coil of 14.5 to 15 mm in diameter was sutured on the sclera under the conjunctiva just in front of the insertion of the rectus muscles, and a torsional coil with a diameter of 7.5 to 8 mm was implanted super-temporally between the lateral and superior rectus muscles and centered on the equator of the globe. The coils were sutured to the sclera with several small sutures.

The superior oblique palsy (SOP) was induced by intracranial sectioning of the trochlear nerve with the monkey under gas anesthesia.29

Through a subtemporal approach, the cavernous sinus and the trochlear nerve were visualized, and the trochlear nerve was then severed, leaving a gap of approximately 10 mm. There was no damage to adjacent structures. After surgery, the animals were given an analgesic (buprenorphine, 0.01 mg/kg by intramuscular injection) for 24 hours but no other medications. The animals were vigorous and active the first day after surgery, eating and drinking well and showing no signs of sedation.

Experimental Protocol and Eye Movement Recording

Control recordings were obtained before surgery. A period of monocular viewing was also tested with the to-be-paretic eye (the left eye in M1, the right eye in M2) covered with an opaque acrylic patch attached to the head plate for 4 (M1) and 7 (M2) days. Then binocular viewing was allowed again. The effectiveness of the patch was verified by showing that the animal was unable to make saccades toward any of the targets used in our alignment paradigms when required to view with a patched eye. Immediately after the trochlear nerve surgery the paretic eye was patched for 6 days in the case of M1 and 9 days in M2, and binocular viewing was then allowed. Eye movements were recorded nearly daily for the first 2 weeks after the SOP, and then three to four times per week for the initial postlesion period of ~35 days.

Alignment was measured pre- and postlesion (straight ahead and to 20° horizontal and vertical eccentric positions) with one eye viewing (i.e., without disparity cues that might aid fusion), and with both eyes viewing unless an eye was habitually patched. The target was a square red light, 0.3° × 0.3°, rear projected onto a tangent screen 66 cm in front of the animal. It stepped randomly across a ±20° (horizontal and vertical) grid with a spacing of 5°. The target jumped after the position of the eye of the animal had been in the fixation window (4°) for 250 ms. Alignment was also measured during spontaneous eye movements made in the completely lit laboratory and during an additional paradigm for measuring vertical saccade dynamics, in which case 10 saccades of the same type were elicited beginning from and ending at the same vertical orbital position.

The response to head tilt was tested with the primate chair tilted 30° to either side within the stationary field coils. The target array was tilted by the same amount, so the eyes kept the same relative orientation in the orbit when the animal was upright.

Data Analysis

Data were analyzed using commercial software (MatLab, The MathWorks, Natick, MA). The position of each eye was described by showing that the animal was unable to make saccades toward any of the targets used in our alignment paradigms when required to view with a patched eye. Immediately after the trochlear nerve surgery the paretic eye was patched for 6 days in the case of M1 and 9 days in M2, and binocular viewing was then allowed. Eye movements were recorded nearly daily for the first 2 weeks after the SOP, and then three to four times per week for the initial postlesion period of ~35 days.

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Results

Eye Alignment Immediately after SOP

Figure 1 shows the alignment of the eyes with normal eye viewing (NEV) in both monkeys (M1 and M2) within several days after the lesion before any binocular viewing was permitted (the paretic eye was patched immediately after surgery when the trochlear nerve was severed). As indicated in the Methods section, the alignment after surgery was corrected for any change in alignment that appeared during prelesion patching. Adduction or abduction always refers to the relative position of the paretic eye (or the to-be-paretic eye) in the orbit; of course, when one eye is in adduction, the other is in abduction and vice versa.

The pattern of misalignment between the two eyes after the lesion was similar in the two animals. There was a VD, with the paretic eye higher, which was greatest with the paretic eye adducted and down. There was a TD with the paretic eye relatively extorted, which was greatest with the paretic eye abducted and down. There was also a horizontal deviation, consisting of an esodeviation (i.e., the eyes are relatively converged) that was greatest with the eyes in the down positions. In M1, the TD was slightly greater relative to the VD in the straight-ahead position. M2 also showed a change in torsion in the normal eye that was greater when the normal eye was in adduction (paretic eye in abduction). This animal, however, also showed some fluctuation in torsion of the viewing eye (and of the torsional phoria) during habitual monocular viewing before surgery.

