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Critical Periods in Vision Revisited

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Abstract

For four decades, investigations of the biological basis of critical periods in the developing mammalian visual cortex were dominated by study of the consequences of altered early visual experience in cats and nonhuman primates. The neural deficits thus revealed also provided insight into the origin and neural basis of human amblyopia that in turn motivated additional studies of humans with abnormal early visual input. Recent human studies point to deficits arising from alterations in all visual cortical areas and even in nonvisual cortical regions. As the new human data accumulated in parallel with a near-complete shift toward the use of rodent animal models for the study of neural mechanisms, it is now essential to review the human data and the earlier animal data obtained from cats and monkeys to infer general conclusions and to optimize future choice of the most appropriate animal model.

1. INTRODUCTION

The notion of critical periods in development emerged from the observation that brief exposure to certain events or chemicals during embryological maturation could alter neonatal morphology. Subsequently, the concept informed understanding of a diverse range of behaviors, including imprinting in chickens and ducks, socialization of domestic animals, the acquisition of bird song, and second language learning in humans. The periods of vulnerability typically had well-defined temporal boundaries surrounding a time of maximum sensitivity. That critical periods may exist in the development of human vision had long been suspected because of clinical experience with reduced visual acuity in one or occasionally both eyes in amblyopia. In amblyopia, a history of unclear and/or unequal images in the two eyes, as can be caused by opaque optical media from monocular cataract, unequal refractive errors (anisometropia), or a squint (strabismus), is the presumed precipitating cause. In a landmark book on strabismus, Claude Worth (1929) described the emergence of amblyopia in 1,729 children and the outcome of their treatment by procedures such as patching of the better eye that are still common today. Outcomes were good in young children and when the strabismus was of recent origin but were "seldom successful" (Worth 1929, p. 112) in children beyond seven years of age, a statement that was arguably the origin of two long-standing beliefs: that amblyopic vision cannot be ameliorated in older children and that critical periods in human vision have finite endpoints.

A biological basis for visual critical periods was uncovered soon after Hubel & Wiesel's (1962) landmark electrophysiological investigations of the visual response properties of cells in the adult cat's primary visual cortex (V1) and their anatomical organization. Certain properties were drastically altered after brief periods of abnormal early visual experience induced by surgical closure of one eyelid (Wiesel & Hubel 1963), a procedure referred to as monocular deprivation (MD). The first publication on this procedure (Wiesel & Hubel 1963) reported huge effects: In contrast to the 84% of cortical cells normally excited by visual stimulation of either eye, after early MD, very few cells could be excited at all through the deprived eye. The effects also appeared to be confined to a period in early postnatal life, since a three-month period of MD imposed on a single adult cat had no effect. Cats reared with equivalent periods of binocular eyelid suture [binocular deprivation (BD)] did not show the drastic alteration: Although cortical cells were not as responsive as usual and were abnormal in other ways, they were far more responsive than after MD (Wiesel & Hubel 1965). The contrasting results ruled out simple disuse as an explanation and led to the suggestion that the changes after MD arise from binocular synaptic competition between cortical afferents from the two eyes onto individual cortical cells.

Because of their long use across many species, including humans, we have focused this review on MD and BD. In addition to a review of the critical period of vulnerability of neurons in the central visual pathway to MD, we examine the link between the deprivation-induced changes in cortical physiology in animal models and the perceptual deficits exhibited by visually deprived humans. Deficits after MD and BD in humans are concordant for tests of visual acuity and other low-level visual tasks but are strikingly discordant for tests of higher-level vision (such as the perception of coherent motion and of global form) that are presumed to reflect operations of extrastriate visual cortical areas. Notably, the deficits on high-level visual tasks in humans are greater after BD than after MD, the precise opposite of the pattern observed on low-level visual tests. The contrary nature of the deficits on low- versus high-level visual tasks is inconsistent with a strict hierarchical cascade of increasing physiological deficits as imperfect input from the primary visual cortex is fed into the extrastriate cortex.

We also examine the relationships between vulnerability to deprivation and two potentially related development events. The most important is its possible relationship to the timing of

normal development of the visual pathway and visual behavior. Initial studies of animals suggested an overlap, but later work conducted on both animals and humans indicated that vulnerability to abnormal early visual input (the critical period for damage) can either extend well beyond the time course of normal development or be surprisingly shorter. A second relationship is between the timing of the critical period for damage and the timing of that for recovery in response to interventions introduced after the visual deprivation (the critical period for recovery).

Exploration of these issues was impeded in the past two decades by events that culminated in a drastic reduction in investigations of cats and monkeys as attention shifted to work on rodent models, in part because of barriers to continuing research on the former species. More importantly, rodent models allowed for the application of powerful molecular and genetic tools that could be used to manipulate individual neurons or classes of neurons to study the molecular mechanisms of cortical neural plasticity. At the same time, new studies of visually handicapped human adults suggest that some capacity for recovery may extend throughout the lifetime. The new data derived from humans and from studies on rodent models make this an opportune time to review both the concept of critical periods in visual system development as it has evolved and the important implications of the results of the new rodent and human studies for the nature of visual plasticity at various ages. Consideration is given first to cats and monkeys because of their historical role in defining the many concepts concerning critical periods in the visual pathways, the large magnitude of the effects observed, and the close similarity of the organization of their central visual pathways to those of humans. Summaries of the early studies and controversies are provided in several past reviews (Daw 2006, Kiorpes 2015, Mitchell & Timney 1984, Movshon & Kiorpes 1990, Movshon & Van Sluyters 1981, Rauschecker 1991, Sherman & Spear 1982, Teller & Movshon 1986).

2. ORGANIZATION

This review is divided into five parts and begins with three sections that summarize studies of the timing of critical periods in the visual pathways of various species with respect to MD, the most studied form of early visual deprivation. Section 3 reviews studies of vulnerability (damage) to the anatomical, physiological, and behavioral consequences of early MD imposed on cats, monkeys, rodents, and mustelids, followed by examination of data on the visual deficits experienced by humans that developed a monocular medial opacity (cataract) in early life. The age-related changes in vulnerability to MD are compared to profiles of development observed in typically reared animals. Section 4 describes insights gained from study of the differential effects of deprivation of one (MD) or both (BD) eyes. Section 5 describes the timing of critical periods for recovery from a prior period of MD followed by various experiential manipulations including reversal of the original deprivation. Sections 6 and 7 describe insights about the underlying mechanisms of early visual plasticity gained from molecular studies on rodents and suggestions for future research, respectively.

3. CRITICAL PERIODS FOR DAMAGE FROM MONOCULAR DEPRIVATION

In contrast to contemporary studies on rodents, for which there are few barriers to the use of many animals, extant data on the timing of visual critical periods in cats and monkeys are based on a few studies that employed small numbers of animals. The duration of the periods of deprivation differed widely among studies, and no single investigation included a sufficient number of deprivation conditions to allow a complete picture of the changing level of plasticity from birth to maturity; conclusions, therefore, depend on composite results from several studies. Moreover,

the sex of the animals was rarely mentioned, nor was information about the allocation of animals from different litters to the experimental conditions. These limitations reflect the small litter sizes; the long gestation times compared to rodents; the rapidly escalating costs of purchase, transport, and housing; and the original need to develop techniques to produce long-term and repeatable manipulations of the early visual input.

The sutured eyelids of cats and monkeys attenuate retinal illuminance by several log units, depending on the wavelength and degree of skin pigmentation (Crawford & Marc 1976), making the retinal image both dimmer and more lacking in spatial detail compared to the fellow eye. It is the degradation of patterned vision that is critical for the effects observed in the kitten's visual cortex (Blakemore 1976, Wilson et al. 1977). However, it is important to note that the degree of deprivation from eyelid suture may not be equivalent across species or even over time, depending on eyelid thickness, the presence or absence of a tarsal plate or nictitating membranes, and possibly the degree of pigmentation of skin and fur.

The enormous effects of early periods of MD were evident from relatively crude subjective measures of ocular dominance (OD) recorded immediately after termination of MD. The OD of each individual neuron was classified on a seven (or five)-point scale representing the relative ability of visual stimuli to elicit action potentials after monocular stimulation of each eye. Across species, the consequences of MD were assessed as the shift of the distribution of OD compared to the distribution observed in normal animals of the same age. The distribution was based on the OD of each sampled cell, which was categorized on the basis of subjective judgments of the frequency of action potentials generated in response to monocular stimulation of each eye in turn. The one exception was the comparatively recent documentation of the critical period of vulnerability to MD in ferrets (Issa et al. 1999), for which computers were used to allow a more objective assessment of OD.

The earliest studies did not distinguish between the effects in granular and in extragranular cortical layers, but most cells would have been encountered in the latter. Given the realization that vulnerability to MD lasts for a much shorter time in layer IV than in the extragranular layers, the effects of MD are now reported separately for the former, especially for monkeys. The data discussed below are for extragranular cortical layers unless otherwise stated.

3.1. Vulnerability to Monocular Deprivation in the Primary Visual Cortex of Cats

Hubel & Wiesel (1970, p. 419) gave the initial definition of the critical period for damage from MD in the cat's primary visual cortex: "Susceptibility to the effects of eye closure begins suddenly near the start of the fourth week, remains high until sometime between the sixth and eighth weeks, and then declines, disappearing finally around the end of the third month." However, this definition of the end of susceptibility rests on data from a single animal with 3 months of MD initiated at 4 months of age who was assessed 16 months later, after a long period with both eyes open during which some recovery could have occurred (Cynader et al. 1980). The pace of the decline in susceptibility is clearer in three later systematic studies (Daw et al. 1992, Jones et al. 1984, Olson & Freeman 1980) that imposed a constant duration of MD on kittens of different ages.

