Early Versus Delayed Repair of Infantile Strabismus in Macaque Monkeys: I. Ocular Motor Effects

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Introduction: The appropriate age for surgical correction of esotropic strabismus in human infants is controversial; some clinicians advocate surgery before age 6 months, and others recommend observation and surgery at older ages. Infantile (congenital) esotropia in humans and monkeys is known to be accompanied by a constellation of eye movement abnormalities caused by maldevelopment of cerebral visual motor pathways. The purpose of this study was to determine how early versus delayed correction of strabismus influences development and/or maldevelopment of these eye movement pathways. ***Methods:*** Optical strabismus was created in infant macaques by fitting them with prism goggles on day 1 of life. The early correction group (2 experimental and 1 control) wore the goggles for a period of 3 weeks (the equivalent of 3 months before surgical repair in humans). The delayed correction group (3 experimental and 1 control) wore the goggles for a period of 3 or 6 months (the equivalent of 12 or 24 months before surgical repair in humans). Several months after the goggles were removed, the monkeys were trained to perform visual fixation, smooth pursuit, and optokinetic nystagmus (OKN) tasks for a juice reward. Eye movements were recorded using binocular search coils. The performance of the early versus delayed infant monkey groups was also compared with that of a group of adult monkeys who had unrepaired, naturally occurring infantile esotropia. ***Results:*** Early correction monkeys developed normal eye movements and exhibited ocular motor behaviors that were indistinguishable from normal control animals. They regained normal binocular eye alignment and showed stable fixation (no latent nystagmus). Monocular horizontal smooth pursuit and large field OKN were symmetric. In contrast, delayed correction monkeys showed persistent esotropia, latent fixation nystagmus, dissociated vertical deviation, and pursuit/OKN asymmetry. Animals who had the longest delay in correction of the optical strabismus exhibited eye movement abnormalities as severe as those of adult animals with uncorrected, natural esotropia. ***Conclusions:*** Early correction of strabismus in primates prevents maldevelopment of eye movements driven by cerebral motor pathways. Our results provide additional evidence that early strabismus correction may be beneficial for brain development in human infants. (J AAPOS 2003;7:200–209)

The appropriate age at which to perform eye muscle surgery for infantile (congenital) esotropia is controversial.[1-3] In North America, the average age of repair ranges from 10 to 18 months.[3,4] Despite surgical repair, deficits of stereoscopic perception, unstable eye fixation, and abnormal smooth eye tracking persist into adulthood.[5-9] Recently, surgeries at or before age 4 months have been advocated. These "very early" surgeries may substantially improve the sensory outcomes (binocular fusion and stereopsis) in children with infantile esotropia,[10-14] but little detailed information is available regarding improvement in ocular motor behaviors.

Behavioral studies have shown that postnatal development of binocular sensory and motor functions in normal infant monkeys closely parallels that of normal infant humans but on a compressed time scale (ie, 1 week of monkey development is equivalent to 1 month of human development).[15-18] Macaque monkeys with infantile esotropia display the constellation of eye movement and visually evoked potential (VEP) abnormalities found in strabismic humans, including defective fusional vergence, latent fixation nystagmus, pursuit/OKN asymmetry, dissociated vertical deviation (DVD), and motion VEP asymmetry.[19,20]

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FIG 1. Infant monkey wearing prism goggles to induce optical strabismus, ie image decorrelation between the right and left eyes.

Thus, infant macaques are an appropriate model to use in studies designed to test the efficacy of early strabismus correction. The specific purpose of this study was to determine how correction of optical strabismus in infant monkeys influenced the development of eye movements, with the "correction" (ie, removal of prism goggles) deliberately timed to mimic early (before age 6 months) versus delayed (age 1 to 2 years) surgical repair of strabismus in human infants.

METHODS

Animals and Goggle-Rearing Groups

Monkeys (*Macaca mulatta*) born at the Yerkes Primate Center in Atlanta, GA, were fitted with goggles on the first day of life (Figure 1). The fitting procedure was an adaptation of that originally described by Crawford.[21,22] The procedure was not stressful to the newborn macaques and did not require anesthesia or fabrication of a head mold. Padded head straps held the goggles firmly in place and prevented the infant from removing the apparatus, which was custom fabricated for each monkey from lightweight plastic. The front piece consisted of 2 lens holders that unscrewed so that ultra-lightweight, 2-mm thick Fresnel plastic prisms could be inserted. Animals were observed several times per day in the primate nursery and during bottle feedings to ensure that the goggles remained clear and in proper position. The goggles did not interfere noticeably with normal play or mingling with other infant macaques. The goggle helmet was removed daily from each monkey for cleaning. During cleaning and, if necessary, adjustment of the goggle, the animal was placed briefly in a dark (light-tight) enclosure to preclude normal binocular experience.

The monkeys were divided into 2 correction groups, early and delayed. In each group, experimental animals wore prism goggles to induce optical strabismus of at least 11.4° (20 PD) in each eye. Five experimental animals (Table 1) wore 11.4° base-down in 1 eye, and 11.4° base-in in the other eye, causing a combined horizontal and vertical strabismus. A sixth experimental animal (SY), wore 11.4° base-in in each eye, causing a 22.8 (40 PD) horizontal strabismus. Normal control animals wore goggles with plano lenses (Table 1). The early correction group (2 experimental and 1 normal control) wore the goggles for a period of 3 weeks (the equivalent of 3 months in humans[16]). The delayed correction group (3 experimental and 1 normal control) wore the goggles for a period of 3 months (the equivalent of 12 months in humans) or for a period of 6 months (the equivalent of 24 months in humans). At 4 to 6 months of age, the monkeys were transported to Washington University in St. Louis MO, where they were trained to perform visual fixation and tracking tasks without prism goggles using a positive-feedback reward (a small bolus of fruit juice).[23] Three adult monkeys who had naturally occurring esotropia with onset ≤4 weeks of age were also studied (Table 1). Cycloplegic refractions showed a refractive error $< +3.00$ spherical equivalent in each of the infant and adult animals. Monocular visual acuity was measured using spatial sweep VEPs[24,25] (without correction for refractive error), documenting approximately equal vision in both eyes of the control and the strabismic monkeys (Table 1).

