

Duration of Binocular Decorrelation Predicts the Severity of Latent (Fusion Maldevelopment) Nystagmus in Strabismic Macaque Monkeys

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PURPOSE. Infantile esotropia is linked strongly to latent fixation nystagmus (LN) in human infants, but many features of this comorbidity are unknown. The purpose of this study was to determine how the duration of early-onset strabismus (or time-liness of repair) affects the prevalence of LN in a primate model.

METHODS. Optical strabismus was created in infant macaques by fitting them with prism goggles on day 1 of life. The goggles were removed after 3 ($n = 2$), 12 ($n = 1$) or 24 weeks ($n = 3$), emulating surgical repair of strabismus in humans at 3, 12, and 24 months of age, respectively. Eye movements were recorded by using binocular search coils.

RESULTS. Each animal in the 12- and 24-week groups exhibited LN and manifest LN, normal spatial vision (no amblyopia), and constant esotropia. The 3-week duration monkeys had stable fixation (no LN) and normal alignment indistinguishable from control animals. In affected monkeys, the longer the duration of binocular decorrelation, the greater the LN: mean slow-phase eye velocity (SPEV) in the 24-week animals was three times greater than that in the 12-week monkey ($P = 0.03$); mean LN intensity in the 24-week monkeys was three times greater than that in the 12-week monkey ($P = 0.03$).

CONCLUSIONS. Binocular decorrelation in primates during an early period of fusion development causes permanent gaze instability when the duration exceeds the equivalent of 3 months in humans. These findings support the conclusion that early correction of infantile strabismus promotes normal development of cerebral gaze-holding pathways. (*Invest Ophthalmol Vis Sci.* 2008;49:1872-1878) DOI:10.1167/iovs.07-1375

Infantile (congenital) esotropia is a convergent misalignment of the visual axes with onset in the first 6-12 months of life.^{1,2} It represents more than 90% of all strabismus occurring

in infancy, and ~40% of all pediatric concomitant strabismus.³⁻⁵ In addition to subnormal fusion and stereopsis, children and adults with infantile esotropia exhibit a defect of stable gaze-holding, evident as fixation nystagmus.² The nystagmus is characterized by a nasally directed, slow-phase drift of eye position when viewing monocularly with either eye.⁶ The severity of the nystagmus (and its conspicuity during clinical examination) increases when one eye is covered, hence the term: latent nystagmus (LN). When the nystagmus is evident under conditions of binocular viewing (i.e., both eyes open) it is called manifest LN.⁶ Although infantile esotropia is the leading cause, any disorder that perturbs development of binocular fusion in infancy (e.g., monocular or severe binocular deprivation⁷) will produce LN and manifest LN. The Committee on Eye Movement and Strabismus (CEMAS) classification has recommended therefore that the terms LN/manifest LN be replaced by the etiologic descriptor: fusion-maldevelopment nystagmus.⁸

The appropriate age for surgical repair of infantile esotropia is controversial.^{9,10} In North America, the average age of repair ranges from 10 to 18 months.^{2,4} Despite surgical repair at this age, deficits of binocular fusion persist permanently, including defective stereopsis, asymmetries of eye tracking, and LN.¹¹⁻¹³ Surgery before age 4 to 6 months (early repair) has been advocated because of an enhanced probability of restoring stereopsis.¹⁴⁻¹⁸ However, little detailed information is known regarding improvement in motor functions.

Behavioral studies have shown that the postnatal development of binocular sensory and motor functions in normal infant monkeys closely parallel that of normal infant humans, but on a compressed time scale (i.e., 1 week of monkey development is equivalent to 1 month in the human).¹⁹⁻²² Infant monkeys with strabismus display the same constellation of perceptual and ocular motor abnormalities found in strabismic humans, including defective stereopsis, abnormal vergence, eye movement asymmetries, and LN.^{7,23-27} Thus, strabismic monkeys are an appropriate animal model for study of the human disorder.

We reported preliminary results describing early versus delayed repair of esotropia in infant monkeys, using a model of optically induced strabismus.²⁸ The repair (i.e., removal of prism goggles) was deliberately timed to mimic shorter (≤ 3 months) versus longer (12-24 months) durations of unrepaired esotropia in human infants. Early repair (shorter duration) was able to restore symmetric tracking, whereas delayed repair (longer duration) caused permanent asymmetries. The purpose of the present study was to determine how the timing of repair influences the severity of LN.