Data for the two studies (Jones et al. 1984, Olson & Freeman 1980) that employed the shortest constant period of MD (28 and 10 days, respectively) are displayed in **Figure 1**. Identification of an upper age at which vulnerability to MD in the cat's visual cortex is undetectable rests upon a single systematic study (Daw et al. 1992) that employed a 3-month period of MD beginning at 8–9, 12, or 15 months of age. Shifts of ocular dominance were evident in the extragranular layers but not in layer IV in kittens deprived at 8–9 months of age. Deprivation had no statistically

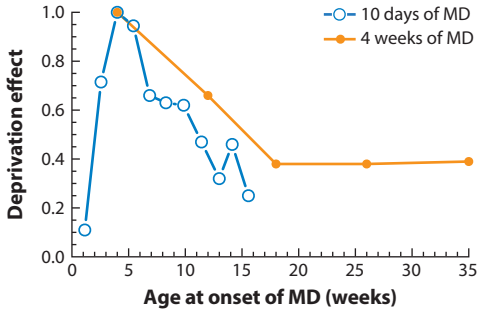

Figure 1

The effects of 10 days (*blue symbols*) or 4 weeks (*orange symbols*) of monocular deprivation (MD) on the ocular dominance of single cells sampled in the cat's V1 as a function of the age at which MD was imposed. The electrophysiological recordings were made in the cortex contralateral to the previously deprived eye. The effects of deprivation are expressed as a deprivation index based on the percentage of neurons dominated by the ipsilateral (nondeprived) eye normalized to the percentage of cells dominated by the ipsilateral eye in normal animals (N) [% cells dominated by the nondeprived eye – N]/[100% – N]. No effect of deprivation would yield a score of zero. Data for 10 days and 4 weeks of MD are replotted, respectively, with permission from Olson & Freeman (1980), for which N was derived from four normal kittens, and from Jones et al. (1984), copyright 1984 Society for Neuroscience, for which N was derived from seven adult cats.

significant effects in the extragranular layers in animals deprived at 12 months, from which the authors concluded that vulnerability to MD ends at approximately 1 year of age. Although not the primary objective of the study, additional relevant data came from cats that received a 3-month period of MD beginning at 4, 7, and 10 months of age (Cynader et al. 1980). The proportion of cells dominated by the nondeprived eye in the contralateral visual cortex fell gradually from 0.56 at 4 months to 0.42 at 10 months of age, a result consistent with the slow decline reported by Jones et al. (1984) and the conclusions drawn by Daw et al. (1992).

In summary, existing studies provide a fine-grained picture for the first 2 months, but the decline thereafter has not been captured with the same detail. The generally accepted view that the critical period of vulnerability to MD extends to approximately 8 months of age rests upon very limited data, namely, results from four animals reared with 1 month of MD (Jones et al. 1984) imposed at 8 months (35 weeks) and from animals reared with 3 months of MD (Daw et al. 1992) starting at 8–9 months ($N = 6$) or at 12 months ($N = 4$). Added to the uncertainty is the potential impact of factors such as the number of hemispheres and cortical layers sampled and whether data from different layers were combined. The overall paucity of data and the variability in duration of MD and ages studied, together with the lack of information on the sex and litter composition of the tested cats, are evident in **Table 1**.

3.1.1. Effects on different cell properties and anatomical locations. Arguably the quintessential demonstration that different functional properties of cortical cells have different critical periods is Daw's work (Daw & Wyatt 1976, Daw et al. 1978) showing the brevity of the critical period for modification of the directional selectivity of cortical neurons, which appears to end by six weeks of age. In an elegant within-animal demonstration, MD and its reversal (reverse occlusion) were combined with exposure to contours moving in a single direction, with the direction of motion switched at the time of reverse occlusion. After these manipulations, the majority of cortical cells were dominated by the eye that was open last but responded preferentially to the motion that was seen first (Daw et al. 1978). This is an elegant demonstration that the critical period for OD is longer than the critical period for directional selectivity.

Table 1 Studies of the critical period of vulnerability to the physiological effects of MD in V1 of various species

Study	Method	Animals[a]	Deprivation conditions (number)	Length of deprivation	Littermates	Sex	Hemispheres studied
Cats							
Hubel & Wiesel (1970)	SCR	15 (+6)	15	3 days–4 months	11	NM	1 (contralateral)
Jones et al. (1984)	SCR	16 (+7)	5	4 weeks	10+	NM	1 (contralateral)
Daw et al. (1992)	SCR	14 (+2)	4	3 months	NM	NM	2
Olson & Freeman (1980)	SCR	14 (+4)	11	10–12 days	NM	NM	1 (contralateral)
Monkeys							
LeVay et al. (1980)	SCR	10 (+16)	10	22 days–18 months	NA	NM	1 (5 contralateral, 4 ipsilateral); 2 (1)
Rodents (rats)							
Stafford (1984)	VEP	NM	4	14 days	NM	NM	2
Fagiolini et al. (1994)	SCR	14	4	10 days or 30 days	NM	NM	1 (contralateral)
Guire et al. (1999)	VEP	22 (+6)	4	5 days	NM	NM	2
Rodents (mice)							
Huang et al. (1999)	VEP	19	4	4 days	NM	NM	NM
Gordon & Stryker (1996)	SCR	25 (+35)	5	4 days	NM	NM	1 (contralateral)
Musceledae (ferrets)							
Issa et al. (1999)	SCR	44 (+9)	18	2, 7, or 14 days	NM	NM	2

[a]The numbers in parentheses indicate additional animals that were studied. In some studies, these were normal adults that provided comparison data for those that received a period of MD. One of the rodent studies (Gordon & Stryker 1996) included data from animals subjected to BD or alternating MD, while another (Fagiolini et al. 1994) also studied dark-reared animals. One kitten study (Hubel & Wiesel 1970) included data from animals that received a period of either binocular vision or reverse occlusion following a prior period of MD. The monkey investigation of LeVay et al. (1980) included 16 animals that were used solely for anatomical study or else received other forms of visual deprivation.

Abbreviations: MD, monocular deprivation; NA, not applicable; NM, not mentioned; SCR, single-cell recordings; VEP, visual evoked potentials.

Only one study has compared the timing of critical periods for the primary visual cortex and a higher cortical area, the lateral suprasylvian cortex (LS) (Jones et al. 1984). Susceptibility to MD peaked at approximately 4 weeks of age in both areas and declined at a similar rate over the following 3 months. However, the decline thereafter was faster in area LS (see **Figure 1**): The primary visual cortex remained susceptible to MD past 35 weeks of age, but area LS in the same animals was resistant to the same duration of MD beyond 18 weeks of age.

3.1.2. Effects on low-level vision. Studies of low-level vision complement the physiological studies. The immediate effects of early MD are so profound that the kittens appear not to possess any form vision; measurable acuity emerges only over the subsequent weeks (Giffin & Mitchell 1978, Mitchell 1988, Mitchell et al. 1977). Substantial recovery of acuity of the deprived eye was observed even following periods of MD that extended from near birth to 4 months of age (Cynader et al. 1980). With increasing duration of MD, the pace of recovery is slower and the ultimate acuity lower (Giffin & Mitchell 1978, Mitchell 1988). When the recovery is binocular, there is no loss of grating acuity of the nondeprived eye.

The profound deficits following extended MD in kittens can be contrasted to the effects of bilateral ablation of both cortical areas 17 and 18, which reduces visual acuity by only approximately an octave (Berkley & Sprague 1979, Mitchell 2002, Mitchell & Lomber 2013). Particularly interesting is the case of an animal that received MD prior to the bilateral ablation of cortical areas 17 and 18 at 4 months of age: The acuity of the nondeprived eye was reduced by just less than an octave, but the deprived eye initially appeared blind and showed a slow and very incomplete recovery of acuity similar to that observed in animals that had not received a cortical lesion (Mitchell & Lomber 2013). It appears that the visual structures (e.g., extrastriate and subcortical) that support vision following ablation of cortical areas 17 and 18 are just as affected by MD as the primary cortical visual areas.

3.1.3. Effects of previous experience. An early discovery was that placing the cat in darkness from birth extends the critical period for damage from MD (Cynader 1983, Cynader & Mitchell 1980). Later studies (Mower 1991, Mower & Christen 1985, Mower et al. 1981) showed that darkness slows the entire time course of the critical period of cortical damage from MD, i.e., both the rise and the decline of the shifts of OD that follow a fixed period of MD imposed at different ages. Additionally, darkness imposed after 6–8 weeks of normal vision also extends the decline of vulnerability to periods of MD (Mower 1991). Binocular eyelid suture does not change the timing of the critical period, a finding indicating that darkness changes cortical plasticity through the complete absence of light and hence of visually driven neural activity in the visual pathways (Mower et al. 1981), likely through changes to the molecular pathways regulating the level of plasticity in the central visual pathways (Levelt & Hübener 2012).

3.1.4. Insights from normal development. In general, cell properties and anatomical features in the primary visual cortex develop over a period shorter than that during which abnormal visual experience can cause disruption. One example of this is the development of binocular interactions between cortical cells measured by phase interactions in response to dichoptic presentation of drifting sinusoidal gratings to the two eyes (Freeman & Ohzawa 1992). Phase interactions of cortical cells mature to adult levels between 3 and 4 weeks of age, thereby providing a possible substrate for the observed early emergence of behavioral stereoscopic vision (Timney 1981). MD can modify these phase interactions long afterward, namely, until at least 10 months of age (Freeman & Ohzawa 1988).

