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Effect of strabismus on the development of vernier acuity and grating acuity in monkeys

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Abstract

The effect of experimental strabismus on the development of vernier acuity and grating acuity was studied in *Macaca nemestrina* monkeys. Six monkeys were studied longitudinally beginning near 10 days after birth. Four of the six monkeys developed amblyopia. As is true for human strabismic amblyopes, the deficit in vernier acuity was larger than the deficit in grating acuity in the amblyopic monkeys. The developmental data reveal that this differential disruption of vernier acuity can be understood as a result of a slowed developmental process associated with amblyopia.

Keywords: Strabismus, Visual development, Vernier acuity, Grating acuity, Macaque monkey, Amblyopia

Introduction

Amblyopia is a deficit in visual function that has no obvious organic cause. Amblyopia develops in association with strabismus, as well as other forms of abnormal visual experience, when present during infancy and early childhood in both humans and monkeys (humans: see von Noorden, 1980; monkeys: Harwerth et al., 1983; Kiorpes et al., 1989; Kiorpes, 1989). Strabismic amblyopia is commonly characterized by a deficit in spatial resolution, as measured by either Snellen acuity or grating acuity, on the order of a factor of 2 difference between the eyes. Recently, psychophysical studies of human strabismic amblyopes have revealed that their deficits in grating acuity are relatively small compared to their deficits in spatial position sensitivity (Levi & Klein, 1982, 1983). Strabismic amblyopes are severely impaired on a variety of spatial-localization tasks like vernier alignment and bisection; they seem to have a distortion of the spatial sense that is not completely captured by measurements of grating acuity (Bedell & Flom, 1981; Hess et al., 1978; Bedell et al., 1985; Fronius & Sireteanu, 1989). Levi and Klein (1985) have further shown that the performance of strabismic amblyopes on spatial localization tasks can be modeled by the performance of the periphery in normal observers.

A variety of neural abnormalities have been proposed to account for the particular distortion of the spatial sense in strabismic amblyopia. For example, recently Levi and Klein (1985) proposed the hypothesis that the central visual field of strabismic amblyopes was spatially undersampled, meaning that the separation of spatial filters (presumably the receptive fields of cortical neurons) is greater than those that serve the central visual field in normal observers. They have likened the sampling grain of the central visual field of strabismic amblyopes to that of the peripheral visual field in normal observers. This and other theories of amblyopic vision can be directly tested in an animal model. The macaque monkey has been demonstrated to be an extremely good model in terms of visual system structure and function. Macaques develop visual acuity and contrast sensitivity in a similar progression to humans, and develop amblyopia in association with strabismus, anisometropia, and form deprivation as do humans (see Boothe et al., 1985, for review). Strabismic amblyopia in monkeys has previously been characterized in terms of grating acuity and contrast sensitivity deficits (Harwerth et al., 1983; Kiorpes et al., 1989; see also von Noorden & Dowling, 1970); no previous studies of spatial localization ability in amblyopic monkeys have been published. To investigate the mechanisms underlying strabismic amblyopia in monkeys, it is important to characterize the performance of strabismic macaques on spatial localization tasks since human strabismic amblyopes are particularly impaired on these tasks.

In the present paper, the time courses for the development of spatial position sensitivity and spatial resolution in experimentally strabismic monkeys are described. The preceding paper (Kiorpes, 1992) established that the developmental time courses for these two visual functions are different in normal monkeys. We reasoned that if these two visual functions depend on different underlying mechanisms, as is suggested by human psychophysical data (e.g. Levi et al., 1985), then they may be disrupted differentially as a result of strabismus. If so, the developmental data might shed light on the character of the underlying mechanisms and the nature of the amblyopic deficit. The present results show that spatial position sensitivity and spatial resolution are disrupted disproportionately in strabismic monkeys. However, the disruption may be understood as resulting from a slowed developmental process rather than a particular disruption of spatial position sensitivity. A summary

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analysis of some of these data has been published previously (Kiorpes & Movshon, 1989).

