CHAPTER 3

Macaque Models of Visual Development and Disability

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Beginning in the 1960s with the work of David Hubel and Torsten Wiesel, Jennifer Lund, Anita Hendrickson, and others, great strides were made in our understanding of visual system organization (see Friedlander and Tootle, 1990). The earliest studies employed the cat as the primary animal model. These studies were followed by physiological and anatomical investigation into the visual system of the macaque monkey. Those ground-breaking studies showed that visual system organization in nonhuman primates, the Old World macaque monkeys in particular, closely mirrors that of humans (see Kaas, 2004; Van Essen, 2004). Since that time the macaque monkey has become the animal model of choice for human vision. Hundreds of studies have used the macaque as a model system for understanding visual system function in normal adults and for studying the origins of dysfunction. To learn how developmental visual disabilities arise, it is important to first understand how the visual system normally develops and to establish that the model system that is best for adults is also appropriate for infants.

NORMAL DEVELOPMENT OF VISION IN MACAQUE MONKEYS

In 1975 Davida Teller, Ronald Boothe, and their colleagues began to document the remarkable similarity between human and macaque monkey infants in the development of vision (see Boothe *et al.*, 1985). They studied visual acuity in both species using the forced-choice preferential looking technique developed by Teller (Teller *et al.*, 1974). They concluded that vision in monkeys develops with the same progression as humans, although the process proceeds four times faster in macaques (Teller and Boothe, 1979). Hence, visual development as measured behaviorally is comparable in monkey and human infants if age is expressed in weeks for monkeys

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and in months for humans. This relationship is shown in Figure 3.1 (also see Teller, 1997). Figure 3.1 (upper data set, open symbols) plots development of grating acuity (similar to acuity as measured with a Snellen eye chart) as a function of age in weeks for monkeys (circles) and as a function of age in months for humans (open triangles). Clearly, the data can be described by the same developmental profile; the weeks-to-months translation is often called the four-to-one rule (see Boothe *et al.*, 1985).

While this four-to-one relationship is a useful metric, it is important to realize it cannot be assumed to necessarily hold for *all* visual processes. Subsequent studies have examined a variety of other measures of spatial vision to see if the rule holds. Two measures that reflect sensitivity to spatial position are Vernier acuity and stereoacuity. These acuities are based on fine spatial positional judgments, the former for co-planar judgments and the latter for localization in depth. Kiorpes (1992a) showed that Vernier acuity is less mature than grating acuity near birth in

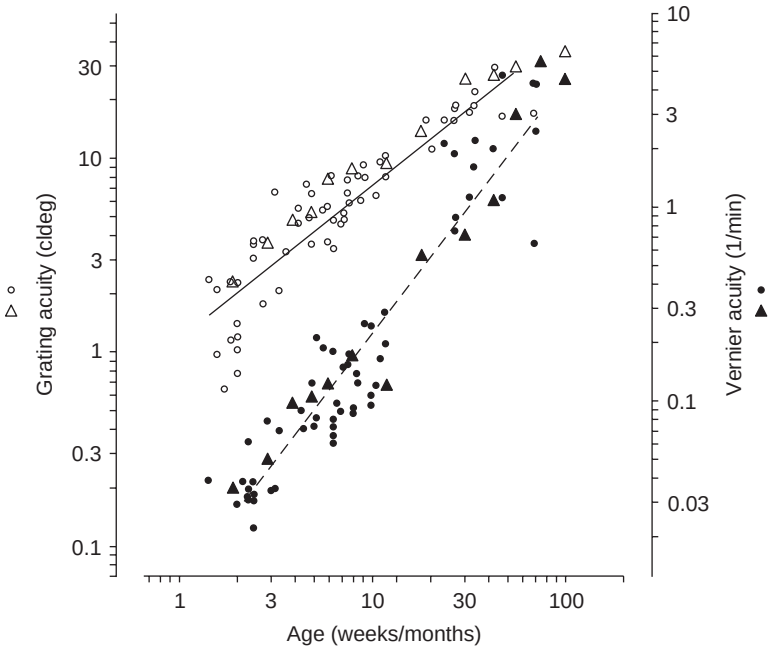

FIGURE 3.1 The development of visual acuity in macaque monkeys and humans. Two measures of visual acuity are plotted together as a function of age, in weeks for monkey data and in months for human data. Grating acuity is referenced to the left ordinate (open symbols) and Vernier acuity is referenced to the right ordinate (filled symbols). The two ordinates are normalized to adult levels of performance for monkeys, and so reflect the relative maturation of Vernier and grating acuity. Monkey data (circles) are from Kiorpes (1992a) with additional unpublished data from the author; human data are from Zanker *et al.* (1992). The lines are regression fits to the monkey data.

macaques, but develops more quickly so that the two functions approach adult levels at similar ages. However, recent studies of Vernier acuity development in children have shown a longer, later developmental profile for Vernier acuity compared with grating acuity (Zanker *et al.*, 1992; Carkeet *et al.*, 1997; Skoczenski and Norcia, 1999, 2002).

The relative development of grating and Vernier acuity is shown in Figure 3.1. The filled symbols represent Vernier acuity data for the same groups of infants from which the grating acuity data were obtained. The scales are normalized to align at adult levels on the log–log plot. Thus the profiles represent the relative maturation of the two visual functions. Once again the developmental profiles match well between the two species, suggesting that the four-to-one rule holds for Vernier acuity as well as grating acuity. Also, although human studies generally conclude that Vernier acuity develops over a longer time-course, the four data sets plotted in Figure 3.1 appear to converge at similar ages. In line with the four-to-one rule, stereoacuity tested using identical techniques across species shows an abrupt onset at 3–4 weeks in macaques (O'Dell and Boothe, 1997) and 3–4 months in humans (Birch *et al.*, 1982). Interestingly, development thereafter appears to proceed at a similar *absolute* rate. This suggests slower relative development of stereoacuity in monkeys than in humans (O'Dell and Boothe, 1997). In neither species is it clear when adult levels of stereoacuity are reached, so the relative rates of development remain to be completely quantified.

The most common and complete descriptor of spatial vision is the contrast sensitivity function. This function describes the sensitivity of the visual system across all spatial scales within the visible range from coarse to fine, describing the ability to detect luminance variations at various spatial scales. Contrast sensitivity functions for monkeys and humans at various ages are shown in Figure 3.2. With age the function shifts from low to high spatial frequency and low to high levels of sensitivity in both species. Adult levels of sensitivity are reached between 40 and 60 weeks in monkeys (Boothe *et al.*, 1988; Kiorpes, 1996) and between 48 and 72 months in humans (Ellemberg *et al.*, 1999). On balance, then, the four-to-one rule seems to be a good metric of relative rates of spatial visual development in macaques and humans.

