1 Sensory processing: animal models of amblyopia

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INTRODUCTION

Wiesel and Hubel launched an era of intense research with their Nobel Prize-winning studies on the effects of visual experience on the development of the visual system. Beginning in the early 1960s, they characterized the functional organization of the primary visual cortex and discovered the vulnerability of this organization to abnormal visual experience in early postnatal life (Wiesel and Hubel, 1963, 1965; see also Hubel et al., 1977; Wiesel, 1982). Their studies focused primarily on the property of binocularity of cells in the primary visual cortex of cats, and later monkeys, and the destructive effects of reduced or absent visual input to one eye on binocular organization. On the basis of these early studies, Wiesel and Hubel suggested that amblyopia might result from a reduction in the number of neurons influenced by the deprived eye in primary visual cortex.

The demonstration of plasticity in the organization of ocular dominance spawned interest in the question of whether other properties of cortical cells could also be modified by early visual experience (see Movshon and van Sluyters, 1981; Movshon and Kiorpes, 1990). It became clear that other functional properties of visual cortical cells, for example orientation preference and direction selectivity, could be influenced by early visual experience. The important question, and the one that is of clinical interest, is: what properties of the visual system are affected by visual abnormalities that are associated with amblyopia in children? We know from clinical experience that anisometropia (a refractive difference between the eyes), strabismus (a misalignment of the two eyes) and unilateral cataract (an opacity in one eye), among other conditions, are associated with the development of amblyopia in children. When these same disorders appear in adults, they do not cause permanent visual deficits. Thus these disorders affect the developmental process. It is important, therefore, to understand the developmental mechanisms by which visual experience exerts its effects.
ANIMAL MODELS

To establish with certainty the causal nature of the relationship between abnormal visual input and the development of amblyopia, and to learn about the neural correlates of amblyopia, it is necessary to study an animal model. There are several important factors that motivate the study of an animal model in this case. First, except in areas where routine screening is conducted, clinicians rarely see infants before a visual disorder becomes obvious, and once the condition presents itself the clinician is typically obliged to begin a course of treatment. However, the clinical profile at the time of presentation may not reflect the original precipitating condition. Numerous studies have shown that abnormal early visual experience can induce strabismus or anisometropia (e.g. Quick et al., 1989; Kiorpes and Wallman, 1995; Smith et al., 1999). Thus it is in many cases difficult to establish the age of onset and the actual cause of the amblyopia, or indeed whether the amblyopia was the result or itself the cause of the child’s condition (Almeder et al., 1990; Kiorpes and Wallman, 1995; see also Tyschen, 1993). Second, because of the need for clinical intervention in the case of an infant or child, it is difficult to study the natural course of amblyopia development in humans. Knowledge of the natural course of amblyopia development would be of particular value for decisions about the necessity of treatment, and the likely outcome and timing of particular courses of treatment. Finally, it is impossible with currently available methods to study the neural basis of amblyopia in human infants and children. To truly understand the condition and effectively treat it, knowledge of the neural mechanisms involved in amblyopia development is essential.

Most animal studies on visual system development are conducted with cats or macaque monkeys as subjects. The macaque monkey visual system is the better model of the two. The early visual pathways in macaques have been shown to be structurally and functionally similar to those in humans. Visual acuity and contrast sensitivity, two basic descriptors of visual function, are similar in macaques and humans (DeValois et al., 1974; Williams et al., 1981; Kiorpes and Movshon, 1990). Moreover, the course of visual acuity development in human and macaque infants is essentially identical if human and monkey age are scaled appropriately: monkey age in weeks is approximately equivalent to human age in months (Teller, 1981, 1997; Boothe et al., 1985; Kiorpes, 1992a; see Figure 1.1). The most important consideration for understanding amblyopia, though, is whether visual conditions that are associated with amblyopia in children also result in amblyopia in monkeys. We have shown that infant monkeys naturally develop strabismus, and do so with a frequency similar to that in humans (Kiorpes and Boothe, 1981; Kiorpes et al., 1985). Amblyopia develops in monkeys in association with naturally occurring strabismus (Kiorpes, 1989); amblyopia also develops when a strabismus is created experimentally under controlled conditions early in life in an otherwise normal animal (von Noorden and Dowling, 1970; Kiorpes and Boothe, 1980; Harwerth et al.,
1983; Kiorpes et al., 1989). Similarly, anisometropia, natural or experimentally simulated, can cause the development of amblyopia in macaque monkeys (Smith et al., 1985; Kiorpes et al., 1987, 1993; Smith et al., 1999).

