Understanding the development of amblyopia using macaque monkey models

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Amblyopia is a sensory developmental disorder affecting as many as 4% of children around the world. While clinically identified as a reduction in visual acuity and disrupted binocular function, amblyopia affects many low- and high-level perceptual abilities. Research with nonhuman primate models has provided much needed insight into the natural history of amblyopia, its origins and sensitive periods, and the brain mechanisms that underly this disorder. Amblyopia results from abnormal binocular visual experience and impacts the structure and function of the visual pathways beginning at the level of the primary visual cortex (V1). However, there are multiple instances of abnormalities in areas beyond V1 that are not simply inherited from earlier stages of processing. The full constellation of deficits must be taken into consideration in order to understand the broad impact of amblyopia on visual and visual-motor function. The data generated from studies of animal models of the most common forms of amblyopia have provided indispensable insight into the disorder, which has significantly impacted clinical practice. It is expected that this translational impact will continue as ongoing research into the neural correlates of amblyopia provides guidance for novel therapeutic approaches.

amblyopia | nonhuman primate | macaque monkey | visual cortex | comparative vision

Vision in newly born infants is poor and develops to maturity over an extended time period. However, the age at which different visual functions reach maturity varies substantially, ranging from several months to many years (1). The neural limitations on this complex developmental process remain incompletely understood. It is known, though, that, without clear, balanced binocular visual input, vision does not develop normally—normal visual experience is required [for reviews, see Movshon and Van Sluyters (2), Movshon and Kiorpes (3), and Birch (4)]. The most common cause of monocular vision loss in children is amblyopia, literally “blunt sight.” This is an experience-dependent, nongenetic developmental disorder. Amblyopia is associated with blur in one eye (anisometropia), misaligned eyes (strabismus), or other impediment to clear vision, such as cataract (form deprivation) or corneal opacity, when these conditions exist during an early period of development—the visual sensitive period. Amblyopia does not result from such conditions when onset in adulthood. The vision loss persists despite correction of any refractive error or misalignment or removal of cataracts; thus, it is a disorder of the brain rather than of the eye. Estimates of the prevalence of amblyopia are on the order of 1% to 4% of children (5–7). It affects many aspects of vision, from basic acuity to high-level form vision, binocular function and stereopsis, reading, and visual-motor coordination, as well as nonvisual factors, such as children’s psychosocial adjustment. High-level perceptual losses include many aspects of vision that are important for everyday life, such as figure-ground segregation, integration of visual information over space and time, motion sensitivity, and object recognition (8, 9). Because amblyopia has such broad implications for children’s visual and social development, it is important to understand the natural history and neural basis for the disorder and to ultimately improve detection and treatment options.

Early Studies of Experimental Amblyopia

The origins of amblyopia were largely a mystery until investigations in animal models were undertaken. As of the early 1970s, it was known that conditions like anisometropia and strabismus were associated with amblyopia, but there was no clear evidence of causality, only a less than perfect correlation. It was difficult to know, for example, whether a refractive error or misalignment of the eyes, identified at the time a child was brought to the clinic, was a cause or a result of an apparent visual loss. Also, except in cases of an obvious strabismus or cataract, it is difficult to know without objective testing whether a child has normal, clear vision or not. Absent regular childhood vision screening, amblyopia often goes undetected until school age—a point at which the residual plasticity of the visual system is already declining, making treatment more difficult (7, 10–12). However, using an animal model, it became possible to identify causal mechanisms, to study the phenomenon under controlled environmental conditions, and, importantly, study the full course of development longitudinally, none of which is possible in humans. Initially studying cats, and later monkeys, Wiesel and Hubel documented the destructive effect of visual deprivation, via monocular eyelid suture, on the postnatal development of neural organization in the primary visual cortex (13–16). Their work demonstrated for the first time that normal, binocular visual experience during development was required in order for the primary visual cortex to achieve normal organization and function in adulthood.

