17 Visual Acuity and Spatial Contrast Sensitivity: Normal Development and Underlying Mechanisms

DAPHNE MAURER
AND TERRI L. LEWIS

ABSTRACT This chapter considers the role of experience and of competitive interactions between the eyes in the development of spatial vision. We first describe the postnatal development of grating acuity and spatial contrast sensitivity in normal infants and the neural changes underlying that development. We then evaluate the role of visual input in driving postnatal development by drawing on evidence from children deprived of patterned visual experience by dense and central cataracts. Animal models allow us to deduce the impact of visual input on different levels of the nervous system. We conclude that experience and competitive interactions between the eyes for cortical connections play a prominent role in the development of spatial vision.

No matter how it is measured, the spatial vision of the newborn is poor. For example, the smallest high-contrast elements to which a newborn responds are 30–60 times larger than the smallest that are visible to an adult with normal vision. In the first half of this chapter, we describe the postnatal development of two aspects of spatial vision—grating acuity and spatial contrast sensitivity—and the neural changes underlying that development. In the second half, we evaluate the role of visual input in driving the postnatal development of spatial vision and draw inferences from animal models about the impact of visual input on different levels of the nervous system. Although various methods have been used to assess spatial vision during infancy, we concentrate on measurements using preferential looking, using results from other methods only to help unravel the neural basis of the observed developmental changes.

DAPHNE MAURER Department of Psychology, McMaster University, Hamilton, Ontario; Department of Ophthalmology, The Hospital for Sick Children, Toronto, Canada.
TERRI L. LEWIS Department of Psychology, McMaster University, Hamilton, Ontario; Department of Ophthalmology, The Hospital for Sick Children, Toronto, Ontario; Department of Ophthalmology, University of Toronto, Toronto, Canada.

Normal development

GRATING ACUITY Preferential looking takes advantage of the fact that young infants look longer at a patterned stimulus than at a plain gray field (Fantz, Ordy, and Udelf, 1962). To measure grating acuity, black-and-white stripes are usually paired with a plain gray stimulus, and the size of stripe is varied across trials, with the stripes appearing randomly on the right or left side of the field. Early versions of the test usually took 20–30 minutes per measure of acuity. They involved psychophysical rules to determine thresholds and cumbersome equipment to reinforce correct responses once the natural preference for patterns waned after early infancy (Birch et al., 1983; Lewis and Maurer, 1986; Mayer and Dobson, 1980, 1982; van Hof-van Duin and Mohn, 1986). A more subjective and portable version of the test, commonly called the Acuity Card Procedure, dispenses with psychophysical rules and typically yields a measurement of grating acuity in less than 5 minutes (McDonald et al., 1985; Teller et al., 1986). On each trial, a tester guesses whether the stripes are on the right or on the left side of the card, based on any reliable cues provided by the child (direction of first look, direction of longest look, etc.). To minimize bias, the tester is kept unaware of the actual location of the stripes. The child's grating acuity is defined as the smallest stripe size that the tester can locate correctly.

Figure 17.1 shows typical changes in grating acuity between birth and 48 months of age as measured by preferential looking. The size of the smallest stripes to which subjects respond at each age is given in cycles per degree of visual angle (c/deg), where one cycle represents one black and one white stripe. The greater the number of cycles per degree, the higher the spatial frequency and the narrower the stripes. Although grating acuity is poor at birth—typically about 40 times worse than that of a normal adult (Brown and Yamamoto,

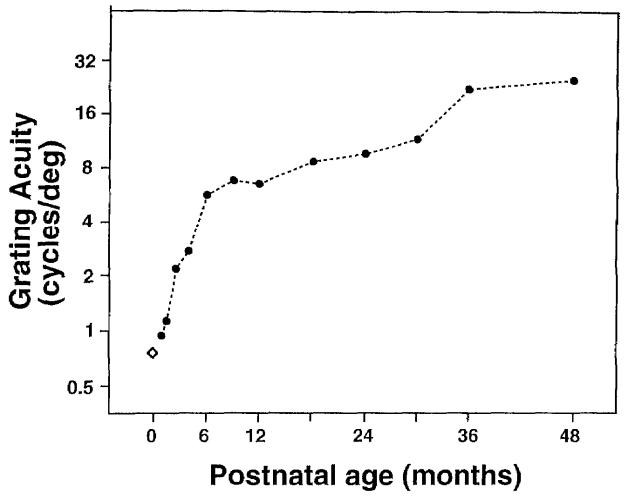

FIGURE 17.1 Typical changes in grating acuity between birth and 48 months. The *y*-axis shows the size of the smallest stripes to which subjects respond, plotted in cycles per degree of visual angle, where one cycle represents one black and one white stripe. Thus, the larger the number, the better the grating acuity. Filled circles represent the mean acuity of 1- to 48-month-olds tested monocularly by Mayer and colleagues (1995). The open symbol represents the log mean grating acuity of newborns tested binocularly (Brown and Yamamoto, 1986; Courage and Adams, 1990; Dobson et al., 1987; Mayer and Dobson, 1982; Miranda, 1970; van Hof-van Duin and Mohn, 1986). Monocular and binocular acuities do not differ prior to 6 months of age (Birch, 1985). Grating acuity is adult-like somewhere between 4 and 6 years of age, depending on the testing conditions.

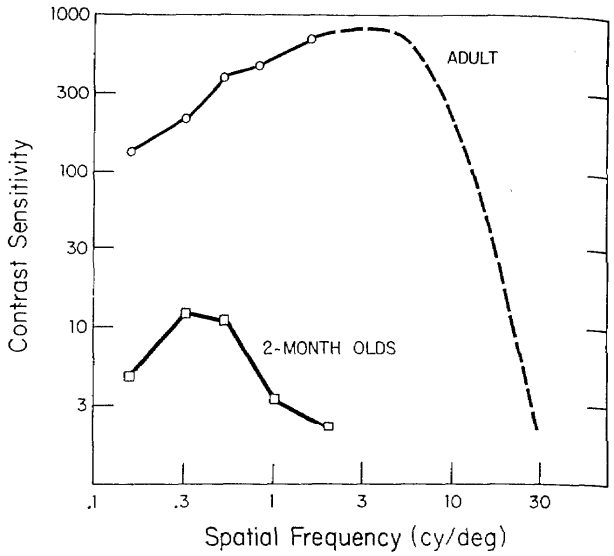

FIGURE 17.2 Typical contrast sensitivity functions for adults (upper curve) and 2-month-olds (lower curve). The *y*-axis plots contrast sensitivity (the inverse of the minimum contrast necessary to resolve the pattern) so that larger numbers represent greater sensitivity to contrast. The *x*-axis plots spatial frequency in cycles per degree of visual angle, where one cycle represents one black and one white stripe. Two-month-olds are about 20 times less sensitive than adults up to about 2–3 c/deg and show no evidence of seeing narrower stripes at even very high contrast. (Reprinted with permission from M. S. Banks and P. Salapatek, 1981. Infant pattern vision: A new approach based on the contrast sensitivity function. *J. Exp. Child Psychol.* 31, Figure 4.)

