Effect of Onset Age of Strabismus on the Binocular Responses of Neurons in the Monkey Visual Cortex

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Purpose. By 6 weeks of age, neurons in the monkey's primary visual cortex acquire qualitatively adult-like binocular response properties and behaviorally stereopsis emerges. In this study, it was determined whether the onset of strabismus has a more severe impact on cortical binocularity before or after this critical developmental age.

Methods. Infant monkeys were fit with a light-weight helmet which held a total of 27 diopters of base-in prisms in front of their two eyes for a fixed period of two weeks. For one group of infant monkeys, prism-rearing began at 2 weeks of age and for a second group, the onset was at 6 weeks of age. Immediately after the rearing period, i.e., at 4 weeks and 8 weeks of age, respectively, extracellular single-unit recording methods were used to determine the nature and severity of alterations in the binocular response properties of V1 neurons. Dichoptic sinewave gratings were used as visual stimuli.

Results. In comparison to normal age-matched infants, V1 neurons in both strabismic groups exhibited reductions in sensitivity to interocular spatial phase disparities (disparity sensitivity) and a higher prevalence of binocular inhibitory interactions (binocular suppression). However, the reduction in disparity sensitivity and the magnitude of binocular suppression were much greater in the late (6–8 weeks) than the early (2–4 weeks) onset group.

Conclusions. Discordant binocular signals due to brief periods of early strabismus have more serious effects on the development of binocular properties of V1 neurons if they occur shortly after rather than before the emergence of stereopsis (i.e., when the binocular connections are relatively more mature but the visual cortex still shows a high degree of plasticity). (*Invest Ophthalmol Vis Sci.* 2000;41:948–954)

Early onset strabismus is known to severely disrupt vision development in a substantial proportion of human infants.[1] One of the most commonly debated issues concerning the management of infants with congenital strabismus is how early (at what age) proper eye alignment needs to be restored to preserve stereoscopic vision and to prevent the emergence of amblyopia. There appears to be very little disagreement with the view that surgical alignment should be performed before 2 years of age.[2–4] However, it has become a matter of debate whether earlier surgery (e.g., before 6 months of age) is of significant benefit for preserving "normal" binocular sensory functions.[5–11]

To gain insight into this critical issue of vision development, we have been investigating how the binocular response properties of neurons in the primary visual cortex (V1) mature in normal monkeys and how binocularly conflicting signals early in life alter their postnatal development. As early as 6 days of age, an adult-like proportion of neurons is sensitive to interocular spatial phase disparities in normal infant monkeys.[12] Over the next 3 to 4 postnatal weeks both binocular and monocular response properties of V1 neurons rapidly mature.[12,13] Consequently, V1 neurons exhibit qualitatively adult-like properties by 4 to 6 weeks of age (equivalent to 4 to 6 months in humans), a critical age during normal development (Fig. 1). This rapid cortical maturation just precedes the age when stereopsis, a sensitive measure of the status of binocular visual functions, normally emerges in monkeys.[14]

Although early strabismus is known to disrupt binocular vision development, it is not clear whether misalignment before or after the emergence of stereopsis causes more serious disruptions in binocular sensory development. In the present study, we investigated this issue by examining the development of binocular response properties of V1 neurons in infant monkeys that were subjected to brief periods of early strabismus.

Methods

All experimental procedures conformed to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Subjects

Eight infant monkeys (*Macaca mulatta*) served as study subjects. In four monkeys, the diplopia and confusion associated with a concomitant strabismus were simulated by placing prisms in front of each eye. Specifically, the infant monkeys

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Supported by Grants RO1 EY-08128, EY-03611, and RR-07146 from the National Institutes of Health (Bethesda, Maryland).

Submitted for publication August 5, 1999; revised October 21, 1999; accepted November 8, 1999.

Commercial relationships policy: N.

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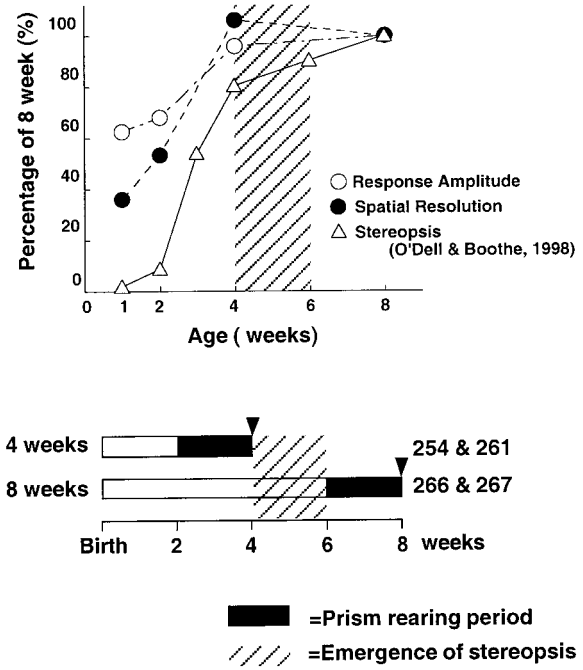

