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Ocular Motor Behavior in Macaques With Surgical Exotropia

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Economides JR, Adams DL, Jocson CM, Horton JC. Ocular motor behavior in macaques with surgical exotropia. *J Neurophysiol* 98: 3411–3422, 2007. First published October 10, 2007; doi:10.1152/jn.00839.2007. To provide an animal model of human exotropia, a free tenotomy of the medial recti was performed in two infant macaques. When the animals were old enough to record eye movements with video eye trackers, we measured their ductions, ocular alignment, comitance, smooth pursuit, fixation preference, and gaze stability. Partial recovery of adduction occurred in each monkey from spontaneous re-attachment of the medial rectus muscle to the eye. However, each animal was left with a relatively comitant, large angle exotropia. The magnitude of the exotropia was not affected by covering one eye. There was no dissociated vertical deviation or any significant "A" or "V" pattern to the horizontal misalignment. Smooth pursuit was more accurate when tracking nasally compared with temporally in both animals. Compensatory catch-up saccades in the tracking eye were always accompanied by conjugate movements in the deviated eye. Despite tenotomy of the medial recti, the velocity of adducting saccades was normal. Both monkeys alternated fixation, preferring to use the left eye for targets on the left side and the right eye for targets on the right. Each animal was capable of switching fixation while making accurate saccades. One of the monkeys developed a vertical pendular nystagmus, which was most prominent in the deviated eye. Macaques with ocular misalignment from medial rectus tenotomy exhibit features that are present in humans with alternating exotropia. These animals will be valuable for probing the cortical mechanisms that underlie visual suppression in strabismus.

INTRODUCTION

Despite the rich literature describing the clinical features of strabismus in humans (von Noorden and Campos 2002), relatively little is known about the abnormalities in cortical function that occur in this disease. To address this issue, strabismus has been modeled in non-human primates to exploit the powerful array of experimental techniques available for animal research. The standard approach has been to disrupt fusion in young animals during the critical period for binocular vision to prevent the development of stereopsis (Kiorpes and Movshon 1990). The earliest animal model relied on a surgical approach: cutting the medial rectus muscle in one eye to produce exotropia (Hubel and Wiesel 1965). Subsequent investigators have performed surgery on multiple muscles using a combination of recession, resection, and extirpation to induce ocular misalignment (Baker et al. 1974; Crawford and von Noorden 1979; Harwerth et al. 1983; Kiorpes and Boothe 1980; Kiorpes et al. 1996; Von Noorden and Dowling 1970).

Strabismus has been created in monkeys using other experimental interventions. The visual axes can be dissociated by placing a prism of sufficient power before each eye to prevent fusion (Crawford and von Noorden 1980; Crawford et al. 1996; Harwerth et al. 1983; Mori et al. 2002; Smith et al. 1997; Wong et al. 2003). Another approach employs complete occlusion of one eye. To avoid amblyopia, the occlusion is alternated between the eyes, usually on a daily basis (Das et al. 2005; Tychsen and Burkhalter 1997; Tychsen and Scott 2003; Wong et al. 2005). Bilateral eyelid suture for a period of several weeks during the critical period also causes strabismus (Mustari et al. 2001; Tusa et al. 2001, 2002). Finally, strabismus can be produced by injection of botulinum toxin to weaken temporarily individual eye muscles (Kiorpes 1992; Kiorpes et al. 1996).

To decide which animal models mimic human strabismus most faithfully, it would be valuable to compare their clinical features. Although eye muscle surgery was the first technique used to create strabismus in animals, no prior study has provided a quantitative description of the eye movements, alignment, and fixation behavior present in monkeys with surgically induced exotropia. Using noninvasive binocular eye tracking, we provide here a detailed account of the oculomotor capabilities of monkeys reared with divergent exotropia following early bilateral medial rectus muscle tenotomy.

METHODS

Animals

Two male macaques (*Macaca mulatta*) were used in these experiments. Both animals were born at the California National Primate Research Center, Davis, CA. At age 4 wk, we performed a tenotomy of the medial rectus muscle in each eye under anesthesia with ketamine HCl (10 mg/kg im). Afterward, the infants were reared normally with their mothers and then pair-housed.

As juveniles, the monkeys were transported to the University of California, San Francisco. After they were trained to sit in a primate chair, a titanium post was attached to the frontal bone (Adams et al. 2007). The implant surgery was performed in *monkey 1* at age 3 yr, 2 mo and in *monkey 2* at age 2 yr, 5 mo. The surgery was performed under general anesthesia induced by ketamine HCl (10 mg/kg im) and maintained by isoflurane (1.5% in a 1:1 mixture of N_2O:O_2). Postoperative analgesia was administered for 48 h, and the monkeys were allowed to recover for 1–2 wk prior to resumption of training. All procedures were approved by the Institutional Animal Care and Use Committee at UC Davis and UC San Francisco.

Retinoscopy was performed in each monkey under light anesthesia with ketamine HCl at age 4 yr. Cycloplegia was achieved with 1% cyclopentolate HCl. The refraction in *monkey 1* was –3.75 sphere in each eye, and the refraction in *monkey 2* was – 4.00 sphere in each eye. Experiments were conducted without refractive correction. The ocular fundi were normal in each animal, as ascertained by indirect ophthalmoscopy.

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Video eye tracking and stimulus presentation

The monkeys' eye movements were recorded while head-restrained in a primate chair (Crist Instrument, Hagerstown, MD). A tangent screen subtending ±45° horizontally and vertically was placed 57 cm in front of the monkey. Computer-controlled stimuli (Cambridge Research Systems, Rochester, UK) were rear-projected onto the tangent screen by a digital light projector (Hewlett Packard, Palo Alto, CA) with a 60 Hz refresh rate. Although the episcleral search coil technique has greater precision and range, a video system was used to record eye movements. A noninvasive system was chosen to avoid any potential restriction of eye movements or change in eye position that might occur from implantation of an episcleral coil. The risk of disturbing eye position with a coil may be greater in animals with strabismus because they lack a normal, compensatory fusional drive. Eye movements were monitored at 60 Hz using two infrared video eye tracking cameras (SensoMotoric Instruments, Teltow, Germany). The cameras were mounted overhead, and an infrared dichromatic interference filter ("hot mirror") was oriented at 45° to acquire video images of the animals' eyes without encumbering their view of the tangent screen. Infrared illumination was provided by a tightly clustered array of 32 light-emitting diodes with a spectral peak at 940 nm. The cameras and infrared light source were invisible to the monkeys. Analog voltages were generated to represent the position of each eye and the location of visual stimuli on the tangent screen. These voltages were recorded digitally at 120 Hz for off-line analysis by a Power1401 data acquisition and control system (Cambridge Electronics Design, Cambridge, UK). For calibration, the gain and offset were adjusted on-line to match eye and target locations while the monkey tracked a spot moving sinusoidally, first horizontally and then vertically. This procedure was carried out for each eye while the other eye was covered. The monkey was rewarded for accurate fixation within an adjustable window (usually set between 2° × 2° and 5° × 5°). When a time criterion for fixation was satisfied, 0.5 ml of a slurry composed of primate biscuit powder, fresh fruit, and juice was delivered. The animals received all their food during experiments; water was available ad lib in the home cage.

The performance of each eye tracker was defined operationally by having two normal human subjects binocularly track a 0.25° target moving horizontally at 10°/s between ±25° for 50 cycles. For this analysis, data near the two points where the eyes reversed direction were not included, because subjects varied slightly from trial to trial in their choice of turn around point. The SD of each time point was calculated ($n = 50$). These values were then averaged over nearly 1,200 time points (10 s/cycle × 120 Hz sampling rate – turn around points) to yield a mean SD. In *subject 1,* the mean SD was 0.44° for the right eye and 0.43° for the left eye. In *subject 2,* the mean SD was 0.51° for the right eye and 0.46° for the left eye. The eye trackers were also tested in a single normal macaque performing exactly the same task. This trained monkey was lent by the Lisberger lab. The mean SD was 0.77° for the right eye and 0.74° for the left eye.