These studies of basic visual development provide reasonable support for the weeks-equals-months relationship for spatial vision, although complete data sets are sometimes unavailable. Most typical day-to-day visual functioning relies less on fine acuity or threshold level vision, and more on global integration of visual information over space and time. Therefore, it is worth examining whether this rule is also obeyed for so-called higher level visual performance. Examples of higher level vision are figure–ground segmentation and motion and form integration. The most commonly studied global ability is motion perception, which requires integration of information over space and time.

There have been many studies of sensitivity to visual motion in human infants, but few that reveal a complete developmental time-course (Braddick *et al.*, 2003).

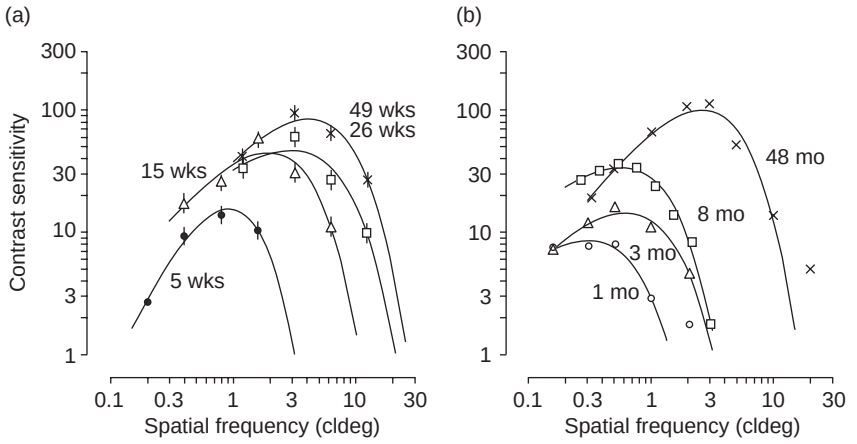

FIGURE 3.2 Development of contrast sensitivity in macaque monkeys and humans. (a) Contrast sensitivity as a function of spatial frequency is plotted for individual monkeys tested at the ages noted in the figure. Data are from Boothe *et al.* (1988). (b) Average contrast sensitivity is plotted for groups of infants tested at the spatial frequencies and ages noted in the figure. Data are from Banks and Salapatek (1978) (1 and 3 months); Peterzell *et al.* (1995) (8 months); Ellemberg *et al.* (1999) (48 months). The smooth curves fit to the data are described in Williams *et al.* (1981) or Kozma and Kiorpes (2003).

Gunn *et al.* (2002) showed a slow maturation of sensitivity for motion integration that reached asymptote around age 10–11 years. A related measure, global form integration ability, had an earlier asymptote at age 6–7 years. Interestingly, Kiorpes and Movshon (2004b) found a similarly long developmental time-course for motion integration in macaque infants. They found that motion sensitivity reached adult levels between 2 and 3 years, which would translate to a maturation rate of 9–13 years in humans by the four-to-one rule. This rate is consistent with the findings of Gunn *et al.* (2002). In macaque monkeys, Kiorpes and Bassin (2003) found earlier asymptotic performance in the range of 1.5–2 years on a form integration task using figure–ground segmentation. These results suggest a slightly earlier maturation of form than motion integration in macaques as well as humans. Thus, the overall pattern of development of integrative visual function, which presumably underlies the ability to extract figures from a visual scene and discriminate common motion among elements in a scene, is similar in macaques and humans and seems to also follow a four-to-one age translation.

VISUAL DISABILITY IN CHILDHOOD

The most common cause of vision loss in children is amblyopia. Amblyopia, literally "blunt sight," is classically defined as a loss of visual acuity in one eye with no obvious

accompanying pathology (von Noorden, 1980). In other words, the child has poor visual performance but there is no obvious impediment to clear vision. On inspection the eye looks normal. However, it is important to realize that vision is accomplished not by the eye alone, but by the visual brain. The eye gathers light from the environment, processes that light energy, and transmits the information to the brain. The estimated incidence of amblyopia ranges from 1% to 6% across many studies, but it is most often in the range of 3–4% in western populations (von Noorden, 1980; Chua and Mitchell, 2004; see also, Simons, 2005).

Amblyopia is typically associated with three primary conditions: congenital cataract, dense opacity in one or both eyes; anisometropia, unequal refractive error in the two eyes; and strabismus, misalignment of the two eyes. These conditions are associated with amblyopia when they occur in infancy and early childhood. It is important to note that these conditions do not result in loss of visual function when they occur in adults. Thus, amblyopia is a disorder of visual development and there is some period of susceptibility, a "critical period," for its development. Although amblyopia was initially considered to affect only visual acuity and binocular function, it is now clear that many other visual abilities are compromised.

A good deal of attention has been paid to the effect of childhood vision loss on the academic and psychosocial development of children (Packwood *et al.*, 1999; Holmes and Clarke, 2006; Koklanis *et al.*, 2006; Williams and Harrad, 2006). Specific effects on reading and math performance have been reported, as well as a general sense that amblyopia interferes with work, school, and sports performance. The poor stereopsis that is associated with amblyopia also affects a child's ability to participate in sports and compromises some motor skills. Although survey results are somewhat inconsistent, amblyopia appears to have a secondary effect on self-esteem. Most recent studies have shown that amblyopia *treatment* is responsible for the greatest negative psychological effects on the child (Choong *et al.*, 2004; Koklanis *et al.*, 2006; Williams and Harrad, 2006), whereas the amblyopia itself has greater long-term consequences for performance. As discussed below, the most common treatment involves eye patching, which itself affects the child's psychosocial well-being. In studying effects on adults, Chua and Mitchell (2004) found that people with amblyopia were less likely to hold university degrees. However, they found no significant effect of amblyopia on occupational choice, although certain occupations such as flying commercial aircraft are closed to those with vision disorders.

One often overlooked consequence of life-long amblyopia is an increased risk of losing sight in the fellow eye. Recent studies have highlighted the increased risk of vision loss in the fellow eye in the amblyopic population (Rahi *et al.*, 2002; Chua and Mitchell, 2004). Taken together, these concerns increase the importance of early childhood vision screening and serious efforts to treat the condition prior to school-age (Williams and Harrad, 2006).

In summary, the normal development of visual function proceeds in a systematic way in both human and nonhuman primates. Three decades of comparative

research shows that the macaque monkey provides an excellent model system for studying the normal development of visual function and mechanisms that underlie visual immaturity in infants (see Kiorpes and Movshon, 2004a). The development of visual function is compromised by abnormal ocular and ocular motor conditions that exist during infancy and early childhood. These conditions result in amblyopia, which is a significant source of concern for pediatric ophthalmologists and compromises many aspects of a child's life in addition to their vision. Research with animal models presents a significant advantage for understanding the processes that underlie the development of amblyopia. In particular, the causal relationship between visual impediment and amblyopia can be studied prospectively, the natural progress of amblyopia development can be studied without the complication of treatment history, age of onset of visual impediment can be completely specified, and studies can be undertaken to directly assess the underlying neural substrate.