Changes in Vertical Eye Alignment during Habitual Monocular Viewing after SOP

Figures 2A and 2B show the time course of the change in VD with the normal eye fixing. Adduction and down, straight ahead, and abduction and down refer to the part of the field where the paretic eye would be located with the normal, fixing eye in abduction and down 20°, straight ahead (0,0), and in adduction and down 20°, respectively. Also shown is the VD before the lesion and the transient changes in vertical phoria that were induced when the monkey had her to-be-paretic eye patched for several days before surgery. M1 had little change in phoria during prelesion patching (left-hand shaded areas). M2 had a small change in phoria during patching before the lesion.
but primarily for fixation in the straight-ahead position in which the to-be-paretic eye became ~2 to 3° higher than the normal eye. In the days after the SOP was created, but before binocular viewing was allowed (right-hand shaded areas), the degree and pattern of vertical misalignment changed. The degree of vertical misalignment lessened most when the paretic eye was in adduction and down gaze, where the VD was initially the largest (Figs. 2A, 2B, triangles), and less when the paretic eye was in abduction and down gaze, where the VD was relatively smaller (Figs. 2A, 2B, asterisks).

**Changes in Vertical Eye Alignment after Binocular Viewing Was Allowed**

Once binocular viewing was allowed, a different pattern of change in alignment emerged (Fig. 2, beyond the right-side shaded areas). The VD increased in both monkeys, especially with the paretic eye in the adducted positions. In M1 the change was relatively gradual, in M2 more abrupt. The deviation grew to the initial postlesion value and, in orbital positions in which the initial deviation was relatively small, exceeded it (e.g., Figs. 2A, 2B, with the eye abducted and down, asterisks).

**Changes in Torsional Eye Alignment with SOP**

Figures 2C and 2D show the time course of the TD in acute SOP. Before the lesion both animals had a small torsional phoria that showed some change while the to-be-paretic eye was patched (left-hand shaded areas). Immediately after the lesion both animals showed a relative extorsion of the paretic eye that was greatest in the abduction, down position (Figs. 2C, 2D, asterisks). Note that in M2 the change in torsional...

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**FIGURE 1.** Postlesion eye alignment with normal eye viewing before binocular viewing was allowed. Tilt angle of short lines with respect to vertical indicates torsion of the eye multiplied ×3. Clockwise indicates intorsion of the paretic eye or extorsion of the normal eye so that the difference in angle between the two lines reflects the cyclodeviation. ADD, paretic eye in adduction (normal eye in abduction); ABD, paretic eye in abduction (normal eye in adduction). Left: M1, 2 days after surgery; right: M2, 3 days after surgery. In each case, alignment was corrected for any misalignment induced during prelesion patching of the to-be-paretic eye for a nearly comparable period of monocular viewing. Note the slight increase in intorsion of the normal eye after surgery in M2. PE, covered paretic eye; NE, normal viewing eye.

**FIGURE 2.** Time course of the change in vertical deviation and torsional deviation with normal eye viewing before and within 30 days after surgery in M1 (A, C) and M2 (B, D). Shaded area: the paretic eye (or to-be-paretic eye) habitually patched. Positive deviation indicates that the paretic eye is relatively higher on extorted. Lesion was induced on day zero. ADD, paretic eye in adduction (normal eye in abduction); ABD, paretic eye in abduction (normal eye in adduction). Ex, extorsion; In, intorsion.
alignment appeared primarily in the abduction, down position, but when compared with the preslesion values when the to-be-paretic eye was patched (left-side shaded areas), there was also a small change in the straight-ahead and adduction, down positions. In contrast to the VD, there was no decrease in TD during the period of patching after surgery and only a limited increase in the deviation during the period after binocular viewing was allowed.

In Figure 3 we compare the changes in VD in the three adducted (paretic eye) positions over time and show the considerable increase in misalignment during the period after binocular viewing was allowed. We used fixation positions from the saccade dynamic paradigm (see the Methods section) to have a larger number of data points at each fixation so that we could also give a sense of variability of the VD. The small standard deviations indicate that the alignment measures were quite consistent.