Performance while tracking a target moving at constant velocity is usually judged by measuring the gain of smooth pursuit (eye velocity/target velocity). This approach was not optimal for interpreting the video eye tracker data obtained in our strabismic monkeys. Both animals had deficient gain, at least during one direction of pursuit, which they compensated for by making frequent catch-up saccades. Position traces recorded by the trackers showed considerable fluctuation, due to a combination of instrument noise and catch-up saccades. Unfortunately, the instrument noise contributed by the video eye trackers often overlapped in magnitude with the catch-up saccades made by the monkeys. The resulting eye velocity traces were noisy. A filter could have been applied to the position traces to reduce the noise, but the choice of filter would have strongly influenced the value of eye velocity.

As an alternative, to measure tracking performance, we measured the mean SD of eye position on repeated cycles of constant velocity horizontal smooth pursuit. This statistical measure of variability provided an indirect index of smooth pursuit quality because a major source of variability was catch-up saccades, which are larger and more frequent during low gain pursuit. This approach required no arbitrary judgment about which oscillations in the position traces constituted noise versus catch-up saccades.

Data analysis

Eye and stimulus positions were analyzed off-line using Igor Pro software (Wavemetrics, Lake Oswego, OR). A running median filter was applied to the position traces to remove segments where accurate eye tracking was interrupted due to blinks or loss of the corneal light reflex. Positive values in degrees represent right gaze for horizontal positions and upgaze for vertical positions. Horizontal deviation is defined as the difference between right eye position and left eye position, resulting in a positive value for an exodeviation.

When displaying stimuli on a tangent screen, there is a discrepancy between the actual gaze angle and the distance measured on the screen from the central gaze point. For experiments involving gaze angles >30° in the fixating eye, data points collected at all eccentricities for eye and stimulus position were corrected post hoc for this source of error. The correction was: $\Delta\theta = \theta_{\text{intended}} - \arctan x/d$, where x = distance on the tangent screen from center gaze position to stimulus position, d = distance from eye to center gaze position on the tangent screen. This correction flattened the peaks on position plots during periodic smooth pursuit.

RESULTS

Range of ductions

Figure 1 shows each monkey looking at a toy presented in the far left or right peripheral visual field. Abduction of each eye appeared normal but adduction was limited, due to the medial

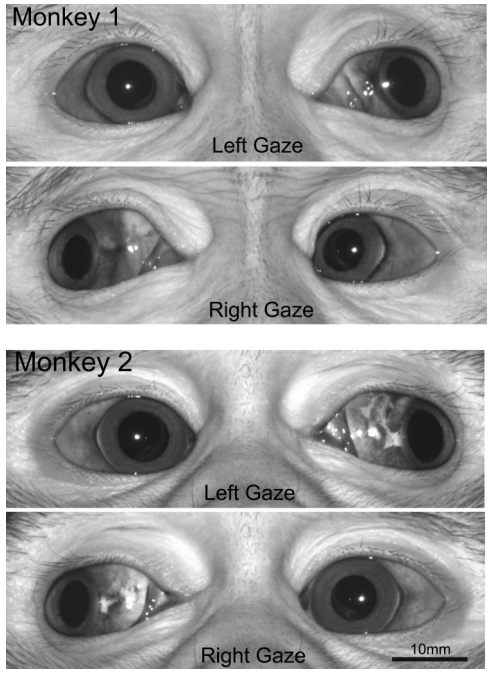

FIG. 1. Horizontal versions after medial rectus tenotomy. *Monkey 1* had nearly full adduction in the left eye but limited adduction in the right eye. Despite this asymmetry, abduction was normal and equal in each eye. *Monkey 2* had symmetric, limited adduction in both eyes. Abduction was normal. Apart from strabismus, the only clinical sign left from the medial rectus surgery is the irregular clumping of pigment cells within the nasal conjunctiva of each eye.

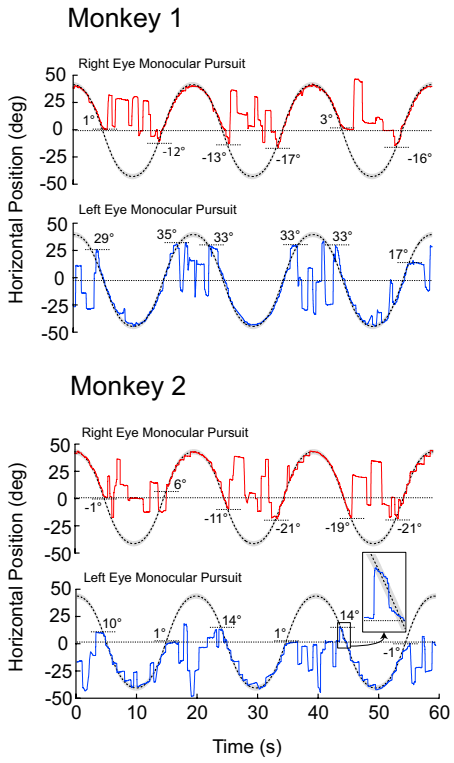

FIG. 2. Monocular range of motion. Ductions evoked by tracking a target moving sinusoidally (0.58 Hz, 15.7°/s peak velocity) in the horizontal plane, while the other eye was covered. *Monkey 1* had better adduction in the left eye than the right eye. *Monkey 2* had poor adduction in both eyes. In general, the monkeys showed a greater range of adduction when saccading to a temporally moving target (*inset*) than when pursuing a nasally moving target. When the target was located outside an eye's range, the monkey made free-viewing saccades. Dashed line, target position; shading, reward window (±2.5°); red, right eye; blue, left eye.

rectus tenotomy performed years earlier. In *monkey 1,* adduction was asymmetric with a better range in the left eye. In *monkey 2,* the eyes had fairly symmetric impairment of adduction. Each monkey was able to fixate and follow 0.25–0.50° targets accurately with each eye, implying relatively symmetric acuity.

To quantify the limitation in adduction we recorded smooth pursuit in both monkeys. With one eye occluded, each monkey tracked a target moving sinusoidally from 43° left to 43° right of center at a mean velocity of 10°/s. Figure 2 shows traces from both monkeys illustrating trials in which they displayed maximum adduction. *Monkey 1* adducted up to −17° with his right eye and up to 35° with his left eye. *Monkey 2* adducted up to −21° with his right eye and up to 14° with his left eye. These recordings confirmed the result documented by photography, namely, that the medial rectus tenotomy produced different results in the two monkeys. In *monkey 1,* the effect on adduction was quite asymmetric, causing a more severe deficit in the right eye. In *monkey 2,* the deficit was closer to equal, being only slightly more pronounced in the left eye.

The traces in Fig. 2 were selected because they illustrate examples of trials in which the monkeys maximally adducted their eyes. On typical monocular trials their performance was poorer. With his right eye, *monkey 1* abandoned smooth pursuit of a nasally moving target at a mean of 2.6 ± 8.2° ($n = 92$ trials), a position that fell short of the midline, although he was capable of tracking to −13°. When the target moved back in the temporal direction, he made a saccade, encountering it significantly earlier, at a mean of −5.8 ± 6.7° ($P < 0.01$ Wilcoxon sign rank). With the left eye, a nasally moving target was tracked to a mean position of 23.6 ± 8.4° ($n = 50$ trials), although the monkey could reach 35°. He made saccades to the target when it was moving temporally at 26.3 ± 5.9°. In the left eye, the difference in adduction range between smooth pursuit and saccades was not significant ($P = 0.17$).