With this background I next review the visual disabilities that have been investigated using the nonhuman primate as a model system. In each disability I highlight the clinical relevance of the work. I also emphasize results that provide insight into the underlying mechanisms, as they are the aspect of our work with animal models that provide unique and otherwise unattainable knowledge. The review is not intended to be exhaustive. Instead, the goal is to illustrate the important contributions that nonhuman primate research has made to our understanding of, and treatment strategies for, developmental sensory disability.

EFFECTS OF VISUAL EXPERIENCE ON VISUAL DEVELOPMENT

A defining moment for understanding the role played by visual experience in visual development came with the early studies of Wiesel and Hubel in kittens (Wiesel and Hubel, 1963, 1965; Hubel and Wiesel, 1965). They found that closing one eye to impose form deprivation, or misaligning one eye to create a strabismus, significantly altered the physiological and anatomical organization of the primary visual cortex (V1, the first cortical area in the visual system hierarchy). They noted anecdotally that after eye closure the kittens appeared blind when using the formerly closed eye following a period – sometimes quite short – of monocular deprivation. Subsequent studies in macaque monkeys showed similar alteration of the structure of V1 (e.g. Hubel and Wiesel, 1977; Wiesel, 1982). Behavioral monkey studies confirmed a devastating loss of visual function (von Noorden *et al.*, 1970; Harwerth *et al.*, 1983).

The normal visual cortex has a balanced representation of the two eyes, known as eye dominance, with regular modulation of binocular and monocular zones. This organization is present at birth in infant monkeys. With normal visual experience it is then refined to some degree over the first few postnatal weeks (Horton and Hocking, 1996). This organization is disrupted following deprivation. The

deprived eye zones are minimized and binocularity is severely compromised (see LeVay *et al.*, 1980; Horton and Hocking, 1997). On the basis of these studies, the authors proposed that impediments to normal visual experience during early postnatal development caused a reduction in the influence of the deprived eye in V1, which in turn led to poor visual function in the adult (see Movshon and van Sluyters, 1981; Movshon and Kiorpes, 1990 for reviews). These findings formed the foundation for a body of work using the macaque monkey as a model system for understanding childhood developmental visual disorders.

Models of amblyopia

Beginning in the 1970s, behavioral studies of macaque monkeys raised under visual conditions that mimic human developmental visual disorders were conducted to determine how well the monkey model reflected the visual losses found in human amblyopia and to explore the underlying neural mechanisms. As mentioned above, three primary conditions are associated with poor visual development in children. In congenital *cataract*, ocular opacities result in form deprivation amblyopia. In *anisometropia*, blur in one eye results in anisometropic amblyopia. In *strabismus*, ocular motor misalignment of the two eyes results in strabismic amblyopia. These conditions are associated with permanent visual loss only when they occur in infancy and early childhood.

Initially, it was not known whether there was a causal relationship between the physical disorders and the behavioral loss of vision. It was only known that there was a correlation. The nature of the association between early visual abnormality and amblyopia was unclear because only about 40–60% of those with strabismus or anisometropia develop amblyopia. The relationship is much stronger for deprivation amblyopia. Furthermore, the condition that the child presents with at the time of diagnosis may not be the same as the original precipitating disorder. For example, anisometropia can cause strabismus. The strabismus is obvious to the parent, but the anisometropia is often not noticed until vision screening at school age.

Animal studies showed direct causality between visual impediment and the development of amblyopia and provided definitive information on the nature of the critical period for vision. They also provided insight into the neural basis of amblyopia and had a direct impact on the way in which amblyopia is treated in children.

Monocular deprivation

The earliest behavioral visual deprivation studies were conducted by von Noorden and colleagues in 1970 (von Noorden *et al.*, 1970; von Noorden, 1973). They showed that early visual deprivation by lid suture, a monkey model for congenital cataract, resulted in a loss of visual acuity in the deprived eye. They closed one eye of young monkeys for various durations and tested acuity using a clinical Landolt-C test,

comparable to letter chart acuity. Amblyopia occurred in all animals deprived prior to the age of nine weeks, even when the period of deprivation was as short as one or two weeks. The data suggested that the critical period for amblyopia development was the first three postnatal months, as only animals deprived before 12 weeks failed to achieve normal visual acuity when tested as adults. It is important to note that in these studies and most others of this kind, the vision was not assessed immediately following the end of the deprivation period. Instead, vision was assessed 1–2 years after the period of deprivation, so it was unclear whether the outcome was purely the result of the early deprivation or reflected much later recovery of function.

Later, more extensive behavioral studies showed that the effect of visual deprivation from lid suture was in fact quite dramatic and largely refractory to recovery following eye opening (Harwerth *et al.*, 1983, 1989). Animals reared with only a few weeks of deprivation, followed by years of normal binocular vision, often developed only limited visual function. Figure 3.3a shows contrast sensitivity data from an animal that was monocularly deprived from the age of 4 months until approximately 18 months (Harwerth *et al.*, 1990). The sensitivity of the deprived eye following early deprivation is substantially poorer than would be expected from even a very young normal infant. This is seen by comparing the deprived eye function to the functions in Figure 3.2. It shows that visual experience is required for normal development of visual function and it is essential to maintain even the rudimentary vision of newly born infants.

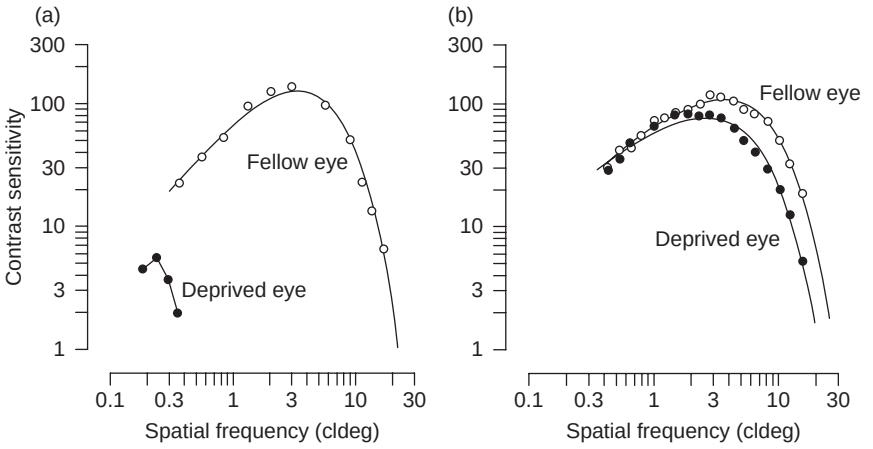

FIGURE 3.3 The effect of monocular deprivation on contrast sensitivity in monkeys. Contrast sensitivity is plotted as a function of spatial frequency for each eye of a monkey monocularly deprived for 18 months from the age of 4 months (a) or 12 months (b). Filled symbols represent data from the deprived eye. Data are from Harwerth *et al.* (1990), figures 5 and 6. The smooth curves fit to the data are described in Williams *et al.* (1981) or Kozma and Kiorpes (2003).