Studies of experimentally induced anisometropia and strabismus in monkeys have shown unequivocally that the presence of unequal refractive error between the two eyes or misalignment of the visual axes during the early postnatal period is sufficient to cause the development of amblyopia. Reports of naturally occurring strabismus and anisometropia in monkeys confirm the close similarity between human and monkey visual systems. Furthermore, it has been demonstrated that naturally strabismic monkeys show visuomotor deficits that are similar to those identified in human congenital esotropes (Distler, 1996; Tyschen and Boothe, 1996). Abnormalities of smooth pursuit eye movements (Kiorpes et al., 1996), binocularity, and stereopsis (Crawford et al., 1983; Harwerth et al., 1997) have been demonstrated in experimentally strabismic monkeys in addition to amblyopia. Collectively, these results strengthen the utility of the monkey model for understanding strabismus, anisometropia and amblyopia.

Cats are less desirable as a model species for amblyopia, primarily because the organization of their visual system is somewhat different from that of primates, and adult visual acuity is considerably poorer than that of humans and monkeys (see Kiorpes and Movshon, 1990). Also, the profile of visual acuity development is quite different from the primate pattern in that acuity improves rapidly over a short period of time following eye opening, and asymptotes by 10–12 weeks at adult levels (Mitchell et al., 1976). However,
visual abnormalities of the kind that lead to amblyopia in monkeys can result in reduced visual acuity in cats as well, although the deficits tend to be small and in many cases the cats become bilaterally amblyopic (von Grünau and Singer, 1980; Holopigian and Blake, 1983; Mitchell et al., 1984; see also Mitchell, 1988).

It must be noted that many studies of the effects of monocular deprivation (by lid suture or occlusion) on visual system development have been conducted in cats and in monkeys. Behavioural studies have shown that residual visual function following monocular deprivation is typically extremely poor, if measurable at all (Harwerth et al., 1983, 1989; see also Movshon and Kiorpes, 1990; Mitchell, 1991). Such dramatic visual deficits are rare in human amblyopia, therefore this paradigm is not especially useful for understanding amblyopia generally. However, monocular deprivation is a reasonable model for understanding the effects of very dense congenital cataracts on visual system development. Also, monocular deprivation and reverse deprivation studies have been important for establishing the effects of particular treatment regimens on recovery of visual system function (Blakemore et al., 1978; Crawford et al., 1989; Harwerth et al., 1989; Mitchell, 1991). A related model that has been especially useful for studying treatment regimes following cataract surgery is unilateral aphakia. Boothe and colleagues have developed a primate model that very closely mimics the human condition of aphakic amblyopia, which develops following removal of the natural lens to correct unilateral congenital cataract (O’Dell et al., 1989; Boothe et al., 1996).

Critical period

As noted above, amblyopia is a disorder of development; the conditions associated with amblyopia in childhood do not result in permanent visual deficits when they appear in adults. Thus there is a critical period for amblyopia development. The extent of the critical period in humans is a matter of some debate, but it is commonly thought to include the first 8 years after birth (von Noorden, 1980). It is important to realize, though, that there are multiple aspects to the critical period (see Daw, 1995, 1998); the critical period is not necessarily synonymous with the period of visual development, and treatment efficacy is not equivalent throughout. Harwerth and colleagues (1986, 1989) have shown, using a deprivation model in monkeys, that different visual functions have different critical periods. For example, spatial vision can be compromised at a later age than spectral sensitivity, and the period of vulnerability of spatial vision extends beyond the period of normal development of spatial vision in macaques. Also, as noted below, we find improvements, as well as losses, in spatial vision of amblyopes beyond the period of normal visual development in macaques.