While these early studies clearly showed the importance of normal visual experience for proper development of the visual cortex, it was unclear what the impact was on functional vision. Anecdotal observations suggested that cats raised with monocular deprivation were blind—they were reported to walk into table legs and other obstacles (13); however, until the 1970s, there was no actual visual assessment. Dews and Wiesel (17), in a behavioral study of cats raised with monocular deprivation, showed a clear effect on acuity and a sensitive period for the effects, as well as a different time course of impact on visual and visual motor ability. The first studies that attempted to mimic visual conditions that were associated with human amblyopia in

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monkeys and assess subsequent consequences for vision were conducted by von Noorden and colleagues in the early 1970s (18, 19). They imposed lid closure or surgically created a large, paralytic eye misalignment in very young macaque monkeys to model congenital cataracts or strabismus and then tested visual acuity in each eye using a Landolt-C task once the animals were several years old. The duration of abnormal visual experience was varied by initiating the intervention at different postnatal ages. In a few animals, in which the abnormality was imposed within the first weeks after birth, they found deficits in visual acuity in the deprived or strabismic eye relative to the nontreated eye. These results suggested that a change in visual experience could itself compromise the function of an otherwise normal visual system but that the effects could only be demonstrated with intervention at very young ages. Subsequent studies tracked the development of visual acuity in each eye of experimentally strabismic macaques longitudinally, revealing that 1) the surgical intervention was not in itself responsible for altering vision (it was the abnormal visual experience that was important) and 2) amblyopia developed gradually—it emerged neither as an arrest of development nor as a deterioration of performance from adult-level vision (20, 21) [in kittens (22)]. This work, and many additional studies conducted during the 1970s and 1980s, also demonstrated quite dramatically that there is a sensitive period for visual development (that is, a time window during development within which the system is vulnerable to abnormal experience) which spans primarily the first 3 mo in cats, the first 1 to 2 y in macaques, and the first 5 to 7 y in humans [see Movshon and Van Sluyters (2), Movshon and Kiorpes (3), Harwerth et al. (23), and Kiorpes (24) for reviews]. Abnormal experience imposed during the sensitive period could have devastating consequences while, if initiated at progressively older ages, the resulting deficit was smaller or, in the limit, led to no deficit in visual acuity at all.

Animal Models of Amblyopia

Since amblyopia is a disorder that arises in association with imbalanced binocular vision during postnatal visual development in humans, it is important to study an animal model that has a similar developmental profile, has similar adult level vision, and has visual system organization that is similar to humans. Moreover, the model species should develop the disorder in ways that reflect the human condition. These criteria are best matched by nonhuman primates: in particular, macaque monkeys. It is well known that the visual system of macaque monkeys is structurally and functionally highly similar to that of humans (25, 26). Importantly, the development of visual function is similar as well (27–29). Fig. 1 shows a direct comparison of the time course of acuity development in human and nonhuman primates. The parallel development across species is clear, given the scaling of age to be 4 times faster in macaques: 1 wk of age in macaques is approximately equivalent to 1 mo in humans. Adult levels of acuity are also similar. A more general descriptor of spatial vision is the contrast sensitivity function (CSF). It is helpful to use the CSF when comparing vision of model species since it describes vision across a broad range of spatial scales rather than just acuity (fine resolution). A comparison of CSFs for a number of species, including human and nonhuman primates, is plotted in Fig. 24. Multiple examples of CSFs are shown for cats and rodents; the primate data are averages of 12 subjects each. There is substantial individual variation, and some across methods, but the distinction among species classes is clear. The fine scale resolution of macaques and humans is quite similar while humans typically have higher sensitivity at the peak (in the midfrequency range) (30–33). Interestingly, as illustrated in Fig. 2, the overall form of the CSF is similar across all species. Cats have comparatively lower acuity and fine scale sensitivity than primates, but they have reasonably high sensitivity in the lower spatial frequency range (34–36). Also