Methods

Subjects

Six *Macaca nemestrina* monkeys were hand-raised from infancy in our primate nursery. The monkeys were supplied by the Washington Regional Primate Center. Care of the animals was provided in accordance with established, approved protocols, which conform to the *NIH Guide for the Care and Use of Laboratory Animals*.

Experimental strabismus

Esotropia was induced by injection of *C. botulinum A* neurotoxin into the lateral rectus muscle of the left eye (Scott et al., 1973; see also Kiorpes et al., 1989). The lateral rectus was exposed by dissection of the conjunctiva; the neurotoxin was injected under visual control with additional EMG guidance *via* the injection needle. The dosage delivered was usually 7–10 units (0.05-ml volume) of *C. botulinum A* toxin per injection. Injections were made while the monkey was lightly anesthetized with ketamine hydrochloride. In two cases, AN and AM, ptosis developed following the injection that at least partially obscured the pupil for 10–13 days. All other animals were given an injection of botulinum antitoxin (1.6×10^{-3} units; 0.2-ml volume) into the superior medial region of the orbit prior to the neurotoxin injection in order to reduce the likelihood of subsequent ptosis (Scott, 1987). Regardless of whether or not the antitoxin is used, the resulting esotropia with this method is of a moderate extent, ranging from 10–40 prism diopters as measured by the Hirschberg method from photographs (Kiorpes et al., 1989). The extent of the esotropia for each monkey in the present study is shown in Table 1. Note that in one case, AP, the neurotoxin injection initially produced a small esodeviation, $5\text{–}10^{\Delta}$, which eventually became an exotropia of 15^{Δ}.

The *C. botulinum A* neurotoxin injections were routinely followed by approximately two weeks of ocular paralysis. Ocular motility following the period of paralysis was quite normal and all animals were able to hold fixation with the injected eye (always the left eye). Refractive errors were measured by cycloplegic retinoscopy for all animals at the beginning of the study (see Table 1). Since our previous work showed that experimental strabismus has no systematic effect on refractive error (Kiorpes et al., 1989), these measurements were not repeated at regular intervals. In all except two cases, the measured refractive errors were within the normal range for this species (Young, 1964). For AO and AN, the refractive errors were larger than normal initially and did not decrease during the first postnatal year.

Table 1. *Refractive status, deviation angle, and age at induction of esotropia are listed for each subject*

Subject	Onset age (days)	Refractive error		Deviation angle (Δ)
		OD	OS	
JS	26	+5.50S	+4.50S	35
OD	22	+3.50-0.25 × 180	+3.75-1.00 × 120	30
AM	32	+2.00S	+4.00S	25
AN	31	+5.00S	+6.00S	20
AO	58	+7.75-0.75 × 180	+7.50S	30
AP	60	+1.25-0.75 × 180	+2.00-0.50 × 180	15[a]

[a]Exotropia.

Behavioral testing

Behavioral testing was begun at about 10 days postnatal and continued through at least the first year after birth; some monkeys were followed for longer periods. As in the preceding paper on development in normal monkeys, we used grating acuity as our measure of spatial resolution and vernier acuity as our measure of spatial position sensitivity. Preferential looking methods were used from near birth to about 15 weeks, thereafter operant methods were used. These methods are fully described in the preceding paper (Kiorpes, 1992). All methods were identical to those used to test the normal monkeys, except that the strabismic monkeys were routinely tested monocularly. Appropriate optical correction was provided as necessary during operant testing. The methods used for behavioral refraction have been described previously (Kiorpes & Boothe, 1984; Smith & Harwerth, 1984). The animals all appeared, on casual inspection, to be capable of steady fixation of the visual targets. Although we have not recorded fixation stability quantitatively, monitoring of oculomotor behavior during testing suggests that they fixated the targets centrally and exhibited a full range of directional eye movements.