Daw (1998) points out that for visual acuity there are really three sub-periods, which are not mutually exclusive, that need to be considered: the period of normal visual development, the period within which amblyopia can develop, and the period within which amblyopia can be successfully treated.
For humans, most studies show that adult levels of visual acuity are reached between 3 and 5 years (Mayer and Dobson, 1982; Birch et al., 1983; Teller, 1997), although improvements in contrast sensitivity and vernier acuity have been noted to continue beyond 5 years (Bradley and Freeman, 1982; Abramov et al., 1984; Carkeet et al., 1997). One recent retrospective study of amblyopia development found that children’s susceptibility to amblyopia development declined by 6 years (Keech and Kutschke, 1995), but it has been reported that treatment for amblyopia can be at least partially effective into the teenage years (see Daw, 1998). To compare monkey and human critical periods we can use the age translation mentioned above, that monkey age in weeks is approximately equivalent to human age in months (Teller, 1981). In monkeys, the development of acuity and contrast sensitivity is complete by the end of the first postnatal year (Boothe et al., 1988), which translates to 4.3 human years, and contrast sensitivity can be degraded by deprivation as late as 18 months (Harwerth et al., 1986), which translates to 6 human years. No data are available on the upper limit for treatment of amblyopia in monkeys. However, it has been demonstrated, across conditions and species studied (including humans), that early intervention can reduce or completely reverse the effects of early abnormal visual experience, whereas later in the critical period treatment becomes less effective (e.g. Crawford and von Noorden, 1979; Crawford et al., 1989; Birch et al., 1990, 1998; Mitchell, 1991). The similarity in developmental profiles and critical periods strengthens the point that the macaque monkey is an excellent model for human visual development and for studying the vulnerability of the human visual system to abnormal visual experience.

**Natural course of amblyopia development**

The natural course of amblyopia development has been documented in strabismic monkeys (Kiorpes, 1989, 1992b; Kiorpes et al., 1989). Naturally strabismic monkeys studied longitudinally showed normal acuity in each eye during the early postnatal weeks, but some time later, beyond 8–10 weeks, most developed amblyopia. A similar pattern was noted by Birch and Stager (1985) in a prospective study of human infantile esotropes. Of the six cases of early onset strabismus studied in monkeys, four cases developed amblyopia and two cases did not (one was an alternating esotrope and the other was an exotrope); two cases that initially developed amblyopia showed a reduction in the degree of amblyopia by 2–3 years of age (Kiorpes, 1989). One other case that was studied developed strabismus and anisometropia following bilateral congenital cataracts; this animal also became amblyopic. One particularly intriguing finding was that the naturally strabismic monkeys seemed to show a protracted developmental time course compared to normal animals. These monkeys continued to show improvement in acuity and contrast sensitivity through the second postnatal year, whereas normal monkeys reach adult levels on these measures by the end of the first postnatal year.

We found a similar pattern of development in longitudinal studies of experimentally strabismic monkeys (Kiorpes et al., 1989; Kiorpes, 1992b). In
Figure 1.2 Acuity development in strabismic monkeys. (a) Grating acuity is plotted as a function of age for amblyopic eyes (filled triangles) and fellow eyes (open triangles) of monkeys with experimentally induced esotropia. Control data (open circles) are from normal infants tested monocularly. (b) Longitudinal acuity development is shown for each eye of two monkeys with surgical esotropia induced at 3.5 weeks postnatal. Open symbols represent fellow eye data; filled symbols represent amblyopic eye data.
these studies, esotropia was induced either by surgical alteration of the horizontal rectus muscles or by injection of *Oculinum* (*C. Botulinum A* neurotoxin) into the lateral rectus muscle at ages ranging from 1 to 15 weeks postnatal. On average, 67 per cent of experimentally strabismic monkeys developed amblyopia, defined as a factor of two or greater deficit in acuity for the deviated eye compared to the fellow eye. Age of onset was an important factor in determining which animals developed amblyopia. Amblyopia developed in 80 per cent of cases when esotropia was induced within the first 4 postnatal weeks, whereas 50 per cent developed amblyopia with later ages of onset. Fixation pattern was another important predictor of amblyopia: those monkeys that alternated fixation were less likely to develop amblyopia than those that adopted a unilateral fixation pattern. The longitudinal acuity data show that the time course of acuity development for the deviated eyes lagged behind that for the fellow eyes (see Figure 1.2); in some cases acuity in the deviated eye actually declined initially, whereas in other cases there was a delay in development followed by a resumption of the developmental time course thereafter. This pattern of delayed or slowed development was also found using other measures of visual function, such as contrast sensitivity and vernier acuity (Kiorpes, 1992b; Kiorpes, 1996).