1986; Courage and Adams, 1990; Dobson et al., 1987; Mayer and Dobson, 1982; Miranda, 1970; van Hof-van Duin and Mohn, 1986), it improves rapidly over the first few months of life, so that by 6 months of age it is only about 8 times worse than that of a normal adult. Thereafter, grating acuity improves more gradually and reaches adult values by 4–6 years of age (Courage and Adams, 1990; Mayer and Dobson, 1982; van Hof-van Duin and Mohn, 1986).

CONTRAST SENSITIVITY Grating acuity provides a measure of the smallest visible stripe size. However, spatial vision is limited not only by size, but also by the difference in luminance between objects and their background. High contrast objects are more easily detected than are lower contrast objects, and the minimum amount of contrast necessary to resolve an object varies with the size of the object. The contrast sensitivity function plots contrast sensitivity (the inverse of the minimum contrast necessary to resolve the pattern) for stripes of various sizes (or, more accurately, for sine waves of different spatial frequency). A typical function for normal adults is shown by the upper curve in figure 17.2. Contrast sensitivity peaks at 3–5 c/deg, drops off gradually for lower spatial frequencies (wider stripes), and declines sharply for higher spatial frequencies (narrower stripes).

Several groups of investigators have used preferential looking to measure contrast sensitivity in young infants (Adams et al., 1992; Atkinson, Braddick, and Moar, 1977; Banks and Salapatek, 1978, 1981; Gwiazda et al., 1997; Peterzell, Werner, and Kaplan, 1995). As with grating acuity, stripes of a particular spatial frequency and contrast are paired with a plain gray stimulus, and the tester looks for evidence that the baby has detected the stripes (e.g., that the baby looks first or most toward the side where the stripes appear). Over trials, contrast is varied to determine the minimum contrast for which babies show a preference for stripes of that spatial frequency. The process is then repeated at different spatial frequencies to derive the contrast sensitivity function.

All investigators agree that contrast sensitivity is very immature during early infancy. The lower curve in figure 17.2 shows typical results from 2-month-olds. Al-

though the function has the same overall shape as that of adults, it is shifted markedly downward and to the left: 2-month-olds are about 20 times less sensitive than adults up to about 2–3 c/deg and show no evidence of seeing narrower stripes even at very high contrast. One-month-olds (the youngest age tested with behavioral techniques) perform even more poorly and produce a function with a different shape, without the low-frequency fall-off typical of adults and older infants (Adams et al., 1992; Atkinson, Braddick, and Moar, 1977; Banks and Salapatek, 1978). After 2 months of age, contrast sensitivity continues to improve, but it is still very immature throughout the first year of life (Adams et al., 1992). In fact, studies of older children using variants of preferential looking or psychophysical techniques designed for adults indicate that contrast sensitivity is not adult-like until middle childhood, with estimates of when it reaches adult levels ranging from 6 years to sometime after 15 years of age (Arundale, 1978; Bradley and Freeman, 1982; Derefeldt, Lennerstrand, and Lundh, 1979; Ellemberg et al., 1999a; Gwiazda et al., 1997; Mantyjarvi et al., 1989; Mayer, 1977).

Mechanisms underlying normal development

What factors might contribute to poor spatial vision at birth and to its subsequent improvement? Nonvisual factors such as changes in motivation or attention are unlikely causes of the rapid postnatal improvement: During early infancy, measurements of contrast sensitivity derived from visually evoked potentials, which presumably are influenced little by motivation or attention, yield values similar to those obtained from preferential looking, provided that stimulus conditions are matched across the two procedures (Atkinson and Braddick, 1989; Harris, Atkinson, and Braddick, 1976; Pirchio et al., 1978). Rather, the important factors seem to be changes with age in the retinal mosaic and in post-retinal factors, with perhaps some contribution from changes in the optics of the eye.

The contribution from changes in the optics of the eye appears to be minimal. First, growth of the eyeball cannot be the main explanation because its rate of growth does not correspond to the rate of improvement in spatial vision (Courage and Adams, 1990; Larsen, 1971; Mayer and Dobson, 1982; Mayer et al., 1995; van Hof-van Duin and Mohn, 1986). Second, changes with age in pupil diameter, in the amount of diffraction, or in the amount of spherical and chromatic aberration probably have negligible effects on spatial vision (reviewed in Banks and Bennett, 1988). Moreover, transmittance through the ocular media is *better* in newborns than in adults, especially at short wavelengths (reviewed in Banks and Bennett, 1988). Finally, inaccurate accommodation does not appear to impose an important limitation because, even at birth, acuity does not vary with viewing distance (Cornell and McDonnell, 1986; Salapatek, Bechtold, and Bushnell, 1976). Taken together, the evidence suggests that postnatal changes in the optical properties of the eye make little contribution to the postnatal changes in spatial vision.

In contrast, retinal development appears to play a major role. Compared to the adult's fovea, in the newborn's fovea, the length of the outer segments of cones is 16-fold shorter and cone-packing density is 4-fold lower (Banks and Bennett, 1988; Hendrickson and Youdelis, 1984; Youdelis and Hendrickson, 1986). Short outer segments of newborns' foveal cones make the cones less efficient in producing isomerization for a given quantum of light. This characteristic limits acuity and spatial contrast sensitivity, both of which decrease as luminance decreases (Allen, Bennett, and Banks, 1992; Brown, Dobson, and Mayer, 1987; Pasternak and Merigan, 1981). Reduced cone packing density causes a reduction in spatial sampling, which limits acuity (Banks and Bennett, 1988; Wilson, 1988, 1993). Immaturities in the newborn's peripheral retina, although less marked, may be a more important limitation during early infancy because normal infants and infants with no anatomical fovea (because of oculocutaneous albinism) have similar grating acuity (Mayer, Fulton, and Hansen, 1985). Although the newborn's peripheral retina beyond about 5 degrees is more mature than the central retina, even in the peripheral retina, the outer segments of cones are much shorter in young infants than in adults (Abramov et al., 1982; Drucker and Hendrickson, 1989; Hendrickson and Kupfer, 1976).

During later infancy, measurements of grating acuity by preferential looking exceed the resolution limits of the peripheral retina and so must be dominated by the central retina and its projections. Although considerable foveal maturation occurs between birth and early childhood, measurements from a 45-month-old indicate that, even at this age, foveal cone packing density is still only half the adult value and the length of the outer segments of foveal cones is still 30–50% shorter than in adults (Youdelis and Hendrickson, 1986). Together, these retinal immaturities can account for at least some of the limitations in acuity and contrast sensitivity at birth and the fact that neither aspect of spatial vision is mature at 4 years of age (Banks and Bennett, 1988; Wilson, 1988, 1993).