Search Coil and Head Restraint Implantation

Detailed descriptions of the training, surgical, and recording methods have been published in previous reports, and for this reason only an abbreviated description is provided here.[23,26] After initial fixation training, scleral search coils were implanted in both eyes, and a custom-built, polycarbonate head restraint device was attached to the skull. The surgical procedure was performed under aseptic conditions using deep general inhalation as well as local infiltration and topical anesthesia. All procedures were performed in compliance with the Association for Research in Vision and Ophthalmology resolution on the use of animals in research and were approved by the Washington University Animal Care and Use Committee.

TABLE 1. Visual and ocular motor characteristics of the 10 macaque monkeys used in the study

Animal/Sex/Age (y) (Species)	Rearing conditions	Eye alignment at testing	Latent nystagmus	Pursuit/OKN asymmetry	DVD	Visual acuity SSVEP (cpd)
Early correction group						
TE/M/1.5 (*M mulatta*)	3 weeks' prism (11.4° BI OD; 11.4° BD OS)	Orthophoric	No	No	No	OD: 19.85 OS: 21.40
SY/M/1.7 (*M mulatta*)	2 weeks' prism (11.4° BI OU)	Orthophoric	No	No	No	OD: 17.95 OS: 22.80
WE/M/1.5 (normal control) (*M mulatta*)	3 weeks' plano lens (0°)	Orthophoric	No	No	No	OD: 22.85 OS: 20.50
Delayed correction group						
YO/M/2 (*M mulatta*)	3 months' prism (11.4° BI OD; 11.4° BD OS)	RET: 16° RHT: 5 °	Yes	Yes	Yes	OD: 21.10 OS: 19.06
HA/F/2 (*M mulatta*)	6 months prism (11.4° BI OD; 11.4° BD OS)	RET: 15° RHT: 4°	Yes	Yes	Yes	OD: 19.23 OS: 18.65
QN/F/2 (*M mulatta*)	6 months' prism (11.4° B1 OD; 11.4° BI OD; 11.4° BD OS)	LET: 12° LHT: 4°	Yes	Yes	Yes	OD: 23.28 OS: 24.01
AY/M/2 (normal control) (*M mulatta*)	3 months' plano lens (0°)	Orthophoric	No	No	No	OD: 18.09 OS: 16.17
Unrepaired naturally strabismic group						
ZE/F/7 (*M mulatta*)	Naturally strabismic	LET: 12° LHT: 8°	Yes	Yes	Yes	OD: 16.80 OS: 18.67
HD/M/12.2 (*M nemistrina*)	Naturally strabismic	LET: 13° LHT: 2°	Yes	Yes	Yes	OD: 19.06 OS: 19.52
TM/M/22 (*M nemistrina*)	Naturally strabismic	RET: 22° RHT: 5°	Yes	Yes	Yes	OD: 17.68 OS: 19.33

OKN, optokinetic nystagmus; *DVD*, dissociated vertical deviation; *SSVEP*, spatial sweep visually evoked potential; *cpd*, cycles per degree; *OD*, right eye; *OS*, left eye; *BI*, base in; *BD*, base down; *OU*, both eyes; *RHT*, right hyperstropia; *LHT*, left hypertropia; *LET*, left esotropia; *RET*, right estropia.

Eye Movement Recordings

Eye movements were recorded using standard magnetic search coil techniques.[27,28] During each recording session, the monkey sat in a primate chair in the middle of field coils and viewed a small laser spot (subtending approximately 0.05°) projected onto the back of a translucent screen located 50 cm in front of the animal. The head restraint was locked to preclude head movement, and the room was lit with dim background illumination. Eye position was calibrated by the use of a calibration coil and by having the animal performed a lever-response task in which it had to detect 50% dimming of the target within 300 milliseconds while the target remained stationary at known horizontal and vertical positions. Previous experiments in normal primates confirmed that foveal fixation was necessary for accurate performance of this task.[23] The calibration sequence was repeated separately for each eye under conditions of monocular viewing. After the initial session, calibrations were rapid and remained stable from day to day. The lever was removed, and accurate fixation was reinforced thereafter by rewarding the animal for keeping eye position within a certain window (see below).

Recordings were performed under conditions of binocular and monocular viewing for each animal. Monocular viewing, when noted in the descriptions that follow, was achieved by positioning an opaque plastic occluder, hinged to the head restraint, in front of either eye. Voltages proportional to horizontal and vertical eye position were digitized at 500 Hz. Eye velocity signals were obtained by passing the eye position signals through a finite impulse response filter (DC to 90 Hz) and differentiated. Angular resolution of the system was approximately 0.05°. Experiments were controlled and the data were acquired and analyzed with the aid of a computer and interactive signal processing software (Spike2 for Macintosh, Cambridge Electronic Design, UK, and Igor Graphics, Wave Metrics, Lake Oswego, OR).

Stimuli for Fixation, Pursuit, and OKN

Eye Alignment. Eye alignment was assessed initially using 35-mm photographs and video recordings of each monkey (Hirshberg method[29,30]) before and during the period of fixation training. After implantation of eye coils, alignment was measured under conditions of binocular viewing to document precisely the magnitude of any intermittent or constant heterotropia. The fixation target was displaced from primary position (straight ahead) to the cardinal positions of gaze to assess concomitance of any misalignment. To reveal the presence of any heterophoria (horizontal or vertical), alignment during periods of bin-

ocular viewing was compared with alignment when viewing with either eye covered.

Stable Fixation. Viewing monocularly, each monkey was required to fixate the laser spot at straight-ahead gaze or at eccentricities of ± 10° horizontally and vertically. The target was presented in repeated trials. To receive a juice reward, the animal had to maintain eye position of the nonoccluded fixating eye within a 2° "fixation window" surrounding the target for a randomized interval of 2 to 5 seconds. The small target size, variability of target location, small fixation window, and random duration of required fixation ensured a high level of visual attention.