3.1.5. Insights from reverse occlusion. In the early 1970s, studies revealed that the physiological consequences of early MD are not necessarily permanent. In the first systematic study of this manipulation, the fellow eye was occluded at the time that normal visual input was restored to the deprived eye, a procedure known as reverse occlusion (Blakemore & Van Sluyters 1974). While 9 weeks of reverse occlusion initiated at 5 weeks of age resulted in a complete shift of OD to favor the eye that was initially deprived, the same period of reverse occlusion initiated at 14 weeks of age produced no change of cortical OD. A subsequent study revealed that most of the shifts of OD occurred in just three weeks and that, if MD is initiated at the peak of the period of vulnerability at approximately 4 weeks, then it was possible to shift OD a second time by again closing the initially deprived eye so as to once again favor the eye that was open first (Movshon 1976). Although reverse occlusion promotes expansive shifts of cortical OD to favor the initially deprived eye, the change occurs at the expense of the fellow eye, which now dominates a minority of cells (Giffin & Mitchell 1978, Mitchell 1988, Mitchell et al. 1977). Moreover, the recovery of the acuity of the deprived eye is often not permanent (Mitchell 1991, Murphy & Mitchell 1987, Mitchell et al. 1984). Some, but not as much, recovery occurs following mere restoration of normal visual input

to the deprived eye even as late as 2 months of age (binocular recovery) (Mitchell et al. 1977, Olson & Freeman 1978) and without a reciprocal drop for the fellow eye, which nevertheless still dominates a higher proportion of cells. Later experiments suggested that different molecular mechanisms may underlie the original effects of deprivation and the subsequent recovery, a conclusion supported by studies that suggest separate critical periods for the effects of MD and the recovery that can occur following various experiential manipulations (Daw 1998, 2006).

Optimum behavioral outcomes occur following a combination of binocular recovery and reverse occlusion: Stable normal acuity of both the deprived and nondeprived eye can be achieved by a daily regimen of occlusion of the fellow eye for 50–70% of the day combined with binocular visual exposure for the remainder of the day (Mitchell 1991, Mitchell et al. 1986).

3.2. Vulnerability to Monocular Deprivation in the Primary Visual Cortex of Monkeys

The studies described below used Old World monkeys, most frequently rhesus macaques (*Macaca mulatta*), unless otherwise specified. The initial study (Baker et al. 1974) revealed that MD beginning at either 7 or 35 days of age and extending to 22 months produced extreme shifts of OD toward the nondeprived eye. Later investigations (Crawford et al. 1975; Von Noorden & Crawford 1978, 1979) by the same group with shorter periods of MD initiated at different times in the first two postnatal months revealed progressively larger shifts with age. However, no studies have employed a constant duration of deprivation over a wide range of ages to allow clear visualization of the declining vulnerability of the primary visual cortex to MD with age. Only a single study provided physiological data on MD begun at different ages but for various durations (LeVay et al. 1980). The data from this study are plotted in **Figure 2** in a form similar to the data for cats plotted in **Figure 1**. As in **Figure 1**, the effects of MD are plotted as a deprivation index against data from normal adult and juvenile monkeys published in a prior study (Hubel et al. 1977, figure 1).

Comparison of the data displayed by gray and colored symbols in **Figure 2** indicates that the effects of very brief periods of MD beginning in the first week are very profound and no less so than those of longer periods of MD beginning at the same age, a pattern suggesting that vulnerability to MD is greatest in the first month. Another interesting result is the apparent lack of any physiological recovery in an animal (M195) that received a 9-day period of MD from P21 to P30 days followed by 4 years of binocular visual exposure, although a strabismus that developed postdeprivation may have interfered with recovery. A decline in vulnerability to MD with age is suggested by the smaller effect observed in the single animal deprived at 12 months for 1 year. Very limited data from a single monkey (M280) deprived at 6 years for 18 months provide the only indication of when vulnerability declines to negligible levels. Data from a *Cynomolgus* monkey (*Macaca fascicularis*) that received MD from 11 to 16 months of age (Blakemore et al. 1978, animal F7603) also show a sizeable shift of OD (0.45 deprivation index, based on a single normal control monkey), similar to the macaque deprived at 12 months (see **Figure 2**).

3.2.1. Effects on different cell properties and anatomical locations. As in cats (Beaver et al. 2001, Daw et al. 1992, Mower et al. 1985, Shatz & Stryker 1978), the effects of MD decline considerably faster in layer IV, the input layer for neurons from the LGN, than in the extragranular layers that project to other cortical areas (Blakemore et al. 1978, 1981; LeVay et al. 1980). For example, MD alters anatomical ocular dominance in monkey layer IVC only minimally by 10 weeks of age, but neurons in the extragranular layers are still very vulnerable at 1 year of age (LeVay et al. 1980). Data from LeVay et al.'s (1980) monkey 240, which received a period of MD at 2 days of age and then reverse occlusion at 3 weeks for 9 months, indicated that layer IVCA, which receives

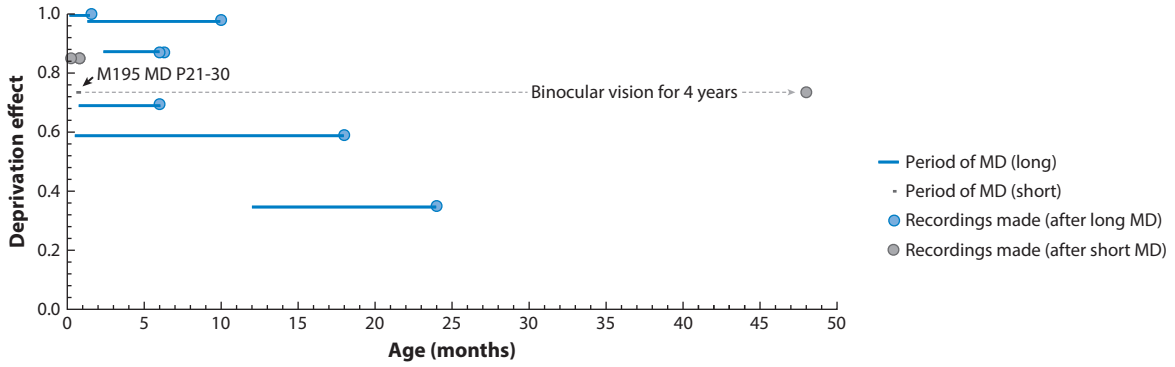

Figure 2

The electrophysiological effects of various periods of monocular deprivation (MD) initiated at different ages in the extragranular layers of the primary visual cortex of macaque monkeys (data taken with permission from LeVay et al. 1980). The deprivation effect is displayed as a deprivation index calculated from the seven-group ocular dominance histograms published by LeVay et al. (1980). The index is calculated as the percentage of cells dominated by the nondeprived eye with respect to the cerebral hemisphere in which the recordings were made (contra- or ipsilateral to the deprived eye) in relation to the percentage of cells dominated by this eye in normal monkeys. For recordings made in the left hemisphere, contralateral to the deprived right eye, the deprivation index is calculated as [(% cells in Groups 5–7) – N_i]/[100 – N_i]; for recordings made in the ipsilateral hemisphere, where N_i and N_c are, respectively, the % of cells in Groups 5–7 (54%) and Groups 1–3 (46%) in normal monkeys, the deprivation index is calculated as [(% cells in Groups 1–3) – N_c]/N_c. The values for N_i and N_c for normal monkeys were calculated from the composite ocular dominance histogram published by Hubel et al. (1977, figure 1; data taken with permission) from data accumulated from 17 normal adult and juvenile monkeys. As with the data for cats displayed in **Figure 1**, the index adopts a value of zero when the ocular dominance histogram is not skewed from the distribution observed in normal animals. Data for seven animals (M282, M206, M365, M202, M157, M307, and M185) that received long periods of MD and that were recorded immediately upon termination of the deprivation are shown by blue symbols at the end of the period of MD, and the duration of the deprivation is indicated by the solid lines. Data from three monkeys, depicted with gray circles, show the effects of very short periods of MD of 9 to 43 days duration. For two of these animals (M164 and M308), electrophysiological recordings were made immediately following the period of MD, but for the third animal (M195), cortical recordings were made four years after the period of MD (from P21 to P30), throughout which time both eyes were open. This animal developed a strabismus that may have reduced the extent of physiological recovery.

input from magnocellular layers of the LGN, was dominated by the eye that was open during the initial period of MD, while layer IVCB, which receives input from parvocellular layers, was dominated by the eye open during the subsequent reverse occlusion. This finding implies that vulnerability to MD may decline faster in the magnocellular-recipient layer IVCA than in the parvocellular-recipient layer IVCB.

3.2.2. Effects on low-level vision. Some insight about the end of vulnerability can be gained from behavioral measurements of monkeys that received 18 months of MD beginning at different ages (Harwerth et al. 1986). As shown in **Figure 3**, when initiated at or before 5 months, MD resulted in an approximately 2-log-unit (100-fold) difference between the acuities of the two eyes. However, when it began at 6 months, there was only a sixfold difference, and thereafter, the effects of MD declined gradually such that, when MD began after 1 year of age, the difference between the two eyes, although measurable, was very small. However, the conclusion that vulnerability to MD ends at approximately 1 year may underestimate the duration of plasticity because there may have been some recovery during the long period of behavioral testing. Moreover, the timing of the critical period in these animals varied with the type of visual function studied. Functions mediated at the retinal level, such as scotopic and photopic spectral sensitivity, were affected by MD only at earlier ages, while vulnerability extended longer for functions mediated at the cortical level, such as contrast sensitivity functions for sinusoidal gratings.