However, retinal immaturities probably do not tell the whole story (Candy and Banks, 1999; Kiorpes and Movshon, 1998). Studies of infant monkeys indicate

that the inputs both from the retina to the LGN and from the LGN to the visual cortex are immature (Blakemore, 1990; Blakemore and Vital-Durand, 1986a; Kiorpes and Movshon, 1998; Movshon and Kiorpes, 1993). These immature connections may account, at least in part, for findings that cortical contrast sensitivity and acuity, as measured by visually evoked potentials, mature no faster than the contrast sensitivity and acuity measured by the electroretinogram (Fiorentini, Pirchio, and Sandini, 1984; Fiorentini, Pirchio, and Spinelli, 1983). Moreover, in humans, many aspects of the geniculostriate pathway are immature until well past infancy. LGN neurons do not reach their adult size until 2 years of age (Hickey, 1977). Within the primary visual cortex, synaptic density increases dramatically, then decreases, and is not adult-like until approximately 11 years of age (Garey and De Courten, 1983; Huttenlocher, 1984; Huttenlocher et al., 1982). This pruning may be related to the reduction in the size of cortical neurons' receptive fields and to the increase in the fine tuning of their selectivity for spatial frequency, all of which have been documented in developing monkeys (Blakemore, 1990). These cortical changes may contribute to the increase in acuity and contrast sensitivity that occurs during childhood (until sensitivity reaches the Nyquist limit set by the retina).

Thus it appears that the development of spatial vision is limited primarily by slow retinal and postretinal development. In the monkey, improvements in behavioral acuity with age closely parallel improvements in the sensitivity of cells in the LGN (Blakemore, 1990); therefore, the main post-retinal limit probably lies in the LGN itself and/or the connections between the retina and the LGN (Blakemore, 1990; Blakemore and Vital-Durand, 1986a; Ellemberg et al., 1999a; Movshon and Kiorpes, 1993). Such limits at the level of the LGN would, of course, restrict the information that reaches the visual cortex and higher levels of the visual system.

The role of visual input

In the rest of this chapter, we consider the role of visual input in driving the postnatal improvements in visual acuity and spatial contrast sensitivity. The data come from children who had dense central cataracts in one or both eyes. A cataract is an opacity in the lens of the eye which, in the children we selected for study, was sufficiently dense to block visual input to the retina and prevent fixation and following. The cataractous lens was removed surgically and the eye given an optical correction, usually a contact lens, to provide nearly normal visual input. This cohort allows us to evaluate the effect of a period of visual deprivation on the development of visual function, and hence to infer the role that visual input plays in normal visual development. By measuring deficits in children treated for congenital cataracts, we can infer the importance of visual input immediately after birth. By measuring deficits in children treated for developmental cataracts, in whom the visual deprivation followed a period of normal visual input, we can infer the importance of visual input during later periods of development and deduce the sensitive period for these visual functions.

Studies of children treated for bilateral cataracts allow inferences about the effects of visual deprivation per se. Comparisons to children treated for unilateral cataract allow additional inferences about the effects of uneven competition between the eyes for cortical connections. For example, worse outcomes after monocular than after binocular deprivation of the same duration after birth provide evidence that the two eyes compete for cortical connections. Because of this competition, parents of children treated for unilateral congenital cataract were instructed to patch the nondeprived eye to force usage of the previously deprived eye, but the amount of patching varied across patients. Better outcomes when there was more patching of the nondeprived eye provide additional evidence for competitive interactions during normal development.

ACUITY IMMEDIATELY AFTER THE END OF VISUAL DEPRIVATION FROM CONGENITAL CATARACT To assess the importance of patterned visual input for the postnatal development of acuity, we measured the grating acuity of 28 infants immediately after the end of deprivation, that is, just after the ophthalmologist inserted contact lens(es) about 1 week after the removal of dense, central congenital cataracts from one (n = 16) or both (n = 12) eyes (Maurer et al., 1999). Whether the deprivation had been monocular or binocular, grating acuity was, on average, like that of normal newborns, despite variation in the duration of deprivation ranging from 1 week to 9 months. As a result, the acuity of deprived eyes fell farther below normal, the later during the first year they were treated. In contrast, the acuity of the nondeprived eyes of unilateral cases was normal and higher, the later during the first year it was tested.

The results indicate that visual acuity does not improve postnatally in the absence of patterned visual input. For deprivation lasting up to 9 months after birth, acuity remains near the newborn level. Even when the deprivation had been monocular so that muted signals from the deprived eye coexisted with signals from a normally developing eye, the acuity of the deprived eye was not degraded below newborn levels. In kittens, spontaneous retinal activity has been shown to influence the

organization of the visual cortex even before eye opening (reviewed in Katz and Shatz, 1996). It is possible that such spontaneous retinal activity provides sufficient cortical stimulation during early deprivation in humans to maintain the connections that were formed prenatally—at least when the deprivation begins at birth and lasts no longer than 9 months.

Development of Acuity after Treatment for Congenital Cataract

After 1 hour of visual input To determine the effect of the onset of patterned visual input, we retested the acuity of the 28 patients after 1 hour of such input, 1 week later, and 1 month later (Maurer et al., 1999). Whether the eye had been treated for monocular or binocular deprivation, there were significant improvements in acuity after the first hour of visual input, with a mean improvement of about 0.4 octaves (an octave is a halving or a doubling of a value). To verify that the improvement was the result of visual input, we conducted a second experiment following the same protocol for the immediate and 1-hour tests except that one treated eye of each of 17 patients was patched after the first test so that it did not receive the hour of patterned visual input. There was no significant improvement in the 17 patched eyes (eight from bilateral cases and nine from unilateral cases). In the six bilateral cases in which we were able to measure changes in acuity for both the eye that had been patched and in the fellow eye that had received 1 hour of visual input, there was significantly more improvement in the experienced eyes than in the patched eyes. Figure 17.3 shows the mean improvement in the 28 patients in the first experiment who received visual input between the immediate and 1-hour tests compared to age-matched normals and the 17 patched eyes in the second experiment.

