Review

Neural mechanisms of recovery following early visual deprivation

Donald E. Mitchell^{1,*} and Frank Sengpiel²

¹*Psychology Department, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J1*

²*School of Biosciences, Cardiff University, Cardiff CF10 3AX, UK*

Natural patterned early visual input is essential for the normal development of the central visual pathways and the visual capacities they sustain. Without visual input, the functional development of the visual system stalls not far from the state at birth, and if input is distorted or biased the visual system develops in an abnormal fashion resulting in specific visual deficits. Monocular deprivation, an extreme form of biased exposure, results in large anatomical and physiological changes in terms of territory innervated by the two eyes in primary visual cortex (V1) and to a loss of vision in the deprived eye reminiscent of that in human deprivation amblyopia. We review work that points to a special role for binocular visual input in the development of V1 and vision. Our unique approach has been to provide animals with mixed visual input each day, which consists of episodes of normal and biased (monocular) exposures. Short periods of concordant binocular input, if continuous, can offset much longer episodes of monocular deprivation to allow normal development of V1 and prevent amblyopia. Studies of animal models of patching therapy for amblyopia reveal that the benefits are both heightened and prolonged by daily episodes of binocular exposure.

Keywords: amblyopia; visual cortex; visual acuity; stereoscopic vision; patching therapy; ocular dominance columns

1. EARLY EXPERIENCE AND DEVELOPMENT OF VISION AND VISUAL PATHWAYS

The influence of early experience on development has been and continues to be a dominant theme in developmental neurobiology. In the context of studies of vision, the modern scientific enquiry into experiential influences on perceptual development is usually thought to have been sparked by Molyneux's seventeenth century question to the philosopher John Locke ([Morgan 1977](#)). The explosion of interest in visual system development was kindled by the investigations in the early 1960s by Hubel & Wiesel of the primary visual cortex and cortical areas beyond. Hard on the heels of their early papers on the primary visual cortex, they published their developmental studies of the state of the neonatal primary visual cortex ([Hubel & Wiesel 1963](#)) and the results of their examination of the effects on cortical ocular dominance of two forms of early selected visual deprivation ([Wiesel & Hubel 1963](#); [Hubel & Wiesel 1965](#)) that destroyed concordant binocular visual input, namely monocular deprivation by eyelid suture and divergent strabismus (exotropia). Whereas monocular deprivation seriously degrades the visual input of one eye, strabismus destroys concordant binocular input without blurring the visual input of either eye. In both cats and monkeys, the former

deprivation leads to pronounced shifts of ocular dominance among cortical cells towards the non-deprived eye (NE) and also increases the size of anatomical domains in layer 4 of V1 controlled by this eye at the expense of domains dominated by the deprived eye (DE). On the other hand, surgically induced exotropia results in a loss of cells in V1 that can be excited by either eye but without any imbalance in the proportion of cells dominated by either eye.

The anatomical and physiological changes observed in V1 as a consequence of early monocular deprivation are accompanied by a loss of visual acuity in the DE, the severity of which depends on when the deprivation began and its duration ([Giffin & Mitchell 1978](#)). On the other hand, the loss of binocularly excitable cells in animals reared with exotropia is accompanied by a loss of stereoscopic vision without any appreciable impairment of the vision of either eye ([Mitchell 1988](#)). The magnitude of the acuity loss, as well as the characteristics of certain of the visual deficits in the DE following early monocular deprivation, resembles those that characterize human amblyopia (e.g. [Murphy & Mitchell 1991](#); [Gingras et al. 2005](#)). Undoubtedly, a major motive for much of the extensive research on visual system development that followed Hubel & Wiesel's pioneering experimental explorations in the early 1960s was the insight that their work provided into the origin and potential treatment of human amblyopia. Indeed, explicit mention of the potential for this work to reveal the origins of amblyopia was made in one of their early developmental papers

* Author for correspondence (d.e.mitchell@dal.ca).

One contribution of 12 to a Theme Issue 'Sensory learning: from neural mechanisms to rehabilitation'.

(Hubel & Wiesel 1965), and as well in their recent book that documents their long collaboration (Hubel & Wiesel 2004).