FIGURE 1. *Top*: Summary data on the development of stereopsis and the monocular response properties of V1 neurons in normal infant monkeys. The function for stereopsis development is based on the data published by O'Dell and Boothe.[14] The monocular response properties of V1 neurons are based on Chino et al.[12] and a recently acquired new data set. Note that the data points indicate the percentage of the respective values at 8 weeks of age. *Bottom*: The timing of the prism-rearing regimen relative to the known age for stereopsis onset in monkeys. MK 254 and MK 261 received optical strabismus before 4 weeks of age, and MK 266 and MK 267 received it after 6 weeks of age. *Triangles* indicate the time of the recording experiments.

were fit with a lightweight helmet, which held 17 and 10 D prisms oriented base-in in front of the left and right eyes, respectively.[15] The total prismatic deviation exceeded the fusional vergence ranges of normal monkeys.[16] The duration of the prism-rearing was for a fixed period of 2 weeks (Fig. 1). In one group, the rearing began at 2 weeks of age (before the known age of stereopsis onset), whereas it began at 6 weeks of age in the second group (after the onset of stereopsis). Immediately after the rearing period, extracellular single-unit recording methods were used to determine the nature and severity of the alterations in the binocular response properties of V1 neurons. The remaining four infant monkeys served as normal age-matched controls.

Preparation

The surgical preparation and the recording and stimulation methods are described in detail elsewhere.[12,13,17] Briefly, monkeys were anesthetized initially with an intramuscular injection of ketamine hydrochloride (15–20 mg/kg) and acepromazine maleate (0.15–0.2 mg/kg), and a superficial vein was cannulated. All subsequent surgical procedures were carried out under sodium thiopental anesthesia. The animals were paralyzed by an intravenous infusion of pancuronium bromide (a loading dose of 0.1 to 0.2 mg/kg per hour followed by a continuous infusion of 0.1 to 0.2 mg/kg per hour) and artificially ventilated with a mixture of 59% N_2O, 39% O_2, and 2% CO_2. Anesthesia was maintained by the continuous infusion of sodium pentobarbital (2–4 mg/kg per hour). The core body temperature was kept at 37.6°C. Cycloplegia was produced by 1% atropine sulfate, and the animals' corneas were protected with rigid, gas permeable, extended-wear contact lenses. Retinoscopy was used to determine the contact lens parameters required to focus the eyes on the stimulus screens.

Recording and Response Analysis Procedures

Tungsten-in-glass microelectrodes were used to isolate activity from individual cortical neurons. Action potentials were extracellularly recorded and amplified using conventional technology. For each isolated neuron, the receptive fields for both eyes were mapped, and ocular dominance was determined using handheld stimuli. For the quantitative analyses of monocular tuning and binocular signal interactions, the receptive fields were projected onto the centers of two matched cathode ray tube (CRT) screens (P-31 phosphores). The CRTs had a space average luminance of 56 cd/m^2. The visual stimuli were drifting sinewave gratings. The neuron's responses were sampled at a rate of 100 Hz (10 msec bin widths) by a laboratory computer and compiled into peristimulus time histograms that were equal in duration to, and synchronized with, the temporal cycle of the sinewave grating. The amplitudes and phases of the temporal response components in the peristimulus time histograms were determined by Fourier analysis. Responses to drifting sinusoidal gratings (TF = 3.1 Hz, contrast = 35%–45%) were measured to determine the orientation tuning, spatial frequency tuning, and direction selectivity of individual units. Cells were classified as simple or complex based on the temporal characteristics of their responses to a drifting sinewave grating of the optimal spatial frequency and orientation.

Binocular Response Properties

To determine the strength and nature of binocular interactions, responses were collected for dichoptic sinewave gratings of the optimal spatial frequency and orientation as a function of the relative interocular spatial phase disparity of the grating pair (Fig. 2).[12,17,18] In addition, monocular stimuli for each eye and one zero-contrast control were included in each stimulus parameter file. For descriptive and analytical purposes, a single cycle of a sinewave was fit to each neuron's phase tuning function. The amplitude of the fitted sinewave was used to calculate the degree of binocular interaction (binocular interaction index [BII] = amplitude of the fitted sinewave/the average response amplitude). Operationally, a unit was considered as "disparity tuned" if its BII value was equal to or greater than 0.3.[12,17–19]

To determine whether binocular signal interactions were excitatory or inhibitory in nature, the binocular response amplitude/dominant monocular amplitude ratios were calculated for each unit. Depending on a cell's disparity sensitivity, two different criteria were used in determining whether a unit was binocularly suppressive. Specifically, if a cell was disparity tuned (i.e., BII $\geq$ 0.3), we took the ratio of the *peak* binocular response amplitude over the dominant monocular response amplitude. For those cells that were non-disparity tuned (BII $<$ 0.3), the *mean* binocular amplitude was compared with the dominant monocular amplitude. If the ratio of the binocular response amplitudes over the cell's dominant monocular response amplitude was less than 1.0 (B/M $<$ 1.0), the cell was considered to exhibit binocular suppression.