The results indicate that the onset of patterned visual input initiates rapid functional development in humans, as it does in kittens (Mitchell and Gingras, 1998). The improvement may be caused by cortical changes similar to those observed in kittens immediately after deprivation. For example, in kittens reared in darkness from birth (Beaver, Mitchell, and Robertson, 1993) or for 1 week beginning at 5 weeks of age (Kaplan, Guo, and Mower, 1996; Mower, 1994), there is expression of Fos, the protein produced by the immediate early genes *fos*, in all layers of the visual cortex after as little as 1 hour of binocular visual input. Because the expression of Fos appears to reflect a step in long-term physiological changes rather than current neuronal activity, at least in the cat (Beaver, Mitchell, and Robertson, 1993; Kaplan, Guo, and Mower, 1996, but see Kaczmarek,

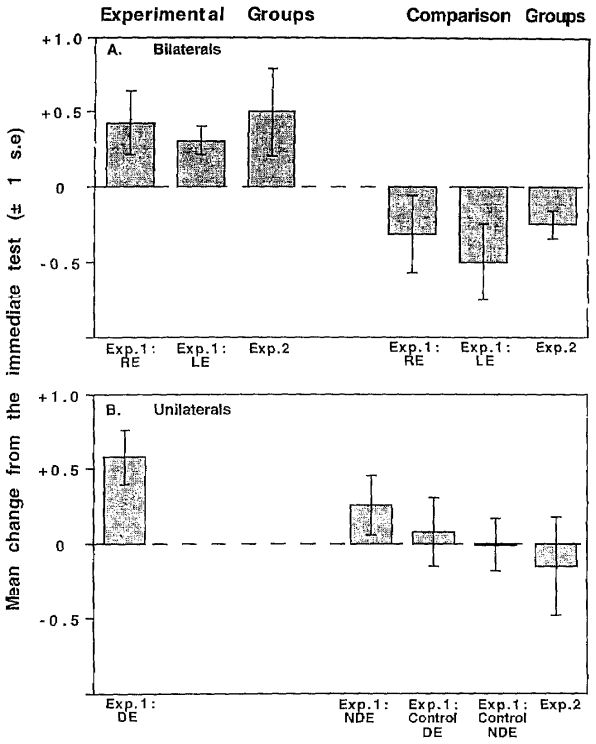

FIGURE 17.3 Mean change in acuity (±1 SE) between the immediate and 1-hour tests. The *y*-axis plots the amount of change in octaves, where one octave is a doubling or a halving of a value. Values above zero represent an improvement from the immediate test; values below zero represent a decline. The left half of each panel shows the results for experimental groups, all of which received their first hour of patterned visual input between the immediate and 1-hour tests. The right half of each panel shows the results for comparison groups, none of which received their first hour of patterned visual experience between the immediate and 1-hour tests either because they were age-matched normals with prior visual experience or because the deprived eye was patched between the two tests. (**A**) The results for bilateral cases and their comparison groups; (**B**) the results for unilateral cases and their comparison groups. In panel A, the three experimental means are, respectively from left to right, from the right eye of bilateral cases in Experiment 1, the left eye of bilateral cases in Experiment 1, and the unpatched eye of bilateral cases in Experiment 2. The three comparison means are from the right eye of age-matched normals for Experiment 1, the left eye of age-matched normals for Experiment 1, and the patched eye of bilateral cases in Experiment 2. In panel B, the experimental mean is from the treated eyes of unilateral cases in Experiment 1. The four comparison means are from, respectively, the nondeprived eye of unilateral cases in Experiment 1, the normal eyes matched to the treated eyes of unilateral cases in Experiment 1, the normal eyes matched to the nondeprived eyes of unilateral cases in Experiment 1, and the patched eyes of unilateral cases tested in Experiment 2. In every comparison, eyes in the experimental groups improved more between the immediate and 1-hour test than did eyes in the comparison groups, a result that indicates that the improvement resulted from receiving patterned visual input for the first time.

Zangenehpour, and Chaudhuri, 1999), these results imply that 1 hour of visual input after dark-rearing is sufficient to induce cortical changes. Similarly, after 5 weeks of monocular deprivation, the kitten's visual cortex shows only small patches of Fos-immunoreactive neurons related to the deprived eye, but those patches are already slightly larger 1 day after the opening of the deprived eye and the suturing shut of the fellow eye (Mitchell, Beaver, and Ritchie, 1995).

One month later By 1 month after treatment, we found significant additional improvement in the visual acuity of the 28 patients such that the deficit was reduced to a mean of about 1 octave compared to normals (Maurer et al., 1999). The amount of improvement was not related to the age of first patterned visual input. Nor, in unilateral cases, was the improvement over the first month related to the amount of patching of the nondeprived eye, which varied from 0 to 7.7 hours/day (M = 4.6 hours/day). The improvement is unlikely to be merely a practice effect because there was no significant improvement over the month in the fellow nondeprived eyes of infants treated for unilateral congenital cataract nor in any of the groups of age-matched controls.

Surprisingly, there was no difference between unilateral and bilateral cases in the amount of recovery either over the first hour or during the first month, and no beneficial effect of patching over that month (Maurer et al., 1999). Unlike the later results (described following), the initial improvements in acuity appear to be determined by visual activity, with no deleterious effects of uneven competition. Mitchell and Gingras (1998) reached a similar conclusion in a study of recovery from monocular deprivation in kittens: The initial recovery was similar whether or not the nondeprived eye was sutured shut (reverse-sutured) to reduce the competitive disadvantage of the previously deprived eye. Mitchell and Gingras concluded that the initial recovery of acuity after monocular deprivation is driven solely by visually evoked cortical activity and that only much later, after a scaffold of connections from the deprived eye has been established in the visual cortex, does uneven competition between the eyes limit the amount of recovery. The implication is that normal development during infancy may also be driven solely or mainly by visual activity and that only later, after a number of robust cortical connections have been established from both eyes, do competitive interactions influence subsequent refinements of acuity.

The recovery after the end of deprivation from congenital cataract might reflect mainly the relative sparing of neurons representing the peripheral visual field. That possibility is suggested by the aforementioned evidence that preferential looking measurements of acuity during the first year of life may be dominated by input from the peripheral retina. It is consistent with evidence that the primary visual cortex of monocularly deprived kittens exhibits a substantial loss of NMDA receptors, which have been shown to be involved in cortical plasticity, only in areas representing the central visual field (Duffy and Murphy, 1999). It also fits with evidence that both the light sensitivity and spatial contrast sensitivity of older children with a history of early monocular deprivation are degraded less in the periphery than in the central visual field (Bowering, 1992; Maurer and Lewis, 1993). Measurements during infancy with techniques that appear to be influenced more by central vision than is preferential looking—optokinetic nystagmus (Lewis, Maurer, and Brent, 1995) and visually evoked potentials (McCulloch and Skarf, 1994)—indicate much less recovery during the first months following treatment for congenital cataract.