We also examined the relationship of the changes in vertical and torsional alignment to changes in horizontal alignment. Figure 4 shows a comparison of the changes in alignment at the straight-ahead 0,0 position. Note that before surgery a slight exophoria developed in both animals when the to-be-paretic eye was patched. There was also some increase in vertical misalignment and fluctuation in torsional alignment. After the lesion under the patch, the exophoria was less than it was before surgery under the patch in M2 but there was little change in M1 in this position. After binocular viewing was allowed, in M1 a slight esophoria developed, and in M2, the exophoria disappeared. There was no relationship between the change in horizontal and either the vertical or torsional alignment.

**Changes in the Relationship of Misalignment to Orbital Position: Comitance**

We evaluated the comitance (i.e., the eye-position dependence, of the vertical and torsional deviations across both horizontal and vertical eye positions by measuring the rate of change of the deviation with orbital position (i.e., the gradient of the deviation). Figure 5 shows examples for the vertical (top) and torsional (bottom) deviations in M1 immediately after the lesion and toward the end of the initial period of habitual monocular viewing before binocular viewing was allowed. Note, for example, in the top panes (for the VDs), that the lengths of the two, perpendicular solid black lines arising from each fixation position (of the normal eye) are the same and both indicate the magnitude of the VD at that fixation point. They are oriented both horizontally and vertically so they can be used to illustrate the change in the size of the VD as a function of vertical or horizontal eye position, respectively. The gray lines with arrows approximate the gradients (slopes) of the deviations.

For the VD across horizontal positions, we compared the slopes of the gray horizontal lines with arrowheads that connected the vertical dark lines across the three horizontal eye positions at different elevations (from abduction to straight ahead to adduction, at up 20°, at 0°, and at down 20°). The slope was always calculated as the ratio between the change in the VD and the change in (horizontal or vertical) fixation position.
position (see the Methods section). For the VD across vertical positions we compared the slopes of the gray vertical lines that connected horizontal dark lines across the three vertical eye positions at different horizontal positions (from elevation to straight ahead to depression, at left 20°, at 0°, and at right 20°). As the connecting lines became more horizontal (across a given elevation) and more vertical (across a given azimuth), the slopes (gradient of comitance) became closer to zero indicating the deviation was less noncomitant.

During patching the patterns of change in comitance of the VDs were similar for both monkeys. Across the horizontal positions, the VDs became less incomitant (Fig. 6) while across the vertical positions there was little consistent change (not shown). After binocular viewing was allowed the VDs across the horizontal positions became more incomitant.

The comitance of the TD as a function of horizontal and vertical position was illustrated and quantified in the same way except the lengths of the horizontal and vertical lines arising from each fixation point reflect the TD. For the TDs (Fig. 6, bottom) there was no consistent change in comitance over time, during the patching period or after binocular viewing was allowed. There was, however, a difference between the two animals in the degree of incomitance for the TDs across the horizontal meridian. For example, in the abduction to center positions for down gaze, the slope for torsional comitance was 0.09 in M1 and 0.3 in M2. Conversely, in the adduction to center positions for down gaze the slope for torsional comitance was 0.18 in M1 and 0.08 in M2.

We also compared the primary VD (normal-eye viewing) with the secondary VD (paretic-eye viewing). As expected, for both monkeys the secondary deviation was always larger than the primary deviation because the deviation was noncomitant, that is, became greater when the paretic eye was rotated farther (which is the case with the paretic eye viewing) into its field of action. In the early period after binocular viewing was allowed, for the straight-ahead target location, the ratio: [(secondary VD − primary VD)/primary VD] was 0.19 in M1 and 0.63 in M2. The ratio was lower in M1 because the degree of incomitance across vertical positions was less (i.e., slopes in M1 were smaller across vertical positions).