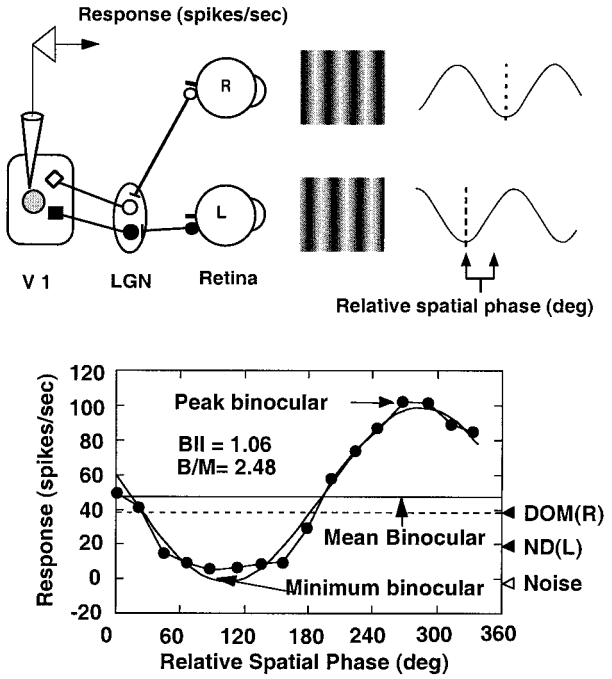

Figure 2. *Top*: Diagram illustrating the methods used to measure the sensitivity of V1 neurons to interocular spatial phase disparities. A pair of identical sinusoidal gratings (corresponding to the cell's optimal orientation and spatial frequency) was drifted in the unit's preferred direction. LGN, the lateral geniculate mucleus. *Bottom*: An example of an interocular spatial phase-tuning function for a simple cell in an adult monkey. The function was obtained by plotting the binocular response amplitude as a function of interocular relative spatial phase disparities. The phase tuning function was fit with a single cycle of a sinewave. DOM(R), the monocular response amplitude of the dominant (right) eye; ND(L), the monocular response amplitude of the non-dominant (left) eye; Noise, the spontaneous activity; BII, the amplitude of the fitted sinewave/the mean response amplitude; and B/M, the binocular amplitude/the dominant monocular amplitude.

Results

The quantitative analysis of binocular interactions was performed for 207 units from the prism-reared monkeys, 88 units for the 4-week-old monkeys and 119 units for the 8-week-old monkeys, and 194 units from the normal age-matched controls. The receptive fields of all neurons were located between 1.0° and 4.0° from the center of the fovea. In each monkey, the electrode traversed all cortical layers of the operculum at similar angles to the surface, and we attempted to study every isolated unit in each penetration.

There was a significant reduction in sensitivity to interocular phase disparities and a higher prevalence of suppressive binocular interactions for both prism-reared groups compared with the normal monkeys. However, the most significant finding was that the binocular deficits were more severe in the 8-week-old prism-reared monkeys than in the 4-week-old monkeys. To illustrate the main points, Figure 3 shows binocular interactions in representative V1 units for the four different subject groups. The unit from a normal 4-week-old monkey (panel A) showed binocular responses similar to those of the adult unit in Figure 2. The unit from a 4-week-old prism-reared monkey (panel B), however, had substantially reduced sensitivity to interocular spatial phase disparities (BII = 0.29) and showed strong binocular suppression. Specifically, the binocular response amplitude of this unit was lower than the dominant monocular amplitude for all disparities (B/M = 0.61). The