Fig. 1. Development of visual acuity in primates. Spatial resolution is plotted as a function of age for macaque monkeys and human infants. Age is plotted in weeks for monkeys (circles) and in months for humans (squares). Snellen equivalent acuity (as it relates to an eye chart) is shown on the right ordinate for reference. Monkey data are from Kiorpes (82); human data are from Mayer and Dobson (83). c/deg, cycles per degree. Reprinted from ref. 1, which is licensed under a [CC BY 4.0](#).

included on this plot is contrast sensitivity in mouse, currently a popular model species for studying some aspects of cortical plasticity, obtained by using psychophysical methods similar to those of the cat studies (37, 38). Mouse acuity is quite poor compared to the cat, approximately a factor of 10 lower, but, again, sensitivity is high at very low spatial frequencies—i.e., very coarse spatial scales.

These large differences in the range of spatial scale sensitivity across species, to a large degree, reflect differences in the size and structural organization of the eye. Fig. 2*B* shows contrast sensitivity data for the same representative species plotted as a function of cycles per millimeter on the retina rather than as a function of cycles per degree of visual angle; this representation is based on retinal distance. The primate data are the same as in Fig. 24; for the other species, a single individual example was chosen. Two features stand out from this plot. First, the range of scale sensitivity and resolution are essentially identical for the primates while the cat is intermediate and rodents are similar to each other (accepting methodological differences between studies) but comparatively lower than cats. Second, even the best behavioral data from rodents reveal substantially poorer resolution than the cat; the difference between them is larger than can be accounted for by retinal magnification. Therefore, there is a limitation on rodent vision that is imposed by later stages of neural processing. Overall, the comparative picture shows that macaques and humans share a similar range of spatial scale and contrast sensitivity while vision in the other species is shifted to progressively coarser ranges, largely but not completely in accordance with eye size and structure, thus reinforcing the nonhuman primate as a valuable model species.

In addition to characteristics of spatial vision, there are other substantial differences between the species highlighted in Fig. 2. Importantly, primates and cats have a central retinal specialization, albeit different ones. In cats, the area centralis forms a zone of increased photoreceptor density, and, in primates, the fovea is a zone where cone photoreceptor density is substantially higher than in more peripheral retina, which accounts for high acuity vision in the central retina. A sophisticated oculomotor system allows purposeful, rapid direction of the foveae to an object of interest. This system typically produces smooth conjugate movements of the 2 eyes, along with convergent and divergent movements, but it malfunctions in strabismus. Strabismus occurs naturally in macaques as well as in humans (39, 40). It occurs in albino cats as well;

Fig. 2. Comparison of behaviorally measured contrast sensitivity in 5 species used in vision research. (A) Contrast sensitivity conventionally plotted as a function of image spatial frequency (cycles per degree [c/deg]). Data are taken from 5 mice [Prusky and Douglas (37), and Histed, Carvalho, and Maunsell (38)], 3 rats [Birch and Jacobs (84), McGill, Douglas, Lund, and Prusky (85)], 3 cats [Bisti and Maffei (34), Murphy and Mitchell (36), Pasternak and Merigan (35)], and the means of 12 monkey and 12 human observers [Harwerth and Smith (32)]. (B) The same data plotted as a function of spatial frequency in units of retinal distance: i.e., transformed by the retinal magnification for each species. Retinal magnification data are taken from Hughes (human and cat) (86), Lapuerta and Schein (monkey) (87), and Remtulla and Hallett (mouse and rat) (88). Single representative cases are shown for each rodent species and cat to avoid clutter. c/mm, cycles per millimeter.

however, in this case, it is related to a genetic disorder. Rodents on the other hand produce only minimal movements of the eyes.

Another significant advantage of primate models and cats is their forward-facing eyes. This organization affords substantial overlap of the visual fields of the 2 eyes, creating a wide zone of binocular vision, which enables stereoscopic vision. Amblyopia is primarily a disorder of binocular vision, due to the impediment to vision in one eye setting up competition between the eyes' inputs to the cortex, thus compromising stereopsis and binocular function generally. While rodents have a zone of binocular overlap, it is extremely small due to their laterally placed eyes, and it is

largely restricted to upper field as would be valuable for predator detection (41). Rodent models of visual deprivation are based on studies of this small cortical segment of binocular overlap, but they have minimal binocular function. Since binocular vision and stereopsis are among the main functions that are deficient in amblyopia, it is important to study species that have good binocular function.