The stimuli were the same as those described in Fig. 1 of the preceding paper (Kiorpes, 1992). For preferential looking testing, the carrier frequency of the vernier pattern was 0.25 cycle/deg and the offset portions were 2 deg high (the same as was used for the normal animals). For operant testing, the vernier acuity stimuli were scaled according to the grating acuity deficit for amblyopic monkeys. To do this, we independently measured the full contrast-sensitivity function for each eye of each strabismic animal. The carrier frequency was in all cases chosen to be near the peak of the contrast-sensitivity function: usually 1–2 cycle/deg for amblyopic eyes and 2–4 cycle/deg for nonamblyopic eyes. The offset portions were proportional to the spatial frequency of the carrier, ranging from 20–80 min high.

The methods used for data analysis were also the same as were described in the preceding paper. However, in this case, we determined a representative psychometric function slope separately for grating and vernier acuity for each eye of each monkey. The results of nested hypothesis testing (Mood et al., 1974) under these conditions were consistent with the assumption that there is a single underlying function for each eye of each monkey on each task.

Results

The developmental time courses for vernier acuity and grating acuity were disrupted in strabismic amblyopia. Four of the six monkeys made esotropic developed amblyopia. In each of these four cases, we found deficits in both grating acuity and vernier acuity. Individual data on the development of vernier and grating acuity are shown in Fig. 1 (A and B) for each eye of two monkeys made esotropic near 4 weeks of age (AN and JS). The