**Binocular Versus Monocular Viewing: Phoria Versus Tropia**

After the patch was removed from the paretic eye, neither monkey could overcome the VD, with both eyes viewing in any position except perhaps the abduction, up position. In M1, early after the restoration of habitual both eyes viewing, over the ±20° visual field, the VD with both eyes viewing was only slightly less (by 0.6°-1.5°) than the VD with normal eye viewing. At the end of the first month after surgery, there was no change in the ability to fuse, with the difference between both eyes viewing and the normal eye viewing still being small (0.4–1.2°). In M2, who adopted the strategy of fixing with the paretic eye, there was little difference (0.7–0.8° decrease) in the VDs between monocular and binocular viewing except at the straight-ahead position (~1.6° decrease), though still well below that necessary to overcome the misalignment. At the end of the 30-day postlesion period, there was about the same degree of difference between monocular and binocular viewing (0.6–1.2°), though the absolute values of the VD had increased considerably. M2 did not appear to fuse in any position. We also compared alignment during binocular viewing between the monkey following the projected targets in an otherwise dark room and spontaneously viewing in the laboratory. The degree of misalignment was about the same, even

**Figure 5.** Comitance of the vertical (VD, A, B) and torsional (TD, C, D) deviations across horizontal and vertical positions for (M1) with normal eye viewing. Length of both of the two perpendicularly oriented thick black lines arising at each fixation point of the normal eye indicates the size of the vertical (A, B) and torsional (C, D) deviations. Thin gray lines with arrowheads show a qualitative approximation to the gradient of the deviation. Slopes were calculated directly from five fixation points at 5° intervals between 0° and 20° (shown in Fig. 6).
where the deviation was relatively small (e.g., in abduction positions, 1.7° in the dark versus 2.0° in the light in M1 and 3.0° vs. 3.3°, respectively, in M2).

Changes in Alignment with Head Tilt

Figure 7 shows the effects of head tilt on the VD. The first postlesion value showed an increase in the VD relative to that in the upright position with tilt toward the side of the SOP, but no change with tilt away from the side of the SOP. M1 showed an increase of ~2°, M2 ~6°. After habitual both eyes viewing was allowed the vertical misalignment with tilt toward the normal side (bottom lines) decreased. In M2, despite an overall increase in the VD of ~5° in the straight-ahead position with the head upright over time, the difference between the VD with the head tilted toward and away from the side of the SOP only changed by a small amount (Fig. 7, Table 1). In M1, however, there was a decrease in the deviation with head tilt toward the normal side just after binocular viewing was allowed (but well before any change in vertical misalignment in the upright position). There was, however, little change in the head-tilt response during the subsequent period of binocular viewing even though there was a slow increase in vertical misalignment in the upright position. In other words, there was a clear dissociation between changes in the VD with the head upright, and the pattern of change in the VD with head tilt.

Changes in the torsional and vertical deviations with head tilt are summarized in Table 1. The most striking finding, when comparing the effect of head tilt toward and away from the side of the lesion, is that M2 showed much larger changes in the VD with head tilt than did M1.

DISCUSSION

The first major goal of this study was to determine the signature of an acute, acquired superior oblique palsy (SOP) uncontaminated by the attempt of central adaptive mechanisms to restore ocular alignment and by any mechanical consequences of sustained ocular misalignment. The opportunity to quantify ocular misalignment in a human patient within a day or two of the onset of acquired SOP almost never arises, and theoretical considerations suggest that even within days the pattern of misalignment reflects more than just the loss of innervation to the superior oblique muscle. The second major goal was to follow the evolution of any changes in alignment over time—be it a decrease or an increase in misalignment—and infer possible mechanisms.

Comparison of Experimental Trochlear Nerve Palsy in Monkey with Acquired SOP in Humans

There is considerable variability in the magnitude and pattern (orbital position dependency and relative amount of torsional versus VD) of ocular misalignment in human SOP, even in patients who are known to have an anatomic abnormality of the superior oblique muscle (e.g., atrophy or absence of the muscle or absence of the tendon). Many factors may account for this variability: (1) different degrees of paresis, (2) inherent anatomic variation in the insertion of the superior oblique tendon on the globe, (3) the actions of central adaptive mechanisms, and (4) mechanical alterations in the periphery due to long-standing misalignment.