As betrayed by its Greek roots, the term amblyopia means blunt or dull vision and is used to describe reduced acuity in usually one but occasionally both eyes that remain after correction of any coexisting refractive condition and which cannot be attributed to a disease. Because it is observed in young children, amblyopia has long been thought of as a result of anomalous development due to a pre- and/or coexisting refractive or oculomotor condition that impairs either the relative clarity or concordance of the two retinal images. Classification of amblyopes into one of the various subtypes of amblyopia, namely anisometropic, strabismic, mixed (i.e. a combination of anisometropic and strabismic) or deprivation, is made according to the nature of the concurrent obstruction to concordant binocular input, whether it is due to a refractive error (anisometropia), deprivation (medial opacity or obstruction) or an oculomotor condition (strabismus). The prevalence is roughly a third each for anisometropic, strabismic and mixed amblyopia with deprivation amblyopia accounting for less than 5 per cent of cases (Holmes & Clarke 2006).

(a) *Conventional clinical treatment of amblyopia*

The most common component of therapy, namely patching of the fellow eye, was advocated in the Western medical literature in the early eighteenth century for strabismic amblyopia but was, in fact, in use much earlier during the heyday of the Arabic empire (von Noorden *et al.* 2002; Loudon & Simonsz 2005). Additional therapies for amblyopia have been added over the years including various visual training regimens such as orthoptic exercises to reinforce binocular vision and/or pleoptic stimulation and training of foveal vision of the amblyopic eye. In addition, many variations of patching therapy have been advocated including the use of lenses or translucent material or even cycloplegic drugs to paralyse accommodation in order to blur rather than to occlude vision of the non-amblyopic eye. Notwithstanding the importance of these various contributions, undoubtedly the greatest advance with respect to successful treatment was provided by the eventual accumulation of knowledge concerning the most appropriate age to initiate treatment, including patching therapy, and the duration and degree of aggressiveness with which the latter was pursued. Arguably, it was the systematic documentation of the outcome of treatment of 2337 children with strabismus or heterophoria by Claud Worth over a 10-year period from 1893, which had the greatest influence on the treatment of amblyopia in the first half of the twentieth century (Worth 1929). For optimum results, he recommended intervention by patching for three to eight weeks between the ages of 3 and 6 years followed by orthoptic exercises, but after 7 years of age 'it is seldom successful, though occasionally good results are obtained' (Worth 1929, p. 112). A measure of the high impact of his clinical recommendations was the fact that this book, initially published in 1903, appeared in nine editions over a period of 56 years. The impression

of an optimum time for treatment and an age beyond which success was limited, which was inculcated into clinical thinking by the work of Worth and others (see review by Tychsen 2005), must have influenced the design and interpretation of Hubel & Wiesel's deprivation experiments that led ultimately to their delineation of a critical period for the effects of monocular deprivation (Hubel & Wiesel 1970; LeVay *et al.* 1980). By his own admission, Worth's (1929, pp. 112–3) suggested upper limit for treatment was influenced more by his experience in the hospital setting in which he worked of reduced chances of children's compliance with patching and lack of interest with orthoptic exercises after 7 years of age than by actual data collected on older children.

The research initiated by Hubel & Wiesel spurred work that established that clinically relevant forms of early visual deprivation in animals (such as different types of strabismus, anisometropia and various forms of monocular deprivation) produced visual deficits similar to those experienced by human amblyopes. In turn, the development of these animal models of amblyopia permitted explorations of procedures for remediation or even prevention of amblyopic deficits and changes of cortical anatomy and function. To begin, we summarize some key findings and concepts that have emerged from the studies of the early development of the central visual pathways of higher mammals relevant to an understanding of the origins of amblyopia.

2. KEY FINDINGS AND CONCEPTS DERIVED FROM EARLY ANIMAL STUDIES RELEVANT TO AN UNDERSTANDING OF THE ORIGIN AND TREATMENT OF AMBLYOPIA

(a) *The choice of animal species*

Although Hubel & Wiesel began their explorations of the visual cortex of monkeys in parallel with their work on cats, the studies on monkeys proceeded far more slowly owing to the more intricate cortex and the need to be more conservative owing to their high cost (Hubel & Wiesel 2004). As a consequence, their first paper on monkeys (Hubel & Wiesel 1968) appeared six years after their pioneering paper on the cat cortex. While the applicability of the latter work to an understanding of human amblyopia is immediately obvious, the high cost and low availability of young animals dictate that developmental studies proceeded at a very slow pace and with very small experimental groups. On the other hand, cats share many important aspects of visual system organization with humans including extensive overlap of the visual fields of the two eyes, semi-decussation of the axons of X- and to a lesser extent, Y-class retinal ganglion cells, good temporal and spatial resolutions and *importantly*, stereoscopic vision. Although it is possible to point to differences between the two species, such as a lesser degree of central retinal specialization in the cat (an area centralis as opposed to a fovea), universal dichromatic colour vision in cats as opposed to trichromacy (in all catarrhines and in some female platyrrhines), the key phenomena of visual cortical development differ very little. Importantly, in both