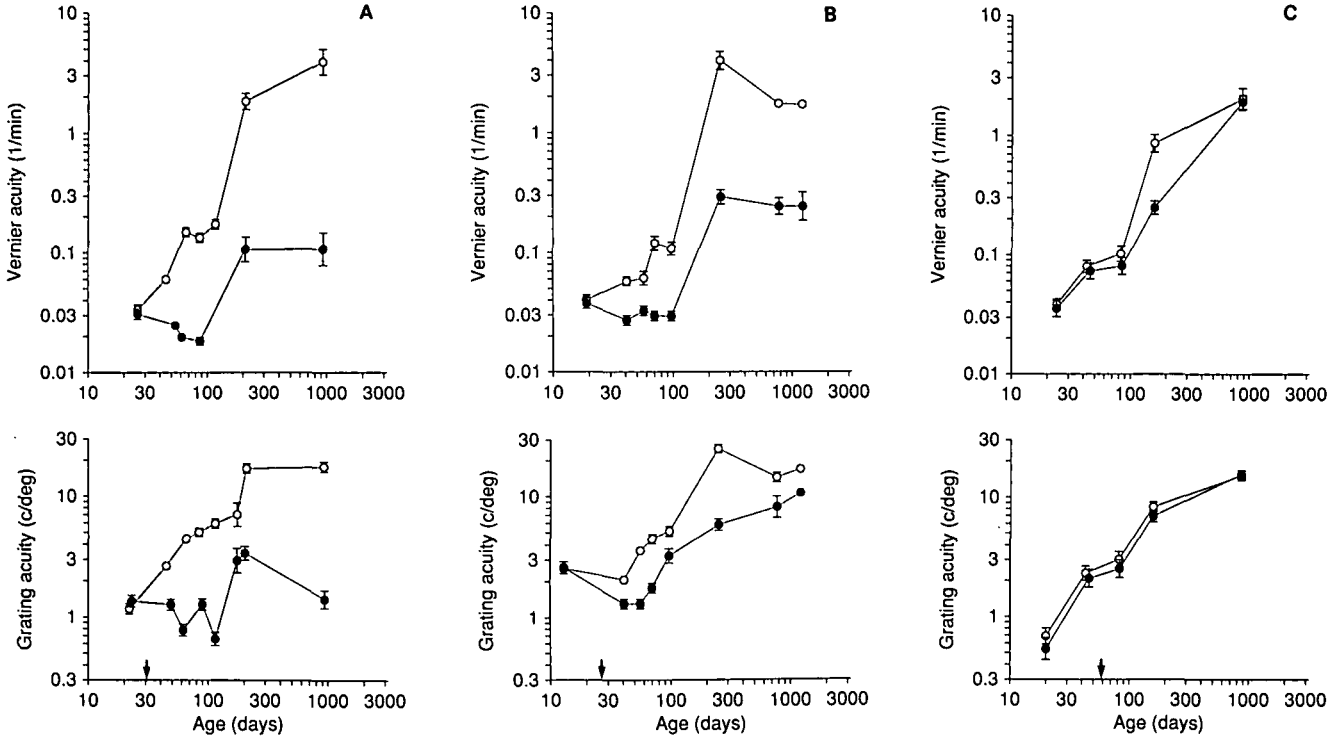

Fig. 1. Longitudinal data for three individual animals showing the developmental time courses for grating and vernier acuity for each eye: A: AN, B: JS, and C: AO. Grating acuity (bottom) in cycles per degree is shown as a function of age in days on log–log coordinates; vernier acuity (top) is shown in inverse minutes of arc on the same age scale as grating acuity (10 in inverse minutes is equal to 6 s). The open circles represent nondeviated eye data; filled circles represent deviated eye data. The arrows indicate the age of neurotoxin injection.

top and bottom panels show vernier and grating acuity, respectively, as a function of age for the deviated (filled symbols) and nondeviated (open symbols) eyes of each monkey. In each case, the development of both visual functions was set back rather immediately by the introduction of the esotropia. The immediacy of the effect is probably due to the paralysis following the neurotoxin injection (Kiorpes et al., 1989). Substantial deficits in the acuity of the deviated eyes were documented at the end of the first postnatal year. The deficit in vernier acuity was in each case larger than the deficit in grating acuity. The effect of ptosis on the developmental pattern was minimal since this pattern of results was characteristic of all four monkeys that developed amblyopia; only two of these monkeys had a post-injection ptosis. It is possible, though, that ptosis contributed to the depth of amblyopia in AN and AM. Three of the four amblyopes were retested later, between 2 and 4 years of age. In each case, the vernier acuity deficit remained greater in extent than the grating acuity deficit.

Two of the monkeys developed normal vernier and grating acuity for each eye. In both of these monkeys, AO and AP, esotropia was created at 8 weeks rather than 3–4 weeks. Developmental data for one animal that failed to develop amblyopia are shown in Fig. 1C. This animal showed a difference between the eyes for vernier acuity at one age, 22 weeks, but the difference was not maintained. Final acuities were similar for each eye on each measure. For AP, equal acuity was found for the two eyes on each measure at all test ages.

Fig. 2 summarizes the relative deficits for vernier and grating acuity for the six strabismic monkeys. The interocular ratio for each monkey for vernier acuity (*VA*) is plotted against that for grating acuity (*GA*) using data from the oldest test age. The data from the oldest test age represents the ultimate extent of the amblyopic deficits. The small open circles are data from normal animals tested monocularly between the ages of 6

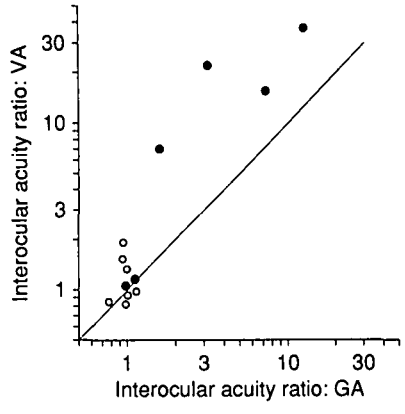

Fig. 2. A comparison between the interocular ratio for vernier acuity (*VA*) and grating acuity (*GA*) measurement for each monkey. The filled circles represent ratios for strabismic monkeys; the open circles represent ratios obtained from normal animals tested monocularly. Interocular acuity ratios were calculated as right (nondeviated) eye acuity divided by left (deviated) eye acuity. The points would fall on the solid line if the interocular ratios for grating and vernier acuity were equal.

months and 2 years. The normal data cluster near 1 on both scales demonstrating relatively small interocular differences. If the deficits for the amblyopic monkeys were proportional for the two measures, the data would fall along the diagonal line. For all except two of the strabismic monkeys, AO and AP, who did not develop amblyopia, the points fall above the dashed line indicating that the deficits in vernier acuity are larger than the deficits in grating acuity.