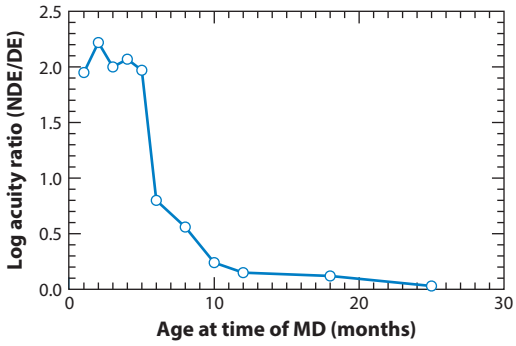

Figure 3

The behavioral consequences of an 18-month period of monocular deprivation (MD) imposed on 11 macaque monkeys at various ages. The ordinate shows the logarithm ($\log_{10}$) of the ratio of the acuities of the two eyes extrapolated from measurements of contrast sensitivity functions. Data taken by permission from Harwerth et al. (1986).

3.2.3. Insights from normal development. Differences in the timing of vulnerability to MD versus the timing of normal development are large. A particularly striking example is OD in layer IV of the primary visual cortex of macaque monkeys, where, despite the fact that neurons appear anatomically fully segregated at birth prior to any visual experience (Horton & Hocking 1996), this mature pattern can be disrupted to favor the nondeprived eye when MD is imposed at up to 10–12 weeks of age (Horton & Hocking 1996, LeVay et al. 1980).

3.2.4. Insights from reverse occlusion. Like the data on vulnerability to MD, studies of the extent of recovery from MD promoted by reverse occlusion are limited in number and employed very few animals and rearing conditions (Blakemore et al. 1978, 1981; LeVay et al. 1980; Von Noorden & Crawford 1978). The two studies (Blakemore et al. 1978, 1981), conducted on *Patas* or *Cynomolgus* monkeys, that followed the design used earlier with kittens (Blakemore & Van Sluyters 1974, Movshon 1976) are the most informative. As with the earlier kitten studies, the four animals received an initial period of MD very early at P1 or P2 days of age (three animals) or at P21 days (one animal) and received comparable durations of reverse occlusion (16 to 21 weeks). Consequently, there was a confound between the age when the animal began reverse occlusion and the duration of the prior period of MD. The MD-induced shifts in OD were reversed completely by the long period of reverse occlusion when it started at 5.5 weeks but only by 50% when it started at 8 weeks, by even less when it began at 9 weeks, and not at all after 9.5 months of age (Blakemore et al. 1978), an age well before an effect of MD is no longer evident (**Figure 2**). As with kittens, the effects of reverse occlusion at 4 weeks of age occur rapidly and appear complete in 2 weeks (Blakemore et al. 1981), but thereafter, the limited extant data suggest that the efficacy of reverse occlusion declines to zero well before the age at which the cortex is no longer vulnerable to MD.

3.3. Vulnerability to Monocular Deprivation in the Primary Visual Cortex of Rodents and Mustelids

Because the geniculostriate pathways of rodents are predominantly crossed [by as much as 95% in mice (Seabrook et al. 2017)], the effects of MD can only be assessed meaningfully in the cortical hemisphere contralateral to the deprived eye. Unlike in cats and monkeys, which demonstrate a near total absence of responsiveness to stimulation of the deprived eye in the binocular zone of the

contralateral hemisphere, in rats after moderate periods of MD, approximately 50% of neurons can still be excited by input to the deprived eye (Fagiolini et al. 1994, Maffei et al. 1992), and in mice, this percentage is even higher (e.g., Dräger 1978, Gordon & Stryker 1996). Deficits in the visual acuity of the deprived eye in rodents are also considerably smaller than in cats and monkeys (Prusky & Douglas 2003, Prusky et al. 2000).

Vulnerability to MD in mice, as assessed by shifts in OD of cortical neurons, begins at around eye opening, at P14–15, peaks at approximately P28, and ends at approximately P32 (Gordon & Stryker 1996), a profile similar to that determined from visual evoked potentials (VEPs) (Huang et al. 1999). The one study in rats (Fagiolini et al. 1994) employed a limited number of deprivation conditions, but these conditions were sufficient to show that vulnerability to MD begins at around eye opening at P12, peaks approximately 10 days later, and disappears completely between P33 and P45. A later study using VEPs (Guire et al. 1999), however, found that MD may affect the rat's visual cortex even at 6 weeks of age.

A comparison of the findings for mice and rats suggests that the period of vulnerability to MD may be somewhat shorter in the former than in the latter. However, these studies provide only a coarse picture because of their small number and, even within the studies, the limited number of animals and conditions, factors that are not very different from the drawbacks of earlier studies conducted on cats and monkeys. The possible contributions of litter differences and sex have been universally ignored, possibly as a reflection of an unstated consensus that such effects, if they exist, are very small.

There has also been a small but impressive set of studies on ferrets, a domesticated form of the European polecat and a member of the family Mustelidae. The interest in ferrets was prompted by the relative immaturity of their visual pathways at birth; the adults' complex visual pathway, which includes OD columns in the visual cortex (Ruthazer et al. 1999); and the eye-specific lamination of the LGN. Issa et al. (1999) studied a notably large number of animals and conditions and used computers both to automate the generation of the stimuli and to assess the neural responses of the two eyes. Following a demonstration that 2+ weeks of MD produces large shifts of OD, they employed short 2-day or 7-day periods of MD to probe the profile of the critical period. MD produced no discernable shifts of OD when imposed at or before P21 but large biases thereafter that peaked when imposed 7–10 days after the time of natural eye opening at P32. After P42, the effects of MD declined gradually to reach negligible values when initiated at P70 or between P70 and P100. Even after those ages, unlike in cats and monkeys, MD reduced the proportion of cortical cells that were binocular (i.e., could be excited by visual stimulation of either eye) without shifting the balance of OD. Indeed, Issa et al. (1999) noted that the proportion of cells classified as binocular is reduced by MD even when imposed on adult ferrets. The cortical plasticity thus revealed in older animals may underlie the physiological recovery observed in ferrets following termination of the period of MD at ages beyond the critical period for OD damage (Liao et al. 2004).

3.3.1. Effects on low-level vision. The effects on visual acuity of MD extending throughout the critical period of vulnerability of the visual cortex have been documented in both Long-Evans rats and C57Bl6 mice by placing the animals in a water box and requiring them to escape from the water by swimming toward a grating rather than a uniform gray field in a two-choice maze apparatus (Prusky et al. 2000). The acuity deficit was surprisingly small in both species, with a reduction of less than an octave, from approximately 0.5 to 0.32 cycles/deg in mice (Prusky & Douglas 2003) and from approximately 1.0 to 0.67 cycles/deg in rats (Prusky et al. 2000). This reduction is much smaller than those observed in either monkeys or cats. As illustrated in **Figure 3**, the acuity of the deprived eye of monkeys is reduced by 1.95 to 2.22 log units (a factor of 90 to

165), or between 6 and 7 octaves following an 18-month period of MD initiated within the first 5 months of life (Harwerth et al. 1986). In cats, long periods of MD initiated near the time of natural eye opening and lasting until 8 to 45 months of age result in profound deficits that range from complete loss of form vision in five animals to an acuity of between 0.16 and 0.8 cycles/deg (or a loss of between 3.2 and 5.5 octaves) in three other animals (Mitchell 1988).

3.3.2. Effects of previous experience. Prior experience with MD can alter the cortical response to subsequent MD (Hofer et al. 2006). For example, an early 4–10-day period of MD introduced at the peak of the critical period in mice apparently enhances the effects of a subsequent period of identical MD in adulthood. The shifts of OD produced by the second period of MD were of the same extent as the first shifts but occurred faster, within 3 days as opposed to 5 days, and were specific to deprivation of the same eye.

3.4. Critical Period for the Effects of Monocular Deprivation on Low-Level Vision in Humans

Analogous to research on lid suture in animals, research in humans has investigated dense unilateral cataracts that blocked all patterned input to the retina until the cataractous crystalline lens was removed surgically and the lost focusing ability replaced with a compensatory contact or intraocular lens. Early studies summarized in a classic book (Von Senden 1960) revealed that, as in cats and monkeys, long-term MD from cataract beginning early in life has devastating effects that are not seen if the deprivation begins in adulthood. Monocular cataracts are a powerful model for studying the effects of MD in humans, but they depend on the natural distribution of onset times and deprivation durations, and their interpretation depends on evidence that the cataract was dense. In this section, we restrict coverage to studies that documented complete blockage of patterned visual input before treatment.

In the 1980s, encouraging clinical outcomes were reported for congenital cases treated at an early age (typically 2–6 months) and studied longitudinally over the first year of life. Despite an initial reduction in the treated eye's acuity, large improvements over the next few months seemed to signal complete recovery (Birch et al. 1986; Jacobson et al. 1981, 1983). However, longer follow-up revealed emergent and persistent acuity deficits (Birch & Stager 1986, Birch et al. 1986, Lewis et al. 1995), which were smaller when treatment (surgery and optical correction) occurred earlier (for treatment before 6 weeks, see Birch & Stager 1996, Birch et al. 1993; for treatment before 8 weeks, see Birch et al. 1998; for treatment before 3 months, see Ma et al. 2017). Studies of spatial contrast sensitivity yielded similar results: an overall reduction in sensitivity and large losses at high spatial frequencies, with better outcomes if treatment occurred before 6–8 weeks of age (Birch et al. 1993, 1998; Ellemberg et al. 2000).