species postnatal cortical development is activity dependent and is governed to a large extent by a process of binocular competition during certain well-defined critical periods that albeit are of longer duration in monkeys. Following Hubel & Wiesel's (2004) lead, we and many of our contemporaries began our studies of rehabilitation of amblyopia in cats so as to cover as much ground as possible before verifying and refining the key concepts on primates. As an aside, we note that this approach may have had an unexpected advantage in that the lower resolution of the cat visual system may reduce the need for highly accurate alignment of the visual axes of the two eyes in situations when both eyes are open after early deprivation. A minor misalignment of the visual axes (a small strabismus) may prevent the substantial cortical and visual recovery that is observed in cats (and humans) but not in monkeys after early monocular deprivation (Mitchell & Timney 1984). In turn, the early focus of developmental research on the cat visual system has in recent years been largely supplanted by work on rodents (particularly mice), in part owing to the obvious advantages of mice for studies of the molecular mechanisms of developmental plasticity.

The voluminous research on visual system development has been summarized in many reviews. The earliest reviews (Movshon & Van Sluyters 1981; Mitchell & Timney 1984; Movshon & Kiorpes 1990; Rauschecker 1991) summarize the early electrophysiological and behavioural studies conducted on cats and monkeys while later ones incorporate the more recent research on rodents and the molecular mechanisms of developmental plasticity (Daw 2002; Hensch 2005; Hooks & Chen 2007; Morishita & Hensch 2008). Other smaller recent reviews either focus upon concepts such as the control of critical periods (Berardi *et al.* 2003) or putative processes of synaptic plasticity (Sengpiel & Kind 2002; Bear 2003). Our objective in this review is also limited and focused upon our interpretation of the impact of four decades of experimental work on animals on our understanding of the clinical condition of amblyopia and its treatment.

Three avenues of exploration are perhaps most relevant with respect to an understanding of the origins of amblyopia. The first and possibly most contentious avenue concerns the state of the primary visual cortex and other visual structures when the animal first receives visual input (at birth or at eye-opening in species where this occurs some time after birth). This issue is particularly relevant as the neonatal state of the visual cortex defines the initial substrate on which visually driven neural activity can potentially modulate its further postnatal development. The second approach documents the effects of early experiential manipulations that influence the anatomical organization of the visual cortex with respect to ocular dominance domains and at a physiological level, the nature of binocular interactions. Together, these studies define conditions that interfere with the capacity for the development of normal binocular vision, especially stereopsis. The third line of studies represents a subset of experiments that define critical periods during which experiential manipulations can either change cortical organization and behaviour or

else permit some degree of recovery from the effects of an earlier period of deprivation. As such, the latter studies represent a first step towards the development and/or refinement of approaches to the rehabilitation of amblyopia.

(b) *The neonatal state of the primary visual cortex*

In recent years, it has become increasingly clear that the visual cortex is far more mature at birth than previously thought. With respect to the development of ocular dominance columns, new data from ferrets (Crowley & Katz 2000), cats (Crair *et al.* 1998; Rathjen & Lowel 2000) and monkeys (Horton & Hocking 1996) reveal that segregated ocular dominance domains emerge earlier than previously thought, at or even earlier than the onset of the time when their dimensions can be altered by monocular deprivation (Crowley & Katz 2002). The change in opinion concerning the neonatal state of the visual cortex raises anew questions concerning the potential influence of visually driven activity on its subsequent postnatal development. Superficially at least, it is easier to consider that such activity may play an active and even guiding role in postnatal development if it is acting upon an immature substrate at birth than if it acts upon a more mature cortex. In the former situation, all visual experience, both normal and unusual, could be considered equipotent; however, in the latter situation it might be thought that normal visual input could exert a greater influence on postnatal development than abnormal input owing to a more vigorous response evoked by such input among the largely specified cortical cells in V1.