The larger deficit in vernier acuity relative to grating acuity suggests that there may be a differential disruption of the developmental time courses for these two visual functions. Fig. 3 shows the developmental time courses for the deviated and nondeviated eyes of all of the strabismic monkeys for both measures of spatial vision. The format of Fig. 3 is the same as for Fig. 1; the symbols represent measured acuity for the deviated (filled circles) and nondeviated (open circles) eyes of each monkey at each age. The dashed and solid lines are regression lines calculated for the nondeviated and deviated eyes, respectively, on each acuity measure. The slopes of the regression functions for log acuity as a function of log age for the nondeviated eyes of these monkeys are similar to those for normally raised monkeys [as determined in the preceding paper (Kiorpes, 1992)]. Table 2 lists each of the regression line slopes. The slope of the deviated eye function for both vernier and grating acuity is shallower than those found for normal eyes and fellow nondeviated eyes. This result suggests that the presence of esotropia generally slows the time course for spatial visual development.

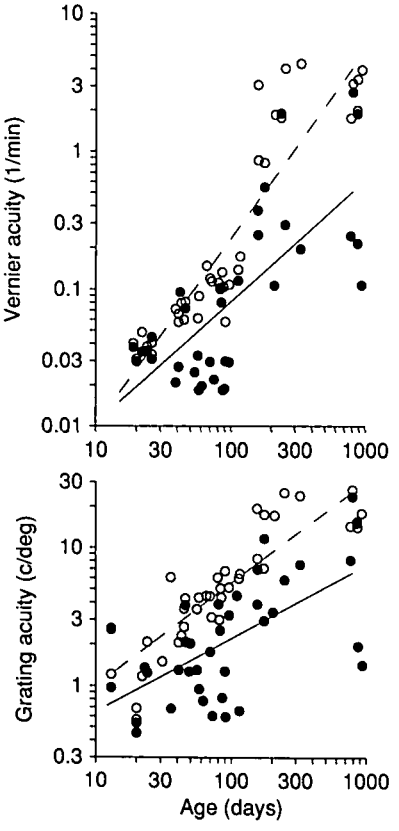

Fig. 3. Developmental time courses for the deviated and nondeviated eyes of all of the strabismic monkeys for both grating (bottom) and vernier (top) acuity. The format and symbols are the same as in Fig. 1. The dashed and solid lines are regression lines calculated for the nondeviated and deviated eyes, respectively, on each acuity measure.

Table 2. *Slopes of the regression lines that describe the relationship between each measure of (log) acuity and (log) age*[a]

Eye	Grating	Vernier
Normal	0.79	1.30
Nondeviated	0.74	1.37
Deviated	0.53	0.89
Amblyopic	0.32	0.64

[a]Slopes are separately calculated for deviated (left) and nondeviated (right) eyes, and for amblyopic eyes alone. The normal measurements are taken from the preceding paper (Kiorpes, 1992).

However, recall that some of the esotropic monkeys did not develop amblyopia. Regression slopes for amblyopic eyes alone are also listed in Table 2. These slopes are substantially shallower even than those calculated for the esotropic eyes together. It is therefore likely that the presence of strabismus does not in itself disrupt the developmental time course. Rather, the disruption of the developmental time course is a feature of the development of strabismic *amblyopia*. Furthermore, the disruption appears not to affect vernier acuity more than grating acuity, but affects them each to a similar degree. This point is illustrated further in Fig. 4. The solid and dashed lines in Fig. 4 represent the normal developmental time courses for grating and vernier acuity, respectively (taken from Fig. 5 in Kiorpes, 1992). Grating acuity (filled symbols) and vernier acuity (open sym-