The benefit of early treatment suggests that the effects of MD may differ between early and middle infancy (before versus after 1.5–3 months). Studies of children with MD that began at different ages indicate that the critical period for damage to the development of acuity, however, extends throughout childhood. With later onset, the deficits in acuity are smaller, but they persist so long as the deprivation began at any time in the first approximately 10 years of life, well past the end of normal development (Lewis & Maurer 2005, Maurer 2017, Vaegan & Taylor 1979; see Taylor et al. 1979 for similar findings for bilateral congenital cataract).

Studies of other visual capabilities demonstrate different periods of vulnerability (see **Table 2**). Unlike acuity, sensitivity to global motion is damaged by MD only when the deprivation begins in the first 6–12 months or so of life. Optokinetic nystagmus tested monocularly has an intermediate pattern: It is asymmetrical at birth, elicited more readily by patterns moving from the temporal

Table 2 Age at which various visual functions emerge and become adult-like and ages during which they are damaged by abnormal visual experience, show subsequent recovery from binocular visual exposure, and show additional recovery with targeted interventions

Visual function	Normal development		Critical period			References
	Emergence	Adult-like	Damage	Recovery (binocular)	Recovery (intervention)	
Acuity	Birth	6–7 years	0–10 years	2 years	Unlimited?	Maurer & Lewis (2001), Lewis et al. (1985, 1989); Jeon et al. (2012) for BD
Spatial contrast sensitivity for low spatial frequencies	Birth	7 years	Unknown	7 years	Unlimited?	Atkinson et al. (1979), Ellemberg et al. (1999); Maurer et al. (2006) and Jeon et al. (2012) for BD
Spatial contrast sensitivity for high spatial frequencies	Postnatal	7 years	Unknown	<5 years	Unknown	Maurer & Lewis (2001), Ellemberg et al. (1999); Maurer et al. (2006) for BD
Peripheral light sensitivity	Birth	>7 years	0→13 years	Unknown	Unknown	Maurer et al. (1991), Bowering et al. (1997)
Binocular vision	3 months	7 years	1–3 years	Unknown	Unknown	Braddick et al. (1983), Birch et al. (2008); Banks et al. (1975) for strabismus
Symmetrical optokinetic nystagmus	3–6 months	~24 months	0–18 months	Unknown	Unknown	Lewis et al. (1992a, 2000); Lewis et al. (1989) for BD
Global motion	<7 weeks but mediation reorganized after 4 months	12 years	0–approximately 1 year	Unknown	Unlimited?	Wattam-Bell et al. (2010), Hadad et al. (2015), Ellemberg et al. (2002); Jeon et al. (2012) for BD

Abbreviation: BD, binocular deprivation.

toward the nasal field than those moving in the opposite direction, and becomes symmetrical for large patterns by 3–6 months of age and for smaller patterns by approximately 2 years of age (Lewis et al. 1992a, 2000). In humans, as in cats (Hoffmann 1979), visual deprivation (for a study of BD, see Lewis et al. 1989) prevents the development of symmetrical optokinetic nystagmus if the onset is anytime in the first 18 months of life, likely by interfering with the development of cortical input to one or more midbrain structures within the accessory optic system. These examples illustrate that, as in monkeys (Harwerth et al. 1986), there are multiple critical periods during which visual deprivation can damage subsequent visual perception.

The removal of the cataractous lens and compensatory contact lens or intraocular implant leaves the patient with focus at a fixed distance, with objects that are closer or farther becoming increasingly out of focus. To offset the fixed focus, patients are also often given bifocal or varifocal glasses either later in infancy or before they enter school. Nevertheless, the fixed focus raises the possibility that emerging deficits are caused by the continuing mild deprivation and not, or not just, by the initial complete pattern deprivation. Studies of rhesus monkeys who suffered no visual deprivation but had the natural lens removed at birth, rendering them aphakic, then had the lens replaced with an extended-wear contact lens or intraocular implant, rendering them pseudophakic, allow an assessment of the effects of this continuing mild deprivation (Wilson et al. 1991). Aphakic monkeys without compensatory correction develop very poor acuity, as would be expected from the severely blurred images that one eye received from birth. So do pseudophakic monkeys, even when the optical correction co-occurs with occlusion of the fellow eye, although the outcomes are better than those for uncorrected aphakic monkeys. These results indicate that the fixed focus of human patients after treatment for monocular congenital cataract may contribute to later deficits.

However, the contribution appears to be small given that rhesus monkeys in which monocular cataract is simulated at birth by an occluding contact lens or diffuser, followed by the removal of the lens and its replacement with multifocal correction, can achieve normal grating acuity (Boothe et al. 2000).

Patterns of findings in the human literature also suggest that the main amblyogenic agent is the initial pattern deprivation, and not the continuing mild deprivation from pseudophakia. On some outcome measures, patients who develop cataracts postnatally and receive the same treatment as congenital patients nevertheless achieve normal vision (e.g., sensitivity to global motion if the onset of deprivation was after approximately 6 months and symmetrical optokinetic nystagmus if the onset was after 18 months; see **Table 2**). In addition, the normal acuity of congenital patients at 1 year of age indicates that poor optics do not limit the development of cortical connections at that stage. In addition, the differential outcomes after MD versus BD (see Section 4.2) cannot be explained by continuing mild deprivation after treatment because both are treated in the same way, i.e., both types of patient are pseudophakic.

These studies also illustrate an additional point: The deficits after early MD are often sleeper effects that emerge long after the deprivation has ended (Maurer et al. 2007). For example, after treatment for monocular congenital cataract, grating acuity begins to improve rapidly, with measurable improvement after just 1 hour of patterned visual input (Maurer et al. 1999) and attainment of normal levels by 12 months of age if there has been extensive patching of the nondeprived eye (Jacobson et al. 1981, 1983; Lewis et al. 1995). Beginning at approximately 2 years of age, the acuity of the treated eyes fails to keep pace with the continuing improvements in visually normal children, leading to deficits in their final acuity. Thus, visual deprivation in the first few months of life prevents the normal improvement in acuity after 2 years of age—a sleeper effect.

3.4.1. Insights from normal development. **Table 2** illustrates that the timing of critical periods of vulnerability to MD is unrelated to the timing of normal development. For example, visual acuity is measurable at birth and improves over the first 6–7 years, at which point it is adult-like, but MD any time during the first 10 years of life leads to subsequent defects in the treated eye, a pattern implying that visual input is necessary not only for the development of mediating neural networks over the first 6–7 years, but also for their consolidation or crystallization for several years thereafter (Maurer 2017). Sensitivity to the direction of motion emerges at approximately 7 weeks of age, with its neural mediation reorganized after 4 months of age, and continues to improve until approximately 12 years of age (Hadad et al. 2012, Wattam-Bell et al. 2010). Nevertheless, it is damaged by deprivation ending before 7 weeks of age and not by deprivation beginning any time after approximately 6–12 months (Ellemberg et al. 2002). These examples illustrate that the timing of vulnerability to MD cannot be predicted from the period during which normal development occurs.

3.4.2. Insights from reverse occlusion (i.e., patching). Deficits in acuity after monocular congenital cataract that was treated early were smaller when there had been extensive patching of the nondeprived eye from the time of treatment (until mid-childhood), a pattern that is already visible by 12 months of age (Drews-Botsch et al. 2012, Lewis et al. 1995). Later spatial contrast sensitivity is also better if there was extensive patching of the nondeprived eye during early childhood (Ellemberg et al. 2000). Unlike in most studies of reverse occlusion in animals, the patching occupied large percentages of waking time but also allowed binocular input each day, mimicking the optimal regimen discovered in kittens. When the onset of deprivation is postnatal because of traumatic cataract, the outcome for acuity was also better with more extensive patching of the fellow eye (Vaegan & Taylor 1979).

4. DIFFERENTIAL EFFECTS OF MONOCULAR VERSUS BINOCULAR DEPRIVATION

4.1. Cats and Rodents

For low-level visual functions, the deficits after MD are larger than those after BD of comparable duration. In kittens, both darkness and binocular lid suture from near birth produce behavioral effects that are initially as dramatic as those affecting the deprived eye after MD: Kittens at first appear blind (Giffin & Mitchell 1978; Mitchell 1988; Timney et al. 1978; Wiesel & Hubel 1963, 1965), then slowly improve at a rate that is slower after longer deprivation. Kittens dark reared to 4 months of age can eventually recover normal grating acuity, but animals deprived longer, to 6, 8, or 10 months of age, attain progressively lower acuity (Mitchell & Timney 1984, figure 12; Mower et al. 1982; Timney et al. 1978). Contrast sensitivity of a cat dark reared to 6 months of age was reduced at all spatial frequencies by a factor of approximately two (Blake & Gianfilippo 1980). The levels of acuity and contrast sensitivity that are recovered are lower after binocular lid suture than after dark rearing, but unless it is very prolonged, the final deficits of either type of BD are smaller than those caused by MD (Giffin & Mitchell 1978, Mitchell 1988, Mitchell & Timney 1984, Mower et al. 1982, Timney et al. 1978). Similar results from rodents show that the acuity deficits following MD are slightly larger than those following equivalent periods of BD (Prusky & Douglas 2003, Prusky et al. 2000). This pattern for low-level vision illustrates that the adverse outcomes after MD result not just from disuse but also from unfavorable competitive interocular interactions.