(c) *The effects of early monocular deprivation*

Two very influential ideas were generated from the initial studies of the effects of early monocular deprivation on the functional properties of cells in V1. The first idea was the concept of a critical period for the effects of deprivation on cortical ocular dominance, a concept that was raised initially from the early demonstration that the ocular dominance shifts were only evident in kittens and were absent in adult cats (Wiesel & Hubel 1963) and confirmed by the studies described below that determined the timing of the effects with greater accuracy. The second idea emerged from Hubel & Wiesel's demonstration of larger effects following monocular as opposed to binocular deprivation (Wiesel & Hubel 1965) and from their studies of the effects of surgically induced exotropia (Hubel & Wiesel 1965). The results from both sets of studies pointed towards the idea that the large effects of monocular deprivation were a consequence of binocular competition rather than disuse. Together, these two ideas permitted the first glimpse into the mechanism and site of origin of amblyopia as well as a tool by which it was possible to optimize the timing of rehabilitative strategies. The early work of Hubel & Wiesel led to a plethora of studies (summarized in the reviews mentioned above) of the effects of various forms of early selected visual deprivation on the anatomical and functional development of the central visual pathways. Limitations of space dictate a

focus here on ocular dominance columns as they provide a very convenient way to assess the relative strengths of the two eyes.

Additional insight into amblyopia and its treatment was provided by studies that explored in more detail than simple assessment of ocular dominance, the impact of early monocular deprivation or strabismus on the binocular characteristics of cells in V1. These studies of the interocular phase sensitivity of cortical cells documented the nature of the residual binocular connections and the remaining selectivity for disparity (Freeman & Ohzawa 1988; Chino *et al.* 1994; Sengpiel *et al.* 1994; Smith *et al.* 1997; Zhang *et al.* 2005). The existence of these residual binocular interactions, which appear to involve predominantly inhibitory mechanisms (Sengpiel *et al.* 2006), provides a potential neural platform for rehabilitation of functional binocular vision in amblyopia.

(d) Critical periods for the effects of monocular deprivation and its reversal

Following Hubel & Wiesel's demonstration that monocular deprivation induced shifts of cortical ocular dominance only when imposed in early postnatal life, there have been a number of attempts to delineate the precise timing of the critical period for this phenomenon (Hubel & Wiesel 1970; LeVay *et al.* 1980; Olson & Freeman 1980; Daw *et al.* 1992). The most informative of these investigations are those (e.g. Olson & Freeman 1980) that employ a constant length of deprivation and vary just the age at which it is imposed so that there is not a confound between length of deprivation and age. Another important point about all of these investigations is that they reveal a very gradual decline in susceptibility to monocular deprivation and that the data are rather sparse with respect to an accurate specification of a critical age beyond which deprivation has no effect.

Early in life it is not just possible to induce cortical changes by monocular deprivation but it is also a time during which these changes can be reversed in whole or in part by inverting the occlusion so that the animal is forced to use its previously DE (reverse occlusion). The extent to which the initial effects of deprivation can be reversed and the speed of the changes depend upon the age at which reverse occlusion begins (Blakemore & Van Sluyters 1974; Movshon 1976a; Blakemore *et al.* 1978, 1981). Indeed, it has been argued that the temporal profile of the declining ability to reverse prior deprivation-induced effects represents a separate critical period for recovery (Daw 1998, 2002, 2003; Lewis & Maurer 2005). Knowledge of the differing temporal profiles of the critical periods for disruption and recovery is of obvious relevance to an understanding of the origin of amblyopia and for hints as to the most effective times for therapeutic intervention.

Although it is not possible to measure the profile of critical periods in the human visual system by use of the same direct methods that have been employed on animals, several notable attempts have been made using indirect methods on selected clinical populations. A landmark study collected visual acuity data from cases of unilateral traumatic cataract immediately following surgical intervention for cataract and correction of the resulting aphakia with contact lenses

(Taylor & Taylor 1979). Owing to the traumatic origin of the cataract, this clinical study is exceptional with respect to the accuracy of the documentation of the start and end of the monocular deprivation. Cataracts that occurred after 10 years of age did not result in an acuity loss suggesting that the longest critical period(s) in the human visual pathway for disruption by monocular deprivation have ended by that age. Other notable attempts to determine critical periods in human vision have targeted the recovery from either monocular deprivation from unilateral cataracts (e.g. Birch & Stager 1996; others reviewed by Mitchell & MacKinnon 2002) or strabismus (Epelbaum *et al.* 1993; Fawcett *et al.* 2005) through an examination of the effectiveness of therapeutic interventions as a function of the age at which they were initiated.