With his right eye, *monkey 2* used smooth pursuit to track a target nasally to −5.4 ± 9.1° and used saccades to acquire targets moving temporally at −14.3 ± 7.0° despite his maximum range being −21°. With his left eye, he tracked a target nasally to 1.7 ± 8.5° and saccaded to a target moving temporally at 7.1 ± 9.2° with a maximum range of 14°. In each eye, this difference in adduction between smooth pursuit and saccades was significant ($n = 50$ trials, $P < 0.01$). To summarize: both monkeys tended to adduct their eyes further when using a saccade to meet an approaching, temporally moving target (Fig. 2, *inset*), than when using smooth pursuit to follow a departing, nasally moving target. The left eye of *monkey 1,* which had the smallest adduction deficit, showed the smallest difference between the nasal ductions measured with a target moving nasally versus temporally. This finding implies that a significant difference in the maximum range of ocular excursions for saccades versus smooth pursuit occurs only when an eye's movement is substantially reduced by recession of an extraocular muscle.

Spontaneous re-attachment of muscles to the eye

Immediately after surgery, photographs taken of each monkey documented an exotropia measuring 40–50° and loss of the ability to adduct each eye. The deviation diminished over several months, eventually stabilizing at the magnitude recorded when the monkeys were several years old. Despite free tenotomy of the medial recti, both eyes of both monkeys recovered a surprising capacity to adduct (Fig. 2). This finding suggested that the medial recti partially regained function after surgery, perhaps by tendon re-insertion into the globe.

To investigate this possibility, an axial computed tomographic (CT) scan was performed in *monkey 2* at age 44 mo (Fig. 3). The medial recti were connected to the globes at a site that was close to their normal anatomical insertion.

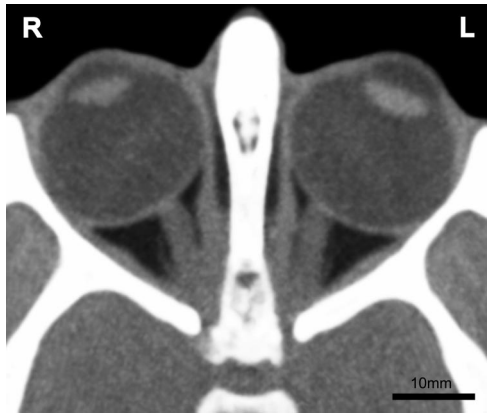

FIG. 3. Re-attachment of medial rectus muscles after tenotomy. Axial CT scan performed in *monkey 2* at age 44 mo showing that the medial rectus mucles have re-inserted into the globe after detachment at age 1 mo.

Spontaneous re-insertion of the medial recti was confirmed histologically in a monkey that underwent a tenotomy of the medial recti at age 10 days. During surgery, the intermuscular septum was dissected posteriorly as far as possible to allow the muscle to retract maximally. A month after surgery an exotropia of 30° was documented photographically. At age 46 mo, the exotropia had diminished to 5° in primary gaze. Unfortunately, this animal suffered from chronic nonbacterial enteritis, which made him unsuitable for awake, behaving recording experiments. After he was killed, both orbits were exenterated for histological examination. Figure 4 shows a horizontal section through the right orbit. The tendon of the medial rectus muscle was inserted into the globe at the normal site, ~5 mm from the limbus.

Binocular smooth pursuit

The magnitude of the exotropia was measured in each monkey by recording simultaneously the movements of both eyes. The eye used for fixation by each monkey depended on the location of targets in the visual field. Figure 5 shows the monkeys with both eyes open binocularly tracking a target moving horizontally back and forth ±40° at nearly constant velocity. They spontaneously switched fixation by making a saccade in a direction opposite to the movement of the target during smooth pursuit. Because both monkeys had impaired adduction, they tended to use the right eye to track the target on the right side of the tangent screen and the left eye to view the target on the left.

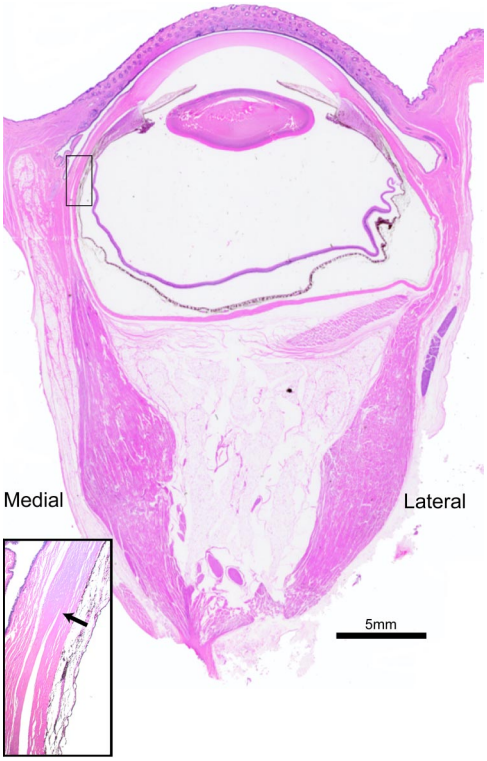

FIG. 4. Histological verification of eye muscle re-attachment. A 10-μm paraffin section stained with hematoxylin and eosin showing the right orbital contents of *monkey 3* at age 4 yr; this monkey underwent bilateral tenotomy of the medial recti 10 days after birth. The tendon of the medial rectus muscle appears inserted into the globe in its normal location, 5 mm from the limbus. *Inset*: magnified view of the medial rectus insertion; ←, actual point of contact between tendon and sclera.

When pursuing to the left, *monkey 1* switched tracking from the right eye to the left eye when the target was between 30 and 15°. He usually made two saccades to acquire the target. When pursuing to the right, he switched from the left eye to the right eye at target positions between −5 and 10°. His saccades were usually a few degrees hypometric, and he simply waited for the target before starting to pursue. The asymmetry in switch points reflected the fact that *monkey 1* could saccade further nasally with the left eye than the right eye to meet approaching targets, as mentioned earlier in the description of his ductions (means: −5.8° right eye, 26.3° left eye). *Monkey 2,* in contrast, had a symmetrical eye switch point at target positions between −10 and 10° under binocular conditions (Fig. 5). This symmetry was due to the nearly equal range of nasal saccades in each eye of *monkey 2* (means: −14.3° right eye, 7.1° left eye). *Monkey 2* also made more accurate saccades than *monkey 1* to switch fixation.

Looking at the traces in Fig. 5, it is evident that variation occurred from trial to trial in the position of each eye during horizontal tracking. To quantify this variation, the SD of each eye's position was calculated for each time bin. The traces were blocked into four pursuit epochs: right eye tracking temporally or nasally, and left eye tracking temporally or nasally. For each epoch, the SDs in eye position for individual time bins (8.33 ms) were averaged to derive a mean SD. For some epochs, there was no difference between the eyes' mean SDs, indicating that the tracking eye and the deviated eye fluctuated in position with each cycle the same amount. For other epochs, the mean SD in position was significantly greater for the deviated eye compared with the tracking eye ($P < 0.01$, unpaired *t*-test, Welch's correction). The tracking eye never showed greater variability in position than the deviated eye for any given epoch.

In both monkeys, the eye engaged in smooth pursuit always had a smaller mean SD in position on repeated trials while moving nasally compared with temporally ($P < 0.01$; Fig. 5). Better performance while tracking nasally may seem surprising, given that the medial recti underwent surgical tenotomy. However, one must bear in mind that the monkeys were free to switch fixation well before their eyes reached their limit of adduction. When the monkeys were required under monocular conditions to track nasally as far as possible, their performance did deteriorate as they reached the limit of their range.

Each monkey showed a difference in accuracy of smooth pursuit between the eyes. In *monkey 1,* the mean SD in position was 0.77° while tracking with the right eye and 1.16° while tracking with the left eye ($P < 0.01$) despite the fact that the monkey preferred to use his left eye for most gaze positions. In *monkey 2,* the mean SD in position was 0.80° while tracking with the right eye and 1.70° while tracking with the left eye ($P < 0.01$). Because of this difference in tracking performance, an eye could sometimes vary more in position while tracking a target than while deviated, over a given range. For example, *monkey 2*'s left eye had a mean SD in position of 0.75° while moving to the left with the right eye engaged in pursuit, whereas the mean SD in position was 2.11° when the left eye tracked over the same gaze angle (Fig. 5). This phenomenon shows that the movement of the deviated eye is limited by the performance of the tracking eye.