Smooth Pursuit. Smooth pursuit was recorded under conditions of monocular viewing using a modification of the "step-ramp" paradigm of Rashbass.[31,32] At the beginning of each trial, the animal fixated on the stationary spot at straight-ahead gaze. When the animal's eye remained within a 2° window continuously for an interval of 2 to 5 seconds, the stationary spot disappeared and a second spot appeared, moving rightward or leftward at 30°/s. The moving spot started either from the point of fixation (zero eccentricity) or from 1 of 8 other initial positions along the horizontal meridian (5° and 10° above, below, to the right, and to the left of zero eccentricity). The "step-ramp" approach allowed us to present target motion at a precise location on the retina as determined by the relative positions of the stationary and moving spots. When viewing with the left eye, rightward target velocities represented nasally directed motion, and leftward target velocities temporally directed stimulus motion in the visual field. To receive the juice reward, the monkey had to track the stimulus within the 2° window for a duration > 750 milliseconds. The onset, direction (up, down, left, right), and speed of the target were controlled by the computer program, which selected combinations of initial target position and direction in a pseudorandom fashion to preclude prediction.

OKN. Large-field OKN was evoked under conditions of monocular viewing using horizontally moving, 100% contrast, vertically oriented, black and white square-wave stripes (0.1 cycle-per-degree) back projected on a tangent screen. The stimulus subtended a visual angle of 90° × 90° horizontally and vertically and moved at a velocity of 30°/s in 60-second trials. The screen was blanked for a period of 90 seconds between all trials to allow dissipation of any OKN after-nystagmus.[33]

Data Analysis

Eye Alignment. Binocular eye alignment was determined from eye position records, with orthotropia defined as the visual axes of each eye aligned on the fixation spot to within 0.1° of target position during more than 90% of rewarded trials. Monkeys who displayed a heterotropia alternated fixation but typically showed a slight preference for fixation with one eye. The preferred eye was designated as the eye aligned on the target during > 50% of rewarded trials. The heterotropic deviations listed in Table 1 represent the mean eye position of the nonpreferred eye measured by at least 20 fixation trials.

Stable Fixation. Fixation was determined to be stable, ie, fixation nystagmus was absent, if eye position tracings showed no evidence of consistent smooth eye drift when the monkey was rewarded for fixating the stationary spot in primary position or at cardinal gaze positions. Latent fixation nystagmus was assessed as present if a nasally directed slow phase drift > 0.10°/s was detected in the tracings of the fixating eye during rewarded trials and accompanied by refoveating temporally directed microsaccades (fast phases). The waveform of nystagmus, when present in our monkeys, was characterized by linear or decreasing-velocity slow phases, which were generally conjugate in the fixating and nonfixating eye.

Smooth Pursuit. Individual "step-ramp" trials were judged acceptable for analysis if the trial contained at least 50 milliseconds of smooth eye velocity after the onset of pursuit. If an accepted trial contained a saccade, the saccade was removed and replaced with a straight line using a cursor-controlled interactive computer program. In cases of the linear interpolation not fitting smoothly into the velocity trace, the trial was excluded from analysis. To assess pursuit performance, we calculated pursuit gain, defined as the ratio of eye velocity to target velocity, during steady-state pursuit (ie, 150 milliseconds after pursuit onset). Nasalward pursuit gains for the right eye (ie, target motion to the left) and the left eye (ie, target motion to the right) are reported as the pooled means of both eyes, as are temporalward gains. Pursuit gains were compared using Wilcoxon signed-rank tests. Values were defined as significant when $P < .05$.

OKN. The beginning and the end points of a slow-phase trace were marked using a cursor to calculate the average velocity for each slow phase. A minimum of 20 slow-phase velocities was averaged within a 60-second trial to obtain mean velocities. OKN gain was calculated as the ratio of mean eye velocity to target velocity for nasalward versus temporalward stripe motion, pooling the responses of the right and left eye. OKN gains were compared using Wilcoxon signed-rank tests. Values were defined as significant when $P < .05$.

RESULTS

Comitant Esotropia and Latent Fixation Nystagmus in Delayed Correction Animals

Early correction monkeys had normal horizontal and vertical eye alignment when tested at age 1 to 2 years. In contrast, each of the 3 delayed correction animals developed a constant comitant large-angle esotropia (Table 1). Delayed correction and naturally strabismic animals also displayed vertical deviations resembling DVD in humans. All normal control monkeys who wore plano lenses had normal eye alignment. Spatial sweep VEPs (Table 1) in-