Over the last 60 y, many studies of experience-dependent visual cortical plasticity have been conducted, not all of which are especially relevant for understanding amblyopia. Animal models for these studies have included cats, ferrets, and rodents (rats and mice), as well as various primate species, although most studies have used nonprimate species. In the vast majority of these cases, plasticity is studied via monocular deprivation, which deprives the eye of all but the coarsest form stimulation and reduces the level of incoming light, providing highly abnormal visual input to the deprived eye and severely disrupting binocular visual experience. Fig. 3 shows CSFs that are representative of the more common forms of amblyopia (Fig. 3A and B) and monocular deprivation (Fig. 3C) in macaques. In visually typical macaques, the CSF for each eye is essentially identical. The curves from amblyopic macaques show a different pattern. Fig. 3A shows an example of strabismic amblyopia—resulting from surgical misalignment of the eyes—and Fig. 3B shows an anisometropic amblyope—arising from rearing with one eye blurred. These data show a pattern of loss in the amblyopic eye (filled symbols in Fig. 3A and B) that is similar to human amblyopia: reduced sensitivity at the finest spatial scales (highest spatial frequencies), which corresponds to the loss of acuity, along with reduced sensitivity at lower spatial scales in some cases as well (as in Fig. 3B). The monocularly deprived case reflects the result of deprivation initiated at ages ranging from 1 to 5 mo after birth (23), which is clearly profound visual loss that far exceeds that commonly seen in amblyopia. For comparison, contrast sensitivity

Fig. 3. Contrast sensitivity in amblyopia. CSFs are plotted for each eye of 3 monkeys and 1 human observer. Filled and open symbols represent amblyopic eye and fellow eye data, respectively. (A) Strabismic amblyopia [data from Kiper and Kiorpes (89)]. (B) Anisometropic amblyopia [data from Kozma and Kiorpes (90)]. (C) Early monocular deprivation [data from Harwerth et al. (23)]. (D) Human congenital cataract [data from Tytla et al. (91)]. c/deg, cycles per degree.

functions for a human with form deprivation amblyopia from cataract is also plotted in Fig. 3*D*. This form deprivation case represents one for which early removal of the cataract and subsequent patching, with optical correction, improved vision substantially; however, residual amblyopia is evident. Even in this case, this individual shows significantly poorer visual outcome than more typical amblyopia but much better vision than a monocularly deprived animal would typically show. Overall, the approach of using primate models of more typical forms of amblyopia, like strabismic and anisometropic, is valuable for further research elucidating the mechanisms underlying the disorder in humans. The monocular deprivation model results in substantially greater visual disorder than is representative of the human case. However, it is of significant value for understanding mechanisms underlying sensitive periods and cortical plasticity, in general.