Graf et al. recently quantified the vertical and torsional deviations in multiple gaze positions of 10 patients with (left) acquired SOP, though there was an interval of at least one year between the onset of the palsy and the time of evaluation. Their values are summarized in Table 2 as are those from our monkeys but at 20° rather than 25° eccentricity. Although the overall pattern between our monkeys and their patients was similar, the maximum values for the deviations in humans were larger than the values for either monkey. Whether this difference is due to inherent differences in function of the superior oblique muscle, to the mechanical effects of a sustained ocular deviation, or to the effects of central adaptive mechanisms that increase, seemingly paradoxically,
the deviation, remains to be shown. In contrast, modeling studies of SOP (e.g., Robinson 18), suggest that a raw acute paralytic SOP in humans would produce a relatively small VD, to a maximum of only $\theta_1 = 10^\circ$ in the straight-ahead position. The values in both of our monkeys for acute SOP were larger, suggesting that there may be a different reciprocal innervation relationship, with a greater innervation to both agonist and antagonist, than is commonly assumed (Quaia et al., manuscript in preparation).

**Difference in SOP between Monkeys**

The general pattern of misalignment created by the SOP was similar in the two animals, though there were a few quantitative differences. The absolute values of the deviations were different, but there was also a dissociation between the relative amounts of torsion versus vertical misalignment. M1 had a relatively smaller VD and M2 a relatively smaller TD. One cause may be the variability (up to $50^\circ$ in humans) in the angle that the superior oblique tendon makes with the sagittal plane, which could lead to relatively more or less torsion versus vertical rotation. M2 also had a change in the torsional orientation of the normal eye. Whether this was in response to the palsy per se or was related to inherent fluctuation in torsion that was also seen before surgery during monocular viewing is unsettled.

**Effects of Monocular Occlusion**

Another cause of variability between monkeys could be a difference in the effects of prolonged monocular viewing, which produces idiosyncratic changes in alignment in both humans and monkeys. Even taking into account the changes in alignment that were associated with patching before surgery, there were still quantitative differences between the two animals in the misalignment produced by severing the trochlear nerve.

**Comitance: Ocular Misalignment as a Function of the Position of the Eye in the Orbit**

A sine qua non of acute paralytic strabismus is that the degree of misalignment worsens when the globe rotates farther in the direction of action of the involved muscle. The rate of change of the deviation with the change in the position of the eye in the orbit, as quantified by a gradient (or slope), is a function of how much that particular muscle contributes to the static forces that hold the eye in that particular position. The gradients for the VD were quantitatively similar in both monkeys though there were small differences in the absolute values of gradients for TDs between the two monkeys, especially across horizontal positions. Perhaps in this case an inherent difference in the angle at which the superior oblique tendon attaches to the globe is responsible for the different gradients across horizontal positions, as was previously suggested for the difference in the ratio of the torsional to the vertical deviation between the two monkeys.

**Changes in Alignment over Time**

A striking finding in both animals was the change in vertical alignment over time. During the immediate postlesion period, when the paretic eye of the monkey was habitually patched, both animals showed a clear *lessening* of vertical misalignment that was greatest in the adduction and down position. Comitance also changed over time. The VD became more comitant but only across the horizontal not the vertical meridians. In contrast, the TD changed much less over time.

The decrease in ocular misalignment during the postlesion patching period was a surprising finding, though there may be a precedent. Viirre et al., using an experimental recession of the horizontal recti in monkeys, studied monocular adaptation of saccades and noted that two of their monkeys, who had their surgical eye patched, showed no ocular misalignment when measured between 4 and 7 days after surgery. It may be that these animals showed a phenomenon—a decrease in

### Table 1. Vertical Deviation and PE Torsion Difference with 30° Head Tilt

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<thead>
<tr>
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<th>Before BEV</th>
<th>After BEV</th>
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<tr>
<td>M1 Day postlesion</td>
<td>5</td>
<td>6° 8° 16° 27° 35°</td>
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<tr>
<td>VDD(NEV)</td>
<td>1.2° 2.5° 4.2° 2.9° 2.8° 2.3°</td>
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<tr>
<td>PETD(PEV)</td>
<td>1.5° 4.1° 3.8° 6.3° 7.7°</td>
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<tr>
<td>M2 Day postlesion</td>
<td>6</td>
<td>9° 25° 35°</td>
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<tr>
<td>VDD(NEV)</td>
<td>6.3° 7.6° 5.5° 6.5°</td>
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<tr>
<td>PETD(PEV)</td>
<td>8.5° 9.0° 7.8°</td>
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VDD, vertical deviation difference with head tilt (tilt to paretic eye minus tilt to normal eye); PETD, paretic eye torsion difference with head tilt (tilt to PE side minus tilt to NE side) relative to prelesion values. See Methods for this calculation; NEV, normal eye viewing; PEV, paretic eye viewing; BEV, both eyes viewing.