**Characteristics of amblyopia in the monkey**

Although amblyopia is most commonly identified clinically as a deficit in acuity, the full contrast sensitivity function is a more complete descriptor of visual function. The contrast sensitivity function provides information about visual sensitivity at all spatial scales, from coarse to fine, whereas acuity provides a measure only of fine resolution. Normal adult monkeys (and humans) show similar contrast sensitivity functions for the right and left eyes and enhanced contrast sensitivity under binocular viewing conditions (Figure 1.3a). Amblyopes show deficits in contrast sensitivity at the high spatial frequencies (fine spatial scale), as would be expected given the acuity deficit, but they also typically show losses for mid-range spatial frequencies and occasionally for low spatial frequencies as well (Figure 1.3b). The binocular enhancement seen in normal observers is typically absent in amblyopic observers (Harwerth and Levi, 1983); our monkey amblyopes also failed to show binocular summation for contrast sensitivity. Similar results have been reported by other labs (Harwerth et al., 1983; Smith et al., 1985). The deficits in contrast sensitivity in amblyopic monkeys are reminiscent of contrast sensitivity profiles in infants. Boothe et al. (1988) showed that infant monkeys have low sensitivity to contrast over the range of spatial scales to which they are sensitive, and that the spatial scale of the infant visual system is shifted to a much lower range than that of adults (Figure 1.3c). As development proceeds, the contrast sensitivity function shifts upward and to the right, to higher spatial scales and higher contrast sensitivity. If we directly compare normal infant and amblyopic adult contrast sensitivity functions, we find that the amblyopic functions resemble data from younger normal monkeys (Kiorpes, 1996). Hence, in terms of this basic descriptor of visual function,
Amblyopia does not represent a completely disordered or abnormal state of visual function. Rather, amblyopia can be characterized as an incompletely developed visual system.

Our studies of the development of vernier acuity led us to a similar conclusion. Studies of human amblyopes had shown that they were particularly impaired on spatial localization tasks in comparison to their deficits in grating and Snellen acuity. Strabismic amblyopes in particular were substantially more impaired on localization tasks compared to anisometropic amblyopes (e.g. Levi and Klein, 1982, 1985; Hess et al., 1990). To investigate whether the development of vernier and grating acuity proceed along the same time course, and to see whether the development of these functions is similarly disrupted in amblyopia, we studied the development of vernier acuity and grating acuity longitudinally in normal animals, and also in animals who had experimentally-induced strabismus (Kiorpes, 1992a, 1992b). We found that vernier acuity in normal infants is relatively less mature than grating acuity, and develops to a greater extent during the first postnatal year. Therefore, the two functions do not show the same developmental profile, although adult levels are approached at similar ages. A recent study in human infants has shown the same developmental relationship between vernier acuity and grating acuity that we found for monkeys (Skoczynski and Norcia, 1999; see also Levi and Carkeet, 1993).

Strabismus disrupted vernier acuity development as well as grating acuity development. The disruption of vernier acuity development was similar to that described above for the development of grating acuity and contrast sensitivity: vernier acuity development in amblyopic eyes lagged behind the fellow eyes and proceeded more slowly. When these monkeys were tested as adults, the deficit in vernier acuity was larger than the deficit in grating acuity, which is consistent with what has been reported in humans. However, this relatively larger vernier acuity loss may be the result of the different developmental profiles we identified for vernier and grating acuity. Since vernier acuity in normal infants is relatively less mature than grating acuity and develops to a greater extent, and since the developmental time course is slower for amblyopes, the relatively greater impairment of vernier acuity over grating acuity may simply be a reflection of a less mature visual system at the end of
the critical period rather than a peculiar deficit in positional acuity (Kiorpes, 1992b).

While our studies showed the expected superordinate loss in positional acuity, we did not find a clear distinction between anisometric and strabismic amblyopes in the relationship between vernier acuity and grating acuity impairment that has been reported in human psychophysical studies (Levi and Klein, 1985; see also Chapter 2). We induced anisometric amblyopia by rearing macaques with unilateral defocus; defocus was imposed with extended-wear contact lenses. While we did not study the development of anisometric amblyopia longitudinally, we measured vernier acuity as well as other visual functions after the end of the rearing period, at about 1 year of age (Kiorpes et al., 1993). Like our strabismic amblyopes, the anisometric amblyopes showed a relatively larger deficit in vernier acuity, although the effect was on balance somewhat smaller for the anisometropes than for the strabismics. To see if this was a fundamental species difference or not, we compared our monkey data directly with data from a population of human amblyopes (Kiorpes and Movshon, 1996). We used data from the Cooperative Amblyopia Classification Study (McKee et al., 1992; Movshon et al., 1996), which included measurements of vernier and grating acuity in a large group of amblyopes with known clinical histories. As shown in Figure 1.4, the amblyopic monkeys fell well within the range of the data from human amblyopes. Interestingly, like our monkeys, this large group of human amblyopes does not show a clear distinction between anisometric and