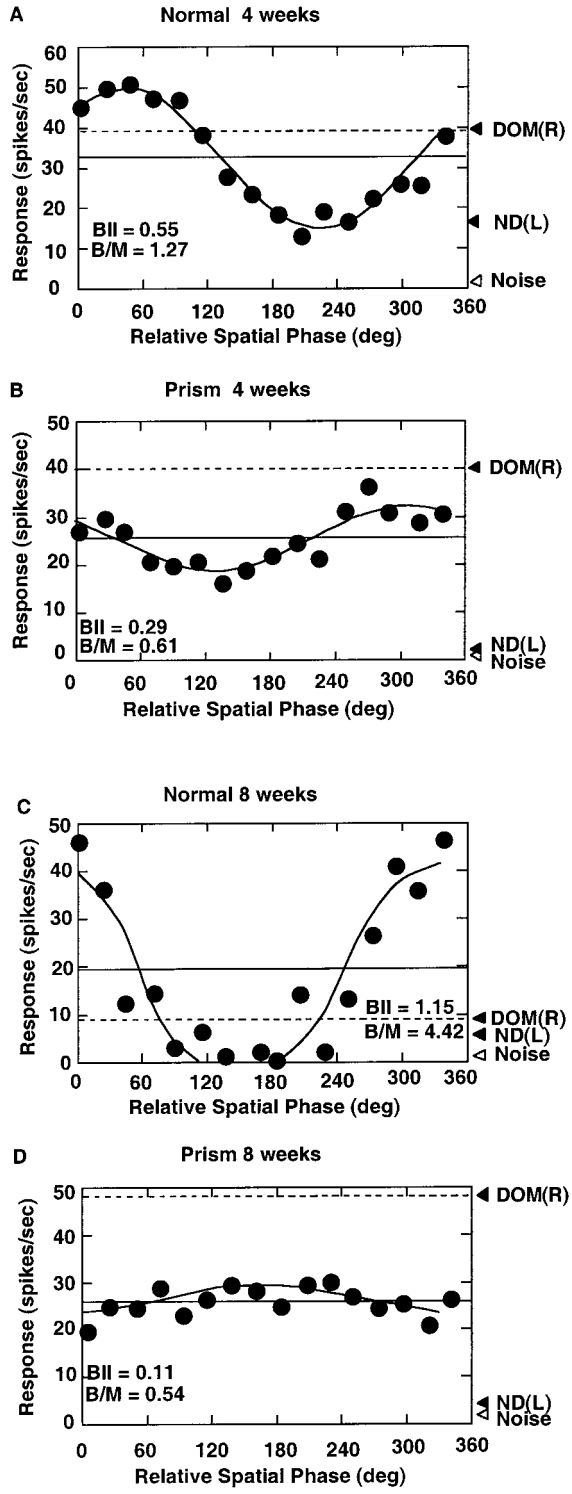

Figure 3. Representative binocular phase-tuning functions for units from a 4-week-old normal monkey (**A**), a 4-week-old prism-reared monkey (**B**), an 8-week-old prism-reared monkey (**C**), and an 8-week-old normal monkey (**D**). See Fig. 2 legend for definitions.

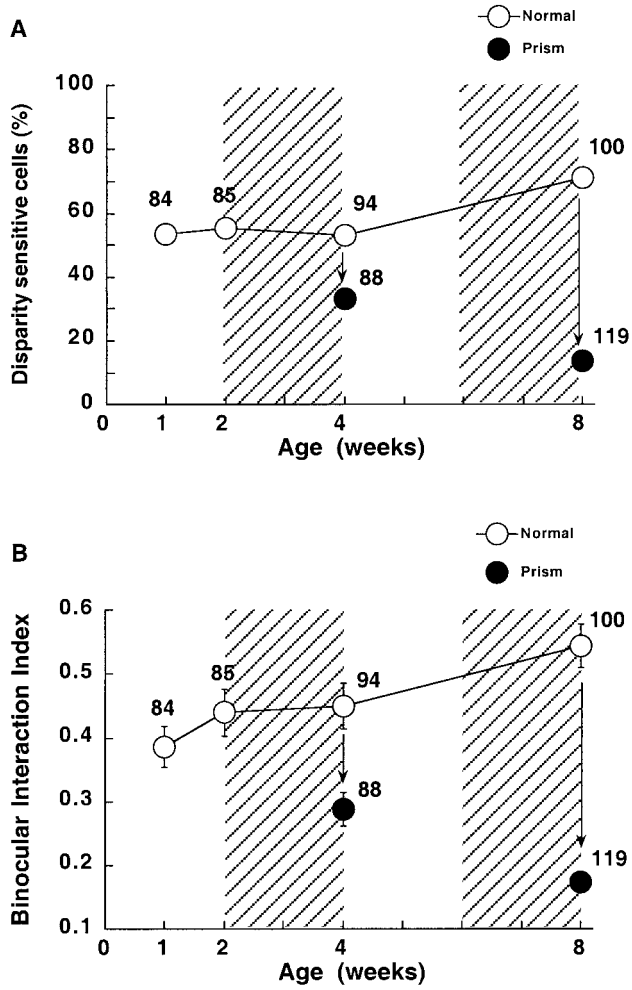

Figure 4. Development of binocular response properties of V1 neurons in normal and prism-reared monkeys. The proportion (%) of disparity tuned units (BII $\geq$ 0.3; **A**) and the mean BII values (**B**) are plotted as a function of age. *Shaded areas* indicate the prism-rearing periods. *Arrows* indicate the magnitude of the prism-rearing effects on the respective response properties. *Small numbers* next to data points indicate the number of sample units.

unit from an 8-week-old normal monkey (panel C) had virtually the same binocular response properties as those in adults (BII = 1.15, B/M = 4.42). In contrast, the unit from one of the 8-week-old prism-reared monkeys had virtually no sensitivity to interocular spatial phase disparity (BII = 0.11) and exhibited overwhelmingly strong binocular suppression (B/M = 0.54).

Disparity Sensitivity

For our populations of simple and complex cells, the reductions in disparity sensitivity were more severe in the 8-week-old prism-reared monkeys than in the 4-week-old monkeys (Figs. 4 and 5). Figure 4A shows that the reduction in the proportion of disparity tuned units (BII $\geq$ 0.3[12,17,18]) was nearly 3 times greater in the 8-week-old prism-reared monkeys than in the 4-week-old prism-reared infants (χ^2 test, $P < 0.005$). The proportion of disparity tuned units in normal monkeys was similar (approximately 60%) at all ages. In Figure 4B, the average BII values were plotted as a function of age. The average BII values in both 4-week-old and 8-week-old prism-reared monkeys were significantly lower than the age-matched controls (ANOVA, $P < 0.0001$). The difference between the normal control groups was not statistically significant. The reduction in the average BII values was also larger in the 8-week-old prism-reared monkeys than in the 4-week-old prism-reared monkeys (two sample *t*-test, $P < 0.0001$).

Figure 5 shows the differences between simple and complex cells in the distributions of the BII values. The most severe loss of disparity sensitivity was found for simple cells in 8-week-old prism-reared monkeys. Specifically, approximately 80% of the simple cells in these prism-reared monkeys, compared with only approximately 10% in control monkeys, did not show sensitivity to interocular phase disparity (i.e., BII $<$ 0.3). In contrast, approximately 60% of normal control units showed high BII values (BII $\geq$ 0.6), whereas only 3% of units from prism-reared monkeys exhibited a high sensitivity to phase disparity. The residual proportion of disparity sensitive units was lowest in complex units from the 8-week-old prism-reared monkeys ($<$10% compared with 50% in the age-matched normal infants). Only one unit in this group of complex cells showed a BII value greater than 0.4. The differences in the BII distributions between the prism-reared and normal control monkeys were significant for both simple and complex cells (Mann–Whitney tests, $P < 0.05$ for 4-week-old monkeys and $P < 0.001$ for 8-week-old monkeys).