* Data taken about 1 to 2 hours after the initial postlesion period of binocular viewing.
misalignment during monocular viewing—similar to our findings.

In our monkeys, after binocular viewing was restored, vertical misalignment changed again but now with a clear increase, though at somewhat different rates in the two animals and in different orbital positions. The deviation again became more noncomitant, with an increase in the gradient for the VDs across the horizontal meridian. Vertical misalignment increased even in the abducting, down position in which there had been only a small decrease in vertical misalignment during the immediate postlesion period of patching. In contrast, after binocular viewing was restored, there was little change in the amplitude and gradients of torsional misalignment.

A Role for Ocular Proprioception in Lessening Ocular Misalignment?

How do we explain the surprising pattern of changes in vertical and torsional misalignment over time? First, why was there a striking improvement in vertical alignment (both in absolute value of the deviation and in the degree of comitance) in the first several days after the creation of the SOP when the paretic eye of the monkey was habitually patched? One possibility is that orbital proprioception provides the error information to produce this type of disconjugate adaptive change in eye alignment.

Although there is considerable controversy about the role(s) for ocular proprioception in localization of targets and control of eye movements, it has been suggested that proprioceptive signals are used for adjusting static eye alignment. The mechanism is unclear, though a unifying hypothesis is that proprioception provides veridical information about the position of the eye in the orbit during fixation. This information would be useful for calibrating central motor commands according to the needs dictated by the normal properties (or acquired abnormalities) of the ocular motor plant.

Previously, Lewis et al. studied monkeys who had artificially induced, vertical paralytic strabismus followed months later by a first division, trigeminal nerve deafferentation to eliminate orbital proprioception. After the proprioceptive lesion, the animals were deprived of binocular disparity cues by patching of the deafferented eye. They developed a slow increase in the amount of vertical misalignment and in the degree of noncomitance of vertical alignment during prolonged monocular viewing after the proprioceptive lesion. This pattern was in essence the reverse of our finding during the period of patching immediately after the lesion and similar to our observation when binocular viewing was restored.

Lewis et al. hypothesized that one of the error signals that drove adaptation of eye alignment was a mismatch between afferent information about the position of the eye in the orbit and an internal estimate of eye position based on an efferent copy signal of the innervation to the eye muscles. In the absence of proprioceptive information, adaptive mechanisms would no longer be able to detect the mismatch between these two signals, and hence some degree of adaptive calibration could be lost, leading to the reemergence or exacerbation of a static misalignment. This interpretation is compatible with our findings that during the initial period of monocular viewing after the SOP the static vertical misalignment improved (due to a proprioceptive-driven adaptive mechanism) and became more comitant.

One might ask why torsional (and horizontal) misalignment did not change over time in a similar way. One may speculate that the proprioceptive mechanism is primarily concerned with foveal misalignment (and does not apply to torsional misalignment) and that it is more important for vertical than for horizontal misalignment because of the inherent limitations of vertical vergence to overcome any but the smallest degree of vertical ocular misalignment. There is evidence that proprioception plays a more important role in the vertical than in the horizontal eye muscle systems.

Worsening of Ocular Misalignment when Binocular Viewing Was Allowed

Less easily explained is why static misalignment worsened and incomitance increased once binocular viewing was restored. One explanation is that it reflects an adaptive strategy for coping with diplopia and visual confusion by driving one of the doubled images farther into the periphery, so that it can be more easily neglected. This explanation has also been invoked to explain a paradoxical head tilt in SOP, which is when a patient habitually tilts the head toward the side of the affected eye to increase the VD. Although our monkeys showed little ability to fuse their deviation in any but the most extreme abducted, elevated eye positions, we did not observe any habitual head tilt, even when they were moving spontaneously in their home cages.

It may also be that during binocular viewing proprioceptive error signals are less effective or ignored. There is evidence of gating of ocular proprioception by the presence or absence of vision in the ocular motor as well as in other motor systems. Such ideas demand testing under carefully controlled viewing conditions.