**Figure 1.4** Comparison between the deficit in vernier acuity and the deficit in grating acuity for human and monkey amblyopes. The extent of the amblyopic deficit on each measure is presented as an interocular ratio: fellow eye acuity/ambyopic eye acuity. The dashed line represents a slope of 1. If the data clustered along the line, the deficits on each measure would be equal. However, since the data are largely scattered above the line, the deficits in vernier acuity are larger than those in grating acuity. Circles represent anisometric amblyopes and triangles represent strabismic amblyopes; filled symbols represent monkey subjects and open symbols represent human subjects. The crosses are data from human combined strabismic-anisometropes. Human data are from McKee et al., 1992; Movshon et al., 1996; see also Kiorpes and Movshon, 1996.
strabismic observers in the relative extent of the deficit in vernier acuity. Mixed strabismic–anisometropic observers tend to show the most extreme deficits in vernier acuity. We have not explicitly modelled this condition, although some of our experimentally strabismic, amblyopic monkeys later developed anisometropia, and some experimentally anisometropic monkeys later developed a natural anisometropia or strabismus (Kiorpes and Wallman, 1995; Kiorpes et al., 1999).

These psychophysical studies of monkeys with strabismic and anisometropic amblyopia show many of the characteristics that are considered basic to human amblyopia. In addition to the deficits in acuity, contrast sensitivity and spatial localization already described, we have identified deficits in spatial phase discrimination (Kiper, 1994), suprathreshold contrast sensitivity (Kiper and Kiorpes, 1994), motion sensitivity (Tang et al., 1998) and contour integration (Kozma et al., 2000). Some of these deficits can be explained on the basis of the primary loss of contrast sensitivity, as is true for many human amblyopes. Furthermore, a psychophysical study designed to determine whether the primary site of the contrast sensitivity deficit in amblyopia is early in the visual pathways or perhaps in the central pathways (cortical) suggested that the loss is predominantly central (Kiorpes et al., 1999). Physiological studies in some of the same animals confirmed that deficits can be found in the visual cortex that reflect, at least qualitatively, the behavioural losses (Kiorpes et al., 1998).

**Neural correlates of amblyopia**

As noted at the beginning of this chapter, the early studies of Hubel and Wiesel and others suggested that the primary neural correlate of amblyopia was a dramatic reduction in the number of neurons in the primary visual cortex (V1) that could be influenced by the deprived eye. However, looking back over several decades of work, we find that a breakdown of binocular function is a ubiquitous result in strabismus, anisometropia and deprivation, but a dramatic deficit in amblyopic eye activity in V1 is not a consistent correlate of amblyopia. The breakdown of binocular function is characterized by a dearth of neurons that can be influenced relatively equally by each eye. Interestingly, recent studies have shown that although the classical test of ocular dominance suggests a lack of binocular function, there can be residual binocular interactions (Sengpiel and Blakemore, 1996; Smith et al., 1997). These studies show that there are indeed deficient excitatory interactions, but that inhibitory, suppressive interactions persist following anisometropic (lensearing) and strabismic (prism-rearing or surgical strabismus) early rearing. The relationship between these residual binocular interactions and the presence of amblyopia is not clear, though. The anisometropic animals studied by Smith and colleagues all showed deficits in contrast sensitivity at high spatial frequencies, but the prism-reared animals had comparatively small deficits or no deficits. Nevertheless, both groups showed measurable binocular interactions at the single-cell level.
The appearance of a shift of cortical ocular dominance away from the amblyopic eye seems to be different for strabismic amblyopia and for blur or deprivation-induced amblyopia. The majority of studies of anisometropic or deprivation-induced amblyopia, in which the presence of amblyopia was behaviourally verified, show a reduction in the number of neurons driven by the amblyopic eye (Baker et al., 1974; Movshon et al., 1987; Kiorpes et al., 1998; but see also Smith et al., 1997). This is not a consistent finding in strabismic amblyopia. Some studies find balanced influence from the two eyes in strabismic amblyopes with mild to moderate amblyopia (see Figure 1.5b; Smith et al., 1997; Kiorpes et al., 1998), whereas others report a shift away from the amblyopic eye even in relatively mild amblyopia (Wiesel, 1982). However, deep strabismic amblyopia does tend to be associated with a reduction of influence by the deviated eye (Baker et al., 1974; Crawford and von Noorden, 1979; Kiorpes et al., 1998). On balance, a shift of cortical influence away from the amblyopic eye seems to be associated with relatively severe amblyopia, deprivation, or blur-rearing, but is not reliably associated with strabismus or mild to moderate amblyopia. Thus, it is important to look beyond the idea of a simple imbalance in cortical influence as the basis of amblyopia.