Binocular Suppression

For the majority of units, the prevalence of binocularly suppressive cells was also higher in the 8-week-old prism-reared monkeys than in the 4-week-old prism-reared monkeys (i.e., the binocular response amplitude was less than the dominant monocular amplitude). This difference was significant for the cells that were not sensitive to interocular spatial phase disparity (Fig. 6, χ^2 tests, $P < 0.05$). Specifically, the prevalence of binocularly suppressive units that were not disparity tuned (BII $<$ 0.3) was similar for both prism-reared groups. However, the age-matched 8-week-old normal monkeys had approximately half as many suppressive units as the 4-week-old normal monkeys. Consequently, the net effect of prism-rearing was greater for the 8-week-old prism-reared monkeys (i.e., a net increase of 50% in 8-week-old versus 25% in 4-week-old monkeys). Similar differences were found for disparity tuned units (Fig. 6A) but were not statistically significant because a much smaller number of binocularly suppressive units maintained disparity tuning as a consequence of early prism-rearing.

Figure 7 illustrates the proportion of suppressive units (%) as a function of age. For both disparity tuned units (panel A) and non-disparity tuned units (panel B), the overall proportion of suppressive neurons in V1 substantially increased after the prism-rearing, whereas in the normal age-matched controls the proportions declined substantially.

Discussion

The major finding of this study was that a brief period of early strabismus causes a greater loss of disparity sensitivity and a higher prevalence of binocular suppression in V1 if it occurs after the age that stereopsis normally emerges (4–6 weeks of age). This is a critical point in normal V1 development. At this time, the binocular connections in V1 have largely become

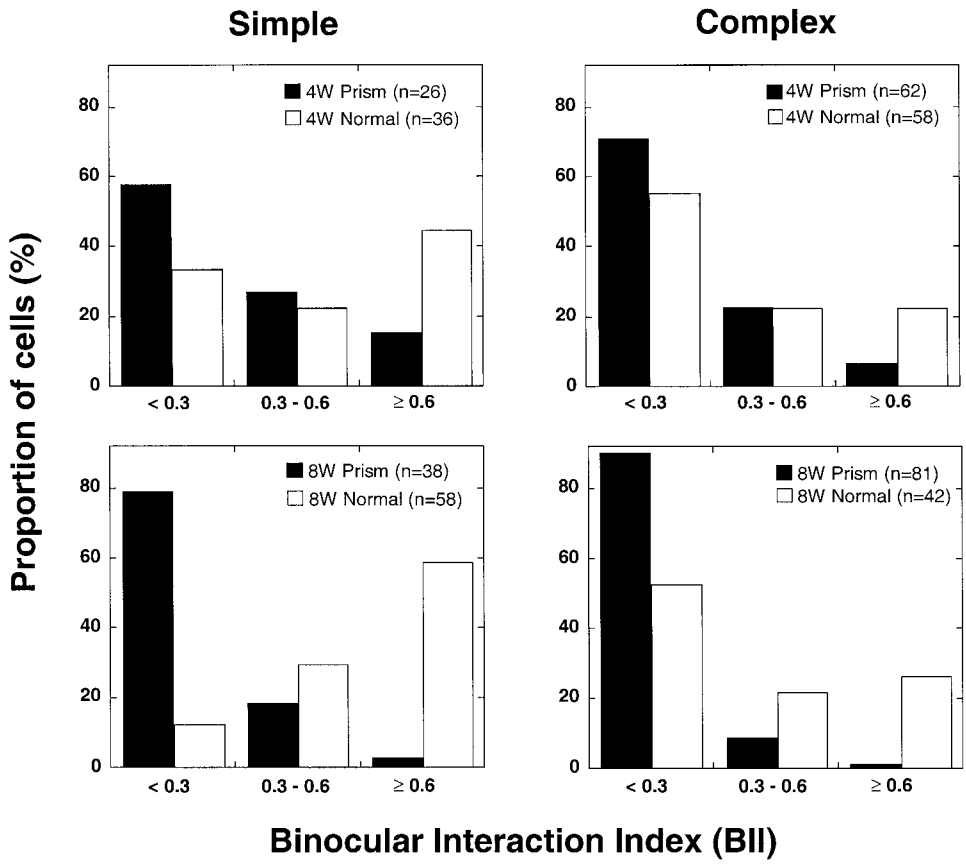

FIGURE 5. Differences between simple (*left*) and complex (*right*) cells in the magnitude of disparity sensitivity reductions for 4-week-old prism-reared (*top*) and 8-week-old prism-reared (*bottom*) monkeys relative to the normal age-matched infants.

functionally mature, yet V1 continues to show a high degree of plasticity.[12,13,20–22]

Why should a misalignment at a later age (after 6 weeks of age) rather than at an earlier age (before 4 weeks of age) cause a more severe breakdown of binocular properties of V1 units? During the first 2 to 3 weeks of life, the functional organization in V1 is dynamic[12] and very mutable, and plasticity is generally thought to decline with age thereafter.[23,24] Thus, abnormal binocular visual experience during this early developmental period would be expected to have a far greater impact on binocular vision development than during later stages of development. This appears to be the case for the effects of early monocular form deprivation on the development of ocular dominance columns in monkey V1.[25] For example, monocular form deprivation at 1 week of age results in a far more severe shrinkage of ocular dominance columns in layer IVC than the deprivation initiated at 3 to 5 weeks of age. Deprivation at 12 weeks of age causes no column shrinkage.