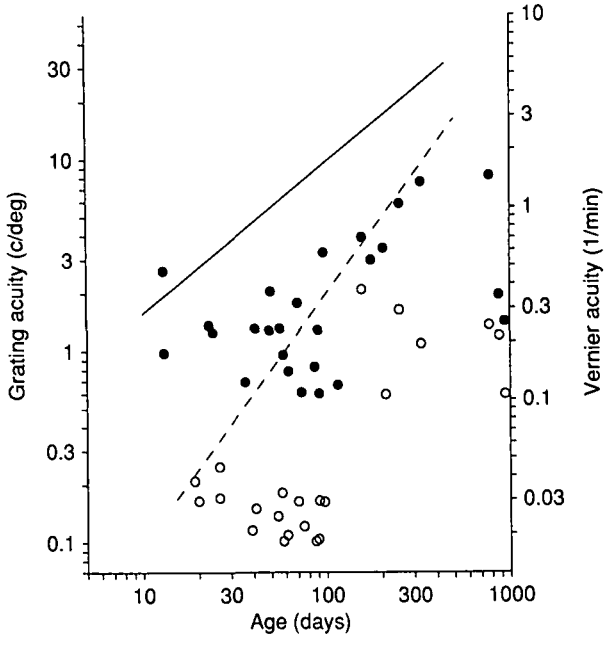

Fig. 4. The development of grating and vernier acuity in amblyopic eyes as compared to normal eyes. Axes are the same as in Figs. 4 and 5 from the preceding paper: grating acuity data relate to the left ordinate; vernier acuity data relate to the right ordinate; the ordinates are aligned at adult performance levels. Filled and open symbols represent grating and vernier acuity data, respectively, for amblyopic eyes only. The solid and dashed lines are the regression lines calculated for normal monkeys on grating and vernier acuity, respectively (from Fig. 5, Kiorpes, 1992).

bols) are shown as a function of age for the deviated eyes of the four strabismic monkeys who developed amblyopia. It is clear that the development of both visual functions is severely impaired relative to normal. For amblyopic eyes, the overall extent of improvement in acuity with age was only about half that seen during the same time period in normal development (bearing in mind that these are log-log axes).

Since in normal development the relationship between grating and vernier acuity changes characteristically with age, it is important to determine whether the disruption of the developmental time courses seen in the strabismic monkeys is accompanied by a distortion of this relationship. Fig. 5 compares the

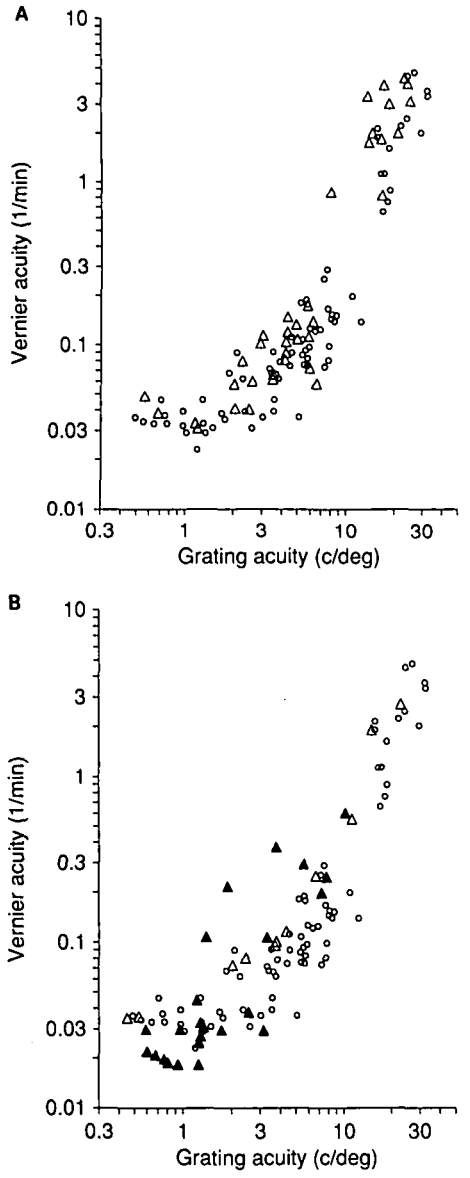

Fig. 5. The relationship between grating and vernier acuity in the strabismic monkeys as compared to normal. Axes are the same as in Fig. 6 of the preceding paper. The small circles show the relationship between grating and vernier acuity for normal monkeys over the course of development (from Fig. 6, Kiorpes, 1992). A: Open triangles show this relationship for the nondeviated eyes of the strabismic monkeys. B: Filled triangles show the relationship for amblyopic eyes; open triangles show the relationship for non-amblyopic deviated eyes.