At 1 year of age By 1 year of age, the acuity of most eyes treated for congenital cataract has improved such that it falls within normal limits (Birch and Stager, 1988; Birch, Stager, and Wright, 1986; Birch et al., 1993; Catalano et al., 1987; Jacobson, Mohindra, and Held, 1983; Lewis, Maurer, and Brent, 1995; Lloyd et al., 1995; Mayer, Moore, and Robb, 1989). By implication, acuity in previously deprived eyes must improve at a rate faster than normal between the time of treatment and the first birthday. Our own data provide information on the largest cohort tested at 1 year of age (Lewis, Maurer, and Brent, 1995). Using inclusion criteria identical to those in the study of acuity immediately after treatment, we measured the preferential looking acuity of the deprived eye of 42 children treated at various ages during the first year of life for unilateral congenital cataract and 88 eyes from 51 patients treated at similar ages for bilateral congenital cataracts. Most (79% of unilaterally deprived eyes and 85% of bilaterally deprived eyes) fell within normal limits. Nevertheless, the mean acuity was below the normal mean and below the mean of the nondeprived eyes of the unilateral cases. In bilateral cases, there was an effect of the duration of deprivation: Acuity at 1 year of age was better the earlier the eye was treated (r = .43 based on one eye of each of the 51 patients, $p < .01$). In other words, during the first year, acuity had improved the most in eyes that had had the most visual input.

In unilateral cases, acuity at 1 year of age was not related significantly to the duration of deprivation after birth, even though it varied from as little as 1 month to as much as 12 months, with a mean of 4.2 months

(Lewis, Maurer, and Brent, 1995). Rather, it was related to the number of hours per day that the nondeprived eye had been patched after treatment: The more hours of patching, the better the acuity ($r = .36$, $p < .05$). In fact, children who had patched the nondeprived eye for less than 3 hours/day had acuity in the deprived eye that was significantly worse than the acuity of children treated for binocular deprivation of comparable duration. Similarly, Mayer and colleagues (1989) found that the difference in acuity between the deprived and nondeprived eyes at 1 year of age was correlated negatively with the amount of patching but, with patching held constant, unrelated to the child's age at surgery. These results imply that by 1 year of age, competitive interactions have begun to influence recovery from deprivation. After monocular deprivation, they have become a stronger influence than the duration of the initial deprivation or the amount of visual activity after deprivation. Thus, the initial recovery appears to be driven by visual activity, perhaps taking advantage of the normal postnatal exuberant proliferation of synapses in the visual cortex (Huttenlocher and de Courten, 1987; Huttenlocher et al., 1982). And once that activity has induced functional changes, presumably by strengthening cortical responses driven by the previously deprived eye, competitive interactions emerge and quickly become the strongest determinant of visual outcome.

At 3 years of age After 1 year of age, the acuity of most patients treated for congenital cataract continues to improve, but does so at a below-normal rate so that most eyes fall outside normal limits after about 2 years of age (Birch and Stager, 1988; Birch, Stager, and Wright, 1986; Lewis, Maurer, and Brent, 1995; Mayer, Maurer, and Robb, 1989; but see Birch et al., 1993; Lloyd et al., 1995). For example, in the cohort we followed longitudinally from 1 year of age, 85% of the 26 eyes treated for unilateral congenital cataract and 74% of the 78 eyes treated for bilateral congenital cataract had preferential looking acuity below normal limits at 3 years of age, with mean deficits of 1.2 octaves in unilateral cases and 1.1 octaves in bilateral cases. These data imply that early visual deprivation caused changes in the nervous system that diminished its ability to profit from visual input during later infancy and early childhood. In children treated for bilateral congenital cataracts, those effects are related to the duration of the deprivation after birth: The longer the deprivation, the worse the acuity at 2.5–3 years of age ($r = .51$ based on one eye from each of 51 patients treated for bilateral congenital cataract, $p = .0001$). The deficits at 3 years of age may reflect damage to neurons with receptive fields involving central vision that dominate measurements of preferential looking acuity at 3 years, but not at 1 year of age (Lewis, Maurer, and Brent, 1995). Alternatively, they may reflect damage to the processes by which cortical synapses are pruned, processes that are especially evident in the visual cortex from 9 to 18 months of age and in higher visual areas after 2 years of age (Huttenlocher, 1979; Huttenlocher and Dabholkar, 1997; Huttenlocher and de Courten, 1987).

As at 1 year of age, we found that the duration of monocular deprivation from birth is not related to the acuity of the affected eyes at 3 years of age (Lewis, Maurer, and Brent, 1995). Rather, as at 1 year of age, the outcome at 2.5–3 years was related significantly to the number of hours per day that the nondeprived eye had been patched since treatment: In the 36 treated eyes that we tested at 2.5–3 years, there was a correlation of .53 between patching and acuity ($p = .001$). Moreover, when the nondeprived eye had been patched for less than 3 hours/day, 3-year acuity was significantly worse than that of children treated for bilateral congenital cataracts. Like the results at 1 year, these findings imply that once visual activity has allowed the previously deprived eye to nearly catch up to the nondeprived eye, competitive interactions between the eyes become paramount. Similarly, Mayer and colleagues (1989) found that interocular differences in acuity at 3 years of age were related to how much the nondeprived eye had been patched and not the age at which the deprived eye was treated. However, there might be a nonlinear relationship between the duration of deprivation, patching, and acuity at 3 years. Consistent with that possibility, Birch and colleagues (1993) found that among children treated for unilateral congenital cataract, all of whom had patched the nondeprived eye for 6–8 hours/day, measured acuity was better at most ages if the affected eye had been treated before 6 weeks of age rather than after 2 months of age.

After 5 years of age By 5 years of age, the grating acuity of normal children has reached (Mayer and Dobson, 1982), or nearly reached (Ellemberg et al., 1999a), the adult level of more than 30 c/deg. Patients treated for congenital cataract almost never achieve such high levels of acuity. For example, in our study of 13 patients treated for bilateral congenital cataract, grating acuity after age 5 ranged from 4.5 to 17.5 c/deg or, on average, 1.5 octaves below normal (Ellemberg et al., 1999b). As in previous studies of patients treated for bilateral congenital cataract (Birch et al., 1998; Mioche and Perenin, 1986; Tytla et al., 1988), these patients showed losses in spatial contrast sensitivity that increased monotonically with spatial frequency, with losses exceeding half a log unit in every eye. Within our small sample, there was

no effect of the duration of the binocular deprivation on the size of the deficit in grating acuity or in contrast sensitivity at 5 c/deg, even though the duration of deprivation had varied from 1.5 to 9 months. This result resembles a similar finding in binocularly deprived monkeys (Harwerth et al., 1991) and previous findings that the duration of binocular deprivation from cataracts does not affect the size of the ultimate deficit in linear letter acuity (Birch et al., 1998; Maurer and Lewis, 1993; but see Kugelberg, 1992). Thus, binocular deprivation for as little as the first 1.5 months of life—a period during which normal infants can see only low spatial frequencies—prevents the later development of normal sensitivity to high spatial frequencies, and causes deficits as large as binocular deprivation lasting far longer into the first year of life. However, there is evidence that after *extremely* early treatment—before 10 days of age—some, but not all, children are able to achieve a linear letter acuity of 20/20 (Kugelberg, 1992).