3. ANIMAL STUDIES ON PREVENTION OF AMBLYOPIA AND RESTITUTION OF FUNCTION WHEN IT OCCURS

(a) Prevention of amblyopia: studies of the effects of mixed early visual input in kittens

The prediction made earlier that normal visual input may be privileged in development was confirmed in a series of experiments in which kittens received mixed daily visual input in which normal and abnormal visual input were pitted against each other in various proportions (Mitchell *et al.* 2003, 2006).

The design of the studies and key rearing conditions are illustrated in figure 1, which depicts the daily visual experience of various groups of kittens for a four-week period beginning at four weeks of age. The animals received only 7 hours of visual experience each day, and for the remaining 17 hours they were housed with their mother and littermates in a large darkroom. The 7 hours of visual experience was split into a portion for which the visual input was normal and another during which it was abnormal, namely monocular. To provide the latter experience (monocular exposure or ME), kittens wore an opaque mask that covered one eye. The mask was removed to permit normal concordant binocular visual exposure (BE). The initial studies examined the consequences of these various rearing conditions on the vision of the two eyes in terms of the visual acuity for square-wave gratings by use of a jumping stand (Mitchell *et al.* 1977). Kittens were trained daily on the jumping stand from approximately five weeks of age for approximately 30 min per day during the period of BE. The acuity of the NE was usually taken as equal to the binocular acuity as measured during the last period of BE on the final day of mixed rearing, an assumption confirmed by monocular measurements made on several animals. The acuity of the DE was measured (with other eye occluded with a hard opaque contact lens) the day after the period of mixed rearing immediately after the animals were removed from the darkroom for the final time.

The outcome from the rearing conditions at the two extremes where the visual experience was either exclusively binocular or monocular (respectively, 7 or 0 hour of BE) was entirely predictable. In the former situation, the acuity of each eye would be expected to be equal to that of a normal eight-week-old kitten

Figure 1. Representation of the daily visual experience of kittens in the form of 24 hours clocks. For four weeks from four weeks of age, kittens received 7 hours of visual experience each day, split between periods of monocular (ME) and binocular (BE) exposure. For the remainder of each day, the kittens were housed in complete darkness (shaded black). The key rearing conditions that were explored include situations where the period of (a) ME preceded or (b) followed BE, conditions where (c) the period of BE was split into two equal intervals that straddled ME and (d) finally situations where the kittens wore masks during the daily period of BE that contained prisms that either had the same orientation for the two eyes (base down or base up) to allow concordant binocular input, or else the opposite orientations so that the visual input was discordant (D). A second cohort of kittens received just 3.5 hours of visual exposure each day.

Figure 2. The visual acuity of the DE (relative to the mean acuity of the NE) measured at the end of the four weeks of mixed daily visual exposure for the two cohorts of kittens as a function of the amount of daily binocular exposure (BE) (a) 7 hours and (b) 3.5 hours. Filled circles depict the animals that received no BE, while the remaining circles show the data from animals that received mixed daily visual input. The half-filled circles are shaded on the left or the right according to whether the period of ME occurred before or after the period of BE, respectively. The open circles show the data from two animals that wore dissociating prisms during the daily period of BE to prevent concordant binocular visual input.

whereas in the latter condition the kitten would be anticipated to appear blind when using the eye that was occluded each day. Various outcomes could be predicted for intermediate mixed daily visual exposures. If the two visual exposures were equally efficacious with respect to their influence on cortical development, the outcome would reflect the relative amount of the two daily exposures. In particular, any amount of daily ME would be expected to result in an impairment of the vision of the occluded eye. On the other hand, if normal binocular visual exposure was weighted heavily, then it might be expected to offset longer daily periods of abnormal exposure to allow the development of normal vision in the DE.

The results, shown in figure 2a in the form of a plot of the normalized acuity of the DE of 14 kittens (as compared with the mean acuity of the fellow eye at eight weeks of age); clearly support the view that binocular visual input was privileged. Animals that received only 2 hours of such exposure each day developed normal visual acuity in the DE in spite of the fact that this eye was occluded for 5 hours each day.