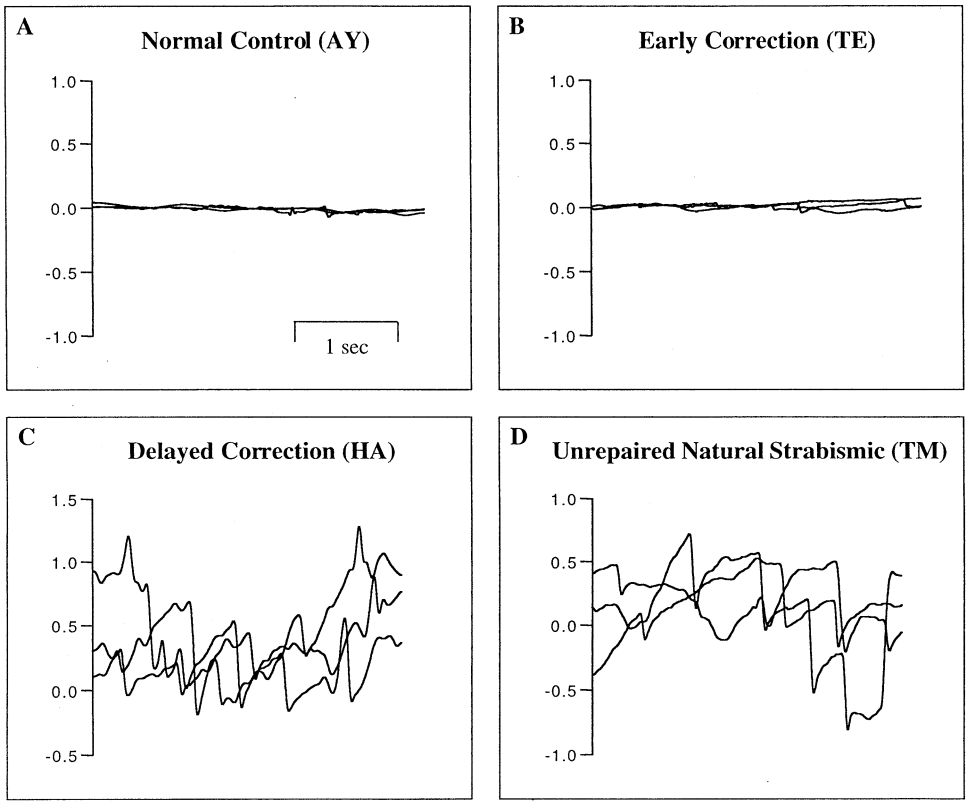

FIG 2. Stable fixation of stationary target versus latent fixation nystagmus. Monocular fixation using the left eye (right eye was occluded) in (A) normal control, (B) early correction, (C) delayed correction, and (D) uncorrected naturally strabismic monkeys. In both normal control (A) and early correction monkeys (B), fixation was steady. In contrast, in both delayed correction (C) and uncorrected naturally strabismic monkeys (D), latent fixation nystagmus was evident as nasally directed slow-phase drifts followed by temporally directed fast phases. Upward deflections indicate rightward movement.

dicated the absence of amblyopia in experimental animals and normal controls.

Figure 2 shows plots of eye position versus time during monocular fixation with the left eye. In both the normal control (Figure 2A) and early correction monkey (Figure 2B), fixation was steady. In contrast, both the delayed correction (Figure 2C) and uncorrected naturally strabismic monkey (Figure 2D) displayed latent fixation nystagmus. The nystagmus was manifested as nasalward slow-phase drifts interrupted by temporalward fast phase jerks (average slow-phase velocity approximately 1°/s).

Nasotemporal Asymmetry of Pursuit in Delayed Correction Animals

Figure 3 illustrates the "step-ramp" strategy we used to present image motion and elicit pursuit. The trials shown in Figure 3A were obtained from a normal control animal (AY) viewing with the right eye. The stationary fixation spot (at 0° straight ahead) disappeared after an unpredictable duration. Simultaneously, the tracking target appeared 5° to the left (for temporalward tracking) or right (for nasalward tracking) and moved in the opposite direction at 30°/s (Figure 3A, top panel). With a latency of approximately 80 milliseconds, the eye accelerated from zero velocity and achieved the velocity of the target (steady state) after approximately 150 milliseconds of pursuit (Figure 3A, bottom panel). Note that pursuit eye velocity was equally strong for both temporalward and nasalward target motion.

The early correction monkey shown in Figure 3B also demonstrated symmetrical pursuit for both temporalward and nasalward stimulus motion. In contrast, in the delayed correction (Figure 3C) and uncorrected naturally strabismic (Figure 3D) animals, a nasotemporal asymmetry of pursuit was evident. Pursuit for temporalward stimulus motion was weak, whereas that for nasalward stimulus motion was strong.

Mean nasalward versus temporalward pursuit gains for all of the monkeys are shown in the bar graphs in Figure 4. Pursuit was symmetrical for both the normal control and early correction groups; mean temporalward pursuit gain was 106% of nasalward gain for the control group and 99% of nasalward gain for the early correction group (P = nonsignificant [NS]). Pursuit gain was asymmetrical in the delayed correction and uncorrected naturally strabismic animals. Mean temporalward gain was 52% of nasalward gain for the delayed correction group ($P < .001$) and 45% of nasalward gain for the uncorrected naturally strabismic group ($P < .001$).

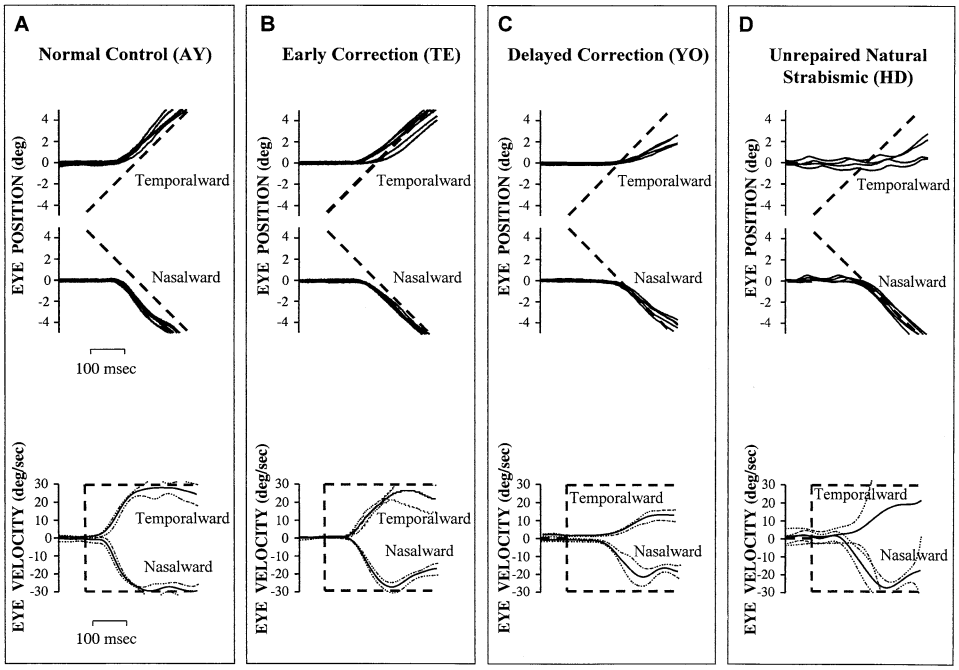

FIG 3. Horizontal smooth pursuit for nasally directed versus temporally directed target motion in (A) normal control, (B) early correction, (C) delayed correction, and (D) uncorrected naturally strabismic monkeys. Monocular viewing using the right eye (left eye occluded). In both normal control (A) and early correction monkeys (B), horizontal pursuit was equally strong for nasalward and temporalward stimulus motion. In contrast, in both delayed correction (C) and uncorrected naturally strabismic monkeys (D), a nasotemporal asymmetry was evident with weaker pursuit in response to temporalward motion. Eye position (upper panels) and eye velocity (lower panels) as a function of time; upward deflections indicate rightward movements.