Our present finding may point to a fundamental difference in how strabismus and form deprivation alter the early development of binocular connections in V1. For strabismic subjects, the very early onset in this study may have been less damaging than the later onset because it may not have caused as large a decorrelation of neural signals between the two eyes as a misalignment in later stages of development. Unlike in monocularly form-deprived subjects, optical strabismus creates two well-focused images that do not match (diplopia). Before 4 weeks of age, the spatiotemporal filter properties of V1

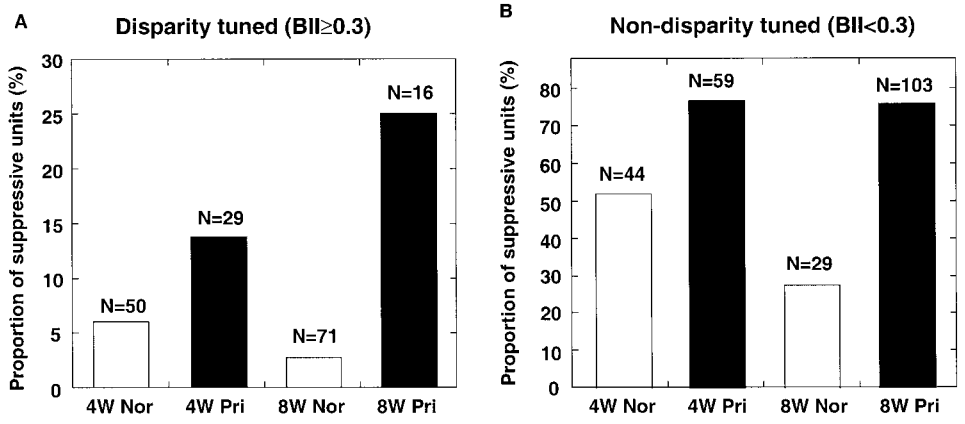

FIGURE 6. Proportions of binocularly suppressive units in V1 of infant monkeys. (**A**) Disparity tuned units (BII ≥ 0.3). Units with the peak binocular response amplitude/dominant monocular amplitude less than 1.0 were considered to be suppressive units. (**B**) Non-disparity tuned units (BII < 0.3). The units with the mean binocular response amplitude/dominant monocular amplitude less than 1.0 are considered to be suppressive units. Nor, normal; Pri, prism-reared.

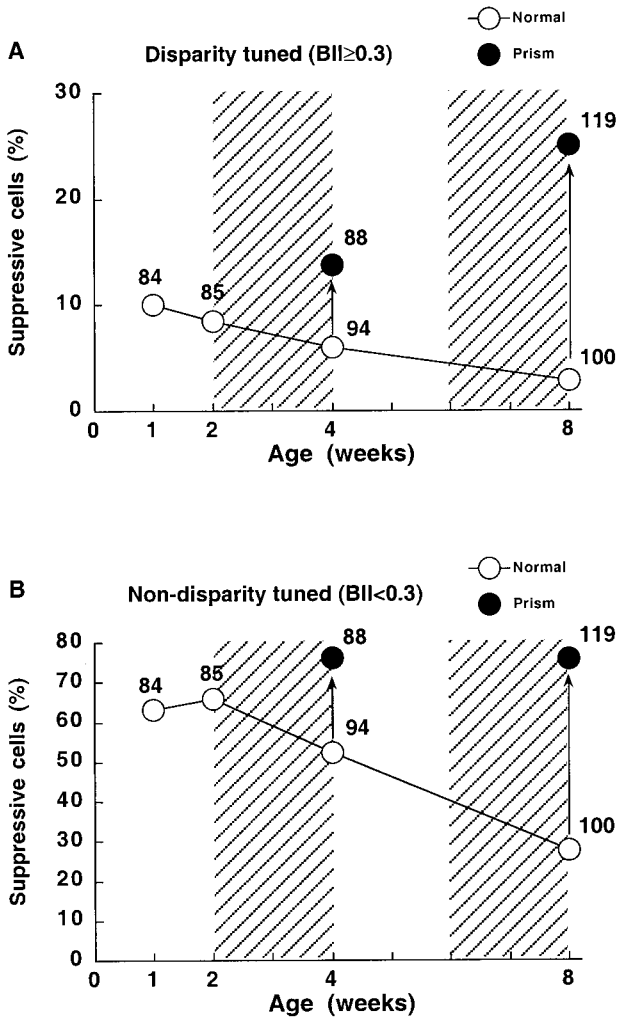

FIGURE 7. The proportions of binocularly suppressive units as a function of age for prism-reared and normal monkeys. (**A**) Disparity tuned units. (**B**) Non-disparity tuned units. *Shaded areas* indicate the prism-rearing periods. *Arrows* indicate the magnitude of the prism-rearing effects on the respective response properties. *Small numbers* next to data points indicate the number of sample units.

neurons are not well developed, and the overall responsiveness of these units is poor (Fig. 1, also see references 12 and 13). As a result, a smaller proportion of V1 units is likely to receive effective uncorrelated input from the two eyes than the better tuned, more responsive V1 neurons in later stages of development, and, thus, the overall impact may have been less severe in the younger group.