METHODS

Animals and Goggle-Rearing Groups

Eight normal infant rhesus monkeys (*Macaca mulatta*, six male, two female) were used. They were born at the Yerkes Regional Primate

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TABLE 1. Rearing Conditions and Visuomotor Findings for the Eight Macaque Monkeys Used in the Experiments

Animal/Age at Testing	Rearing Conditions (RE Prism; LE Prism)	Eye Alignment at Testing	Latent Nystagmus	Pursuit/OKN Asymmetry	DVD	Visual Acuity SSVEP (cyc/deg)
Normal control						
WE/1.5 y	Plano lens 3 wk	Orthophoric	No	No	No	RE: 22.8 LE: 20.5
AY/2 y	Plano lens 12 wk	Orthophoric	No	No	No	RE: 18.1 LE: 16.2
3-Wk duration						
TE/1.5 y	11.4° BI; 11.4° BD	Orthophoric	No	No	No	RE: 19.9 LE: 21.4
SY/1.7 y	11.4° BI; 11.4° BD	Orthophoric	No	No	No	RE: 17.9 LE: 22.8
12-Wk duration						
GO/1.5 y	11.4° BI; 11.4° BD	ET: 8°/LHT: 4°	Yes	Yes	Yes	RE: 8.3 LE: 10.6
24-Wk duration						
HA/2 y	11.4° BI; 11.4° BD	ET: 15°/RHT: 4°	Yes	Yes	Yes	RE: 19.2 LE: 18.6
QN/2 y	11.4° BI; 11.4° BD	ET: 12°/LHT: 4°	Yes	Yes	Yes	RE: 23.3 LE: 24.0
EY/1.5 y	11.4° BI; 11.4° BD	Alter 12° ET	Yes	Yes	Yes	RE: 8.9 LE: 7.7

BI, base-in Fresnel prism; BD, base-down Fresnel prism; RE, right eye; LE, left eye; ET, esotropia; HT, hypertropia; OKN, optokinetic nystagmus; DVD, dissociated vertical deviation; SSVEP, spatial sweep VEP.

Research Center and fitted with goggles on the first day of life. The fitting procedure, similar to the method described by Crawford et al.,²⁹ was not stressful to the monkeys and did not require anesthesia. Padded head straps held the goggle helmet firmly in place, preventing the infant from removing the apparatus. The lens holders unscrewed to allow thin plastic Fresnel prisms (Fresnel Prism and Lens, Eden Prairie, MN) to be inserted and secured in place before each eye. The animals were observed during bottle feedings and periodically in the primate nursery, to ensure that the goggles remained clear and in proper position. Normal play and interactions with other infant monkeys were not affected noticeably by the goggles. Once daily, the goggle helmet was removed for cleaning and, if necessary, adjustment. During these brief periods, the animal was placed in a dark enclosure to prevent normal binocular viewing.

The goggles created a combined horizontal and vertical strabismus to prevent fusion. As listed in Table 1, the experimental animals viewed through an 11.4° base-in prism in the right eye and an 11.4° base-down prism in the left eye. The two control animals (WE, AY) wore the same goggle apparatus but with plano lenses in place of prisms. The experimental animals wore the prism goggles for durations of 3, 12, or 24 weeks, corresponding to durations of unrepaired strabismus in human of 3, 12, and 24 months, respectively. Once the defined period of goggle-rearing ended, the monkeys were transported to Washington University where they were trained to perform visual fixation tasks without goggles with fruit juice used as a positive feedback reward.³⁰ Six animals used in the present study were also subjects of an earlier report²⁸; Figure 2 of that report showed tracings of fixation with one eye in three animals.

Monocular visual acuity was measured using spatial-sweep visually evoked potentials (SSVEP)³¹ without correction for refractive error. Cycloplegic refractions revealed a refractive error $\leq +3.00$ spherical equivalent in each of the experimental and control animals. In the months before coil implantation, eye alignment was assessed with 35-mm photographs and video recordings of each monkey (Hirshberg method³²). All procedures were performed in compliance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and were approved by the Washington University Animal Care and Use Committee.