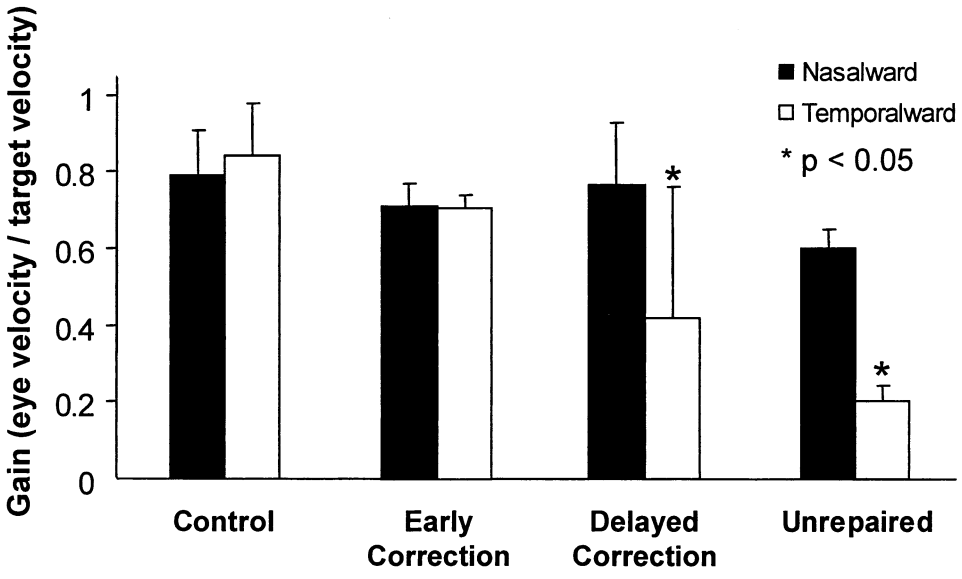

FIG 4. Mean smooth pursuit gain as a function of time of correction. No nasotemporal asymmetry of pursuit gain was evident for control or early correction monkeys, but nasalward gains were significantly greater in delayed correction and unrepaired monkeys. Data were pooled from each animal in each group and between eyes for each animal.

Nasotemporal Asymmetry of OKN in Delayed Correction Animals

Figure 5 shows representative OKN responses viewing with the left eye. In both normal control (Figure 5A) and early correction monkeys (Figure 5B), OKN responses were equivalent for both nasally directed and temporally directed target motion, with no directional asymmetry. However, delayed correction (Figure 5C) and uncorrected naturally strabismic (Figure 5D) monkeys exhibited a directional asymmetry. OKN was robust for nasally directed

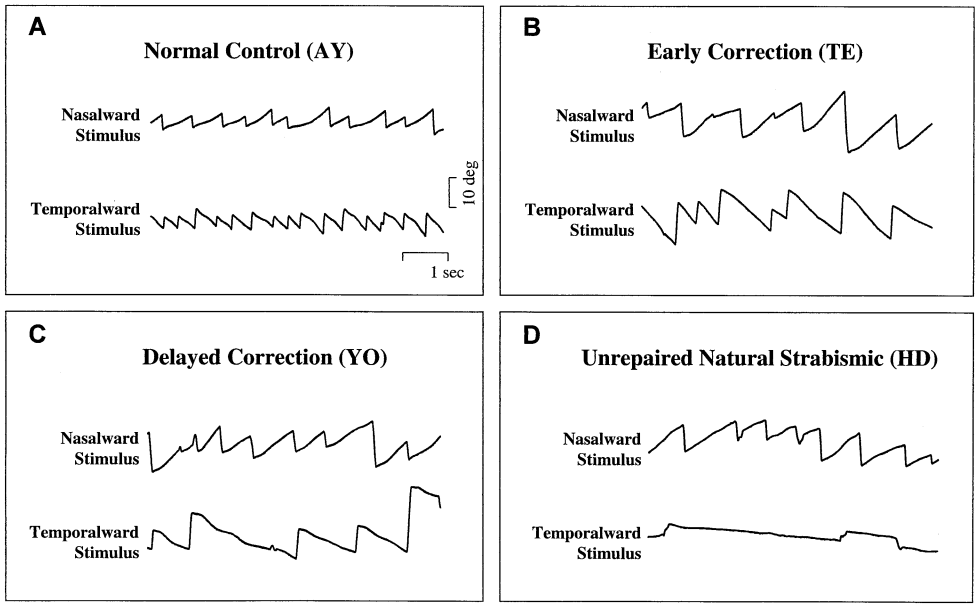

FIG 5. Horizontal OKN for nasally directed versus temporally directed target motion in (A) normal control, (B) early correction, (C) delayed correction, and (D) uncorrected naturally strabismic monkeys. Monocular viewing of large-field stimulus using the left eye (right eye occluded). In both normal control (A) and early correction monkeys (B), horizontal OKN was equally strong for nasalward and temporalward stripe motion. In contrast, in both delayed correction (C) and uncorrected naturally strabismic monkeys (D), a nasotemporal asymmetry was evident as a weaker OKN response for temporalward motion. Upward deflections indicate rightward movement. OKN, optokinetic nystagmus.