The variability in eye position from trial to trial arose in part due to the limited resolution of the eye tracker, measured at

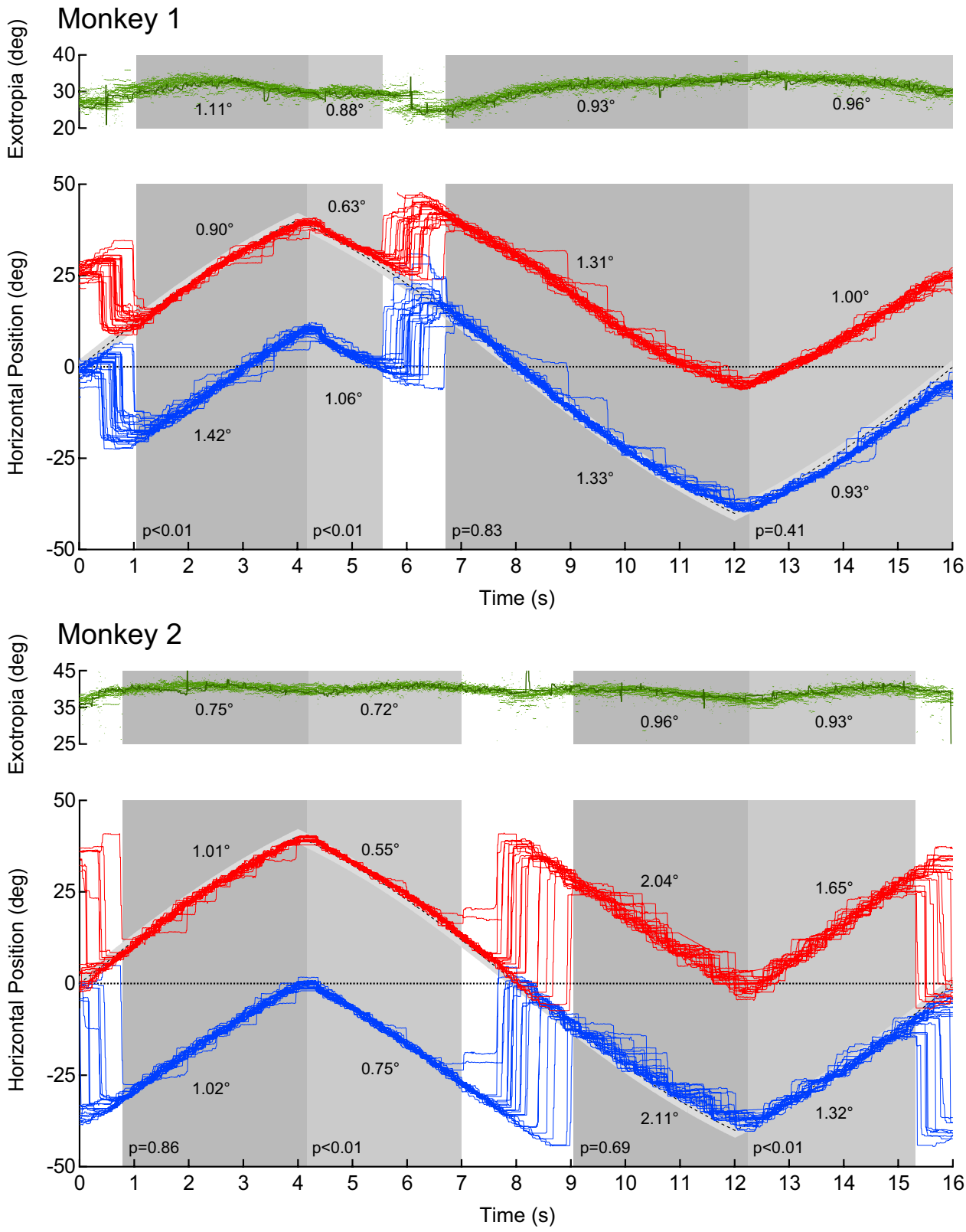

FIG. 5. Binocular smooth pursuit. These traces show ~20 cycles of each monkey tracking a 0.5° target (highlighted dashed line) moving horizontally from +40° to −40° at 10°/s. Food reward was offered for being on target with either eye. The animals spontaneously switched fixation to avoid having to track too far with their adducted eye. In *monkey 1,* the switch in fixation from left eye to right eye occurred at a different orbital position than the switch from right eye to left eye. The mean SD of each eye's position for all 4 epochs is shown next to each trace; for some epochs, the deviated eye had a significantly greater mean SD in position ($P < 0.01$). The intervals containing fixation switches were excluded to calculate the SDs. For each monkey, the mean SD in position was less while tracking nasally (light gray) compared with temporally (dark gray) ($P < 0.01$). The green traces plot the angle of exotropia, calculated by subtracting left eye position from right eye position. The exotropia values for a single cycle are shown by the dark trace. These data were replicated for each monkey in recording sessions done on 5 different days. Dashed line, target position; shading, reward window (±2.5°); red, right eye; blue, left eye.

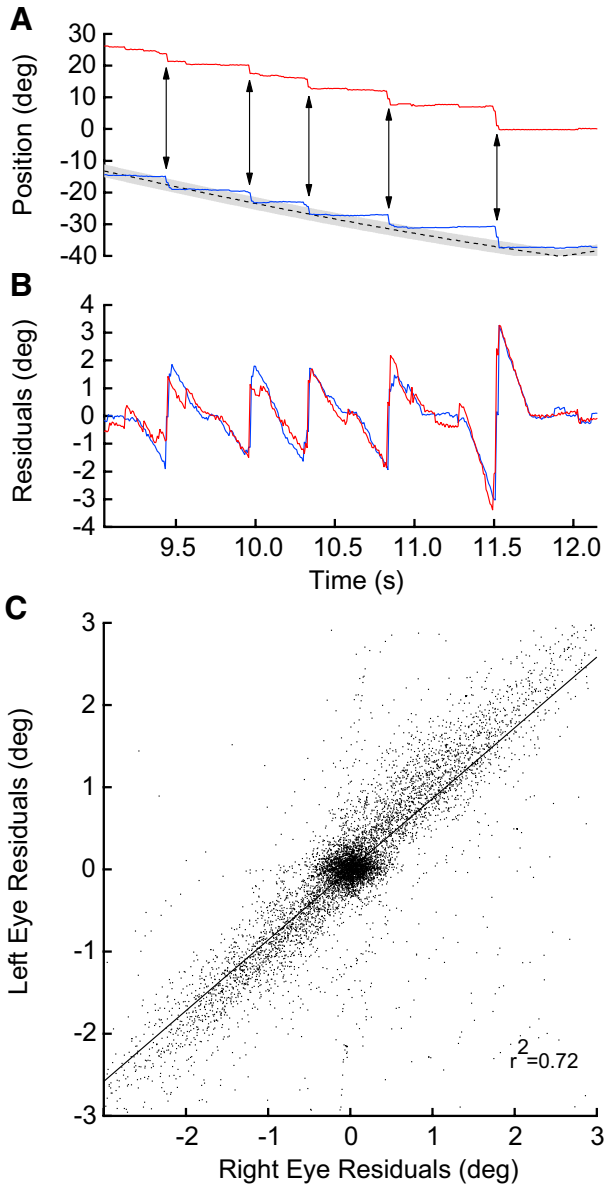

FIG. 6. Catch-up saccades are coordinated in strabismus. *A*: single position traces from *monkey 2,* between 9–12 s, from Fig. 5. The 5 catch-up saccades (arrows) made by the tracking left eye (blue) are mimicked perfectly by the deviated right eye (red). *B*: position residual values obtained by subtracting the running mean value (averaged over 50 time bins) from each position trace. *C*: right eye versus left eye position residual values, showing a high correlation, reflecting the similar timing and magnitude of catch-up saccades. The slope of the regression line is 0.86.

about ±0.7°. The most important source of variability was catch-up saccades. When catch-up saccades were larger and more frequent during an epoch, the mean SD in eye position increased. Inspection of individual traces showed that catch-up saccades were highly correlated in timing and amplitude in the two eyes (Fig. 6*A*). To confirm this impression quantitatively, we calculated a running mean for each individual position trace to remove the offset due to the exotropia. The running mean derived by averaging 50 time bins was subtracted from the actual eye position in each time bin to derive a residual position value (Fig. 6*B*). A scatter plot of right eye versus left eye position residual values showed a high correlation ($r^2 = 0.72$), with a slope of 0.86 (Fig. 6*C*). This result means that the catch-up saccades made by the tracking eye were replicated by the deviated eye. Similar results were obtained in both monkeys for all epochs that contained large, frequent catch-up saccades. For epochs when the monkeys tracked more efficiently, the correlation was lower, but still significant. It was reduced because there were fewer catch-up saccades, which resulted in smaller residual values. In addition, with fewer catch-up saccades, the tracker noise became a more influential factor, and of course, it had no correlation between the eyes.