Eye Movement Recording

Detailed descriptions of the surgical and recording methods have been published in previous reports; an abbreviated description is provided herein.³⁰ After induction of deep general inhalation anesthesia (supplemented by local infiltration and topical anesthesia), scleral search coils were implanted in both eyes and a custom-built, polycarbonate head-restraint device was attached to the skull.

Eye movements were recorded with standard magnetic search coil techniques.^{33,34} The monkey sat in a primate chair in the middle of field coils. The head restraint was locked to preclude head movement, and the room was lit with dim background illumination. Eye position was calibrated at the start of each recording session by using a calibration coil and by having the animal maintain eye position within a 2° window of target position. The target was a laser spot subtending $\sim 0.05^\circ$ projected onto the back of a translucent screen located 50 cm in front of the animal. The calibration sequence was repeated separately for each eye.

Recordings were performed under conditions of binocular and monocular viewing. Monocular viewing was achieved by use of liquid-crystal shutter goggles which cycled from transparent to opaque (or the reverse) in 80 μ s (0.08 ms).³⁵ Voltages proportional to horizontal and vertical eye position were digitized at 500 Hz. Eye velocity signals were obtained by differentiating the eye position signals, which were then passed through a finite impulse response filter (DC to 90 Hz). 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).

Visual Stimuli, Trial Design, and Data Analysis

While viewing monocularly, each monkey was required to fixate the laser spot at straight-ahead gaze or at eccentricities of $\pm 10^\circ$ horizontally and vertically. The target was presented in repeated trials. To receive a juice reward, the animal had to maintain the 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.³⁰

Fixation was determined to be stable (i.e., 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. LN was assessed as present if a nasally directed, slow-phase drift of >0.10 deg/s was detected in the tracings of the fixating eye during rewarded trials, accompanied by temporally directed microsaccades (fast phases) which repositioned the target on the fovea. The analysis was conducted by two independent observers masked to the animal group. Eye velocity tracings verified linear or decreasing-velocity slow phases (none of the animals had evidence of pendular nystagmus in the velocity records). Horizontal and vertical components of slow-phase eye velocity (SPEV) were calculated for each cycle of nystagmus by dividing amplitude by slow-phase duration, measured from a minimum of 50 eye position epochs ≥ 500 ms for fixation with each eye in each animal. Nystagmus frequency was calculated as the number of cycles per second. Nystagmus intensity was calculated as the product of amplitude and frequency. The angular direction of each slow phase was calculated as the arc tangent of vertical and horizontal amplitudes, defining the beginning of each slow phase as the origin. The angle for the right-eye viewing was plotted as counterclockwise rotation from the polar axis and for the left eye, as clockwise. Differences among means for the animal groups were compared using analysis of variance (ANOVA). Significance was defined as $P < 0.05$.

RESULTS

Visual Acuity and Eye Alignment

Table 1 summarizes the ocular findings for the eight animals at the time of testing, 1.5 to 2 years after prism goggle rearing. The control and prism 3-week-duration monkeys had normal eye alignment. The 12- and 24-week duration monkeys all had constant esotropia and vertical deviations, with the largest magnitudes recorded in the 24-week animals. None of the strabismic monkeys had amblyopia (defined as an interocular acuity difference ≥ 0.25 octave).³⁶ Grating visual acuity thresholds, as measured by SS VEP (Table 1), varied idiosyncratically from animal to animal, but interocular acuity differences were comparable in experimental and control monkeys. Grating visual acuity was not related to minor variations in refractive error from animal to animal.

Fixation Nystagmus: LN and Manifest LN

The control and 3-week monkeys had stable fixation when viewing monocularly or binocularly (Figs. 1A, 1B). The 12- and 24-week monkeys, however, showed LN (fusion maldevelopment nystagmus³⁵), more pronounced in the 24-week animals. The nystagmus was evident as nasalward slow-phase drifts, with respect to the fixating eye, interrupted by temporalward fast-phase jerks (Figs. 1C, 1D). When the subject was fixating with the left eye (right eye occluded), both eyes drifted to the right; when fixating with the right eye (left eye occluded), both eyes drifted to the left. The wave form of the slow-phase—decreasing or linear velocity—conformed to standard LN criteria.⁶ The nystagmus appeared conjugate during inspection of fixation videotape (the equivalent of clinical examination of human infants): The direction and frequency were the same in both eyes. Analysis of eye position tracings, however, revealed mild-to-moderate disconjugacies of velocity and amplitude between the two eyes. In Figure 1C, for example, the nystagmus was more pronounced in the (esotropic) left eye of monkey GO when the animal fixated with the right eye. In Figure 1D (monkey HA), the nystagmus was more pronounced in the esotropic right or left eye. Figure 1D also illustrates (BE traces) that the nystagmus intensity tended to be less pronounced under conditions of binocular (neither eye occluded) viewing (i.e., LN was more intense than manifest LN).