The effects of even short periods of daily BE were quite profound; even 30 min of BE each day permitted the recovery of some vision in the DE. Also, the order of exposure (BE first or second each day) had no obvious influence on the outcome and so it seems unlikely that consolidation by sleep at the end of the daily period of visual experience conveyed any advantage on the exposure received last each day. Included in figure 2a is the data (open circles) from the two animals that wore dissociating prisms (each five prism dioptres, one base up, the other base down) before the two eyes during a 2 hours daily period of BE. These animals developed an acuity in the DE that was only half of normal values or that achieved by control animals (data not shown) that wore the same prisms but with the same orientation for the two eyes during the 2 hours period of BE. This result leads to the important conclusion that for the development of normal vision, the vision during the 2 hours daily period of BE period must be both simultaneous and concordant.

A similar experiment (Mitchell *et al.* 2005) has been conducted on a second cohort of 12 kittens that received

just 3.5 hours of total visual experience each day in order to explore further some of the temporal parameters of the protective effects of concordant binocular exposure. The results, shown in [figure 2b](#), indicate that with this cohort, only 1 hour of BE each day was sufficient to permit the development of normal visual acuity in the DE. This result is consistent with the view that the outcome for vision is defined the best by the proportion of the total daily exposure that is binocular as opposed to a fixed amount of such exposure.

Another important temporal parameter that was observed with both the 3.5 and 7 hours cohorts concerned the manner in which the daily period of BE was distributed in time. The benefit of, respectively, 1 and 2 hours of BE for the two cohorts was obtained only when the period of BE was consolidated in one exposure; when the exposure was distributed in two equal episodes delivered on either side of the period of ME ([figure 1c](#)), the outcome was very similar to that observed with just one of the two exposures as if the second exposure had no effect ([Mitchell et al. 2006, fig. 5](#)). In this respect, the outcome is the opposite to what is observed in classic studies of learning and LTP induction where spaced trials are in general more effective than when they are massed (see review by [Silva et al. 1998](#)).

The effectiveness of daily periods of BE in offsetting much longer daily episodes of visual deprivation was not restricted to grating acuity but was also reflected by normal contrast sensitivity functions and alignment accuracy ([Mitchell et al. 2006](#)). Thus, the degree of protection afforded to the vision of the DE by the daily period of BE is very profound and possibly complete as alignment accuracy (a form of vernier acuity) is affected far more than grating acuity by deprivation in both cats ([Gingras et al. 2005](#)) and humans ([Hess & Holliday 1992](#)). The requirement that the visual input to the two eyes be concordant during the daily periods of BE to maximize its protective effect raises the possibility that as well as allowing normal visual acuity in both eyes, such input may also permit the development of some level of stereoscopic vision. We are at present exploring this possibility at a behavioural level but as noted below, a recently completed physiological study ([Vorobyov et al. 2007](#)) of the reliability of cells in the visual cortex to spatial phase disparity suggests that stereopsis may not be at normal levels even in those animals that received sufficient daily BE to develop normal visual acuity in both eyes. Nonetheless, the presence of even rudimentary stereopsis raises the potential for subsequent improvement with further targeted binocular stimulation.

Although very substantive, the behavioural findings alone do not permit the identification of the level(s) in the visual pathway where the protective effects of daily periods of BE are exerted. To investigate this issue, we have carried out a parallel study of the physiological consequences of mixed daily visual input in the primary visual cortex (V1), both in terms of cortical territory devoted to processing input from each eye and in terms of single-neuron responses ([Schwarzkopf et al. 2007](#); [Vorobyov et al. 2007](#)). Ocular dominance maps in the region of V1 representing the central visual field were obtained using optical imaging of intrinsic signals,

Figure 3. Ocular dominance maps in the primary visual cortex of cats subjected to selective rearing consisting of daily monocular and binocular exposure periods. Each of the three kittens shown had 7 hours of total daily visual exposure, of which different amounts were binocular exposure (BE), as indicated above each maps. Percentages give the amount of cortical territory averaged across both hemispheres that were dominated by the DE. Each map shows the left cortical hemisphere on the left, the right hemisphere on the right, separated by the inter-hemispheric cleft. The top row (*a*(i)–(iii)) of maps shows as dark patches the regions of visual cortex responding to stimulation of the DE (the left eye in this case). The bottom row of maps (*b*(i)–(iii)) shows as dark patches the regions of visual cortex responding to stimulation of the NE (the right eye in this case). (i) DE activity patches are very sparse in the absence of any BE, (ii) they are reduced compared with the NE at 0.5 hours BE, (iii) but close to normal at 1 hours BE per day.

a technique that uses differences in absorption and scatter of incident red light between more active and less active areas of the cortical surface ([Bonhoeffer & Grinvald 1996](#)).