The deficits are greater in children treated for unilateral congenital cataract unless treatment was early *and* followed by aggressive patching of the nondeprived eye (Birch et al., 1993, 1998; Ellemberg et al., 2000; Mayer, Moore, and Robb, 1989; Tytla et al., 1988). When treatment was very early (before 6 weeks) and followed by aggressive patching (at least 75% of waking time), a few treated eyes achieve a linear letter acuity of 20/20 and normal contrast sensitivity at all spatial frequencies (Birch et al., 1993). When treatment is delayed and followed by little patching, there are profound losses in grating acuity and in contrast sensitivity at all spatial frequencies (Ellemberg et al., 2000). For example, in two children with monocular deprivation lasting more than 8 months followed by little patching of the nondeprived eye (<3 hours/day), we found deficits in grating acuity of about 1.5 log units (5–6 octaves) and losses of about 1 log unit in spatial contrast sensitivity even at 0.5 c/deg, losses that were much larger than those seen in a child treated for binocular deprivation of the same duration (Ellemberg et al., 1999b). As at earlier test points (Birch et al., 1993), among good patchers, there appears to be a nonlinear relationship between outcome and the duration of the monocular deprivation: The outcome is better if treatment occurred anytime during the first 6 weeks of life than if it occurred later, with no effect of the duration of deprivation during the first 6 weeks (Birch and Stager, 1996). Only when treatment occurred after 6 weeks of age (and was followed by aggressive patching) is there a linear relationship, such that the outcome is worse the longer the deprivation lasted. [When there was little patching, the outcome is poor, regardless of how long the monocular deprivation lasted (Maurer and Lewis, 1993).] The emergent influence of the duration of monocular deprivation after 6 weeks of age may be related to the increasing cortical influence over infants' visual behavior beginning at about 2 months of age (Birch and Stager, 1996; Braddick, Atkinson, and Hood, 1996; Johnson, 1990).

NONDEPRIVED EYE OF CHILDREN TREATED FOR UNILATERAL CONGENITAL CATARACT As in our previous study (Lewis et al., 1992), we found small losses in the grating acuity of nondeprived eyes, even though the eyes appeared normal on repeated ophthalmological examinations. The losses ranged from 0.3 to 0.8 octaves and were unrelated to the amount of patching (Ellemberg et al., 2000). Similarly, most nondeprived eyes show small losses in contrast sensitivity, but only at high spatial frequencies (Ellemberg et al., 2000; Lewis et al., 1992). These findings complement previous reports of a shift in the distribution of letter acuities in the nondeprived eye toward values that are slightly lower than normal (Lewis et al., 1992; Thompson et al., 1996) and of abnormalities in some aspects of the nondeprived eye's VEP response to small checks (McCulloch and Skarf, 1994). [Birch and colleagues (1993) may not have observed these deficits because they tested the nondeprived eyes at age 5, an age at which sensitivity to high spatial frequencies is not yet adult like on their test and/or because their test of recognition acuity did not include the 20/15 line, which many normal children, but few patients, are able to read.] The subtle deficits in the nondeprived eye—which we observed even in patients who did little patching of the nondeprived eye—suggest that uneven competition between the eyes adversely affects the development of connections from both the previously deprived and the "normal" eye. Interestingly, when the "normal" eye is paired with an eye that does not transmit visually driven signals (e.g., when a serious uniocular disorder like a dense cataract or optic atrophy remains untreated), there is no evidence of such deficits (Thompson et al., 1996).

SENSITIVE PERIOD Like the improvements in acuity during infancy, studies of children treated for cataract indicate that the later refinements in acuity also depend on visual input. Evidence comes from children who were born with apparently normal eyes but who subsequently developed cataracts that blocked all patterned visual input in one or both eyes until the cataracts were removed surgically and the eyes given contact lenses or glasses to focus input on the retina. When the cataract was caused by an eye injury, we can be confident about

when the blockage began and hence the age of onset and duration of complete patterned deprivation. We cannot be so confident when the cataract was caused by a metabolic or genetic disorder, because such cataracts usually develop gradually and block more and more visual input as they become larger. Nevertheless, permanent deficits in visual acuity after treatment for developmental or traumatic cataracts signal the importance of patterned visual input after early infancy.

The *y*-axis in figure 17.4 shows the asymptotic linear letter acuity achieved by the deprived eyes of 29 children treated for unilateral developmental or traumatic cataract and, for comparison, 31 children treated for unilateral congenital cataract. Each dot is plotted at the age when we estimate that the cataract was sufficiently dense to block all patterned visual input. Filled circles indicate that the child had had the nondeprived eye patched for at least 3 hours/day from the time of treatment until 5 years of age. The figure indicates that no child whose deprivation began before about 8 years of age developed normal or nearly normal letter acuity, even though the good eye had, in some cases, been patched aggressively. Figure 17.5 shows similar results for 33 children treated for bilateral congenital cataract and 40 children treated for bilateral developmental cataract. It illustrates the asymptotic linear letter acuity for one eye per child, in panel A for the eye with the better prognosis based on eye alignment and in panel B for the eye with the worse prognosis. With later onset of deprivation, the asymptotic acuity is generally better but it does not reach nearly normal levels unless the deprivation began after about 7–9 years of age. Thus, visual input is necessary throughout the 5–6 years that it takes letter acuity to reach adult levels. It is also necessary to consolidate connections for several years after the age at which normal development is complete.

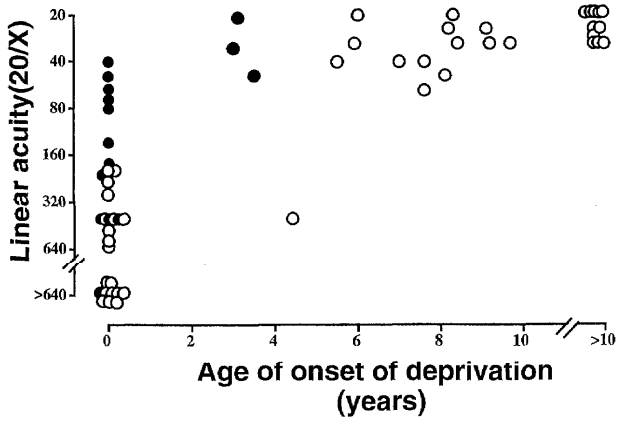

FIGURE 17.4 Asymptotic linear letter acuity as a function of age of onset of monocular deprivation. The *y*-axis plots the denominator of the Snellen fraction such that 20 represents 20/20 vision, which is normal. Larger numbers represent increasingly poor letter acuity. Each dot represents the result for one deprived eye. Data are for the deprived eyes of children treated for unilateral cataract whose deprivation began at birth or who had a normal early visual history and then developed a dense cataract in one eye sometime after 3 months of age. Filled circles are for children who had patched the nondeprived eye more than 3 hours/day from the time of treatment until 5 years of age.