Differences in the relative maturity of V1 neurons at the onset of strabismus may also explain why binocularly suppressive interactions were more prevalent in the 8-week-old prism-reared monkeys than in 4-week-old monkeys. In strabismus suppressive interactions were thought to become more prevalent in V1 neurons because conflicting binocular inputs early in life selectively reduce the effectiveness of excitatory binocular connections, both local and long-range,[26–28] while largely sparing, at least relatively, inhibitory connections.[20,29–31] In comparison to inhibitory connections, excitatory connections may be more susceptible to abnormal visual experience, because these connections typically exhibit a higher degree of stimulus specificity than inhibitory connections.[32–35] Because the specificity of excitatory connections is far better developed at 6 weeks of age,[12,13,36,37] misalignment might have caused a more severe breakdown of the excitatory connections for the late-onset group. Consequently, binocular suppression was more prevalent in the 8-week-old prism-reared monkeys than in the 4-week-old prism-reared monkeys.

It is likely that the deficits that were found in the 8-week-old prism-reared monkeys are permanent. We have previously studied two adult monkeys that were subjected to the brief period of early strabismus that was similar to the regimen for the 8-week-old prism-reared monkeys in this study. These older monkeys showed comparable deficits in the binocular response properties of their V1 neurons.[20] Behaviorally, these adult monkeys also showed a loss of binocular summation and stereodeficiencies. Thus, brief periods of early strabismus can cause permanent deficits of cortical binocularity that are comparable to those found immediately at the end of the prism-rearing despite years of undisturbed visual experience. However, it has not yet been experimentally tested whether the removal of prisms before 4 weeks of age followed by long periods of normal visual experience leads to improved binocular functions in adult monkeys.

At what age should eye alignment be achieved for congenital esotropes? It depends on a variety of clinical and/or scientific factors. However, if improving the odds for maintaining better binocular sensory function (e.g., achieving better stereoacuity) is the primary objective, the present findings are more consistent with the view that corrective procedures for congenital esotropes should be considered as early as the misalignment is detected (i.e., before 4 to 6 month of age).[6–8] Besides maintaining better overall disparity sensitivity and reducing the prevalence of suppression in the visual cortex, earlier alignment provides a relatively longer duration of normal visual experience during the early plastic period. In this respect, the age at which realignment is achieved may be as important a variable to consider as the age when esotropia is detected.

Although V1 units alone may not be sufficient to support stereoscopic vision,[38] the presence of highly sensitive disparity encoding mechanisms in the early stages of cortical processing (e.g., in V1) is a prerequisite for stereopsis in normal subjects.[39] Even if residual disparity sensitive units in strabismic subjects are not sufficient to support stereoscopic vision, these cells may provide critical information on image disparities that are necessary for vergence eye movements.[40] Harwerth et al.[41] reported that monkeys that experienced similar periods of optical strabismus early in life showed significant stereodeficiencies but were able to maintain normal interocular alignment, and they showed relatively normal disparity vergence eye movements. In this context our present findings suggest that earlier surgical alignment may increase the odds for maintaining better alignment at later stages of development.

Acknowledgments

The authors thank Dennis Levi and Ronald Harwerth for comments on an earlier version and Akihiko Tamai for his continuing support.

References

1. von Noorden GK. A reassessment of infantile esotropia: XLIV Edward Jackson Memorial Lecture. *Am J Ophthalmol.* 1988;105:1–10.