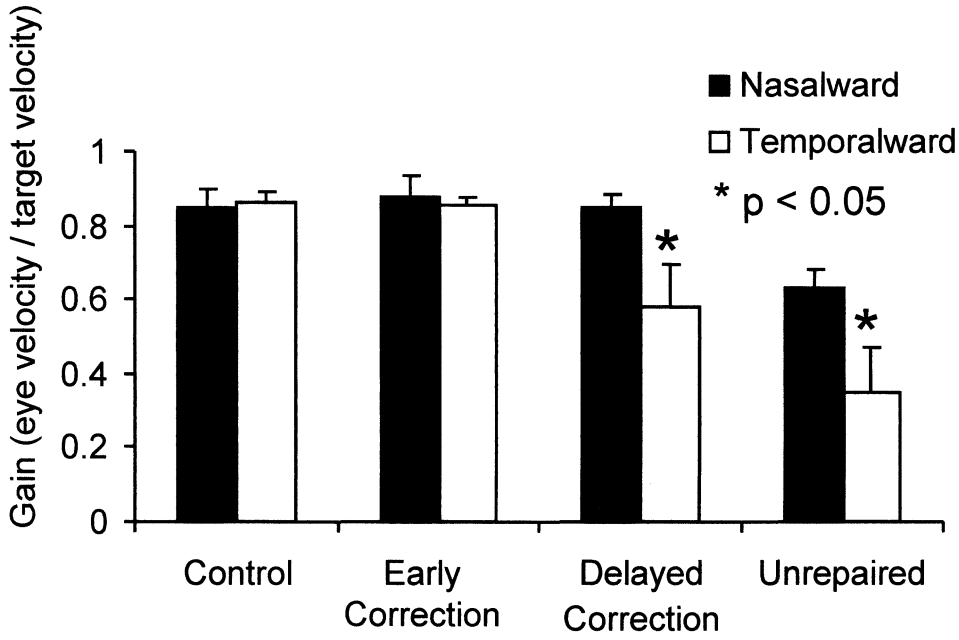

FIG 6. Mean OKN gain as a function of time of correction. No nasotemporal asymmetry of pursuit gain was evident for control of early correction monkeys, but nasalward gains were significantly stronger in delayed correction and unrepaired monkeys. Data were pooled from each animal in each group and between eyes for each animal. OKN, optokinetic nystagmus.

motion and weak to absent for temporally directed motion. The weaker response to temporalward motion was evident as lower slow-phase velocities and fewer epochs of sustained nystagmus beats (Figures 5C and 5D).

Figure 6 shows mean nasalward versus temporalward OKN gain for all studied animals. This graph shows with greater clarity that OKN was symmetrical in both normal control and early correction monkeys. Mean temporalward gain was 101% of nasalward gain for the controls and 97% of nasalward gain for the early correction group (P = NS). In contrast, OKN gain was asymmetrical in the delayed correction and uncorrected naturally strabismic

groups. Mean temporalward gain was 68% of nasalward gain in delayed correction monkeys ($P < .001$) and 56% of nasalward gain in uncorrected naturally strabismic animals ($P < .001$).

DISCUSSION

Our study provides detailed ocular motor information that would be difficult or impossible to obtain from human infants in randomized clinical trials. Using a primate model of esotropic human, we found that early correction of strabismus allowed the ocular motor pathways to re-establish normal eye alignment (fusional vergence) and stable fixation. Monocular horizontal smooth pursuit and large-field OKN eye movements were symmetric, normal, and robust. In contrast, delayed correction resulted in persistent heterotropia, latent fixation nystagmus, DVD, and pursuit/OKN asymmetry. Correction of the optical strabismus within the first 3 weeks of life in the monkeys (the equivalent of 3 months in humans) prevented the constellation of ocular motor defects that typify infantile esotropia in humans.[19,20]

Fresnel prisms were used in the experimental monkeys and plano lenses in the normal controls. In addition to misalignment of the visual axes (ie, image decorrelation), Fresnel prisms can cause image blur and mild chromatic aberration. The Fresnel prisms in our monkeys did not impair development of visual acuity and cause amblyopia. Acuity measured using spatial sweep VEPs were comparable in the experimental and control groups. Our results indicate that chronic image decorrelation in the sensory pathways of the central nervous system was the critical factor causing maldevelopment of the ocular motor pathways.

Early Strabismus Repair in Human Infants

Esotropia represents more than 90% of all strabismus that develops in human infants.[3,34] The timing of surgical corrections for infantile esotropia is controversial.[1-3] In North America, the mean age of surgical repair ranges from 10 to 18 months,[3,4] and in many parts of western Europe, surgical repair is delayed to age 2 to 4 years.[35] Stereopsis is restored in only 40% to 50% of infants undergoing surgery at age 10 to 18 months and seldom to normal threshold levels.[5,7] Motion VEP asymmetries and, to a lesser degree, pursuit/OKN asymmetries tend to be improved, but seldom resolve, in infants undergoing surgery at these ages.[6,8,9]

In the last decade, advances in outpatient infant anesthesia and surgical technique have made it possible to realign the eyes of strabismic children at just weeks or months of age. Reports of infants who have had "very early" surgery, ie, at or before age 6 months, are few, but the outcomes of these children when tested at older ages appear to be substantially better than those in the delayed-surgery groups.[11,12,14,36] Animal studies provide additional support for early surgery by showing that a brief period of strabismus, as short as 3 to 4 weeks, results in permanent loss of binocular cortical cells.[21,37-40] The controversy surrounding early surgery inspired the Congenital Esotropia Observational Study (CEOS) and the Early Surgery for Congenital Esotropia (ESCET) collaborative clinical trial.[13,41] Critics of early surgery argued that the strabismus may have resolved spontaneously in infancy if it had been left untreated. The CEOS found that the strabismus in fact persisted in 98% of infants who had large-magnitude ($\geq$ 40 PD) constant esotropia.[13,41] The CEOS defined a clinical profile of infants most likely to benefit from early surgery.[13] The ESCET was abandoned because experience from the CEOS indicated that recruitment for eligible patients would be too low to make a randomized clinical trial feasible.

The risks versus benefits of early surgery should be carefully evaluated when extrapolating our findings to strabismic human infants. The potential for early surgery to enhance ocular motor and sensory outcomes must be weighed against the possibility of spontaneous resolution. Because the likelihood of spontaneous resolution is exceedingly low (less than 2%) in the presence of constant, large-magnitude esotropia, the presence of a large, constant deviation should be confirmed before surgery is performed.[13]

Early surgery is believed to enhance sensory outcomes by re-establishing alignment during an early critical period for the development of stereopsis.[14,42,43] Although both age at alignment and duration of misalignment are correlated with long-term stereoacuity outcome, the duration of misalignment appears to be the more important factor.[14,43] In the present study, the normal ocular motor behaviors observed in the early correction monkeys most likely resulted from both earlier age at alignment and shorter duration of misalignment.