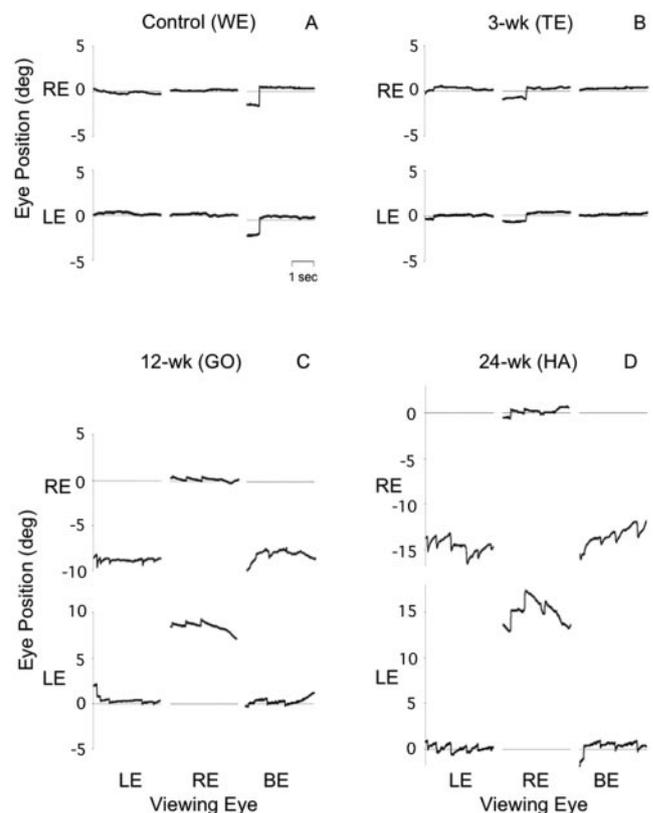


FIGURE 1. Stable fixation versus latent (LN)/manifest latent nystagmus (MLN) in horizontal eye position tracings from four representative monkeys. Monocular viewing with the left eye (LE) or right eye (RE) and binocular viewing (BE, both eyes). The nonviewing eye was occluded during monocular viewing. (A, B) Stable fixation in control monkey WE and 3-week monkey TE, who had normal eye alignment. (C) LN and MLN in 12-week monkey GO, who had alternating esotropia of $\sim 8^\circ$. The slow phase is directed nasalward with respect to the viewing eye. (D) LN and MLN in 24-week monkey HA, who had alternating esotropia $\sim 15^\circ$. Upward, rightward eye position.

Slow-Phase Eye Velocity

Average SPEVs the LN (monocular viewing) and manifest LN (binocular viewing) are plotted in Figure 2. LN SPEV showed an increasing trend with longer durations of optical strabismus (ANOVA, $P = 0.02$). The largest mean velocity, 2.4 deg/s, was recorded during monocular viewing in the 24-week monkeys. Mean SPEV in the 24-week monkeys was three times greater than that in the 12-week monkey, and 16 times greater than baseline fixation eye velocity fluctuations in the 3-week and control monkeys. In animals exhibiting LN, mean horizontal slow-phase amplitude during monocular viewing ranged from 0.21° to 1.66° and mean nystagmus frequency ranged from 0.98 to 4.26 cycles/s. During binocular viewing, the control and 3-week animals showed stable gaze holding, while all longer-duration animals exhibited manifest LN. Nystagmus velocity during binocular viewing was 26% to 51% slower than during monocular viewing.