Figure 3.3b shows comparable data for an animal that was monocularly deprived for a similarly long period of time, but beginning at the later age of 12 months. Note that sensitivity at middle and high spatial frequencies is depressed for the deprived eye, but only moderately so compared to the fellow non-deprived eye. Thus, the visual system of the monkey is vulnerable to deprivation well beyond the first three months after birth, the period originally proposed by von Noorden. Furthermore, there is a gradation in susceptibility with age. This work had a direct impact on management of infants born with congenital cataracts. It led to a dramatic reduction in the age at surgery to remove the cataract and stimulated prospective studies on the effect of age at surgery on visual outcome in humans (Birch and Stager, 1996).

The lid suture model was instrumental in establishing the nature of the critical period for the development of amblyopia. The initial work of von Noorden and colleagues identified the early postnatal weeks as a period of extreme vulnerability to abnormal visual experience. This period of susceptibility declines gradually over the succeeding year. Harwerth *et al.* (1986, 1989, 1990) systematically charted the period of vulnerablility to deprivation of spatial, temporal, and chromatic visual functions over the first two postnatal years in monkeys. They clearly showed that different visual functions have different critical periods. Similarly, different levels in the visual pathway have different critical periods. Subcortical structures show less vulnerability than cortical levels (Levitt *et al.*, 2001) and cortical layer IV shows a shorter period of susceptibility to deprivation than other layers (LeVay *et al.*, 1980; Horton and Hocking, 1997).

These and similar studies of monkeys and humans, as well as kittens, revealed that the concept of a critical period needs to be refined. This is because there are different sensitive periods for normal development, for the disruptive effects of deprivation, and for recovery from deprivation (Daw, 1998; Mitchell and MacKinnon, 2002; Lewis and Maurer, 2005). As argued by Daw (1998), there are different, but not mutually exclusive, critical periods for the disruptive effects of abnormal visual experience on development and for the efficacy of treatment. In neither case is the critical period completely coincident with the period of normal visual development. This principle is illustrated clearly in a publication showing different but overlapping sensitive periods for the susceptibility of stereopsis to abnormal binocular visual experience in humans (Fawcett *et al.*, 2005). Thus, these distinctions hold true for humans as well as for animal models and for binocular as well as spatial vision.

The lid suture model has been very important for our understanding of constraints on visual development and the nature of critical periods in vision. Neurophysiological and anatomical investigation of the visual pathways and properties of single neurons following lid suture have shown shrinkage of cells associated with the deprived eye at the level of the lateral geniculate nucleus (LGN) and a nearly complete loss of influence by the deprived eye in primary visual cortex. The degree of the abnormality reflects the amount and timing of the deprivation

(e.g. von Noorden and Crawford, 1978; LeVay *et al.*, 1980; Horton and Hocking, 1997). However, because the deep amblyopia that results from lid suture occurs relatively infrequently in human clinical practice, and because the representation of the deprived eye in cortex following lid suture is minimal at best, the lid suture model is not the best one for understanding the development of and neural basis for amblyopia. More clinically relevant models for amblyopia are those that are associated with moderate visual loss and permit maintained representation of the deprived eye in the primary visual pathways.

Anisometropia and strabismus

Models of amblyopia that create or simulate strabismus or anisometropia are preferred over lid suture because they are associated with more moderate visual loss. Early studies of vision following surgically induced strabismus in young monkeys established a clear, causal relationship between strabismus onset and the development of amblyopia in the otherwise normal visual system (von Noorden and Dowling, 1970; Kiorpes and Boothe, 1980; Harwerth *et al.*, 1983; Kiorpes *et al.*, 1987, 1989). These studies showed that strabismus created surgically, or anisometropia produced by unilateral blur, reliably resulted in amblyopia when imposed during the height of the critical period. Longitudinal studies, easily conducted in monkeys but difficult to conduct in humans, showed that amblyopia develops over time as a gradual set-back or slowing of the developmental program. This is followed later by a resumption of development. Figure 3.4 illustrates one pattern, showing acuity development in each eye of one strabismic monkey. Interestingly, prospective and retrospective studies using these animal models have

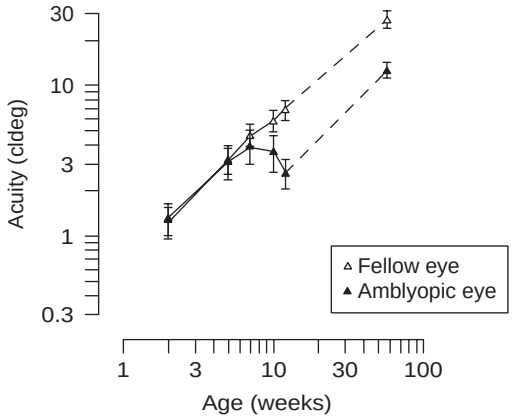

FIGURE 3.4 The effect of strabismus on acuity development. Acuity is plotted as a function of age for each eye of a monkey made strabismic by surgery at 3 weeks of age. Filled symbols represent data from the strabismic eye. Data are from Kiorpes *et al.* (1989), figure 2b.

shown not only that strabismus and anisometropia cause amblyopia, but also that amblyopia can cause strabismus and anisometropia (Quick *et al.*, 1989; Kiorpes and Wallman, 1995; Smith, Hung and Harwerth, 1999). It is important to note that, similar to humans, macaque monkeys naturally develop strabismus, anisometropia, and cataracts, allowing study of the natural history of these disorders (see Kiorpes, 1989, 2002; Horton *et al.*, 1997).