Neural Mechanisms for Pursuit/OKN Asymmetry and Latent Nystagmus

The nasally directed asymmetry of pursuit and the nasal drifts of latent-fixation nystagmus represent a directional bias encoded within the immature ocular motor pathways of the cerebral cortex. The mechanism for this nasal bias has been partly elucidated by electrophysiological and anatomic studies.[19,44-48] The pursuit motor area of extrastriate cortex in each cerebral hemisphere is innately wired so as to receive input from visual motion neurons that command pursuit in a nasal direction. This innate wiring is monocular and does not require binocular visual connections. In contrast, for temporally directed pursuit, binocular excitatory connections and absence of active suppression between ocular dominance columns of opposite ocularity are necessary for postnatal development of temporally directed pursuit. If binocularity fails to develop, the system will be incapable of activating normal temporally directed pursuit.[19,47,49,50] An innate monocular nasal bias is also present in a closely related cerebral

system, ie, the gaze-holding system, manifested by latent fixation nystagmus with nasal drifts of eye position.[19,50]

The cause of infantile strabismus is unknown. Ocular motor recordings in strabismic humans and monkeys show no primary abnormality of the extraocular muscles or cranial nerves.[19,20,49,50] It is conceivable that an innate defect of binocular connectivity in the visual cortex or a primary convergence motor neuron abnormality, or both, may play a causative role.[19] The present study showed that early disruption of binocular fusion in primates causes defects in ocular motor behaviors known to be mediated by cerebral visual pathways. It will be important to know whether this early disruption of binocular fusion causes maldevelopment of binocular connections in visual area V1 as has been documented in monkeys with natural infantile strabismus.[9,51,52] Neuroanatomical experiments designed to answer this question are the subject of our next report.

References

1. Jampolsky A. When should one operate for congenital strabismus? In: Brockhurst RJ, Boruchoff SA, Hutchinson BT, Lessell S, editors. Controversy in ophthalmology. Philadelphia: Saunders; 1977. p. 416-422.
2. Parks MM. Operate early for congenital strabismus. In: Brockhurst RJ, Boruchoff SA, Hutchinson BT, Lessell S, editors. Controversy in ophthalmology. Philadelphia: Saunders; 1977. p. 423-430.
3. von Noorden GK. Binocular vision and ocular motility: theory and management of strabismus. St. Louis (MO): Mosby; 1996.
4. von Noorden GK. A reassessment of infantile esotropia. XLIV Edward Jackson Memorial Lecture. Am J Ophthalmol 1988;105:1-10.
5. Birch EE, Stager DR, Berry P, Everett ME. Prospective assessment of acuity and stereopsis in amblyopic infantile esotropes following early surgery. Invest Ophthalmol Vis Sci 1990;31:758-65.
6. Tychsen L. Improvements in smooth pursuit and fixational eye movements after strabismus surgery in infants. Ophthalmology 1991; 98(suppl):94.
7. Birch EE, Stager DR, Everett ME. Random dot stereoacuity following surgical correction of infantile esotropia. J Pediatr Ophthalmol Strabismus 1995;32:231-5.
8. Norcia AM, Hamer RD, Jampolsky A, Orel-Bixler D. Plasticity of human motion processing mechanisms following surgery for infantile esotropia. Vision Res 1995;35:3279-96.
9. Tychsen L, Burkhalter A, Boothe RG. Neural mechanisms in infantile esotropia: what goes wrong? Am Orthoptic J 1996;46:18-28.
10. Ing MR. Early surgical alignment for congenital esotropia. Trans Am Ophthalmol Soc 1981;79:625-63.
11. Wright KW, Edelman PM, McVey JH, Terry AP, Lin M. High-grade stereo acuity after early surgery for congenital esotropia. Arch Ophthalmol 1994;112:913-9.
12. Ing MR. Surgical alignment prior to six months of age for congenital esotropia. Trans Am Ophthalmol Soc 1995;93:135-46.
13. Birch E, Stager D, Wright K, Beck R, Pediatric Eye Disease Investigator Group. The natural history of infantile esotropia during the first six months of life. J Am. Assoc Pediatr Ophthalmol Strabismus 1998;2:325-8.
14. Birch EE, Fawcett S, Stager DR. Why does early surgical alignment improve stereopsis outcomes in infantile esotropia? J AAPOS 2000; 4:10-4.
15. Atkinson J. Development of optokinetic nystagmus in the human infant and monkey infant: an analogue to development in kittens. In: Freeman RD, editor. Developmental neurobiology of vision. New York: Plenum; 1979. p. 277-87.
16. Boothe RG, Dobson V, Teller DY. Postnatal development of vision in human and nonhuman primates. Ann Rev Neurosci 1985;8:495-546.
17. O'Dell C, Boothe RG. The development of stereoacuity in infant rhesus monkeys. Vision Res 1997;37:2675-84.
18. Brown RJ, Wilson JR, Norcia AM, Boothe RG. Development of directional motion symmetry in the monocular visually evoked potential of infant monkeys. Vision Res 1998;38:1253-63.
19. Tychsen L. Infantile esotropia: current neurophysiologic concepts. In: Rosenbaum AL, Santiago AP, editors. Clinical strabismus management. Philadelphia: Saunders; 1999. p. 117-38.
20. Tychsen L, Yildirim C, Anteby I, Boothe R, Burkhalter A. Macaque monkey as an ocular motor and neuroanatomic model of human infantile strabismus. In: Lennerstrand G, Ygge J, editors. Advances in strabismus research: Basic and clinical aspects. Vol 78. Wenner-Gren International Series. Portland Press Ltd, London UK; 2000. p. 103-19.
21. Crawford MLJ, von Noorden GK. Optically induced concomitant strabismus in monkeys. Invest Ophthalmol Vis Sci 1980;9:1105-9.
22. Crawford M. Optical control of early visual experience in monkeys. Behav Brain Res 1996;79:201-5.
23. Foeller P, Tychsen L. Eye movement training and recording in alert macaque monkeys: 1. Operant visual conditioning. 2. Magnetic search coil and head restraint surgical implantation. 3. Calibration and recording. Strabismus 2002;10:5-22.
24. Norcia AM, Tyler CW. Spatial frequency sweep VEP: visual acuity during the first year of life. Vision Res 1985;25:1399-1408.
25. Norcia AM. Vision testing by visual evoked potential techniques. In: Isenberg SJ, editor. The eye in infancy. St. Louis (MO): Mosby-Year Book; 1994. p. 157-73.
26. Wong AMF, Tychsen L. Effects of extraocular muscle tenotomy on congenital nystagmus in macaque monkeys. J AAPOS 2002;6:100-7.
27. Robinson DA. A method of measuring eye movement using a scleral search coil in a magnetic field. IEEE Trans Bio-Med Electronics 1963;10:137-45.
28. Fuchs AF. Saccadic and smooth pursuit eye movements in the monkey. J Physiol 1967;191:609-31.
29. Quick MW, Boothe RG. Measurement of binocular alignment in normal monkeys and in monkeys with strabismus. Invest Ophthalmol Vis Sci 1989;30:1159-68.
30. von Noorden GK. Binocular vision and ocular motility. St. Louis (MO): Mosby-Year Book; 1996.
31. Rashbass C. The relationship between saccadic and smooth tracking eye movements. J Physiol 1961;159:326-38.
32. Lisberger SG, Westbrook LE. Properties of visual inputs that initiate horizontal smooth pursuit eye movements in monkeys. J Neurosci 1985;5:1662-73.
33. Leigh RJ, Zee DS. The neurology of eye movements. New York: Oxford University Press; 1999.
34. Tychsen L. Binocular vision. In: Hart WM, editor. Adler's physiology of the eye: Clinical applications. St. Louis (MO): Mosby; 1992. p. 773-853.
35. The Early vs. Late Infantile Strabismus Group. The early vs. late infantile strabismus surgery study: first monitoring report. Strabismus 1994;2:87-102.
36. Ing M, Costenbader FD, Parks MM, Albert DG. Early surgery for congenital esotropia. Am. J Ophthalmol 1966;61:1419-27.
37. Crawford M. Binocular neurons and binocular function in monkeys and children. Invest Ophthalmol Vis Sci 1983;24:491-5.
38. Crawford M, Harwerth RS, Smith EL, von Noorden G. Loss of stereopsis in monkeys following prismatic binocular dissociation during infancy. Behav Brain Res 1996;79:207-18.
39. Crawford M, Harwerth RS, Chino YM, Smith EL, III. Binocularity in prism-reared monkeys. Eye 1996;10:161-6.
40. Smith EL, Chino YM, Ni J, Cheng H, Crawford ML, Harwerth RS. Residual binocular interactions in the striate cortex of monkeys