Since amblyopia is predominantly a disorder of spatial vision, it is important to evaluate the spatial properties of neurons in the visual pathways. Only a few studies have made quantitative assessments of spatial properties of neurons in amblyopic animals. Movshon and co-workers (1987) studied spatial tuning properties of V1 neurons in monkeys raised with chronic unilateral defocus from daily instillation of atropine in one eye; behavioural testing of contrast sensitivity showed that these animals developed amblyopia (Kiorpes et al., 1987). Consistent with the behavioural deficits in contrast sensitivity, neurons driven by the treated eyes were found to have a reduction in overall contrast sensitivity, preferred spatial frequency and spatial resolution compared with neurons driven by the untreated eyes. These deficits were not reflected in the physiological properties of neurons earlier in the visual pathways, in the LGN (see also Blakemore and Vital-Durand, 1986). Eggers and Blakemore (1978) reported similar results in cats reared with monocular optical defocus. They found a reduction in contrast sensitivity and spatial resolution of V1 neurons driven by the treated eye; however, they did not test their animals behaviourally to verify the presence of amblyopia.

Kiorpes and co-workers (1998) studied spatial tuning properties of V1 neurons in animals that were behaviourally verified to be strabismic or anisometropic amblyopes. Strabismus was induced surgically (Kiorpes et al., 1989); anisometropia was simulated during rearing with defocusing contact lenses (Kiorpes et al., 1993). Full contrast sensitivity functions were measured to document the presence of amblyopia (see Figure 1.5a). This study showed a clear correlation between the behavioural deficits in spatial vision and reduced spatial frequency sensitivity in V1 neurons. For animals with moderate to severe amblyopia, the range of preferred spatial frequency and spatial resolution for amblyopic eye neurons was shifted to lower spatial scale with respect to those for fellow eye neurons (Figure 1.5c). A similar reduction
Figure 1.5 Comparison of behavioural and physiological correlates of amblyopia. (a) Contrast sensitivity functions for one strabismic (top) and one anisometropic (bottom) amblyopic monkey (filled symbols represent fellow eye data; open symbols represent amblyopic eye data). Note that the depth of amblyopia is similar for each case. (b) Ocular dominance histograms for the monkeys in (a). These histograms show the proportion of cells in primary visual cortex that could be influenced by either eye. The strabismic monkey (top) showed equal representation of the fellow (dominance category 7) and amblyopic (dominance category 1) eye, while the anisometropic monkey showed a skewed distribution: many fewer cells could be driven by the amblyopic eye than the fellow eye. For both monkeys, relatively few cells were binocular (dominance categories 2–6). (c) Distributions of optimal (preferred) spatial frequency, contrast sensitivity, and spatial resolution for neurons tested through the amblyopic (dark bars) and fellow (light bars) eye of the same two monkeys. The distributions of optimal frequency and spatial resolution for amblyopic eye neurons of each monkey were significantly lower than the distributions for fellow eye neurons. The distributions for contrast sensitivity were not significantly different for amblyopic and fellow eye neurons in these cases. (d) Quantitative comparison of the extent of the behavioural and physiological deficits in anisometropic and strabismic amblyopes. For each measure, the interocular ratios for physiologically assessed neural sensitivity are plotted against those for behavioural sensitivity. Open and filled circles represent data from anisometropic and strabismic animals, respectively. If the behavioural and physiological deficits were commensurate, the data would cluster along the diagonal drawn through each plot; the data fall largely below the diagonals indicating a larger behavioural than physiological deficit. Data are from Kiorpes et al., 1998.
in neuronal acuity has been reported in strabismic cats with behaviourally documented acuity losses (Chino et al., 1983; Crewther and Crewther, 1990). The shift to lower preferred spatial frequency and resolution mimics that seen behaviourally, with the shift of the contrast sensitivity function to a lower spatial scale for the amblyopic eye. As Figure 1.5d shows, there was a reliable relationship between the extent of the behavioural deficit and the extent of the physiological one, although the physiological shift was typically smaller than the behavioural deficit. Consistent with the finding that the physiological deficits were smaller than the behavioural deficits, the mildest amblyopes showed no reliable difference between the amblyopic and fellow eye distributions. Curiously, unlike the earlier study (Movshon et al., 1987), there was no consistent effect on neuronal contrast sensitivity even in the deepest amblyopes. Overall, the range of contrast sensitivities for amblyopic eye neurons was similar to that for fellow eye neurons. This latter result, and the finding that the spatial deficit apparent in the neuronal population is smaller than the behavioural deficit, led us to conclude that neural correlates of amblyopia can be seen at the level of single neurons in V1, but that it is likely that these deficits are amplified and probably compounded at subsequent levels of processing either within or beyond V1.