Nystagmus Intensity

Nystagmus intensity (frequency \times amplitude) is shown in Figure 3. LN intensity increased with longer duration of optical strabismus (ANOVA, $P = 0.03$), and the relationship followed the same pattern as SPEV: mean horizontal intensity in the 24-week monkeys was 3 times greater than that in the 12-week monkey, and 16 times greater than baseline velocity deflec-

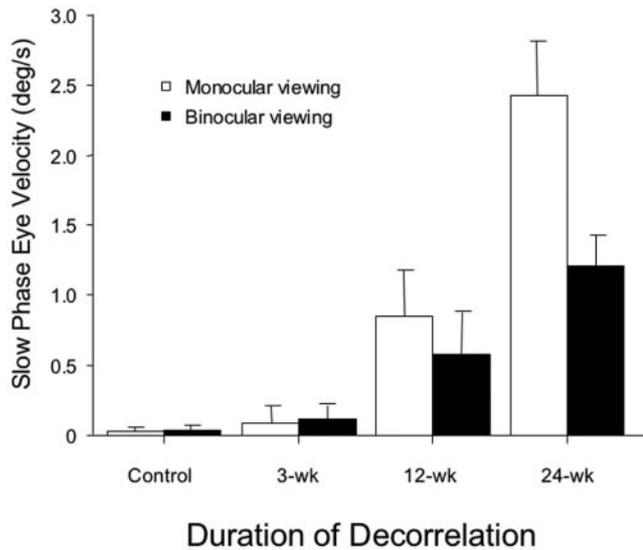


FIGURE 2. SPEV of LN (monocular viewing) and MLN (binocular viewing) as a function of duration of binocular decorrelation in the four groups of monkeys. Group means \pm SD; pooled responses of the right and left eyes.

tions in the 3-week and control monkeys. Under binocular viewing conditions, the 12- and the 24-week animals showed a reduced-intensity nystagmus. No systematic relationship was found between gaze direction ($\pm 10^\circ$ along the horizontal and vertical meridians) and SPEV or nystagmus intensity.

Directional Vector of Slow Phases

Vector plots of mean horizontal and vertical slow-phase LN are shown in Figure 4, which pools the results of the 12- and 24-week monkeys. Slow-phase drift in the fixating eye was dominated by a nasally directed horizontal component, with a smaller upward vertical component. The mean vector, combining the right and left eyes, was 20° (range, 14° - 27°) above the horizontal axis. There was no significant difference in mean slow-phase direction of the vectors in the four monkeys with

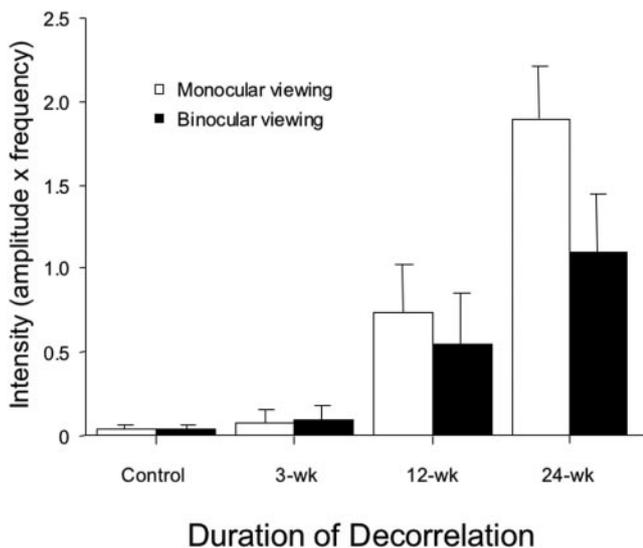


FIGURE 3. Intensity of LN (monocular viewing) and MLN (binocular viewing) as a function of duration of binocular decorrelation in the four groups of monkeys. Group means \pm SD; pooled responses of right and left eyes.

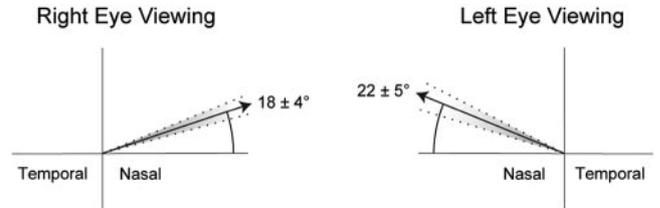


FIGURE 4. Directional vector of LN when viewing with the right versus left eye in the strabismic monkeys. The vector was predominantly nasalward and mildly upward in each animal; pooled responses, mean \pm SD.

nystagmus (ANOVA, $P = 0.43$). The angular direction of these vectors is similar to that reported previously by Kiorpes et al.²³ in monkeys with infantile-onset esotropia created by muscle tenotomy.