MECHANISMS UNDERLYING THE PERMANENT DEFICITS

The deficits in patients treated for congenital cataract are not likely to arise from optical factors because they are not observed in patients with similar optics after treatment for cataracts with onset in adulthood (Ellemberg et al., 1999b). Nor are they likely to arise from the nystagmus or strabismus commonly associated with congenital cataracts because the same pattern of deficits is

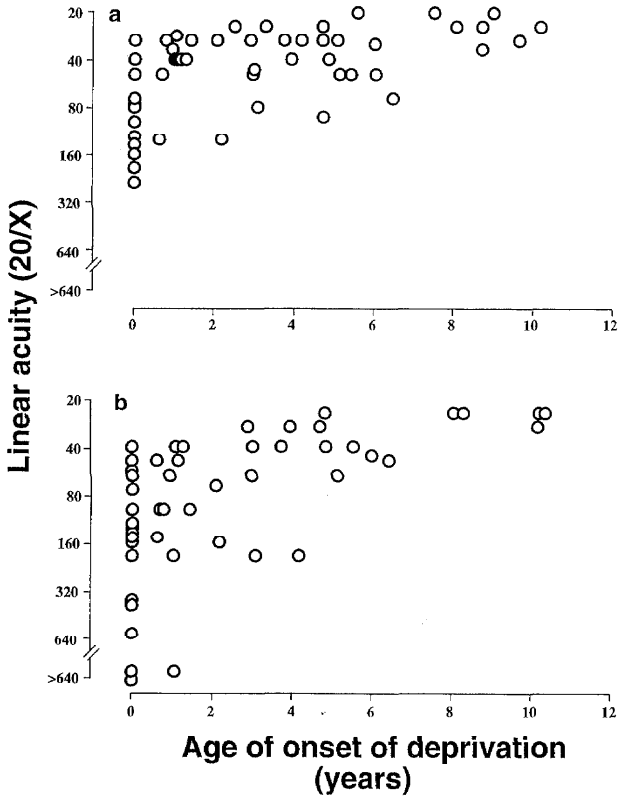

FIGURE 17.5 Asymptotic linear letter acuity as a function of age of onset of binocular deprivation. Data are from children treated for bilateral cataracts whose deprivation began at birth or who had a normal early visual history and then developed dense cataracts sometime after 7 months of age. (**a**) Results from the better eye of each patient, determined on the basis of the history of eye alignment; (**b**) results from the worse eye. Other details as in figure 17.4.

observed in patients without these associated conditions (Ellemberg et al., 1999b, 2000; Lewis, Maurer, and Brent, 1995; Maurer and Lewis, 1993). Rather they are likely to reflect neural damage caused by the visual deprivation.

Studies of monkeys that were deprived of visual input by lid suture allow inferences about the likely site of the neural damage. As in the children treated for cataract, the later acuity and contrast sensitivity of such monkeys are degraded, with the deficit worse after monocular than after binocular deprivation unless the monocular deprivation was short and followed by extensive occlusion of the fellow eye (Harwerth et al., 1983a,b, 1989, 1991). In monkeys, visual deprivation during infancy causes damage to the primary visual cortex, but not to earlier levels of the geniculostriate pathway. There are no changes in the topography of photoreceptors (Clark, Hendrickson, and Curcio, 1988; Hendrickson and Boothe, 1976) or in the electroretinogram (Crawford et al., 1975). Unless the deprivation extended from birth past 2 years of age (which is probably comparable to more than 8 years of deprivation in humans), the morphology of retinal ganglion cells is normal (reviewed in Boothe, Dobson, and Teller, 1985). (Very long-term deprivation may cause retinal damage in humans: The electroretinogram for the deprived eye was abnormal in a patient with 13 years of monocular deprivation from birth; see Levi and Manny, 1982.) Cells in the monkey's lateral geniculate nucleus are smaller than normal but nevertheless have normal physiological properties, even after 5 years of monocular deprivation from birth (Blakemore and Vital-Durand, 1986b; Levitt et al., 1989). Thus, LGN cells presumably send normal signals to the primary visual cortex.

There are marked abnormalities in the primary visual cortex of monkeys after early visual deprivation. After early binocular deprivation, a few cells respond normally, but most respond more sluggishly than normal, have receptive fields that are abnormally large, and are poorly tuned to orientation and spatial frequency (Blakemore, 1990; Blakemore and Vital-Durand, 1983; Crawford et al., 1975, 1991). Across the population of cells, there is a large reduction in sensitivity to higher spatial frequencies and low contrast (Blakemore, 1990; Blakemore and Vital-Durand, 1983). Thus, reductions in acuity and spatial contrast sensitivity after early binocular deprivation probably reflect abnormalities in neurons in the primary visual cortex and their projections, abnormalities that can be induced even by short periods of binocular deprivation. That interpretation is strengthened by evidence that in monkeys (Miller, Pasik, and Pasik, 1980)—unlike cats (Lehmkuhle, Kratz, and Sherman, 1982)—lesions to the primary visual cortex drastically reduce contrast sensitivity for all spatial frequencies. Similarly, humans with damage to the primary visual cortex show marked losses of grating acuity in the affected regions of the visual field (Weiskrantz, 1986). After early binocular deprivation in humans, the visual abilities that develop normally may be mediated by the few remaining normal cells in the primary visual cortex, by the many visual cortical cells that respond abnormally, or by cells in extrageniculostriate pathways that appear to play a greater role than normal in mediating some visual functions after binocular deprivation—at least in cats (Zablocka and Zernicki, 1996; Zablocka, Zernicki, and Kosmal, 1976, 1980).

After early monocular deprivation in monkeys, abnormalities in the primary visual cortex are even more marked. Although the periodicity of the areas dominated by each eye (the "ocular dominance columns") is unchanged (Crawford, 1998), the width of columns driven by the deprived eye is decreased and the width of those driven by the nondeprived eye is correspondingly increased (Horton and Hocking, 1997; Hubel, Wiesel, and LeVay, 1977; LeVay, Wiesel, and Hubel, 1980), with larger changes, the earlier the deprivation started (Horton and Hocking, 1997). The changes are greater in layers that receive input from parvocellular cells of the LGN (which are known to mediate sensitivity to high spatial frequencies) than in layers that receive input from magnocellular cells (Horton and Hocking, 1997). Even after very short periods of monocular deprivation, the deprived eye can drive very few cells in the primary visual cortex (Crawford, 1988; Crawford et al, 1991; Hubel, Wiesel, and LeVay, 1977; LeVay, Wiesel, and Hubel, 1980). The cells that can be driven by the deprived eye exhibit sensitivity to spatial frequency and contrast similar to (or even worse than) cells in the primary visual cortex of a newborn monkey (Blakemore, 1988). Reverse suture—closing the fellow eye at the same time that the originally deprived eye is opened—increases the proportion of cells in the primary visual cortex that can be driven by the originally deprived eye (Blakemore, Garey, and Vital-Durand, 1978; Crawford et al., 1989; LeVay, Wiesel, and Hubel, 1980; Swindale, Vital-Durand, and Blakemore, 1981). These changes in the primary visual cortex may explain the greater deficits in grating acuity and spatial contrast sensitivity after monocular than binocular deprivation in humans, unless there was aggressive patching of the nondeprived eye. The mild deficits even in the nondeprived eye may be related to an absence of functional connections in the zones into which its axons have expanded (Horton and Hocking, 1997).