The extraordinary deficit in spatial localization ability in amblyopia, which is particularly apparent in strabismic and mixed amblyopes, cannot easily be explained on the basis of this physiological deficit in spatial frequency sensitivity. Several psychophysical theories have been proposed to explain the spatial localization deficit, most notably that there is a topographical jitter or disarray in the amblyopic eye neurons' receptive fields, or that there is under-sampling of the amblyopic visual world at fine spatial scales (see, for example, Hess et al., 1999; Kiorpes and McKee, 1999; Levi et al., 1999; and Chapter 2). Our finding that the range of spatial scale sensitivity of amblyopic eye neurons is lower than for fellow eye neurons could provide a substrate for under-sampling at fine spatial scales. However, while receptive fields for amblyopic eye neurons did not appear to be disordered with respect to nearby fellow eye neurons, it would be difficult to capture disarray at the single unit level without finer sampling. The question of topographic disarray may be better addressed at a higher, perhaps extrastriate, level of the visual system where receptive fields integrate over larger areas of visual space.

Finally, it is informative to compare the physiological properties of amblyopic neurons to those of normal infants. Physiological studies of foveal V1 neurons in 1–4-week-old monkeys show that, on average, preferred spatial frequency is two to three times lower than that found in adult monkeys, while orientation and direction selectivity are essentially adult-like in newborns (Movshon et al., 1999, 2000; see also Chino et al., 1997). Spatial resolution of infant V1 neurons is about a factor of 5 lower than in adults (Blakemore, 1990; Chino et al., 1997). In our amblyopes, spatial resolution and preferred spatial frequency was a factor of 1.5–2 lower for neurons driven by amblyopic eyes compared to neurons driven by the fellow eyes, while orientation and direction selectivity were normal in all cases. These results suggest that receptive field properties that are immature in infants are affected by the
abnormal visual input that leads to amblyopia; these properties develop from newborn levels, but do so more slowly, or perhaps incompletely, in the presence of abnormal visual input. Thus, as indicated by our longitudinal behavioral studies of strabismic and anisometric monkeys, a slowed developmental time course may leave the visual system in an immature state at the end of the critical period.

CONCLUSION

This chapter has attempted to convey the utility of the primate model for amblyopia, describe the relationship between strabismic and anisometric amblyopia in monkeys (both experimentally induced and naturally occurring) and that which has been characterized in humans, and provide some insight into the developmental mechanisms that may underlie amblyopia. These studies have shown that amblyopia is a disorder of the developmental time course, and the slowed development is reflected initially in the spatial properties of V1 neurons. Numerous animal studies have been directed at the molecular mechanisms that control the period of visual plasticity and the progress of development (see Daw, 1995). Progress in this area may allow us to understand more completely the mechanisms of plasticity, and perhaps eventually allow us to extend the critical period, to more effectively treat amblyopia in children.

REFERENCES


Amblyopia: A Multidisciplinary Approach