DISCUSSION

Using a primate model of infantile esotropia, we found that reduction of binocular decorrelation by 3 weeks of age (equivalent to 3 months of age in humans) allowed recovery of stable gaze-holding. Longer durations of decorrelation resulted in permanent maldevelopment of the gaze pathways, evident as LN during monocular viewing and as manifest LN during binocular viewing. The severity of the ocular motor defect—measured either as SPEV or nystagmus intensity—increased systematically with the duration of decorrelation. The primate model allowed us to: (1) impose strict periods of binocular decorrelation and (2) record precisely large blocks of trials to compare the behavioral deficits. This information would be difficult or impossible to obtain from human infants in clinical trials. Extrapolated to humans, these results imply that timely surgery for infantile esotropia prevents the development of nystagmus, while delayed surgery promotes nystagmus.

A concern with the animal model is that it may not adequately mimic the effects of strabismus surgery in children. Strabismus surgery entails muscle tenotomy and repositioning on the globe, with adaptations of muscle length and tension.³⁷ These factors are not replicated in monkeys by prism goggle removal. However, strabismus surgery in children that does not achieve restoration of fusion appears to have no salutary effect on reducing or eliminating LN.^{11,12} Likewise, muscle tenotomy does not reduce or eliminate pendular nystagmus or LN in naturally strabismic monkeys.³⁸

The nystagmus in the strabismic animals was similar to that observed in strabismic children.^{2,11} It was characterized by a linear or decreasing-velocity, slow-phase waveform; the slow-phase was directed nasalward with respect to the viewing eye; and the nystagmus was reduced under conditions of binocular viewing. Each of these features is also consistent with LN or manifest-LN associated with naturally occurring strabismus in macaque monkeys, and with disruptions of binocularity caused by monocular deprivation in both infant monkeys and humans.^{23,25,26,39}

Paucity of Binocular V1 Connections and Nasotemporal Gaze Instability

The nasalward drifts of LN represent a directional imbalance of conjugate-gaze pathways. The conjugate-gaze pathways of the visual cortex include visual areas V1 (striate cortex), medial temporal (MT), and medial superior temporal (MST).⁴⁰ Efferents from V1 and MT feed to area MST in each cerebral hemisphere.⁴¹⁻⁴⁵ Area MST neurons in turn drive ipsilateral, brain stem premotor gaze neurons (within the nucleus of the