Figure 5 plots the magnitude of the exotropia as a function of gaze angle in each monkey. From trial to trial, the exotropia was remarkably constant at any given gaze angle, usually having a SD of <1°. For example, while using his left eye to track leftward, *monkey 2* had a SD in eye position of 2.11°, but a SD in exotropia of only 0.96°. Exotropia generally varied less than eye position because the biggest source of variability in eye position—catch-up saccades—cancelled in the two eyes. The cancellation was not perfect because one tracker sometimes recorded a catch-up saccade a single video frame before the other tracker, resulting in an artifactual spike in the exotropia trace. The other sources of exotropia variability were tracker noise and slow drifts of <1° in ocular misalignment which occurred over seconds to minutes on repeated trials.

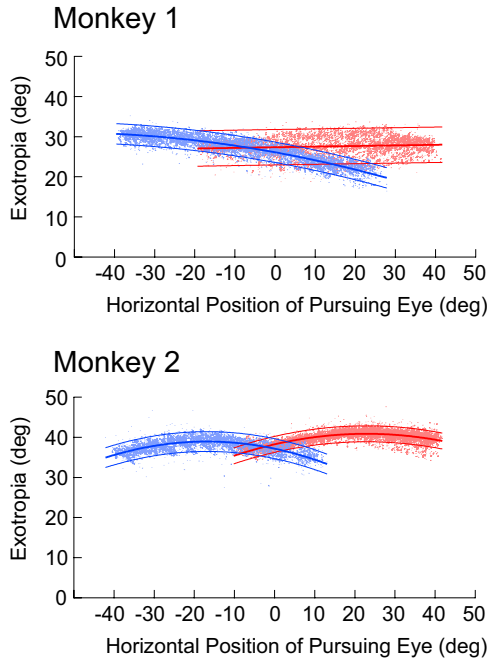

FIG. 7. Exotropia as a function of the orbital position of the pursuing eye (red, right; blue, left). Each point represents a calculation of exotropia (right eye position minus left eye position) compiled every 16.7 ms during constant velocity pursuit of a blue 0.5° target moving at 10°/s, while the deviated eye's view was blocked by a red filter. *Monkey 1* showed incomitance during pursuit with the left eye, manifested by increased exotropia on left gaze, due to deficient adduction of the right eye. The exotropia was comitant while the right eye tracked because over the right eye's range of pursuit, the left eye had full movement. Right eye pursuit time = 153 s, left eye pursuit time = 199 s. *Monkey 2* showed an equal range of horizontal ductions for each eye, because its adduction deficit was relatively symmetric. The exotropia was nearly comitant with either eye pursuing, although it increased by several degrees in the middle of each eye's travel. Right eye pursuit time = 293 s, left eye pursuit time = 165 s. Plots show means ±95% prediction bands.

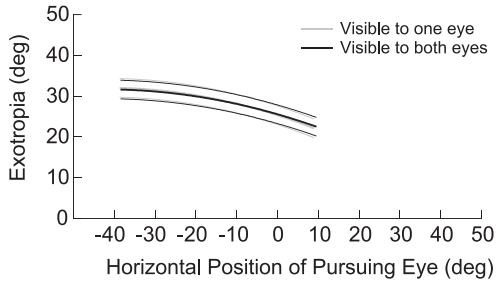

FIG. 8. Target visibility in the deviated eye has no effect on exotropia magnitude. *Monkey 1* tracked a target with his left eye from −40 to 10° that alternated between red and blue on successive cycles. The right eye was covered by a red filter, making only the red target visible to it. The 95% prediction bands are plotted for red target trials vs. blue target trials. There was no difference in the size of the exotropia between these 2 conditions.

Horizontal misalignment and comitance

Naturally occurring strabismus is usually comitant, i.e., the misalignment of the eyes remains fairly constant with shifts in gaze angle. To assess comitancy in our monkeys, the angle of strabismus was determined with both eyes open while each eye tracked over its maximum range. The monkeys were reluctant to adduct fully because they preferred to switch fixation to the other, abducted eye. To overcome this problem, the strategy we employed was to place a red dichroic filter in front of one eye while using a blue target. The filter passed only wavelengths >600 nm. Consequently, only the eye without the red filter could see the blue target, but both eyes could be imaged by the video eye tracker. Under these conditions, the monkeys tracked the blue target over the maximum range of ductions that each eye could execute.

Figure 7 plots the magnitude of the exotropia while either the left eye or the right eye was engaged in smooth pursuit of a target moving horizontally at nearly constant velocity. In *monkey 1,* when the left eye tracked the moving target, the exotropia ranged from 30.7° on far left gaze to 19.7° on far right gaze. The incomitance was due to the poor ability of the right eye to adduct. When the right eye tracked, the exotropia averaged 27.5°. It was nearly comitant, because the left eye had nearly full excursions over the range of motion of the right eye. Curiously, the 95% prediction band was wider when the right eye tracked (±4.41°) than when the left eye tracked (±2.53°). This difference was due to the fact that the exotropia was slightly greater when the right eye tracked rightwards compared with leftwards (see the exotropia trace in Fig. 5). This phenomenon had no obvious explanation but was reproducible in multiple recording sessions.

Monkey 2 had a larger exotropia despite undergoing the same surgery as *monkey 1* (Fig. 7). With the left eye tracking, the exotropia averaged 37.8° over the eye's range of motion with a 95% prediction band width of ±2.47°. With the right eye tracking, it averaged 39.9° with a 95% prediction band width of ±1.98°. The exotropia was relatively comitant, due to the symmetric adduction defect in each eye. In the mid-range of each eye's travel, the exotropia increased by 3–4° for unknown reasons.