Of course, the increase in the VD may not be purposeful. Rather, mechanical factors related to the sustained deviation of the eye in a new position may supervene to change the mechanical properties of the denervated and lengthened SOM, and possibly the other vertical muscles in that eye. Contracture of the superior rectus muscle and overacting of the vertical rectus and inferior oblique muscles have been invoked to explain these unexpected changes in alignment, but there is little solid supporting evidence for these mechanisms. Our data argue against a mechanical explanation for the worsening of alignment. First, once habitual binocular viewing was allowed, the increase in misalignment was

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**TABLE 2. Comparison of Vertical and Torsional Deviations between Humans and Monkeys**

<table>
<thead>
<tr>
<th></th>
<th>Straight ahead</th>
<th>Adduction and Down</th>
<th>Abduction and Down</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VD</td>
<td>TD</td>
<td>TD/VD</td>
</tr>
<tr>
<td>Human</td>
<td>4 (10)</td>
<td>5 (13)</td>
<td>1.25</td>
</tr>
<tr>
<td>M1</td>
<td>5.23</td>
<td>4.28</td>
<td>0.82</td>
</tr>
<tr>
<td>M2</td>
<td>7.95</td>
<td>1.41</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data are in degrees and are from humans (Graf et al.) and from M1 at day 2 and M2 at day 3 after surgery. Abduction and adduction refer to the position of the paretic eye in the orbit. For the human data, median values are shown with the maximum values in parentheses. The deviations for the monkey are corrected for the phoria values during the prelesion patching period.
relatively rapid, beginning within days. Second, the two monkeys showed different rates for the increase in the VD. Third, the changes in VD were independent of changes in the TD. Whether this dissociation between torsional and vertical alignment is related to central innervation factors or to secondary changes in the location of orbital ‘pulleys’ remains to be shown.5,6 One final factor is that M2 opted to fix with the paretic eye. This strategy could have contributed to the initial abrupt increase in misalignment after binocular viewing was allowed.

Regardless of mechanism, the overall changes in the pattern of ocular misalignment, both in the immediate postlesion period of monocular viewing, and after habitual binocular viewing was allowed, were striking and qualitatively similar for both monkeys.

Bielschowsky Head Tilt Test

A time-honored feature of SOP is a positive Bielschowsky head tilt test. The VD increases when the head is tilted toward the side of the lesion and diminishes when the head is tilted away from the side of the lesion. The usual explanation is that with head tilt, an ocular counterroll is induced due to otolith stimulation, requiring an intorsion of the lower eye during head tilt. In the absence of contraction of one of the intorting muscles, in this case the superior oblique, the elevating action of the other intorting muscle, the superior rectus, is no longer counterbalanced by the depressing action of the superior oblique muscle. This imbalance leads to decreased torsion and increased elevation of the paretic eye when it is tilted toward the side of the lesion.5,67

In our animals, there was a difference in the response to head tilt, being much smaller in M1 than in M2. In both monkeys there was no correlation between changes in the pattern of the head tilt response and changes in the magnitude of the vertical misalignment during viewing in the straight-ahead position. This dissociation suggests that the mechanism of increasing vertical misalignment with the head upright is neither related to, nor causes, the relative change in the response to head tilt to the side of the normal and to the paretic eye.

The changes in the VD with head tilt (+45°) have recently been reported in a series of 10 patients with (left) acquired SOP.7 The values for our monkeys fall within the range of values reported by Graf et al.,7 though in their study there were many subjects with much larger head tilt responses than in our monkeys. Why human beings appear to show such striking increases in the head tilt responses over time has long been debated. Changes in the actions of other vertical muscles6,15,17,18 and inherent variability and adaptation of static otolith-ocular reflexes7,19,58,93 have been invoked to explain the large range of values for the changes in the ocular deviation with head tilt.

In sum, we have described the ocular motor signature of acute, acquired SOP in monkeys with its characteristic pattern of changes in 3-D alignment, including variation in amplitude and the comitance of the deviation. We have shown striking early changes in vertical misalignment. When initial viewing is monocular, misalignment lessens and when binocular viewing is allowed, misalignment worsens. One implication of these findings is that manipulating viewing conditions in patients immediately after the onset of acquired strabismus or after corrective strabismus surgery may be of therapeutic benefit.

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References