reared with abnormal binocular vision. J Neurophysiol 1997;78: 1353-62.
41. Pediatric Eye Disease Investigator Group. Spontaneous resolution of early-onset esotropia: experience of the congenital esotropia observational study. Am J Ophthalmol 2002;133:109-18.
42. Birch EE, Gwiazda J, Held R. Stereoacuity development for crossed and uncrossed disparities in human infants. Vision Res 1982;22:507-13.
43. Ing MR, Okino LM. Outcome study of stereopsis in relation to duration of misalignment in congenital esotropia. J AAPOS 2002;6: 3-8.
44. Dursteler M, Wurtz R, Newsom W. Directional pursuit deficits following lesions of the foveal representation within the superior temporal sulcus of the macaque monkey. J Neurophysiol 1987;57: 1262-87.
45. Hoffmann K-P, Distler C. The optokinetic reflex in macaque monkeys with congenital strabismus. IV Symposium of the Bielschowsky Society for the Study of Strabismus. Eye Clinic Heidelberg of the Ruprecht-Karls University, Germany, 1992. Vol. 1. Aeolus Press.
46. Fuchs AF, Mustari MJ. The optokinetic response in primates and its possible neuronal substrate. In: Miles SA, Wallman J, editors. Visual motion and its role in the stabilization of gaze. New York: Elsevier; 1993. p. 343-69.
47. Kiorpes L, Walton PJ, O'Keefe LP, Movshon JA, Lisberger SG. Effects of artificial early-onset strabismus on pursuit eye movements and on neuronal responses in area MT of macaque monkeys. J Neurosci 1996;16:6537-53.
48. Mustari MJ, Tusa RJ, Burrows AF, Fuchs AF, Livingston CA. Gaze stabilizing deficits and latent nystagmus in monkeys with early-onset visual deprivation: role of the pretectal NOT. J Neurophysiol 2001; 86:662-75.
49. Tychsen L, Hurtig RR, Scott WE. Pursuit is impaired but the vestibulo-ocular reflex is normal in infantile strabismus. Arch Ophthalmol 1985;103:536-9.
50. Tychsen L, Lisberger SG. Maldevelopment of visual motion processing in humans who had strabismus with onset in infancy. J Neurosci 1986;6:2495-2508.
51. Tychsen L, Burkhalter A. Neuroanatomic abnormalities of primary visual cortex in macaque monkeys with infantile esotropia: preliminary results. J Pediatr Ophthalmol Strabismus 1995;32:323-8.
52. Tychsen L, Burkhalter A, Boothe R. Functional and structural abnormalities of visual cortex in infantile strabismus. Klin Monatsbl Augenheilkd 1996;208:18-22.

An Eye on the Arts – The Arts on the Eye

Very few people—most notably, actors and politicians—are able consciously to control all of their facial expressions. Lies can often be caught when the liar's true feelings briefly leak through the mask of deception.

One of the most difficult facial expressions to fake—or conceal, if it is genuinely felt—is sadness. When someone is truly sad, the forehead wrinkles with grief and the inner corners of the eyebrows are pulled up. Paul Ekman, professor of psychology at the University of California, San Francisco, who has been studying facial expressions for the past thirty years, found that fewer than 15 percent of the people he tested were able to produce this eyebrow movement voluntarily. By contrast, the lowering of the eyebrows associated with an angry scowl can be replicated at will by almost everybody. 'If someone claims they are sad and the inner corners of their eyebrows don't go up,' Ekman says, 'the sadness is probably false.'

The smile, on the other hand, is one of the easiest facial expressions to counterfeit. It takes just two muscles—the *zygomaticus major* muscles that extend from the cheekbones to the corners of the lips—to produce a grin. But there's a catch. A genuine smile affects not only the corners of the lips but also the *orbicularis oculi*, the muscle around the eye that produces the distinctive 'crow's-feet' associated with people who laugh a lot. A counterfeit grin can be unmasked if the lip corners go up, the eyes crinkle but the inner corners of the *oculi* that is difficult to fake. The absence of lowered eyebrows is one reason why false smiles make a person look constipated rather than happy.

—James Geary (from *The Body Electric: Anatomy of the New Bionic Senses*)