4.2. Humans

The impact of congenital cataracts that were bilateral, dense, and diagnosed early in infancy has been confirmed in studies from three labs, those of Daphne Maurer and Terri Lewis (e.g., Lewis & Maurer 2009, Maurer 2017), Eileen Birch (e.g., Birch & Stager 1996), and Brigitte Röder (e.g., infants with early diagnosis and treatment) (Bottari et al. 2015), and to a lesser extent from the lab of David Taylor (e.g., Vaegan & Taylor 1979). In these studies, the preop blockage of all patterned vision was confirmed by criteria such as the baby's inability to fixate or follow a light and the ophthalmologist's inability to visualize the retina through the cataract by ophthalmoscopy. In every case, the diagnosis was at or near birth. Recently, other studies have appeared from research in India (e.g., Bottari et al. 2018, Ganesh et al. 2014, Gogate et al. 2014, Ostrovsky et al. 2009, Paryani et al. 2012) and Africa (e.g., De Smedt et al. 2016, Gogate et al. 2016, McKyton et al. 2015). These studies include children discovered to have cataracts at a later age that were labeled congenital, sometimes despite the absence of confirming medical records. Like in early case studies, some of these children likely had some patterned visual input during infancy. Indeed, when Gogate et al. (2014) used medical records to divide their sample from Maharashtra, India into a group with a cataract that was congenital (i.e., diagnosed before 6 months) versus a group with a cataract that was developmental (i.e., diagnosed after 7 months), they had to classify nearly half (116 of 246) as congenital/developmental because there were no available records before the child presented for surgery at an average age of 9 years. In addition, when measurements of vision had been made before the surgery, some of the putatively congenital patients had measurable vision. For example, one recent study found measurable preop contrast sensitivity in all 10 of the children studied, aged 8 to 16, with a median high spatial frequency cutoff of 1.8 cycles per degree (McKyton et al. 2015). Despite this measurable preop pattern vision, the children were described as suffering from dense bilateral cataracts from early infancy. These cases are interesting for what they reveal about the progression of recovery after treatment for childhood visual impairment, but they are not a valid source of information on the effect of complete deprivation of patterned visual input at or near

birth, nor do they provide information on later-onset developmental cataracts with a documented age of onset.

4.2.1. Low-level vision. In studies that documented that dense cataracts were present from birth, patients later exhibited deficits in low-level visual capabilities (acuity, peripheral vision, spatial and temporal contrast sensitivity, sensitivity to local motion) irrespective of whether the cataracts were monocular or binocular. When treatment is delayed (e.g., past approximately 12 weeks of age), the outcome for acuity and contrast sensitivity is worse if the deprivation was monocular rather than binocular (Birch et al. 1998). Even with shorter deprivation, the outcome is worse after MD than after BD if there was not aggressive patching of the nondeprived eye following treatment (Birch et al. 1998, Lewis et al. 1995). This pattern replicates that found in animal behavioral, electrophysiological, and anatomical studies showing that, compared to deprivation alone, deprivation combined with unbalanced input leads to more damage to low-level vision and to the primary visual cortex.

Not surprisingly, stereopsis is also more likely to develop when the deprivation from birth was binocular rather than monocular (Yamamoto et al. 1998). MD prevents the development of normal binocular stereoscopic vision even when it lasts only 1–2 months after birth, that is, when it ends before the normal onset of stereopsis at approximately 3 months (see **Table 2**), providing another example of a sleeper effect (Brown et al. 1999, Hartmann et al. 2015, Jeffrey et al. 2001, Lambert et al. 2016, Magli et al. 2017, Writ. Comm. Pediatr. Eye Dis. Investig. Group et al. 2019). The common postoperative strabismus may partly explain this outcome, since misalignment of the eyes anytime during the first four years of life prevents the development of normal stereopsis (Birch et al. 1990, Fawcett et al. 2005). Stereopsis is more likely to develop when the MD was shorter (surgery before 7 weeks); when the eyes are (close to) straight; when the acuity of the previously deprived eye is better; and, among those with good acuity, when the good eye had been patched for fewer hours per day after treatment (Hartmann et al. 2015, Jeffrey et al. 2001, Lambert et al. 2016). When the onset of either MD or BD occurs after birth, the prevalence of binocular fusion is higher, and that of strabismus is lower (Magli et al. 2016, 2017; but see Vaegan & Taylor 1979). Together, these findings suggest the importance of binocular input near birth (better outcomes after shorter deprivation or postnatal onset) and of coordinated input between two balanced eyes after birth (better outcomes when there is better acuity, less patching, and straight eyes). Additional clues come from studies of the good eye, that is, the fellow eye of children treated for monocular congenital cataract. Its acuity tends to be slightly depressed (Lewis et al. 1992b), and its sensitivity to global motion is as deficient as that of the previously deprived eye (Ellemberg et al. 2002). These findings suggest that the deficits when viewing with the previously deprived eye are, in part, a manifestation of a binocular problem. In fact, when the fellow eye becomes blind in patients treated for unilateral congenital or traumatic cataract, thereby preventing abnormal binocular interactions, acuity improves to much higher levels (Vaegan & Taylor 1979).

4.2.2. High-level vision. For higher-level visual capabilities mediated beyond the primary visual cortex, there is a striking reversal: Children treated for congenital monocular cataract have smaller deficits when viewing with the previously deprived eye than do children treated for congenital binocular cataract when viewing with either eye, and the extent of patching after MD does not modulate the outcome. For example, thresholds for perceiving the direction of global motion are elevated 1.5-fold when viewing with either eye in children treated for monocular cataract but 4.9-fold in children treated for binocular cataract (Ellemberg et al. 2002; see also Bottari et al. 2018). Similarly, thresholds for perceiving the global form made by pairs of dots are slightly elevated when viewing with the previously deprived eye in monocular cases (1.26-fold)

but significantly more elevated in binocular cases (1.65-fold), again with no benefit from more aggressive patching (Lewis et al. 2002; see also Putzar et al. 2007). (The smaller deficits for global form than for global motion may be a manifestation of decreased vulnerability in the ventral than in the dorsal extrastriate pathway.) The relative sparing of higher-level visual functions after MD indicates that higher-level deficits are not the simple result of a hierarchical cascade of increasing deficits as imperfect input from the primary visual cortex is fed into the extrastriate cortex (see Daw 1998). Instead, converging input across eyes to neurons in the extrastriate cortex, many with low spatial resolution, appears able to effect a relative sparing of function after MD. When there is no input to either eye, however, as happens during BD, there is not only damage to the primary visual cortex, but also surprisingly large damage to functions mediated in the extrastriate cortex. Event-related potentials from cataract-reversal patients support this supposition (Sourav et al. 2018): The polarity of the C1 wave reverses normally for stimuli in the upper versus lower visual field, consistent with retinotopic organization in early visual cortical areas, although its broader distribution in these areas suggests less precise tuning than normal. In contrast, the P1 wave that is believed to originate from the extrastriate cortex is attenuated significantly. A benefit from converging input may explain why patients treated for monocular or binocular congenital cataract develop normal sensitivity to biological motion—which involves converging input from the dorsal and ventral pathways, as well as several subcortical structures, some of which may have been unaffected by the deprivation (Bottari et al. 2015, Hadad et al. 2012, Rajendran et al. 2020).

4.2.3. Cross-modal reorganization? Visual capabilities mediated by the extrastriate visual cortex may be damaged more severely by binocular than by monocular congenital cataract because cross-modal reorganization of the type documented in the congenitally blind might be precipitated during the initial period of BD. Recent studies have documented similarities between BD patients and the congenitally blind in the processing of auditory stimuli. When BD patients hear various auditory stimuli in a functional magnetic resonance imaging (fMRI) scanner, they are as accurate as controls at detecting an occasionally longer sound and show differential activation in the normal auditory pathways. However, in addition, like the congenitally blind (Collignon et al. 2013), they show activation in the visual cortex, bilaterally around the cuneus (V3), that is not seen in controls and that appears to originate directly from the primary auditory cortex (Collignon et al. 2015). The possible functionality of this pathway is suggested by the transfer from adaptation to the sound of a looming object to adaptation to the sight of a looming object (Guerreiro et al. 2016b), as well as evidence that such patients switch attention faster than controls from vision to audition, with no difference for switches in the opposite direction (de Heering et al. 2016). Like the congenitally blind, BD patients are also faster than controls to detect auditory stimuli, are more sensitive to auditory motion, and show patterns of fMRI and electroencephalogram (EEG) activation suggesting more efficient auditory processing (Bottari et al. 2018, de Heering et al. 2016, Guerreiro et al. 2016a). These recent findings support the hypothesis that auditory recruitment of the putatively visual cortex during the period of BD may contribute to the later visual deficits in higher-order visual processing seen in BD patients. In contrast to the situation following BD, during MD, input from the good eye to the higher cortical areas where most cells receive input from both eyes may prevent such intersensory remapping, thereby leading to larger deficits after BD than after MD. In the congenitally blind, such cross-modal recruitment occurs mainly in higher cortical areas (Frasnelli et al. 2011) and thus would not be expected to affect low-level vision, where the BD deficits are smaller than the MD deficits.