We were curious to learn whether the magnitude of the exotropia in each monkey was influenced by the visibility of the target in the deviated eye. The experiment shown in Fig. 7 was repeated, but the color of the target was switched between red and blue on alternating cycles. Both eyes could see the red target, but only the eye without the red filter could see the blue target. The target excursion was limited to the range over which each monkey voluntarily maintained fixation with the same eye. Figure 8 shows an example of *monkey 1* tracking from −40 to 10°, which was the range over which he preferred to use his left eye. The size of the exotropia was not affected by target visibility in the deviated right eye. The same result was obtained under conditions of right eye fixation in *monkey 1* and with either eye engaged in fixation in *monkey 2.*

The red dichroic filter hid the blue target, but a dim red view of the tangent screen was still visible to the deviated eye. To eliminate all visual feedback, these experiments were repeated with a infrared filter (RG780) in front of the deviated eye. The magnitude of the exotropia at different gaze angles was un-

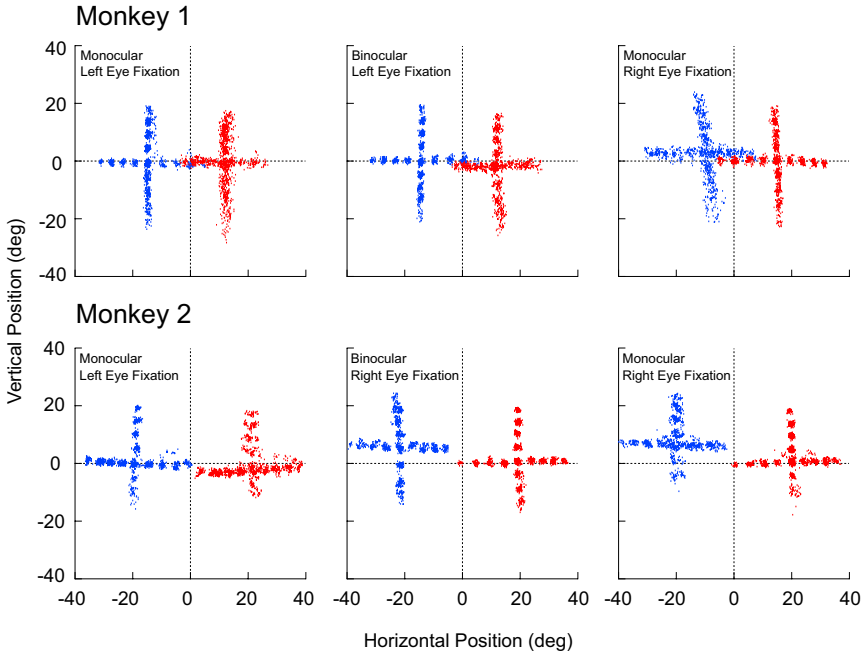

FIG. 9. No A/V pattern or dissociated vertical deviation. The monkeys were rewarded for fixating static targets spaced 5° apart for 500 ms. Data were randomly culled to reduce each plot to 1,000 points. For monocular viewing conditions, the other eye was occluded by an infrared filter. *Monkey 1* had a left hypertropia of 2–3°, and *monkey 2* had a left hypertropia of 6–7°. The horizontal deviation did not change more than 5° between up and down gaze, indicating absence of a significant A or V pattern. Occlusion of either eye did not induce a dissociated vertical deviation. Red, right eye; blue, left eye.

changed (data not shown). Short-term occlusion of one eye did not alter the exotropia in these two monkeys.

Vertical misalignment

Although surgery was confined to the medial recti, each monkey developed a small vertical deviation (Fig. 9). This was ascertained by having each animal fixate a series of targets presented at ±20° around a point 15° (*monkey 1*) or 20° (*monkey 2*) from the origin. The horizontal deviation remained nearly constant with shifts in vertical gaze in each monkey, excluding an "A" or "V" pattern.

In some forms of strabismus, monocular occlusion causes "dissociated vertical deviation" or elevation of the occluded eye. This phenomenon did not occur in either *monkey 1* or *2* (Fig. 9). In fact, ocular misalignment was similar with both eyes viewing or with one eye occluded by an infrared filter.

Eye fixation preference

Under the conditions illustrated in Fig. 5, the monkeys switched fixation for a target moving in a predictable fashion. To probe their eye preference under more natural search conditions, we trained them to initiate trials by fixating with either eye for 500 ms on a 0.5° target located at the center of the tangent screen. The center target was then extinguished and replaced by a peripheral target that appeared at a random location within a 40 × 70° area. The monkey was rewarded for fixating the peripheral target with either eye for 500 ms. *Monkey 1* initiated 96% of the trials by fixating with his left eye on the central target (Fig. 10). The strong bias probably reflected the fact that he could adduct the left eye better than the right eye, making it easier for him to acquire central targets with the left eye. A sharp line divided the visual field into regions where peripheral targets were acquired either by the left eye or the right eye. Intermingling of target acquisition between the left eye and the right eye occurred only between 5 and 12°.

Monkey 2 initiated 57% of the trials with his left eye. He used his right eye to initiate trials more often than *monkey 1* because his adduction deficit was more symmetric. In fact, it was surprising that he did not initiate more trials with his right eye, given that adduction and smooth pursuit were slightly better in the right eye than the left eye (Figs. 2 and 5). The dividing line between peripheral target acquisition by the left eye versus the right eye was quite sharp as in *monkey 1*. The dividing line was pushed over to the left when he initiated trials by fixating the central target with the right eye, as one would anticipate.

For these recordings the monkeys' heads were stabilized with a post, allowing only eye movements. When able to move about freely in their cages, the monkeys typically adopted a 10–20° head turn away from the viewing eye. This maneuver brought the viewing eye near the middle of its horizontal range. Presumably, this mid-orbital position was preferred because it required less effort to sustain fixation on objects located directly in front of the animal. It also equalized the range of abduction and adduction available to the fixating eye, for any subsequent eye movements. When the monkeys switched fixation they simultaneously turned their heads, producing a characteristic to-and-fro head swivel.

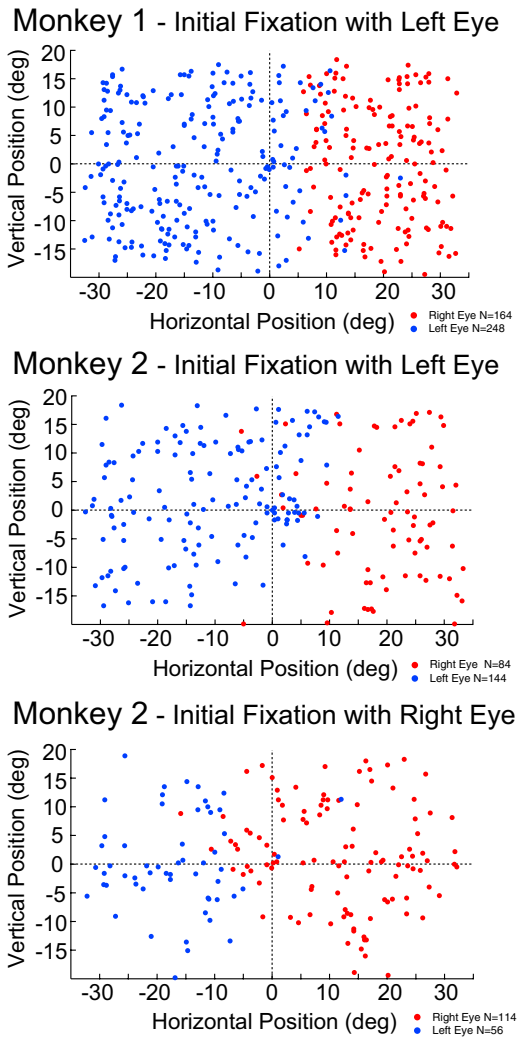

FIG. 10. Eye preference for target acquisition. After fixating a central target with either eye, monkeys were rewarded for saccading to a peripheral target and holding fixation for 500 ms. *Monkey 1* initiated virtually all trials with the left eye and used the left eye to fixate all peripheral targets in the left visual field and the central 5° of the right field. *Monkey 2* preferred to initiate trials with the left eye (57% trials) and then used the left eye to acquired peripheral targets in the left visual field. When he elected to start trials with the right eye, his dividing line for eye preference was shifted leftwards about 10°. Red, right eye; blue, left eye.

Velocities of adducting and abducting saccades

One might expect tenotomy of the medial recti to reduce the velocity of adducting saccades. To examine this issue, eye movements were recorded in both monkeys during a task that required them to fixate targets that appeared between ±30° along the horizontal meridian. The monkeys were rewarded for making a saccade to the target with either eye. Figure 11 shows scatter plots of peak velocity versus saccade amplitude for abducting saccades and adducting saccades in each monkey. Exponential fit lines were generated for each data set with the following function that describes the main sequence relationship: peak velocity $= V_{max}(1 - e^{Amplitude/C})$ where V_{max} is the asymptotic velocity and C is a constant offset term (Leigh and Zee 2006).