In addition to the acuity loss in amblyopia, sensitivity to contrast across spatial scales from coarse to fine is compromised. The fine spatial scales representing sensitivity to fine detail are affected most deeply (Kiorpes, 1996). Contrast sensitivity functions for each eye of two amblyopic monkeys, one strabismic and one anisometropic, are shown in Figure 3.5. Note the relatively greater loss of sensitivity at the high spatial frequency ranges near the acuity limit, represented by the extrapolation of the curves to the abscissa. The range of visual deficits following experimental strabismus is similar to that found in the human population and experimentally produced amblyopia occurs with similar frequency to natural amblyopia. Thus, somewhat surprisingly, only about 60% of those with experimental strabismus actually develop amblyopia (Kiorpes *et al.*, 1989; Kiorpes, 2002). Experimentally produced anisometropia created by rearing with defocus of one eye either by spectacle lenses, contact lenses, or dilation of the pupil, also results in clinically relevant depths of amblyopia (Boothe *et al.*, 1982; Smith *et al.*, 1985; Kiorpes *et al.*, 1987; Kiorpes *et al.*, 1993; Smith *et al.* 1999). Taken together, this work

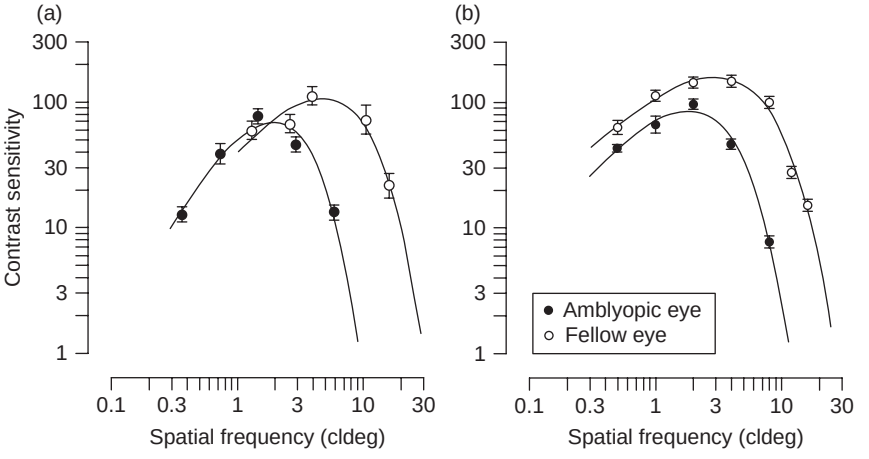

FIGURE 3.5 The effect of strabismus and anisometropia on contrast sensitivity in monkeys. Contrast sensitivity is plotted as a function of spatial frequency for each eye of a monkey (a) made strabismic at 3 weeks of age or (b) made anisometropic at 3 weeks of age. Filled symbols represent data from the deprived eye. Data in (a) are from Kiper and Kiorpes (1994), figure 1d; data in (b) are from Kozma and Kiorpes (2003), figure 5c. The smooth curves fit to the data are described in Kozma and Kiorpes (2003).

established experimental amblyopia in macaque monkeys as an excellent model for human amblyopia, and identified many of the constraints on its development.

Neural mechanisms in amblyopia

To identify the neural basis for amblyopia, Movshon *et al.* (1987) and Kiorpes *et al.* (1998) evaluated the response properties of neurons in the primary visual cortex of monkeys with behaviorally documented amblyopia. Both studies revealed losses of neuronal "acuity" in cells responding to stimulation of the amblyopic eye, results which were reminiscent of those seen behaviorally. No loss was found at earlier levels of the visual pathway (Movshon *et al.*, 1987), even following severe form deprivation (Blakemore and Vital-Durand, 1986; Levitt *et al.*, 2001). These studies established for the first time that, in addition to disruption of the binocular organization of the visual cortex, there were effects of abnormal visual experience on the spatial response properties of neurons.

Acuity loss at the neuronal level was reflected in the tuning properties of the cells in V1 that are driven by the amblyopic eye. These cells responded to lower ranges of spatial frequency compared with cells driven by the fellow eye. There were varying degrees of loss in contrast sensitivity of individual neurons driven by the amblyopic eye in addition to the reduction in acuity, but these were not consistent across animals and studies. Other properties of these cells, such as their selectivity for orientation and direction of motion, were uniformly normal. A direct comparison between the degree of behaviorally measured amblyopia and the extent of the neural deficit showed a strong correlation, supporting the conclusion that the neural deficits were actually related to the behavioral losses (Kiorpes *et al.*, 1998; Kiorpes and Movshon, 2004a). However, the cortical losses tended to be smaller than the behavioral ones and did not explain the contrast sensitivity deficit. Thus, the properties of amblyopic neurons at this early cortical stage cannot completely account for even the basic loss in spatial vision. These studies established that the primary visual cortex is the first site in the visual pathway that reflects developmental disruption related to amblyopia and that abnormalities early in the visual system may be amplified in downstream visual areas.

While the effect of abnormal visual experience on the spatial properties of V1 neurons is more modest than might be expected, amblyopic V1 does reflect dramatic abnormalities of binocularity similar to those found following lid suture (e.g. Movshon *et al.*, 1987; Crawford *et al.*, 1996a; Kiorpes *et al.*, 1998). Anisometropic rearing results in a shift of ocular dominance away from the defocused eye, but strabismic rearing generally results in relatively balanced ocular dominance as measured physiologically. In all cases, regardless of the type of model used, there is a reduction in the number of binocularly driven neurons (see Kiorpes and Movshon, 2004a). Amblyopic neurons appeared to be monocular with the standard procedure of testing each eye independently. However, Smith *et al.* (1997) showed that residual binocular interaction could be

demonstrated in a large proportion of amblyopic neurons when the cells were tested dichoptically by stimulating both eyes at the same time.

These interactions were more often than not suppressive rather than excitatory, particularly following strabismic rearing. Suppressive interactions developed quickly following the onset of abnormal binocular visual experience. They are present following as little as 3 days of binocular decorrelation (Zhang *et al.*, 2005) and correlate well with deficits of binocular vision assessed behaviorally (Smith *et al.*, 1997; Wensveen *et al.*, 2001, 2003; Zhang *et al.*, 2003). These findings serve as a caution to clinicians that infants with strabismus should be treated as early as possible in order to preserve normal binocular function.

To summarize, neurophysiological investigation into the neural correlates of amblyopia show that V1 is the first site along the visual pathway reflecting behaviorally documented abnormalities of vision. In the case of binocular function, the neural abnormalities at the level of V1 closely correlate with those measured behaviorally. However, in the case of spatial vision, the neural deficits are qualitatively similar but not quantitatively sufficient to account for the vision losses. The inevitable conclusion is that the neural basis for the spatial visual deficits that characterize amblyopia lies further along the visual pathway in higher order processing areas. If that is the case, there should be a range of perceptual deficits in amblyopes that reflect processing disruption at higher levels of the visual pathways.

Perceptual disorder in amblyopia

Behavioral studies of amblyopia in nonhuman primates and psychophysical studies of adult human amblyopes have shown that amblyopia affects far more than acuity and contrast sensitivity (see Kiorpes, 2006; Levi, 2006). There is a disruption of the position sense, as exemplified by measurements of Vernier acuity (Kiorpes, 1992b). There is also a loss of binocular vision, in particular stereopsis, in amblyopic monkeys (Crawford *et al.*, 1996b; Wensveen *et al.*, 2003). Moreover, there is disruption of higher level perception in amblyopes that cannot be understood only on the basis of the acuity loss. An example of such a function is figure–ground segregation as measured by contour integration (see Kozma and Kiorpes, 2003). Contour integration is the ability to extract a coherent structured form from a field of background noise elements. It is disrupted in strabismic and anisometropic amblyopia in both monkeys and humans. Whether this task relies on areas beyond V1, or on V1 itself, is a matter of controversy, but performance is clearly not predictable from knowledge of the depth of the acuity loss.