In a cohort of cats that had received a total of 7 hours daily visual exposure, animals with 1 hour or 2 hours of BE per day exhibited close to normal OD maps, with roughly equal territory responding to each eye. However, when daily binocular exposure was further reduced, the patched eye was under-represented in the visual cortex, as shown in [figure 3](#). With 0.5 hour of BE, this under-representation was modest but it became pronounced with further reduction of the daily period of BE. In parallel, orientation maps revealed normal responses through both eyes after 1 hour of daily BE or more but reduced signals through the patched eye when daily BE was 0.5 hour or less; this reduction was mainly due to a loss in responsiveness rather than a loss of orientation selectivity ([Schwarzkopf et al. 2007](#)). In another cohort of animals that received only 3.5 hours of daily visual exposure, the binocular exposure needed to maintain a normal balance between left- and right-eye cortical responses was not reduced proportionally (i.e. it was not half of that in the 7 hours group) but remained approximately the same as in the 7 hours cohort. As with visual acuity, there was no effect of the order of exposure (BE first or second each day) on the outcome, arguing against consolidation by sleep of

Figure 4. DE territory in V1. The relative cortical area (averaged across both cortical hemispheres) dominated by the DE in each animal is plotted against the daily amount of binocular exposure. Cortical area is normalized relative to the value expected for normal rearing which is set to 100 per cent. Data from the cohort of animals that received a total of 7 hours visual exposure per day are represented by circles and those from the 3.5 hours cohort by squares. The shading of symbols indicates whether binocular experience preceded or followed monocular deprivation (filled squares, 3.5 hours BE before ME; open squares, 3.5 hours BE after ME; filled circles, 7 hours BE before ME; open circles, 7 hours BE after ME). There was no significant effect of the sequence of daily visual experience in either the 3.5 hours cohort or the 7 hours cohort. All data represent mean ± 1 s.e.m. An exponential function, described by the equation $f(t) = -70.70e^{-1.824t} + 99.02$, is fitted to the combined data (dotted line).

the type of visual experience received last each day. The fit of an exponential curve to the combined group data (figure 4) revealed that approximately 1 hour 49 min of daily BE were required for the DE to attain 95 per cent of the 50 per cent territory for each eye expected for normal rearing (Schwarzkopf *et al.* 2007); this value is in good agreement with the results of our behavioural studies (Mitchell *et al.* 2003, 2006).

By analogy to our behavioural studies, we further assessed the effects on visual cortical ocular dominance maps of splitting the daily period of binocular exposure into two equal parts, one given before and one after the period of ME. We found that just as in terms of visual acuity, the outcome was essentially the same as giving a single BE period of half the length, i.e. the two exposure periods did not add up in their effectiveness (Schwarzkopf *et al.* 2007). We do not yet know whether the detrimental effect of ME alone is similarly affected if this exposure is broken up into more than one episode a day. It is important to note that very brief periods of BE are not *per se* insufficient to allow normal cortical responses to be maintained, since animals reared with just 15 min of daily BE in the absence of any other visual experience developed normal ocular dominance and orientation maps (Schwarzkopf 2007; Schwarzkopf *et al.* 2007). As in our behavioural studies, binocular experience had to be concordant to be efficacious, since an animal reared with base in prisms in front of both eyes and 1 hour of BE exhibited a level of deprivation evident from its ocular dominance maps that was akin to animals that had just 15 min of concordant BE (Schwarzkopf 2007).

Single-cell recordings from the same animals that had been imaged were directed at left- or right-eye

dominated as well as binocular regions of V1. These revealed a moderate reduction in binocularity with decreasing daily amounts of BE (Vorobyov *et al.* 2007) but little effect on orientation selectivity of neurons dominated by the part-time DE (Schwarzkopf 2007). More significantly, analysis of responses to binocular disparity stimuli showed that the proportion of truly disparity selective cells declined with decreasing daily BE. At the same time, the depth of phase modulation of the population of disparity selective cells decreased, as did the intertrial reliability with which a selective cell's optimal phase was signalled. Thus, subtle deficits in the presumed cortical substrate of stereopsis were detected in rearing conditions where visual acuities and functional maps appeared to be normal (Vorobyov *et al.* 2007). This result indicates that other visual functions may be affected in cases where visual acuity and its presumed neurophysiological substrate is not (see below for further discussion).