normal sequence, which characterizes the changing relationship between vernier and grating acuity during maturation as described in the preceding paper (Kiorpes, 1992; Fig. 6), with the relationship between vernier and grating acuity in strabismic monkeys. The two acuity measures are plotted against each other, collapsing across age and animals; the small open circles reproduce data for normal animals from the preceding paper. In Fig. 5A, the open triangles represent nondeviated eye data for the strabismic animals. These nondeviated eye data are well described by the normal sequence. The deviated eye data are also reasonably well described by the normal sequence although the scatter of the data is greater in this case. Fig. 5B shows the relationship between vernier and grating acuity for the deviated eyes along with the normal sequence. The filled triangles represent data from amblyopic eyes, while the open triangles represent the non-amblyopic deviated eyes. The relationship between vernier and grating acuity appears to be preserved rather than decoupled in the strabismic monkeys. The strabismic amblyopes perform like younger normal monkeys with their deviated eyes, while the monkeys that did not develop amblyopia perform like their normal peers.

Discussion

The present study shows that, like human strabismic amblyopes, macaque strabismic amblyopes have relatively greater deficits in vernier acuity than grating acuity. However, the developmental time courses for vernier and grating acuity appear to be disrupted in parallel, rather than differentially. These deficits seem to result from a slowing of the development of spatial vision generally for the deviated eye since the relationship between vernier and grating acuity found was typical of younger normal animals.

On the surface it may appear that the major findings are contradictory. The findings of a greater deficit in vernier acuity than in grating acuity, but a comparable disruption of the developmental time courses for these two visual functions, can be understood by recalling the pattern of normal development discussed in the preceding paper (Kiorpes, 1992). In normal animals, vernier acuity is relatively less mature at birth but develops more rapidly than grating acuity, with both functions approaching adult levels at the end of the first postnatal year. Since vernier acuity is relatively "poorer" near birth, slowed development will appear to have a greater effect on vernier acuity than on grating acuity. Suppose strabismus were to slow development generally so that it proceeded at a proportional rate that was half that of normal (a reasonable guess based on Fig. 4). By the end of the critical period, given the range of normal development found for each measure, grating acuity for the deviated eye might reach 6.5 cycle/deg and vernier acuity might reach 0.4 min^{-1}. Assuming that the nondeviated eye achieved normal levels of performance, as is usually the case, the deficit in vernier acuity would be larger than the grating acuity deficit. Thus, it seems reasonable to conclude that amblyopia results from a slowed developmental process that leaves many aspects of visual function in a relatively immature state at the end of the critical period.

Given these findings, it seems worthwhile to reconsider the predominant theory regarding the limitations on grating resolution and vernier performance. On the basis of psychophysical data from human adults, it seems that the retinal mosaic limits grating resolution while positional sensitivity is related to

cortical magnification (Westheimer, 1982; Levi et al., 1985; Fahle & Schmid, 1988). However, as discussed in the preceding paper, cortical magnification may simply be a reflection of ganglion cell density (Wässle et al., 1990). Even if this distinction holds true for adults, it is not necessarily the case in infants. While in adult central vision grating resolution is well matched to the resolution limit of the retinal mosaic, infant spatial resolution is well below the resolution limit imposed by the photoreceptor mosaic (Brown et al., 1987; Banks & Bennett, 1988; Wilson, 1988). This is not simply a failure of behavioral methods to tap true sensitivity since the resolution potential of the retina exceeds the resolution of the best lateral geniculate nucleus (LGN) and cortical cells as well (Jacobs & Blakemore, 1988; Movshon & Kiorpes, 1992). The development of spatial resolution in macaques follows a time course similar to the development of spatial resolution of central-field LGN and cortical cells (Blakemore & Vital-Durand, 1986*a*; Jacobs & Blakemore, 1988; Kiorpes, 1992), although these changes may in turn reflect changes in the retinal mosaic. There is evidence that some portion of the development of both spatial resolution and vernier sensitivity depends on photoreceptor immaturities (Banks & Bennett, 1988). However, it is also clear that postreceptoral factors are to some unknown degree necessary to account for the full extent of development.