Another example of higher level processing is motion perception. This requires integration of motion signals over time and space and is thought to depend on a visual area downstream from V1 known as MT, the middle temporal area (Newsome and Pare, 1988; Britten *et al.*, 1992). Kiorpes *et al.* (2006) studied motion sensitivity of amblyopic monkeys and found substantial losses when viewing with the amblyopic

eye. The deficits were apparent in both the spatial and temporal domains. The spatial losses could be ascribed to the reduced range of spatial frequency sensitivity of the amblyopic eye, but the temporal losses could not be related to any known V1 abnormality. This finding strongly supports the idea that additional amblyopic processing deficits arise in downstream visual areas.

A now common finding in studies of higher order perception in amblyopia is that the perceptual losses identified for the amblyopic eye extend to the fellow "normal" eye (e.g. Giaschi *et al.*, 1992; Kozma and Kiorpes, 2003). Performance using the fellow eye is poorer than for normal controls, but not as poor as the amblyopic eye. In the past, it was typically assumed that the fellow eye was unaffected in amblyopia. The combination of the findings of subnormal performance with the fellow eye in monkey models and abnormal performance with the fellow eye in human studies stimulated caution in the clinical community. Simons (2005) makes this point and urges reference to the fellow eye not as "normal" or "sound" but as the "better" eye.

To summarize, investigations into the ability of amblyopes to perform higher order perceptual tasks have found substantial deficits that cannot be predicted from contrast sensitivity and acuity deficits and often extend to the fellow eye. This behavioral profile is consistent with the neurophysiological findings discussed above, suggesting that the development of visual cortical areas well beyond V1 is disrupted by abnormal postnatal visual experience. To date, no studies of neuronal sensitivity in extrastriate areas have been conducted in amblyopic macaque monkeys, although one study has noted abnormal binocular organization in an extrastriate area following early monocular defocus (Movshon *et al.*, 1987). Nevertheless, the nonhuman primate work is consistent with recent psychophysical studies of human amblyopes showing high order perceptual losses that are not explained by losses in contrast sensitivity (Simmers *et al.*, 2003; Simmers *et al.*, 2005; Levi, 2006). Also, functional imaging studies show abnormal activity in brain areas beyond V1 in amblyopes (Anderson and Swettenham, 2006).

Treatment of amblyopia

Patching has been the treatment of choice for amblyopia in children for more than a century (see von Noorden, 1980; Simons, 2005). Patching therapy involves occlusion of the fellow eye with an eye patch, forcing use of the amblyopic eye. One important corollary of the lid suture studies discussed above is that deprivation amblyopia can result from this common treatment. In the animal model, recovery from early deprivation was typically effected by "treatment" likened to patching, a procedure called reverse occlusion. This involves closure of the previously nondeprived eye with concurrent opening of the initially deprived eye. Monkey studies showed that the visual "recovery" of the initially deprived eye occurred at the expense of the fellow eye (Harwerth *et al.*, 1989).

Examples of the consequences of reverse suture on contrast sensitivity are shown in Figure 3.6. Harwerth *et al.* (1989) closed one eye of monkey subjects at about 1 month of age, then performed the reverse occlusion at various time points thereafter. The data in Figure 3.6a are from a monkey "treated" after 60 days of monocular deprivation. The filled symbols represent data from the *initially* deprived eye. Clearly there has been a complete reversal of the deprivation effect, with the initially deprived eye showing almost normal contrast sensitivity and the initially open, fellow eye, showing deep amblyopia. The data in Figure 3.6b reflect "treatment" at a later age after 90 days of deprivation. In this case, contrast sensitivity is similar in the two eyes, but not normal for either eye. The treatment has resulted in a bilateral loss of visual function.

These data are reminiscent of findings from a longitudinal study in kittens as a model of patching therapy (Mitchell, 1991; Mitchell and MacKinnon, 2002). The study revealed a gradual trade-off of acuity between the initially amblyopic eye and the initially "normal" eye resulting from reverse occlusion. Similarly, studies of recovery of vision following removal of the lens of the eye in monkeys were conducted to explore treatment options for children with congenital cataract. This work documents a dramatic trade-off of acuity in nonhuman primates when the fellow eye is continuously occluded (see Boothe, 1996). Neurophysiological

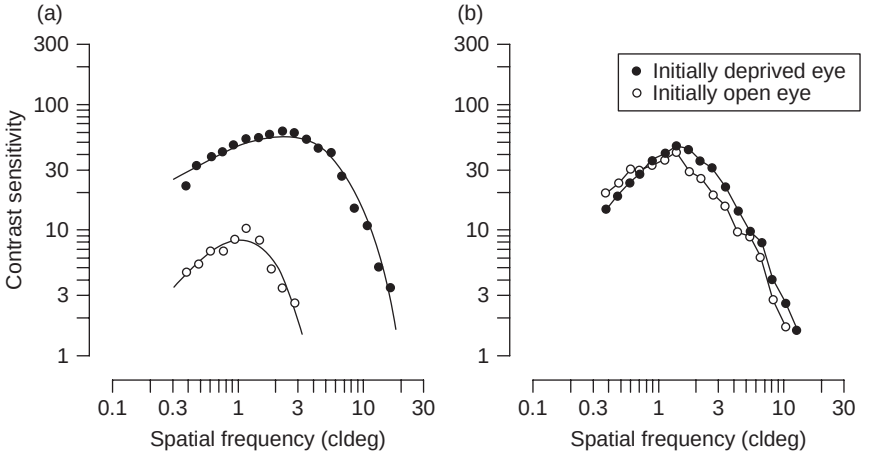

FIGURE 3.6 The effect of "treatment" of amblyopia on contrast sensitivity in monkeys. Contrast sensitivity is plotted as a function of spatial frequency for each eye of two monkeys monocularly deprived at the age of 4 weeks. (a) The initially deprived eye was opened after 60 days of deprivation and the initially open eye was closed for 120 days. (b) The initially deprived eye was opened after 90 days of deprivation and the initially open eye was closed for 120 days. Thereafter, both monkeys received normal binocular visual experience until tested at approximately one year of age. Filled symbols represent data from the initially deprived eye. Data are from Harwerth *et al.* (1989), figure 1c and d. The smooth curves fit to the data are described in Williams *et al.* (1981); the data in panel b could not be fit by our function.

recordings from monkey visual cortex neurons following reverse occlusion treatment confirm that the initially open eye, once continuously patched, loses dominance to the initially deprived eye (Blakemore *et al.*, 1978; Wiesel, 1982; Crawford *et al.*, 1989). Depending on the age of the reverse occlusion, the result is a greater or lesser takeover of cortical territory by the initially deprived eye. These animal studies clearly showed that covering the fellow eye can itself cause amblyopia to develop and often the long-term outcome is poor vision in both eyes.