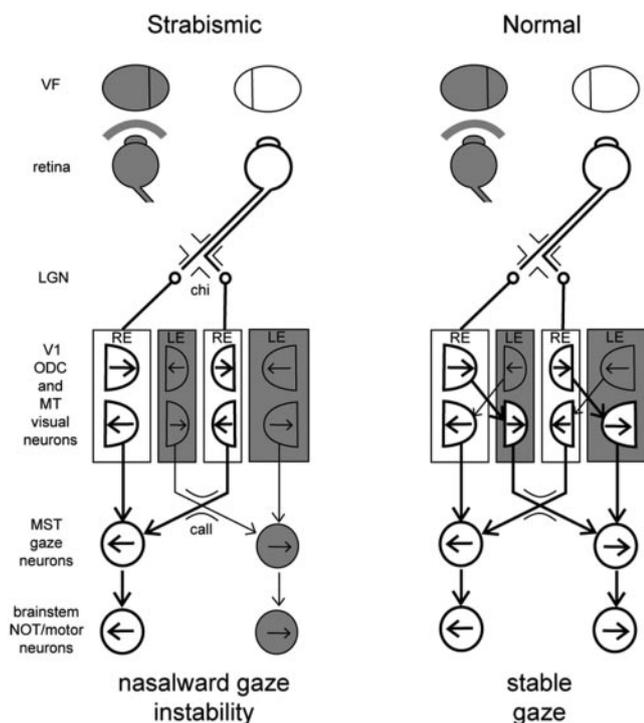


FIGURE 5. Diagram of the circuit mediating gaze-holding in primates and the role of binocular connections. Shaded structures indicate less active visual and motor neurons caused by occlusion of one eye and/or interocular suppression. Strabismic: flowing top to bottom, starting from monocular visual field of viewing right eye. RGC fibers from the nasal and temporal hemiretinas decussate at the optic chiasm (chi), synapse at the lateral geniculate nucleus (LGN), and project to alternating, monocular right eye (RE) and left eye (LE) ODCs in V1. In each V1, ODCs representing the nasal hemiretinas (temporal visual hemifield) occupy slightly more cortical territory than those representing the temporal hemiretinas (nasal hemifield), but each ODC contains neurons sensitive to nasalward versus temporalward motion (neurons, *half circles* match corresponding hemi-field; *arrows*, directional preference). Visual area neurons (including those beyond V1 in area MT) are sensitive to both nasal- and temporalward motion, but only those encoding nasalward motion are wired innately, through monocular connections, to gaze neurons in area MST. MST in each cerebral hemisphere encodes ipsiversive gaze, which is nasalward gaze in relation to the contralateral eye. Normal: access to MST for temporalward gaze requires binocular connections to homoversive neurons within neighboring ODCs that have opposite-ocularity (i.e., LE ODC neurons when viewing with the RE). Binocular horizontal connections: *diagonal lines* between RE and LE neurons. Call, efferent projections through splenium of corpus callosum. MST efferents project to the ipsilateral brain stem nucleus of the optic tract (NOT) and ipsiversive motor nuclei.

optic tract, NOT) and, via projections from NOT, the motor neurons (medial vestibular, abducens, and oculomotor nuclei) that drive conjugate gaze.^{7,40}

The mechanism for the nasalward gaze bias has been elucidated by electrophysiologic and anatomic studies of normal^{46,47} and strabismic primates,^{23,48-50} as summarized in neural circuit models.^{2,7,23} In brief, area MST in each cerebral hemisphere appears to be wired innately to receive input from nasalward visual motion neurons of areas V1/MT. This innate wiring (Fig. 5) is monocular; binocular visual connections are not required. In contrast, the V1/MT neurons that command temporalward gaze gain access to area MST predominantly through binocular connections. If binocular connections fail to develop properly, area MST in the hemisphere contralateral to the viewing eye will be more active, becoming evident as the nasalward gaze imbalance of LN.

Decorrelation of activity during an early critical period of development is known to cause loss of binocular connections in V1 of strabismic kittens.⁵¹⁻⁵³ Binocular connections in V1 have also been shown to be deficient in monkeys with natural infantile esotropia and LN.^{54,55} The deficit of binocular connections is accompanied by suppression of metabolic activity between ocular dominance columns (ODCs) of opposite ocularity (interocular suppression).^{56,57} The systematic relationship between the severity of LN and the duration of binocular decorrelation in the present study suggests that the severity of LN may be a behavioral marker for the severity of anatomic, binocular deficits in V1.

Implications for Early Strabismus Repair in Human Infants

The timing of surgical corrections for esotropia in human infants is controversial.^{9,10,58} Critics of early surgery have argued that the esotropia may have resolved spontaneously in infancy if left untreated. The initial Congenital Esotropia Observational Study found that the strabismus in fact persisted in 98% of infants who had large-magnitude (≥ 40 PD) constant esotropia.^{59,60} A follow-up study of infants with small and variable-angle constant esotropia revealed that, over a period of months, all progressed to larger misalignment and required surgery.

Early surgery in humans (i.e., at or before age 4-6 months) is believed to enhance sensory outcomes by re-establishing correlated binocular activity during an early critical period for the development of stereopsis.^{18,61,62} The stereopsis outcomes of infants who have early surgery are better than those in the delayed-surgery groups.^{15,17,18,63} Both age at alignment and duration of misalignment are linked to enhanced stereoacuity outcomes, but the duration of misalignment appears to be the more important factor.^{62,64} Durations less than a total of 3 months in human infants are associated with the best outcomes. The effect of early versus delayed surgery on ocular motor behaviors is less clear. Early surgery children tend to need fewer reoperations to restore horizontal alignment and may have slightly lower rates of vertical deviation, but little is known about the effects on tracking and gaze stability. The results of the present study provide indirect support for early surgery by showing that restoration of correlated binocular images, by the equivalent of 3 months of age in human, facilitates development of stable gaze.

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