Additional studies reveal that patients treated for bilateral congenital cataract have abnormal patterns of interaction between sound and sight, abnormalities that, to the extent tested, are smaller or nonexistent in patients treated for unilateral congenital cataract. For example, BD

patients perceive a flash and beep as simultaneous even when the beep occurred considerably later, consistent with faster auditory processing (Chen et al. 2017), and they are less susceptible to the McGurk illusion, that is, lip movements are less likely to bias their hearing of speech, consistent with their visual impairment (Putzar et al. 2007, 2010, 2012). However, in other paradigms, sound has a paradoxically small influence on their visual perception. They are less susceptible to the fission illusion, in which the sound of two beeps biases perception of a single flash toward perception of two flashes (Y.-C. Chen, T.L. Lewis, D.I. Shore and D. Maurer, unpublished observations); to auditory influences on judgments of when a flash occurred (Putzar et al. 2007); and to auditory stimuli when making temporal order judgments (Badde et al. 2020). When tested with fMRI, such patients do not show the normal enhanced activation in auditory and visual cortices when the sight of lip movements accompanies the sound of spoken words, and in fact less activation occurs in the visual cortex for the bimodal than the visual-only condition (Guerreiro et al. 2015). Combined, these findings indicate that normal audiovisual integration, like normal visual perception, requires visual input from birth, presumably in conjunction with normal auditory input. In its absence, auditory perception may be enhanced but fail to integrate normally with visual perception.

Unlike BD patients, MD patients, whether viewing with the previously deprived or the fellow eye, show normal susceptibility to the fission illusion, in both the center of the field and the periphery, where it is enhanced to a normal extent (Y.-C. Chen, T.L. Lewis, D.I. Shore and D. Maurer, unpublished observations). Although they do not make normal judgments of the simultaneity of auditory and visual stimuli, their pattern is qualitatively normal: Like visually normal children (younger than 9 years old), they judge a flash and beep to be simultaneous over wider intervals than do typical adults (Chen et al. 2017). Together, these results are consistent with the hypothesis that input from the good eye prevents auditory remapping of the visual cortex during the initial period of deprivation, but obviously, more data on cross-modal interactions after MD are needed before conclusions can be drawn.

5. CRITICAL PERIODS FOR RECOVERY

As reviewed above, across species, some recovery is observed immediately after the end of MD imposed during the critical period for damage. Longer-term recovery after MD is also facilitated by occlusion of the nondeprived eye. In recent work, interventions have been tested that induce additional recovery, even sometimes after the end of the critical period for damage. In this section, we review those interventions and the age limits on their efficacy, which we call the end of the critical period for recovery.

5.1. Cats and Rodents

Fast and substantial recovery from MD has been reported recently following a novel experiential intervention in which animals were placed for a time in total darkness. Initial studies on adult rats indicated that 10 days of total darkness can reintroduce vulnerability to a 3-day period of MD at an age (P70–110 days) well beyond the age at which MD alters OD in normal animals (He et al. 2006, 2007). In addition, the effects on OD and acuity of a long period of MD from eye opening until adulthood (P70–100) can be reduced substantially and quickly by 10 days of darkness (He et al. 2007). Shortly thereafter, the potential benefits of this intervention were explored in kittens that had received a 7-day period of MD at the peak of the critical period of vulnerability, that is, at P30 (Duffy & Mitchell 2013, Mitchell et al. 2016). The interlude of darkness was introduced 8 weeks after the MD ended, when the acuity of the deprived eye had reached a stable but subnormal acuity, which happened after 4–5 weeks. However, following 10 days in darkness, the acuity of the deprived eye improved rapidly to normal levels in approximately 1 week with no

deleterious effects on the fellow eye. When 10 days in darkness occurred immediately after the MD, initially, the kittens appeared blind in both eyes, followed by slow lockstep improvement to normal levels in approximately 7 weeks. The different immediate effects of darkness on the vision of the fellow eye in the two situations was unexpected: When the darkness was imposed early, the vision of the fellow eye was reduced to blindness, while when it started later, it had no effect, a finding that points to a short critical period for the effects of darkness on vision in normal kittens (Mitchell et al. 2015). The different speeds of recovery of acuity of the deprived eye following early versus late imposition of darkness suggest that the functional recovery of the deprived eye may depend on the level and pattern of neural activity in established anatomical connections with the nondeprived eye at the time that the darkness ended (at P47 versus P103 days). When darkness occurred early, kittens appeared blind in both eyes, a pattern suggesting that, initially, visually driven neural activity was equal and weak from both eyes. An important role for connections with the nondeprived eye is supported by observations that brief occlusion of the fellow eye in the immediate aftermath of the period of darkness can stop recovery of the acuity of the deprived eye in its tracks (Mitchell et al. 2019a).

Although a 10-day period of darkness promotes recovery from MD in adult rats and young kittens, the same duration of darkness is ineffective in adult cats (Holman et al. 2018), implying that there is a critical period for recovery from MD effected by this manipulation. A later study (Mitchell et al. 2019b) revealed an abrupt end to the efficacy of a 10-day period of darkness in promoting recovery from MD between P186 and P191 days of age in kittens. Whereas darkness eliminates all visually driven neural activity in the visual pathways, some spontaneous (i.e., nonvisually driven) neural activity remains. It is possible to eliminate it by intraocular injection of the sodium channel blocker tetrodotoxin (TTX). Five spaced TTX injections into both eyes, each blocking input for 2–4 days, promote rapid recovery from MD in kittens and also promote physiological recovery in the visual cortex of young mice (Fong et al. 2018). By contrast, 7 days of darkness produced only a modest recovery in young mice compared to simple restoration of visual input to the deprived eye (Erchova et al. 2017), possibly underlining the benefit of complete silencing of retinal visual activity.

5.2. Humans

There are no systematic studies of the critical period for recovery after MD in humans. Three studies of children treated for bilateral congenital cataract suggest that there is considerable potential for recovery after treatment and that the critical period for recovery may be lengthy. The first was a study of the first 5 days after treatment at 44 months of a Tibetan child with what were probably bilateral congenital cataracts, given that the family and their friends had noticed bright white pupils at 3 months of age and that the child always appeared to be blind (Chen et al. 2016). Over the first 5 days after treatment, she responded more and more to visual objects, looking at them for the first time from 6 minutes after the surgical patches were removed, reaching for and grasping objects with increasing accuracy from the first reach at 13 minutes until 60 minutes, and learning to avoid obstacles while walking by the end of the first day. On the second day, she could choose a designated object (differentiated by size) based on visual cues after experiencing it first with visual and tactile cues but failed at the same task if the transfer was visual to visual or tactile to visual. By the third day, she was at ceiling on both visual-to-visual and tactile-to-visual transfers but continued to have difficulty with a tactile-to-tactile pairing, a common finding with blind children, suggesting that vision normally teaches touch but that touch can teach vision after deprivation lasting until 3.5 years of age. On the fourth day, she learned the names of colors. This rapid improvement is similar to that seen in acuity immediately after treatment for unilateral or bilateral congenital cataracts in the first year of life (see Sections 3.4 and 4.2).

The second study was a longitudinal study of the spatial contrast sensitivity of children treated during infancy for bilateral congenital cataract beginning when they were between 5 and 18 years of age (Maurer et al. 2006). When the baseline measurements were taken at 11+ years of age, there were no changes during the subsequent 2 years. However, when the baseline was measured between 5 and 9 years of age, sensitivity to low spatial frequencies ($\leq$1.0 cycles/deg) improved faster than normal, eliminating all or most of the deficit. Importantly, this benefit was seen even after 7 years of age, the age when children with normal eyes achieve adult levels of spatial contrast sensitivity. Thus, in addition to periods of normal development that are driven by experience and separate critical periods for damage, there are periods during which some recovery is possible. There are clearly limits on this recovery process: There was no improvement in sensitivity to mid and high spatial frequencies ($\geq$5.0 cycles/deg) and, when observations began at age 9 or later, no improvement even at low spatial frequencies.

The third study suggests that some plasticity after BD continues even into adulthood. Inspired by demonstrations of improvements in visually normal adults, Jeon et al. (2012) used an action video game to improve the vision of 7 adults treated for bilateral congenital cataract. Specifically, adult patients played a first-person shooter game, *Medal of Honor*, that had been shown to improve acuity, as well as several other visual capabilities, in adults with normal eyes and in adults with strabismic or anisometropic amblyopia (Green & Bavelier 2003, 2006a,b; Li et al. 2009). The protocol involved a baseline assessment, 10 hours of play a week for 4 weeks, and a post-test. After playing the video game, most patients had improved acuity, spatial and temporal contrast sensitivity, and sensitivity to global motion, although none of these capabilities normalized. There was no improvement in stereopsis or useful field of view. Thus, a mere 40-hour intervention was sufficient to induce multiple improvements in adults treated for bilateral congenital cataracts, improvements that were still apparent 9 months later. What is unclear is whether a longer intervention would induce additional improvements, and whether the improved performance reflects changes in functional neural connectivity that produce clearer signals and/or improved ability to attend to unchanged, noisy signals. Regardless, the results indicate that the critical period for recovery of some visual functions extends into adulthood.

There are also case studies of patients treated as older children and adults for cataracts of long duration and uncertain age of onset. Whatever the etiology, such patients are initially confused by the novel visual input, but, as in the case of the Tibetan child described above, their vision improves over the first few days and months after treatment (Gandhi et al. 2017, Ganesh et al. 2014, Kalia et al. 2014, Ostrovsky et al. 2009, Von Senden 1960), with improvements documented in visual acuity, spatial contrast sensitivity, face detection, and segmentation of occluded objects. At least for such segmentation, there is more improvement when movement is added as a cue (Ostrovsky et al. 2009), a pattern suggesting that plasticity lasts longer for some visual functions than for others.