The primary backup treatment for amblyopia is a procedure called penalization. Penalization involves instillation of a drop of atropine into the fellow eye daily. This dilates the pupil and paralyzes accommodation, thereby inducing blur. Penalization of the preferred fellow eye is intended to shift the child's fixation preference to the amblyopic eye. Unfortunately, this procedure also has been shown to induce amblyopia in young nonhuman primates (Boothe *et al.*, 1982; Harwerth *et al.*, 1983; Kiorpes *et al.*, 1987). The resulting amblyopia is similar in character to anisometropic amblyopia following rearing with blur from defocusing lenses. The effect of penalization during development on cortical neurons is to reduce the acuity and contrast sensitivity of neurons driven by the treated eye (Movshon *et al.*, 1987). Studies such as these alerted the clinical community to the negative effects of patching and penalization, generating a quest for better therapeutic options.

Amblyopia secondary to occlusion and penalization therapy continues to be a concern for treatment (Simons, 2005; Levi, 2006). Recent retrospective studies in treated and untreated amblyopic humans show that contrast sensitivity of the fellow eye is often compromised, but it is difficult to know for sure whether or not this is the result of patching (e.g. Lew *et al.*, 2005; Chatzistefanou *et al.*, 2005). One recent study in monkeys has shown a clear advantage of part-time occlusion strategies for prevention of occlusion amblyopia (Wensveen *et al.*, 2006). It has recently become possible to conduct controlled randomized clinical studies of treatment effectiveness. Several large-scale prospective clinical studies have been implemented to assess the efficacy of alternative strategies such as part-time patching and penalization in amblyopic children (see Holmes and Clarke, 2006; PEDIG, 2005, 2006).

Another concern with typical treatment strategies is that they prolong the period of abnormal binocular visual experience. As described above, amblyopia not only affects spatial vision but also binocular vision. A lack of correlation between the information from the two eyes creates a rapid loss of binocular function at the level of the visual cortex. Patching and penalization further disrupt binocular vision, thereby preventing any opportunity for rescue of binocular vision. Treated human amblyopes often lack binocular function and the poor binocularity may in fact be primary in determining the nature of amblyopic adult spatial vision (McKee *et al.*, 2003). Motivated by the findings in animals, prospective studies in human infants show that early surgery for strabismus and cataracts improve the chances of recovery of binocular function (Birch and Stager, 2006). Minimizing the amount of occlusion therapy further improves binocular outcome (Jeffrey *et al.*, 2001). In addition to revealing the detrimental effects of common therapeutic strategies on

the vision of the fellow eye and binocular function, one clear impact of animal work on clinical practice is demonstrating the importance of continued examination of visual acuity during and after treatment for amblyopia.

Treatment of congenital cataract

Cataracts are opacities of the lens that prevent form vision. Either bilateral or unilateral congenital cataracts have a devastating effect on development of vision (see Birch and Stager, 1996; Maurer *et al.*, 1999; Sjöström *et al.*, 1996). The parallels between visual outcomes in monkeys deprived of vision during infancy by lid suture and children deprived in infancy by cataract was obvious by the late 1970s. Since then it has been clearly demonstrated that amblyopia develops as a result of even more moderate levels of form deprivation than lid suture. Smith *et al.* (2000) raised monkeys with varying degrees of image degradation. They found that the resultant depth of amblyopia was directly related to the degree of image degradation. Work with animal models combined with accumulating evidence from human studies has revealed a strong correlation between duration and degree of form deprivation and depth of vision loss (see Mitchell and MacKinnon, 2002; Lewis and Maurer, 2005). It has now become standard practice to remove cataracts as early as possible in infancy to minimize the period and degree of early visual deprivation.

The primary difficulty with the management of cataracts in infancy is that removal of the cataract requires removal of the lens of the eye. This results in a condition called aphakia, in which the eye has no power to focus. Removal of the cataract thus results in continuing form deprivation after surgery. Prior to about 1980 spectacle lenses were typically prescribed to correct the defocus. There were two problems with this approach. First, it was difficult to keep glasses on young children. Second, the correction required high magnification to compensate for the missing lens. High magnification correction was sometimes difficult to achieve and created aniseikonia, unequal image size in the two eyes. The visual outcome for the aphakic eye was generally poor.

The introduction of contact lenses for use with infants presented a significant advantage over spectacle lenses, but a high degree of compliance and monitoring was required for successful therapy. Contact lenses also require relatively high magnification for proper correction, although less so than with glasses. However, the problem of aniseikonia remained and often the result was still a suboptimal visual outcome (Birch *et al.*, 1986; Lambert *et al.*, 1994). Contrast sensitivity data from each eye of a child with deprivation amblyopia are shown in Figure 3.7. This child had a unilateral congenital cataract that was removed at four months and wore contact lens correction essentially continuously thereafter. In spite of a substantial amount of patching therapy she had significant amblyopia when tested at age 6 years.

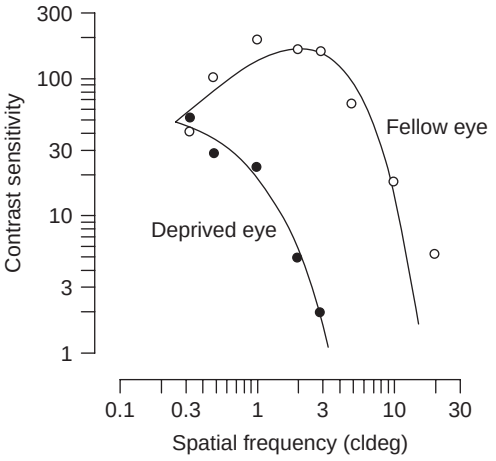

FIGURE 3.7 The effect of congenital cataract on contrast sensitivity in humans. Contrast sensitivity is plotted as a function of spatial frequency for each eye of a child who had a congenital cataract. The cataract was removed at about 4 months of age. Thereafter, the child's vision was corrected by contact lenses and patching therapy; testing took place when the child was about 6 years old. The data are from Tytla *et al.* (1988), figure 1, static gratings. The smooth curves fit to the data are described in Williams *et al.* (1981).