The amblyopic deficits found in the present study are likely to depend on the properties of striate cortical cells. Several physiological studies of amblyopic monkeys have shown that the primary site of the amblyopic deficit is cortical. Movshon et al. (1987) quantitatively studied spatial properties of cells in LGN and striate cortex from monkeys made amblyopic by chronic instillation of atropine to one eye. They found deficits in spatial resolution and contrast sensitivity in cortical cells but not in LGN cells. Similarly, normal spatial resolution has been found for LGN cells in monocularly deprived monkeys (Blakemore & Vital-Durand, 1986*b*) even if the deprivation conditions existed for extended periods of time (Levitt et al., 1989). There is no evidence to suggest an anatomical effect on retina in amblyopic monkeys (Hendrickson et al., 1987); although no studies of retinal physiology in amblyopic monkeys have been published. Therefore, it is reasonable to assume that strabismic amblyopia also exerts its effects primarily at the level of the cortex. One quantitative physiological study of strabismic monkeys found a dramatic reduction in the number, spatial resolution, and contrast sensitivity of cortical cells driven by the deviated eye, but did not examine LGN cells (Eggers et al., 1984).

The longitudinal data from the strabismic monkeys suggest that in amblyopia there is a single factor that affects the development of both vernier acuity and grating acuity: the developmental time courses for vernier and grating acuity seem to be similarly affected in the amblyopic monkeys and the relationship between vernier and grating acuity is similar to that found in young normal monkeys. These data argue against the idea that vernier acuity is peculiarly disrupted in strabismic amblyopia. Rather it seems likely that some factor acting at the level of the cortex retards the development of spatial and contrast-response properties of single cells and that the behavioral data reflect these neuronal deficits. Validation of this idea awaits further physiological study and, of course, the nature of this factor is open to speculation. Clearly the presence of strabismus is not in itself uniquely responsible since some monkeys and humans with strabismus do not develop amblyopia. The development of amblyopia following strabismus in animals has been shown to depend primarily on the fixation pattern adopted and the age of onset of the strabismus (Kiorpes et al., 1989).

The developmental patterns for vernier and grating acuity in normal and strabismic monkeys taken together suggest that there is a rather tight relationship between these two visual functions. It is possible that these functions reflect different processing aspects of the same cells, and/or depend to a different degree on the development and organization of the photoreceptors. For example, suppose that the spatial resolving power of central-field cells at the retinal, geniculate or cortical levels limits grating resolution (Blakemore & Vital-Durand, 1986*a*). And suppose that the contrast-response properties of neurons at the level of the cortex or earlier limit vernier performance (Parker & Hawken, 1985). The spatial properties of single neurons may develop to a different degree or at a different rate than contrast-response properties. The differential development of behaviorally measured visual functions would then not necessarily reflect development at different levels in the visual pathway. Behavioral development could reflect the development of physiological properties of cortical cells and amblyopia could reflect disruption of development at this level.

In summary, vernier acuity and grating acuity develop over different time courses in normal animals and are similarly disrupted in strabismic amblyopia. The resulting behavioral status in strabismic amblyopes is similar to that of young normal animals where vernier acuity is relatively less mature than grating acuity. These results argue against the notion that vernier acuity is particularly affected in strabismic amblyopia. They also extend previous studies of amblyopia in monkeys, showing additional similarities between macaques and humans. Further physiological and anatomical investigations will be needed to address the underlying basis for the deficits in spatial vision of strabismic amblyopes.

Acknowledgments

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