Implications for Clinical Practice

As a result of the many animal studies showing dramatic visual loss following visual deprivation, clinical practice changed (42). Common, long-standing treatment approaches include patching (occlusion of the stronger eye), imposed blur on the stronger eye (often via daily instillation of atropine), and a variety of optical strategies for maintaining good alignment and clear vision to both eyes. Historically, interventions were delayed until after age 2 even when detected in infancy. Congenital cataracts are now removed from infants at very young ages, typically under 6 mo but before 2 y (<https://www.aao.org/disease-review/pediatric-cataracts-overview>), to provide the best opportunity for normal development of spatial vision and to preserve binocular vision to the extent possible (43, 44). Form deprivation amblyopia is now comparatively rare in most Western countries and progressive Asian societies in humans. However, in many other societies, access to health care—including vision care—is limited. In particular, early congenital cataracts may remain untreated for many years (45). Programs such as Project Prakash (45) have provided a mechanism through which many children have been treated at older ages. The degree of plasticity that remains in these children is heartening, but functional visual recovery remains limited (46–48). Recent prospective studies of amblyopia treatment in children show results that are consistent with animal studies of critical periods and treatment strategies, in which intervention and treatment at young ages produce the best visual outcomes in cases of unilateral vision loss [see Holmes et al. (49) and Koo et al. (50)]. Postsurgical treatment of form deprivation amblyopia, following cataract removal, has changed following a series of studies on the efficacy of various treatment options in macaques and prospective work in human infants. Odell et al. studied visual acuity development following early unilateral lensectomy in infant macaques, creating aphakia as a model for congenital cataracts (51). They tested a variety of treatment options, including combinations of fellow eye patching and various types of aphakic eye correction. The best outcomes were obtained by part-time patching and near-point correction, which allowed normal levels of visual acuity to be achieved with both eyes. Studies of amblyopia treatment outcomes in children show that part-time patching, sometimes in combination with near-activity, typically results in a good visual outcome which is comparable to full-time patching but reduces the risk of occlusion amblyopia (52–54). The problem of occlusion amblyopia was demonstrated dramatically in early kitten and monkey studies that used reverse deprivation as a proxy for patching (22, 23). Often, subnormal vision in both eyes was the result. Thus, the move toward shorter periods of occlusion is likely to be beneficial in general practice as recent randomized-controlled studies of amblyopia treatment have shown (6, 55). While the use of atropine “penalization” treatment to reduce the strength of input from the fellow, nonamblyopic eye as an alternative to patching had fallen out of favor, it has been revived of late and is now more commonly used as one of the standard treatment options (5). However, 2

noteworthy studies in nonhuman primates suggest that atropine use can cause the development of amblyopia (56) and exert effects on the natural process of emmetropization of the eye (57). It is hoped that this work will serve as a caution and lead to tempering the use of this approach.

Neural Correlates of Amblyopia

The nonhuman primate model for amblyopia, with its clear relevance to human amblyopia, has afforded the opportunity to directly investigate the neural mechanisms underlying amblyopia. Early ideas were based simply on diminished representation of the affected eye in the primary visual cortex (V1) (13–16, 58, 59). Fig. 4*A* shows eye dominance data for each of the different amblyopia types discussed above. Although, in each case, there is poor representation of binocularly driven neurons (eye dominance categories 3 to 5), not all types result in a dearth of neurons driven by the amblyopic eye (eye dominance category 1). Therefore, this idea fails to account for even the basic acuity loss in amblyopia, let alone the broad range of additional deficits associated with amblyopia. Subsequent investigations addressed the possibility that the abnormal visual experience affects the development of receptive field properties of individual neurons, in addition to their eye preference (60–63). These studies identified neural losses in spatial resolution and, in some cases, contrast sensitivity that were reminiscent of the behaviorally documented ones. However, the extent of the physiological deficits was insufficiently strong to account for the depth of amblyopia on an individual animal comparison (61, 64, 65), as shown in Fig. 4*B*. In each *Top* panel of Fig. 4*B*, the ratio of performance between the amblyopic and fellow eye is plotted for the location of the peak of the CSF as measured behaviorally (Fig. 4*B*, *Top Left*) and physiologically (Fig. 4*B*, *Top Right*). These ratios are not consistently different for the 2 eyes. In each *Bottom* panel of Fig. 4*B*, on the other hand, the physiological measure is compared with the behavioral one for peak spatial frequency (Fig. 4*B*, *Bottom Left*) and peak contrast sensitivity (Fig. 4*B*, *Bottom Right*). It is easy to see that, overall, the behavioral losses are larger than the neural ones. These results suggested several possibilities: that there was an amplification of those deficits in downstream visual areas or perhaps that de novo abnormalities arose in subsequent visual areas to account for the higher level perceptual losses that are present in amblyopia, beyond acuity and contrast sensitivity, or that there were additional neural abnormalities at the level of the primary visual cortex. There is now evidence to support each of those possibilities.