The problems associated with glasses and contact lenses are alleviated by use of intraocular lenses (IOL) following removal of the natural lens. An extensive series of studies by Lambert and colleagues in macaque monkeys was instrumental in evaluating the effect of aphakia on visual development and efficacy of various regimes of treatment following removal of the natural lens. They modeled treatment regimes involving lens removal followed by implantation of either monofocal or multifocal intraocular lenses, with or without subsequent full or part-time patching (Lambert *et al.*, 1994; Boothe, 1996; Boothe *et al.*, 1996, 2000). Grating acuity was longitudinally measured in each eye and assessed by Landolt-C acuity and contrast sensitivity after 1 year of age. The best visual outcomes were produced by a combination of IOL implantation of either kind and subsequent use of contact lenses for optical correction. Part-time patching further improved visual outcomes, but patching of less than 70% of the day produced subnormal grating acuity in the treated eye. Interestingly, although grating acuity reached normal adult levels under optimal treatment conditions, contrast sensitivity and Landolt-C acuity were never normal.

These studies demonstrated the advantage of IOL for good visual outcome, alone or in combination with extended wear contact lenses, over lens removal without subsequent IOL implantation. The results led directly to altered clinical practice. Subsequent clinical studies confirmed the benefit of this regime for visual outcome in human infants (Lambert *et al.*, 2001), although good compliance with contact lens wear can produce equivalently good outcomes (Birch *et al.*, 2005b).

To summarize, congenital cataracts present a significant challenge to the developing visual system. They leave devastating visual losses if left untreated, often resulting in life-long deprivation amblyopia even if treated aggressively. Monkey studies have been used to establish optimal treatment ages and strategies and have changed clinical practice accordingly.

NUTRITION AND VISUAL DEVELOPMENT

Although it has long been known that diet and nutrition affect growth and development, it took primate research results to make specific recommendations on amino acid and fatty acid content in infant formula. Taurine is an important amino acid normally present at high levels in the retina, brain, and other tissues throughout the body. Some early soy-based infant formulas lacked taurine. A series of studies by Neuringer and colleagues evaluated the effect of feeding taurine-free soy formula on visual development in macaque infants (Neuringer and Sturman, 1987; Neuringer *et al.*, 1987; Imaki *et al.*, 1987). They found reduced visual acuity in infants fed the taurine-poor diet. Infants fed a diet lacking taurine also had degeneration of cone photoreceptors in the retina and disorganization of the normally regular photoreceptor matrix. These studies provided evidence that dietary taurine is essential for normal visual system development. Soy-based infant formulas are now enhanced to include several amino acids including taurine.

There is accumulating evidence that some lipids are important for normal development of vision and the brain. Neuringer *et al.* (1986) studied the effect of dietary $\omega 3$ fatty acid concentration on the developing retina and brain of macaque monkeys. Pregnant monkeys were fed either control or $\omega 3$ fatty acid-deficient diets. Following parturition, the presence or absence of $\omega 3$ fatty acids in the diet was maintained in a manner consistent with the prenatal exposure. Biochemical changes were found in the level of long-chain fatty acids in the brain and retina of those fed deficient diets. Moreover, the infants deprived of $\omega 3$ fatty acids showed poorer visual acuity and abnormal photoreceptor function evidenced by longer times to recover from a bright flash of light. Infant formulas were in general lacking in $\omega 3$ fatty acids until the early 1990s, when manufacturers began to add specific ones to their formulas. Subsequent prospective studies of full-term human infants showed the importance of docosahexaenoic acid (DHA), among others, for supporting normal visual and cognitive function (see Neuringer, 2000; Auestad *et al.*, 2003; Birch *et al.*, 2005a).

CONCLUSIONS

The Old World macaque monkey has been shown to provide an excellent model for normal visual development in humans and for understanding clinically important

developmental disorders of vision. Animal studies in general have contributed greatly to our understanding of the vulnerability of the visual system to early abnormal visual experience.

While it has been known for over a century that conditions like strabismus are associated with poor vision in adults, no data existed to demonstrate a direct causal relationship prior to a longitudinal study in infant monkeys by Kiorpes and Boothe (1980). The work of Wiesel and Hubel identified, for the first time, anatomical and neurophysiological correlates of abnormal visual experience on the visual system. This work inspired many subsequent studies that revealed the existence and nature of critical periods in vision. In particular, studies of monocular deprivation during development illustrated the extreme devastation to visual system structure and function created by form deprivation. The work in aggregate identified the nature of the critical period for normal visual development, showing varying degrees of vulnerability over different age ranges and showing different periods of susceptibility for recovery after deprivation. Retrospective analyses of this literature led to a revision of the concept of the critical period, suggesting that there are three conceptually separate, but overlapping sensitive periods; namely for normal development, for disruption of function, and for recovery of function. The results of studies with the lid suture model led directly to a shift in clinical practice in two ways. First, they led to treatment of children with vision disorders, in particular those with cataracts, at the youngest possible ages. Second, they led to a major re-evaluation of classical treatment strategies such as full-time patching of the fellow eye. Current recommendations are to use part-time patching, if possible in combination with focused activity to improve the vision in the amblyopic eye.

Other macaque models of amblyopia, such as experimental strabismus and anisometropia, characterized the nature of amblyopia in relation to the losses in acuity and contrast sensitivity. This work revealed the extent of loss in spatial, temporal, and binocular vision and showed additional significant loss in perceptual vision. Macaque models have also been used to evaluate treatment strategies for recovery of function. The basic neural mechanisms underlying amblyopia have been identified in macaque monkeys. The unexpected finding was that in addition to correlates of amblyopia at the level of the primary visual cortex, there must be additional sites of dysfunction further along the visual pathways. This is surprising because since the early studies of Wiesel and Hubel it has been assumed that V1 is the primary site of developmental plasticity in the visual system. Future work must address the possibility of additional, perhaps escalating, deficiency at higher levels of the system. This idea has important implications for treatment. Given the clear impact of amblyopia on higher order perceptual visual functions, and finding that these problems remain even when acuity measures reflect successful treatment,we should be developing clinical tests for perceptual dysfunction and extending treatment over a longer time period than might be dictated by acuity measures alone (Simons, 2005).

One subtle but none-the-less important result of studies of visual development in cat and monkey models of amblyopia was to show the necessity of following

visual function in children undergoing treatment. Longitudinal studies in animals showed the progression of visual acuity development in the presence of amblyogenic factors and revealed the gradual trade-off of good visual function between the two eyes during occlusion therapy. The use of quick visual assessment tools, such as the Teller Acuity Cards (Teller *et al.*, 1986), in the practitioner's office is becoming commonplace, thus improving the ability of clinicians to track visual acuity during treatment without a major investment of time and effort. Finally, this body of work in aggregate has led to increased attention to the importance of early childhood vision screening programs to identify and treat visual disorders with optimal success (Hartmann, 2000; Williams and Harrad, 2006).

The primary challenge remaining for future studies of visual dysfunction in macaque monkeys is to identify the nature of neural plasticity in areas of the visual system beyond V1. The critical periods for these downstream areas are likely to be longer than for V1. This may provide a better opportunity for the successful treatment of amblyopia.

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