To compare the velocity of saccades, the 95% confidence interval for the main sequence of the abduction plot was

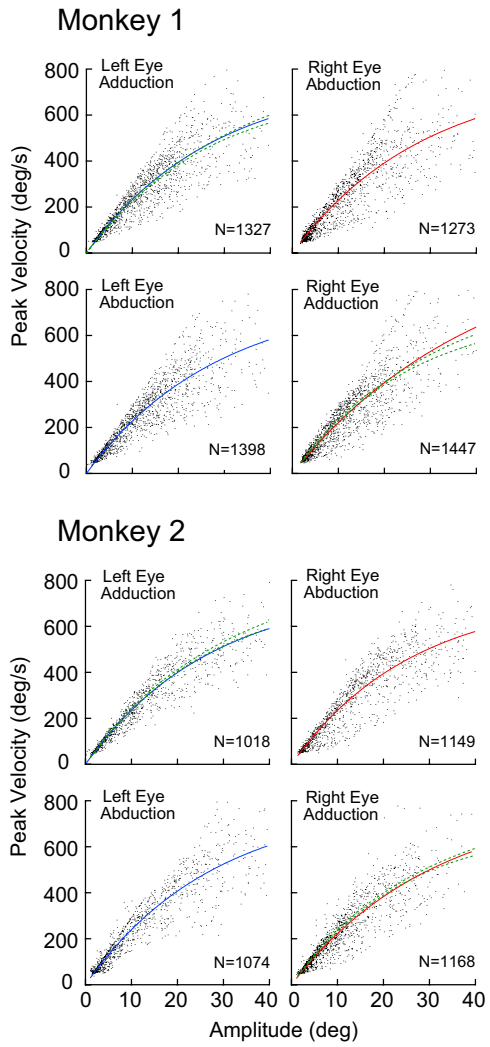

FIG. 11. Comparison of velocity of adducting vs. abducting saccades. Scatter plots show peak velocity vs. amplitude for saccades made to targets appearing at locations within ±30° of the origin. The monkey was rewarded for fixating the target with either eye. There is little difference in the velocity of abduction versus adduction. The 95% confidence intervals for the main sequence fit of the abducting saccades is shown on the plot of the adducting saccades for each eye. The criterion for identification of saccades was an eye velocity exceeding 50°/s.

superimposed on the adduction plot for the same eye. In each case, the adduction fit line fell within the 95% confidence interval of the abduction fit line. The lone exception occurred in *monkey 1,* in whom adducting saccades were actually slightly faster than abducting saccades in the right eye for amplitudes >20°. Overall, in *monkey 1,* the V_{max} for adducting saccades was 819°/s (95% CI = ±53°/s) and the V_{max} for abducting saccades was 743°/s (95% CI = ±43°/s). In *monkey 2,* the V_{max} for adducting saccades was 796°/s (95% CI = ±43°/s) and the V_{max} for abducting saccades was 775°/s (95% CI = ±31°/s). There was no evidence that tenotomy of the medial recti slowed saccadic velocities, at least over the range of saccades that were evoked by these test conditions.

This experiment was designed to test velocities for saccades made under circumstances that simulated the monkeys' natural viewing behavior. They were rewarded for acquiring the target with either eye. In addition, targets were located a maximum of ±30° from the origin because we knew that when head free, the monkeys usually avoid making adducting saccades that go much beyond the vertical midline. Saccades made by the tenotomized medial recti were no slower than those made by the lateral recti. Had the animals been tested monocularly, and required to adduct maximally, we might have found slowing of saccades as the eyes reached the limit of their nasal excursion.

Nystagmus

Pathological nystagmus was exhibited only by *monkey 1.* He had downbeat nystagmus in both eyes when he was inattentive or placed in the dark (Fig. 12*A*). The slow phases had a velocity of 2–3°/s and a magnitude of 5–10°. In addition, there was a finer vertical pendular nystagmus. Sine wave fits to the oscillations were used to measure the amplitude, frequency and phase of the pendular nystagmus. It averaged 0.9°, had a frequency of 3 Hz, and was ~180° out of phase in the two eyes.

Fixation on a target stopped the downbeat nystagmus in both eyes and damped the pendular nystagmus in the fixating eye

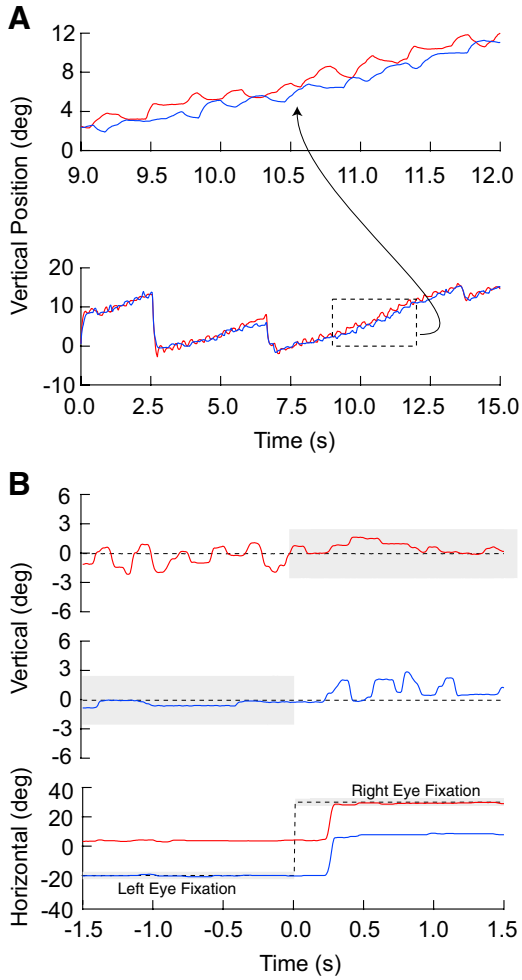

FIG. 12. Downbeat and pendular nystagmus. *A, bottom*: vertical position while *monkey 1* was staring at a blank tangent screen in a dimly illuminated room. There is fine, rapid pendular nystagmus superimposed on a coarse, slow, synchronous downbeat nystagmus. *Top*: pendular nystagmus is out of phase in the two eyes. *B*: target eliminates the downbeat nystagmus and damps the pendular nystagmus in the fixating eye. Red, right eye; blue, left eye.

(Fig. 12*B*). The pendular nystagmus persisted in the deviated eye and became larger with adduction.

DISCUSSION

After failure in 10 infant monkeys, Von Noorden and Dowling (1970) reported that permanent strabismus cannot be produced by free tenotomy of a single horizontal muscle. The operation produced a temporary impairment of motility, but the animals were able to regain normal ocular alignment within 3–4 wk. To generate strabismus by monocular surgery, they had to weaken one horizontal rectus by extirpation and advance the resected antagonist to the limbus. All subsequent investigators have employed some variant of a monocular recess/resect technique when using surgery to induce strabismus in monkeys (Crawford and von Noorden 1979; Harwerth et al. 1986; Kiorpes 1989; Kiorpes and Boothe 1980; Kiorpes et al. 1996, 1998). Their objective was to create an esotropia, often with amblyopia in the operated eye.

Our goal was to produce an alternating strabismus, without amblyopia, to explore the neurophysiology of visual suppression. From the experience of Von Noorden and Dowling (1970), it was evident that surgery on two muscles would be required. We chose to perform symmetric surgery on each eye because this strategy seemed most likely to achieve a deviation without a strong eye fixation preference or amblyopia. After bilateral lateral rectus tenotomy, there is a chance that a monkey may avoid strabismus by fusing on near targets until ocular motility recovers. In contrast, after bilateral medial rectus tenotomy there is no potential for fusion as long as adduction remains limited. Accordingly, we decided to adopt this approach.