2. Taylor DM. How early is early surgery in the management of strabismus? *Arch Ophthalmol.* 1970;70:752–756.
3. Ing MR. Early surgical alignment for congenital esotropia. *Trans Am Ophthalmol Soc.* 1981;79:625–663.
4. Ing MR. Early surgical alignment for congenital esotropia. *Ophthalmology.* 1983;90:132–135.
5. Birch EE, Stager DR, Everett ME. Random dot stereoacuity following surgical correction of infantile esotropia. *J Pedatr Ophthalmol Strabismus.* 1995;32:231–235.
6. Wright KW, Edelman P, Terry A, McVey J, Lin M. High grade stereoacuity after early surgery for congenital esotropia [ARVO Abstract]. *Invest Ophthalmol Vis Sci.* 1993;34:**S**710. Abstract nr 32.
7. Wright KW, Edelman PM, McVey JH, Terry AP, Lin M. High grade stereoacuity after early surgery for congenital esotropia. *Arch Ophthalmol.* 1994;112:913–919.
8. Helveston EM. Esotropia. *Trans Am Ophthalmol Soc.* 1988;85: 441–460.
9. Ing MR. Outcome study of surgical alignment before six months of age for congenital esotropia. *Ophthalmology.* 1995;102:2041–2045.
10. Ing MR, Costenbader FD, Parks MM. Early surgery for congenital esotropia. *Am J Ophthalmol.* 1996;61:1419–1427.
11. Ing MR. The timing of surgical alignment for congenital (infantile) esotropia. *J Pediatr Ophthalmol Strabismus.* 1999;36:61–68.
12. Chino YM, Smith EL III, Hatta S, Cheng H. Postnatal development of binocular disparity sensitivity in neurons of the primate visual cortex. *J Neurosci.* 1997;17:296–307.
13. Hatta S, Kumagami T, Qian J, Thornton J, Smith EL III, Chino YM. Nasotemporal directional bias of V1 neurons in young infant monkeys. *Invest Ophthalmol Vis Sci.* 1998;39:2259–2267.
14. O'Dell C, Boothe R. The development of stereoacuity in infant rhesus monkeys. *Vision Res.* 1998;37:2675–2684.
15. Crawford MLJ, von Noorden GK. Optically induced concomitant strabismus in monkeys. *Invest Ophthalmol Vis Sci.* 19;1980:1105–1109.
16. Boltz RL, Harwerth RS. Fusional vergence ranges of the monkey: a behavioral study. *Exp Brain Res.* 1979;37:87–91.
17. Smith EL III, Chino YM, Ridder WH III, Crawford MLJ. Binocular spatial phase tuning characteristics of neurons in the macaque monkey's striate cortex. *J Neurophysiol.* 1997;78:351–365.
18. Ohzawa I, Freeman RD. The binocular organization of simple cells in the cat's visual cortex. *J Neurophysiol.* 1986;56:221–242.
19. Ohzawa I, Freeman RD. The binocular organization of complex cells in the cat's visual cortex. *J Neurophysiol.* 1986;56:243–259.
20. Smith EL III, Chino YM, Ni J, Cheng H, Crawford MLJ, Harwerth RS. Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *J Neurophysiol.* 1997;78: 1353–1362.
21. Kiorpes L, Kiper DC, O'Keefe LP, Cavanaugh JR, Movshon JA. Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci.* 1998;18:6411–6424.
22. Movshon JA, Kiorpes L. The role of visual experience in visual development. In: Coleman JR, ed. *Development of Sensory Systems in Mammals.* New York: J Wiley; 1990:156–202.
23. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey striate cortex. *Phils Trans R Soc Lond (Biol).* 1977;278:377–409.
24. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. *Nature.* 1982;299:583–591.
25. Horton JC, Hocking DR. Timing of the critical period for plasticity of ocular dominance columns in macaque striate cortex. *J Neurosci.* 1997;17:3684–3709.
26. Lowell S, Singer W. Selection of intrinsic horizontal connections in the visual cortex by correlated neuronal activity. *Science.* 1992; 255:209–212.
27. Tychsen L, Burkhalter A. Neuroanatomic abnormalities of primary visual cortex in macaque monkeys with infantile esotropia: preliminary results. *J Pediatr Ophthalmol Strabismus.* 1995;32:323–328.
28. Singer W. Effects of monocular deprivation on excitatory and inhibitory pathways in cat striate cortex. *Exp Brain Res.* 1977;30: 25–41.
29. Chino YM, Smith EL III, Yoshida K, Cheng H, Hamamoto J. Binocular interactions in striate cortical neurons of cats reared with discordant visual input. *J Neurosci.* 1994;14:5050–5067.
30. Sengpiel F, Blakemore C. Interocular control of neuronal responsiveness in cat visual cortex. *Nature.* 1994;368:847–850.
31. Sengpiel F, Blakemore C. The neural basis of suppression and amblyopia in strabismus. *Eye.* 1996;10:250–258.
32. Ts'o DY, Gilbert CD, Wiesel TN. Relationships between horizontal interactions and functional architecture in cat striate cortex as revealed by cross-correlation analysis. *J Neurosci.* 1986;6Z:1160–1170.
33. Weiliky MK, Katz L. Patterns of excitation and inhibition evoked by horizontal connections in visual cortex share a common relationship to orientation columns. *Neurons.* 1994;15:541–552.
34. Somogyi P, Kisvarday ZF, Martin KAC, Whitteridge D. Synaptic connections of morphologically identified and physiologically characterized large basket cells in the striate cortex of cat. *Neuroscience.* 1983;10:261–294.
35. Bonds AB. Role of inhibition in the specification of orientation selectivity of cells in the cat striate cortex. *Vis Neurosci.* 1989;2: 41–55.
36. Levitt JB, Lund JS. Asynchronous development of receptive-field properties and clustered horizontal connections in macaque striate cortex. *Neurosci abstr.* 1996;22:491.
37. Shaw CL, Cameron D, March M, Cynader B, Zielienski B, Henndrickson A. Pre- and postnatal development of GABA receptors in Macaca monkey visual cortex. *J Neurosci.* 1991;11:3943–3959.
38. Parker BG, Cumming AJ. Responses of primary visual cortical neurons to binocular disparity without depth perception. *Nature.* 1997;389:280–283.
39. Marr D, Poggio T. A theory of human stereopsis. *Proc R Soc Lond B Biol Sci.* 1979;204:301–328.
40. Masson GS, Busttini C, Miles FA. Vergence eye movements in response to binocular disparity without depth perception. *Nature.* 1997;389:283–285.
41. Harwerth RS, Smith EL III, Crawford MLJ, von Noorden GK. Stereopsis and disparity vergence in monkeys with subnormal binocular vision. *Vision Res.* 1997;37:483–493.