Experiments that targeted areas further along the visual pathway, downstream of V1, have reported larger deficits and abnormalities that extend beyond basic spatial receptive field properties. Chino and colleagues have found greater effects of strabismus on ocular dominance and spatial resolution in V2 neurons compared to V1 (63). V2 receptive fields also show spatial disorder in amblyopic animals and spiking variability that is higher than in the typical cortex (66, 67). Similarly, middle temporal (MT) area neurons show generally more dramatic abnormalities in strabismic and anisometropic amblyopia in that ocular dominance is strongly disrupted in what is typically a highly binocular area (68). In addition, populations of neurons in MT show losses in motion sensitivity that capture well behavioral deficits on an individual animal comparison. Moreover, in V2, de novo abnormalities have been found in the processing of higher order structural information that represents the organization of natural images (69). The latter result suggests that, developmentally, compromised and/or imbalanced information feeding forward from the amblyopic eye representation in V1 leads to additional deficits in downstream areas that process specific aspects of the visual image, perhaps accounting for the high-level perceptual losses that are characteristic of amblyopia.

Further studies of area V1 in amblyopic macaques have identified a number of important additional abnormalities that

Fig. 4. Physiological measurements in amblyopic macaques. (A) Eye dominance distributions from 5 populations of macaque monkeys raised either normally or with different forms of abnormal visual experience, as indicated at the top of each histogram. The normal control data and those from the anisometropic and strabismic groups are from Kiorpes et al. (61); data from the deprived group are from Movshon et al. (60); data from the atropine-treated group are from LeVay, Wiesel, and Hubel (16). (B) Comparison of interocular differences in performance as measured physiologically and behaviorally in individual amblyopic macaques. Data are represented as the ratio of performance between the amblyopic and fellow eye on each of the indicated metrics of the contrast sensitivity function. Data are from Kiorpes et al. (61) and Movshon et al. (60). Reprinted with permission from ref. 64, *The Visual Neurosciences*, © 2004 Massachusetts Institute of Technology.

reflect disruption of local circuitry in V1. A number of findings provide greater depth of understanding of the abnormal binocular organization and interactions that accompany amblyopia. Structurally, local wiring is disrupted such that metabolic activity in cortical columns driven by the amblyopic eye is altered (70–73). Although classically defined ocular dominance may be skewed away from the amblyopic eye and binocular representation is weak or absent, as shown in Fig. 4, significant residual interactions persist that are predominantly suppressive (62, 63). The appearance of this strong suppression actually results from the reduced excitatory drive from the amblyopic eye, altering the excitatory/inhibitory balance at the local circuit level (74). Moreover, the imbalance of interocular suppression that is evident psychophysically (75–79), such that the amblyopic eye is more strongly suppressed by the dominant eye than vice versa, is reflected in asymmetric suppression of inputs to binocularly activated neurons in V1 (80). Finally, a recent study shows that correlated firing patterns among populations of neurons driven by the amblyopic and fellow eye of strabismic amblyopes are different (81). Specifically, lower correlated firing among groups of neurons results in increased signal-to-noise ratios, which is advantageous for improving visual signal detection. The amblyopic monkeys were found to have higher

correlated firing among amblyopic eye neurons relative to fellow eye populations, which may contribute to the poorer sensitivity to visual stimuli of amblyopic eyes. These additional deficits found at the level of V1, together with downstream abnormalities, provide a new basis for understanding the broad range of perceptual losses in amblyopia.

Conclusion

Amblyopia is a significant sensory developmental disorder affecting many children around the world. Research with animal models, especially nonhuman primate models, has provided much needed insight into the brain mechanisms that underlie this disorder and has significantly impacted clinical practice. Additional translational research which builds on current knowledge is allowing development of novel therapies for amblyopia, with the aim of substantially reducing its incidence and impact.

Data Availability Statement

There are no original data in this article.

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