When infant macaques are exposed to only a short period of strabismus, they can recover normal binocular function (Wong et al. 2003). Optical misalignment that lasts only 2 wk, rather than 8 wk, has less impact on the disparity sensitivity of cortical neurons (Kumagami et al. 2000; Mori et al. 2002). Thus it was important that the adduction deficit in our monkeys last beyond the critical period for establishing fusion and stereopsis, which spans age 4–12 wk in the macaque (O'Dell and Boothe 1997). Although each animal showed partial recovery of adduction after medial rectus tenotomy, their deficit lasted long enough to induce a permanent exotropia.

Free tenotomy of the medial recti produced strabismus in all three monkeys, but the results were inconsistent. The same surgery resulted in different deficits in different monkeys and even in the same monkey. For example, *monkey 1* recovered 35° of adduction in his left eye but only 17° of adduction in his right eye, leaving him with a 20–30° exotropia. On the other hand, *monkey 3* regained nearly full adduction and had just 5° of residual exotropia. Such variability is a potential drawback for an animal model, but at least exotropia was predictable in every monkey. In monkeys raised with alternating monocular occlusion, either esotropia or exotropia can occur (Das et al. 2005). Such animals can even be esotropic while fixating with one eye and exotropic while fixating with the other (Tychsen et al. 2000).

In humans, it is well known that partial recovery of muscle function can occur after free tenotomy (Knapp 1978). However, the muscle usually remains "lost," and can be extremely difficult to locate during orbital exploration (Murray 1998). The force it exerts on the globe is transmitted via fascial attachments, such as the muscle capsule or Tenon's capsule. In macaques the globe occupies a much greater proportion of the orbit than in humans, which means that there is less room for the severed tendon to recoil into the orbital apex. We showed by computed tomography and histology that the tenotomized muscle reattaches spontaneously to the globe in macaques, close to its normal insertion (Figs. 3 and 4). How this process occurs is unknown, but perhaps the scleral insertion site secretes a trophic factor that attracts the muscle tendon. Horizontal rectus muscle anatomy is normal in macaques with natural strabismus, and in those raised with prisms or alternating daily monocular occlusion (Narasimhan et al. 2007).

Comitancy is considered one of the hallmarks of infantile strabismus. Bimedial rectus tenotomy had the advantage of inducing a relatively comitant strabismus (Fig. 7). A recess/resect procedure confined to one eye would have produced a far more incomitant strabismus with a sharp increase in the exotropia on lateral gaze away from the operated eye. Neither monkey had a dissociated vertical deviation. This feature is classically associated with infantile esotropia but can also occur with exotropia in humans (Hunter et al. 2001) and monkeys (Das and Mustari 2007). Had more monkeys been studied, an animal with dissociated vertical deviation might have been encountered. In strabismus, some features occur inconsistently; all the observations in this report are limited by the fact that we have tested only two animals in detail.

Smooth pursuit is not an obligatory binocular function: normal subjects track moving targets just as efficiently under monocular compared with binocular conditions (Kiorpes et al. 1996). Nonetheless, both monkeys showed a clear deficit in smooth pursuit from disruption of binocularity. In each animal, one eye was capable of tracking with greater fidelity than the other, a consistent result across dozens of recording sessions. Curiously, this was not necessarily the eye preferred by the monkey for fixation. In the eye with poorer smooth pursuit, catch-up saccades were prominent. They occurred simultaneously in the deviated eye (Fig. 6), a feature not demonstrated before in strabismus. Although smooth pursuit and binocular function are impaired in strabismus, the coordination of catch-up saccades remains intact.

The quality of smooth pursuit in the tracking eye governed the movement of the deviated eye. When one eye had better smooth pursuit than the other, the eye with poorer pursuit moved more smoothly when serving as slave than functioning as master (Fig. 5). In addition, the fidelity of the tracking eye was better while tracking nasally, compared with temporally in both monkeys. In humans and monkeys with esotropia, smooth pursuit is known to be more accurate in the nasal direction (Tychsen and Lisberger 1986; Wong et al. 2003). It would be worthwhile to test more exotropic subjects, looking for a naso-temporal asymmetry in pursuit. It is possible that this abnormality occurs in exotropia more frequently than has been appreciated (Tychsen et al. 1985).

Saccadic gain adaptation and amplitude-peak velocity relationships are normal for horizontal saccades made by strabismic monkeys raised with alternating monocular occlusion (Das et al. 2004; Fu et al. 2007). In animals raised with tenotomy, shortening of the muscle might be expected to slow saccades. However, we found a normal main sequence relationship after free tenotomy (Fig. 11). A similar finding has been reported in

humans with a "slipped" extraocular muscle (Chen et al. 2005). Normal peak velocities were probably achieved through reattachment of the severed muscle and by adaptive modification of pulse and step gains by the CNS (Optican and Robinson 1980). Despite recovery of normal peak velocities, each tenotomized medial rectus muscle showed some reduction in adduction range. Interestingly, this limitation was less for saccades than for smooth pursuit. This reason for this difference is unclear but could reflect either a difference in muscle length/tension properties during saccades versus smooth pursuit or more efficient CNS compensation for saccadic weakness (Hazel et al. 2002; Sylvestre and Cullen 1999).

In subjects with strabismus, covering one eye may alter the magnitude of the ocular deviation. The latent component of strabismus is thought to be held in check by residual binocular sensory mechanisms when both eyes are open (von Noorden and Campos 2002). In our monkeys, short-term monocular occlusion made no difference to the angle or direction of strabismus (Figs. 8 and 9). Under both monocular and binocular conditions, the monkeys maintained a remarkably constant deviation ($\pm 1°$) for any given angle of gaze. Their deviation must be controlled entirely by the oculomotor system, given the lack of any apparent effect of monocular occlusion.

The monkeys in this report displayed a behavior typical of humans with a large angle exotropia: they alternated fixation by saccading to left-sided targets with the left eye and to right-sided targets with the right eye (van Leeuwen et al. 2001). In principle, this behavior means they could acquire peripheral targets more rapidly than normal subjects because smaller saccades were generally required. To randomly presented targets, each monkey displayed a sharp, consistent dividing line separating portions of the visual field where targets were acquired by the left eye versus the right eye (Fig. 10). Consequently, it was possible to predict which eye the monkeys would use to saccade to a target and to control eye fixation through appropriate choice of target location.

The most interesting behavior was evoked by stimulus conditions that required the monkeys to switch eyes during a saccade, which they did accurately. It remains unclear how they program saccades under such circumstances (van Leeuwen et al. 2001). One possibility is that the fixating eye detects the new target in its peripheral retina, and the correct saccade amplitude is calculated for the other eye by adding the size of the exotropia. This mechanism would require that the animal have access to an internal representation of the exotropia, which can vary as a function of gaze position (e.g., *monkey 1,* left eye fixating). Another possibility is that the new target is picked up in the peripheral retina of the deviated eye, and the appropriate saccade is calculated directly. The third possibility is that both eyes participate in programming the saccade. Experiments are underway to settle this issue.

The best animal model for human strabismus is provided by macaques with naturally occurring strabismus (Kiorpes et al. 1985). But such animals can be obtained only by mass colony screening, and their ocular history is usually unknown. Early bilateral medial rectus tenotomy in macaques produces a clinical syndrome that resembles human exotropia in many respects (Donahue 2007). There is a large angle exotropia, free alternation between the eyes, little evidence of amblyopia, and limitation of adduction. Only the latter feature is not found regularly in primary human exotropia but does occur in some children with esotropia who are rendered exotropic by excessive recession of the medial recti (a more frequent complication than generally realized). Another important distinction is that primary exotropia in humans usually arises after gradual decompensation of an exophoria, with an intermediate stage of intermittent exotropia (Govindan et al. 2005; Nusz et al. 2006). In the macaque model, the onset of exotropia is sudden and permanent.

A major advantage of any surgical model of strabismus is that after a single operation early in life, no further intervention is required until the animal is ready for experiments. Prism rearing and alternate monocular occlusion require daily intervention and monitoring for months. Although no existing model incorporates all the elements present in any form of human strabismus, bimedial rectus tenotomy produces a fairly comitant, alternating exotropia that is a good facsimile of human exotropia.

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