Studies of monocularly deprived kittens have begun to elucidate the mechanisms underlying competitive interactions between a deprived and nondeprived eye. Some results support a model of spatial competition governed by competition for a scarce resource, such as neurotrophins, that play a role in the stabilization of developing axons and the supply of which is limited and activity-dependent (Cabelli, Hohn, and Shatz, 1995). Supplying more of that scarce resource appears to mitigate the effects of monocular deprivation. Thus, infusion of neurotrophins into the visual cortex during monocular deprivation prevents shrinkage of LGN cells and leaves the deprived eye still able to drive a nearly normal number of cortical cells (Carmignoto et al., 1993; Galuske et al., 1996). It also preserves normal acuity (Carmignoto et al., 1993; Fiorentini, Berardi, and Maffei, 1995). However, evidence that cells near the site where the neurotrophin was infused lack normal orientation tuning and cannot be driven in normal numbers by the *nondeprived* eye (Galuske et al., 1996) suggests that the mechanism of monocular deprivation extends beyond competition between geniculocortical afferents for neurotrophic support.

Other results indicate that competition might be better thought of as temporal competition between patterns of activity (Blais, Shouval, and Cooper, 1999; Hata and Stryker, 1994). These models subsume Hebb's original postulate that cortical connections are strengthened by use that leads to correlation between pre- and postsynaptic activity (Hebb, 1949). They go beyond Hebb in postulating that monocular deprivation alters the cortex not because of the absence of input from the deprived eye but because of an actual mismatch of pre- and postsynaptic activity. The mismatch arises when spontaneous activity in the deprived eye drives presynaptic activity out of synchrony with the postsynaptic activity driven by the nondeprived eye. The mismatch leads to long-term synaptic depression, which is normally observed as a shift in ocular dominance, that is, a reduction in the proportion of cells that can be driven by the previously deprived eye. The mismatch may continue even after the monocular deprivation has ended if visual signals from the previously deprived eye are transmitted more slowly than signals from the nondeprived eye, as they appear to be (Kasamatsu et al., 1998; McCulloch and Skarf, 1994). The strongest evidence for this model comes from demonstrations that manipulations that reduce the mismatch between pre- and postsynaptic activity reduce the effects of monocular deprivation. For example, 2 days of monocular deprivation around 7 weeks of age are sufficient to induce a shift in ocular dominance toward the nondeprived eye. However, using tetrodotoxin (TTX) to block retinal activity in the deprived eye during the 2 days of monocular deprivation prevents the shift in ocular dominance, presumably because it prevented any signals from the deprived eye from reaching the cortex and hence any mismatch between pre- and postsynaptic activity (Rittenhouse et al., 1999). There are similarly paradoxical findings when monocular deprivation of 2–4 weeks beginning around 4 weeks of age is accompanied by injections of muscimol, which binds selectively to GABA receptors on postsynaptic sites and blocks their activity (Hata and Stryker, 1994; Hata, Tsumoto, and Stryker, 1999). Near the site of infusion, the deprived eye is able to drive more than the normal number of cells and its normal-looking axons cover an expanded area. Axons serving the nondeprived eye are shorter and less elaborate than normal and look worse even than axons serving the deprived eye in untreated cortex (Hata, Tsumoto, and Stryker, 1999). The shrinkage of axons serving the nondeprived eye presumably reflects the frequent mismatch between presynaptic activity induced by visual stimulation and the inhibited postsynaptic activity. Axons serving the deprived eye would have been spared by the infrequency of its spontaneous activity. The likelihood of a mismatch is also affected by the modification threshold of the postsynaptic neuron, which varies with the overall level of cortical activity (Kind, 1999). Binocular deprivation may have weaker cortical effects than monocular deprivation because it lowers the overall level of cortical activity and hence lowers both the modification threshold of the postsynaptic neuron and the probability of a mismatch between pre- and postsynaptic activity (Blais, Shouval, and Cooper, 1999; Kind, 1999; Rittenhouse et al., 1999).

The competitive interactions underlying the deleterious effects of monocular deprivation are likely to vary with the timing and duration of the deprivation. For example, a short period of monocular deprivation at the height of the sensitive period in kittens causes a radical shift in ocular dominance toward the nondeprived eye, such that the deprived eye stimulates few visual cortical cells when it is stimulated monocularly. It also causes a shrinkage of geniculocortical axons serving the deprived eye (Antonini and Stryker, 1996). Nevertheless, for most cells, input from the deprived eye alters the cortical response during binocular (dichoptic) stimulation, both suppressing and enhancing the response stimulated by the nondeprived eye on its own, depending on the relative phase of input to the two eyes (Freeman and Ohzawa, 1988). These results imply that the deprived eye, although unable to drive most cortical cells when

stimulated monocularly, nevertheless remains sufficiently connected to influence them during binocular viewing. A similar conclusion arises from evidence of responses to stimulation of the deprived eye after removal of the nondeprived eye or injections of $GABA_A$-receptor antagonist (reviewed in Kasamatsu et al., 1998). After very long monocular deprivation (more than 11 months beginning at 3 weeks), evidence of such residual connections is virtually absent (Freeman and Ohzawa, 1988). After such long periods of monocular deprivation, the deprived eye appears to be disconnected.

Conclusions

In summary, spatial vision improves rapidly during early infancy but takes many years to reach adult levels. Much of this improvement can be explained by the postnatal development of the retina and primary visual pathway. However, the improvement depends on patterned visual input, the onset of which alters the nervous system rapidly and sufficiently to support better acuity as early as 1 hour later. The initial improvements in acuity appear to be determined solely by visually evoked cortical activity, and only later, after sufficient numbers of cortical connections have been established from both eyes, do competitive interactions influence subsequent refinements of spatial vision. Permanent deficits in visual acuity after treatment for developmental or traumatic cataracts signal the importance of patterned visual input for consolidating connections, even after the age at which spatial vision is normally mature.

The permanent deficits in spatial vision after early deprivation probably reflect abnormalities in and beyond the primary visual cortex, deficits that are larger after monocular than after binocular deprivation, unless the competitive disadvantage of the previously deprived eye was ameliorated by reverse suture or occlusion. Binocular deprivation may have weaker effects because it lowers the overall level of cortical activity and hence lowers the probability of a mismatch between pre- and postsynaptic activity. Whatever the underlying mechanisms, it is clear that experience and competitive interactions play a prominent role in the development of spatial vision.

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