Unlike the dearth of studies on late recovery from MD or BD in humans, there is a substantial emerging literature on effective interventions for adults with strabismic and/or anisometropic amblyopia, that is, reduced vision in one eye secondary to misaligned eyes and/or unequal refractive errors early in life that produced a barrier to clear binocular input. Most strikingly, adults with either form of amblyopia who lose the use of the fellow eye sometimes recover better vision in the amblyopic eye, a finding suggesting that the requisite connections had been formed but were previously suppressed (El Mallah et al. 2000; for a review, see Levi 2020). Interventions such as perceptual training of sensory discrimination yield improvements that usually transfer to improved acuity (for a meta-analysis, see Tsirlin et al. 2015). As with patients treated for BD, playing an action video game with first-person perspective also improves acuity; this intervention is effective in fewer hours and with more general transfer than perceptual training (for a review, see

Levi 2020). Surprisingly, patching the amblyopic eye for 2 hours a day can also lead to long-lasting improvements in acuity and stereoacuity, especially if combined with physical exercise, perhaps because patching increases the excitability of the amblyopic eye, thereby improving the balance between eyes (Lunghi et al. 2019, Zhou et al. 2019).

In small clinical studies, these interventions (perceptual training, action video games, occlusion, binocular therapy with dichoptic stimuli) generally lead to a small, 1–2-line improvement in acuity, often with greater improvement in patients who began with worse vision. However, in standardized randomized clinical trials, the effects have been smaller (Falcone et al. 2021). Much greater improvement was observed in an earlier study in which amblyopes were hospitalized to receive an intensive 6-week intervention with 100% patching of the fellow eye and various kinds of fixation training with small targets (Kupfer 1957). There are similar reports from vision therapy, although the details of the treatment vary from patient to patient (Press 1997). Across all of these interventions, the basis of the improvements is also unclear and may differ between interventions. Candidates for the basis include changing neuromodulators, unmasking of primary visual cortex neurons connected to the amblyopic eye, formation of new connections, and high-level improvements in attention to unaltered noisy signals.

6. MOLECULAR STUDIES

In the past 20 years, investigations of visual critical periods have been increasingly dominated by a search for the underlying molecular mechanisms of the effects of MD (for reviews, see Daw 2006; Hensch 2004, 2005; Levelt & Hübener 2012; Morishita & Hensch 2008). Although some early work was done with cats, the majority of studies were done with rodents. These studies indicate that the onset of plasticity coincides with the maturation of inhibitory GABAergic innervation, while the subsequent declining plasticity originates from a change in the balance of excitatory and inhibitory neurotransmission, as well as several other molecular events (Hensch 2005, Murphy et al. 2005). Included among the latter is an increase in the expression of diverse proteins that are referred to as braking molecules because they act collectively to reduce plasticity in the visual cortex. Such proteins include myelin proteins (McGee et al. 2005), the cholinergic brake Lynx1 (Morishita et al. 2010), neurofilament proteins (Duffy & Mitchell 2013), and chondroitin sulphate proteoglycans within the perineuronal nets that surround inhibitory interneurons (Pizzorusso et al. 2002). Behavioral or environmental interventions such as exposure to darkness may act in part through their effects on the expression of some or all of these braking molecules (e.g., Duffy & Mitchell 2013, Stryker & Lowell 2018).

Although it is still early days, knowledge of the molecular underpinnings of cortical plasticity in mice has not yet had any translational impact such as increasing the level of cortical plasticity in adult humans or the treatment of human amblyopia. For example, recent repurposing of existing approved drugs known to influence the expression of molecules implicated in cortical plasticity in mice has so far proved ineffective in increasing perceptual learning or the effectiveness of behavioral interventions in remediating amblyopia (for a review, see Levi 2020).

7. ISSUES TO BE ADDRESSED IN THE FUTURE

Notwithstanding the fewer barriers to the use of rodents as compared to other species, detailed documentation and temporal sampling of the profile of critical periods in rats and mice are at present incomplete. Not only is such knowledge for rodents essential for the design of studies of the benefits of genetic, pharmacological, and other interventions for alleviation of cortical and behavioral deficits due to early MD, but also it is important to have better knowledge of the variability associated with eyelid suture, the most common means for implementation of

MD. Because the small dimensions and thickness of the eyelids of mice makes it difficult to maintain MD for long durations, it may be worthwhile to explore new procedures for MD. With respect to the use of rodents as animal models for amblyopia, it is important to establish the extent of anatomical, physiological, and behavioral recovery from MD of various durations that occurs both passively following alleviation of the deprivation (binocular recovery) or after more active interventions such as occlusion of the fellow eye, as such data are a necessary baseline for comparison with the recovery promoted by new pharmacological or experiential interventions.

This review not only highlights the incomplete data concerning the timing of critical periods in various visual cortical regions in cats and monkeys, as well as rodents, but also directs attention to exciting new data on the contribution of cross-modal plasticity to the visual deficits in humans. Future study of both issues will require the choice of appropriate animal species for study. As also argued most recently by Tyschen (2020) and Kasamatsu & Imamura (2020), many of the phenomena summarized in this review cannot be studied adequately in rodent models, and thus studies of such species must be complemented by investigations of other species, including nonhuman primates. The ability to study species other than rodents has become increasingly constrained and even fragile, not only because of pressure exerted by animal-rights activists and university administrators. Granting agencies and their adjudication panels have possibly inadvertently contributed to this shift by placing more weight on the one superior feature of rodent models, namely, their ability to address molecular mechanisms of plasticity, at the expense of similarity to humans along other dimensions that include the organization of the visual pathways, the visual and other sensory cortical regions affected, and the size and nature of the effects of early deprivation. It is imperative that the relevance to human anatomy, physiology, and vision not be downplayed in consideration by funding agencies of the appropriate animal models for study.

Although the use of both New and Old World monkeys faces many barriers, the past two decades have seen growing utilization of marmosets, a nonhuman primate species that holds considerable promise for the study of visual system plasticity. As summarized recently (Mitchell & Leopold 2015, Mitchell & Sengpiel 2018), marmosets possess many attributes that favor their adoption, including visual cortical areas that lie close to the cerebral surface, a high foveal cone density, a relatively short gestational time (approximately 140 days), and multiple (one–four) animals in a litter, while the ability for social housing in groups of five–six animals reduces colonization costs. Unlike use of rodents, use of marmosets or other nonhuman primates will allow exploration of the interactions of low-level visual cortical regions with high-level cortical regions that are lacking in rodents, as well as with other sensory cortices, which recent human work has shown is crucial to understanding the full effects of early BD.

SUMMARY POINTS

1. Initial studies of the timing of critical periods were conducted mainly on the visual pathways of cats and, to some extent, monkeys that had received a period of MD. Although enormous effects on OD were evident, insufficient animals and conditions were used to be confident about the timing of the period of vulnerability.
2. The composite results of four systematic studies of OD in the extragranular layers of the cat's visual cortex suggest that susceptibility to MD begins in the second week, reaches a peak at between 4 and 5 weeks, and then declines slowly to disappear finally at one year of age.

3. Even more limited data from macaque monkeys indicate that MD effects profound changes in cortical OD when it begins in the first month after birth and continues to have large effects even at 1 year of age, the oldest age examined to date.
4. Comparable data from humans who suffered visual deprivation because of dense cataracts indicate that the vulnerability of low-level visual abilities can last until 10 years of age, although the period of vulnerability varies with visual function, as it does in cats and nonhuman primates.
5. In both cats and monkeys, the functional effects in the visual cortex, as well as those on low-level visual functions, are far greater after MD than after BD. The same pattern holds in humans for low-level visual functions.
6. The timing of critical periods cannot be predicted from the timing of normal development, with examples both of vulnerability continuing several years after normal development is complete and of vulnerability ceasing while development is still in progress. In addition, recent work suggests that some recovery from visual deprivation may be possible outside both of these periods.
7. For higher-level visual functions in humans, such as global motion, early MD causes smaller deficits than does BD, a reversal of the pattern seen for low-level visual functions. This reversal may result from cross-modal recruitment of putatively visual areas during BD, as has been documented in the congenitally blind and for which there is increasing evidence in bilateral cataract reversal patients.
8. In recent years, studies of visual deprivation have shifted to rodents, in part to assess molecular mechanisms. However, the effects of MD on OD and acuity in rodents are considerably smaller than in cats or monkeys, and it is not possible to study in rodents the higher-level effects that have revealed novel insights in recent human studies.

FUTURE ISSUES

1. The lack of adequate temporal sampling of the effects of MD at different ages observed in past studies of all species should be addressed. Such detailed documentation may be easiest to accomplish in rodents.
2. Studies on rodents should also address additional issues such as the variability of the electrophysiological and behavioral deficits associated with periods of MD of different duration, as well as the pace and extent of recovery that occurs afterward. In addition, different methods for producing stable periods of MD should be explored.
3. Just as the phrase "horses for courses" reflects the higher success of certain horses in particular race locations, advances in our understanding of the myriad of molecular, anatomical, and functional events that underlie the timing of critical periods in human visual development may depend crucially on the choice of appropriate animal species for study or for tests of particular hypotheses, an idea captured by the phrase "species for theses."
4. Because of the many barriers to the use of Old World monkeys such as macaques, the use of marmosets should be promoted to facilitate study of the neural basis of the effects of early deprivation on higher-level visual functions, as well as for study of the basis for the cross-modal changes observed in human cataract patients.

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Errata

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