(b) Studies of the effects of mixed early visual input in monkeys

Results quite similar to ours have been obtained from macaque monkeys that wore diffuser lenses in front of one eye for all but 1, 2 or 4 hours each day during which time the animals had unrestricted binocular vision. However, in contrast to the strict limits placed on the total visual experience of the cats in our studies, the monkeys were kept in their usual colony room with a fixed 12 hours light: dark cycle. A noteworthy aspect of the rearing was the fact that the period of BE occurred in the middle of the 12 hours light cycle so that the period of ME was effectively split in two which may have reduced its efficacy. This regimen of mixed visual input was maintained from 3 to 21 weeks of age, followed by normal vision until approximately 4 years of age. Behavioural tests of contrast sensitivity were started at 18 months of age. Compared with animals without any daily binocular vision, 2 hours were found to reduce the deficits by 90 per cent, and 4 hours preserved near-normal contrast sensitivity (Wensveen *et al.* 2006). In line with the behavioural results, ocular dominance distributions among single cells recorded from V1 approached normal with between 2 and 4 hours of binocular exposure. The critical duration of daily BE required to allow the development of normal vision in the two eyes of monkeys was very similar to that observed in cats when this duration is expressed as a proportion of the total daily visual exposure (4 out of 12 or 33%). Moreover, as with cats, binocular interactions elicited by gratings of varying relative disparity were notably abnormal in all groups, even with 4 hours of daily binocular exposure (Sakai *et al.* 2006). Although the interpretation of these data is complicated by the long period of normal binocular experience intercalated between the rearing and testing phases, which might have given rise to either or both unquantified recovery as well as intervals of discordant input due to the development of a temporary strabismus, the agreement between the data from cats and monkeys is quite remarkable in terms of the protective effects of daily periods of BE and the proportion of the daily input that this daily input represents. Moreover, in both species, there appears to

be limits to the protective effects as the abnormal binocular interactions of V1 neurons predict that the protective effects of daily BE on spatial vision may not extend to measures of stereoscopic vision.

4. ANIMAL STUDIES ON REHABILITATION OF DEPRIVATION AMBLYOPIA

(a) *Studies of different patching regimens*

In addition to the powerful ability of daily periods of binocular visual input to prevent the development of amblyopia, animal studies have also revealed that such input can also be of benefit when added as a component of conventional patching therapy following the development of amblyopia. Study of the effectiveness of occlusion of the fellow eye in promoting recovery from amblyopia in humans is made notoriously difficult owing to the issue of compliance with any prescribed patching regimen. Until the recent development of methods that allow documentation of the actual amount of daily occlusion of young children (Fielder *et al.* 1995) it was difficult if not impossible to measure dose–response curves for the benefits of occlusion or for that matter investigate the potential benefits of daily binocular input in a systematic manner. Such studies have long been possible in animals and were in fact begun over 25 years ago on kittens that had been monocularly deprived from near birth to generate a model of deprivation amblyopia.

The first experiments (Mitchell *et al.* 1984a,b) explored the consequences of full-time occlusion (by eyelid suture) of the non-amblyopic eye. Unlike previous studies of early administration of such occlusion ‘therapy’ (Blakemore & Van Sluyters 1974; Movshon 1976a,b; Blakemore *et al.* 1981), the new studies investigated the permanence of any recovery after full-time occlusion was terminated to allow visual input to both eyes. The very surprising finding was that much of the vision recovered by the amblyopic eye during occlusion of the fellow eye was lost quite quickly in approximately three weeks, while the vision of the recently occluded eye improved but at a slower pace (Mitchell *et al.* 1984a,b). Subsequent systematic study of the consequences of full-time occlusion of the NE imposed for different lengths of time and on kittens of various ages revealed that these events were virtually ubiquitous although of different magnitude (Murphy & Mitchell 1987; Mitchell 1991). Significantly, the eventual outcome in many situations was that both eyes finished up amblyopic (bilateral amblyopia) with the depth of amblyopia usually greatest in the initially DE that started amblyopic. In only a very rare set of circumstances did both eyes develop normal vision (Mitchell 1991).

At first, this outcome would be thought to be at variance with clinical experience, although similar effects have been reported in the clinical literature (von Noorden 1985). Moreover, clinicians counsel (e.g. von Noorden 1996, pp. 514–6) against the use of protracted periods of patching since this can lead to an impairment of the vision of the patched eye (occlusion amblyopia). However, there was a very important difference between the animal experiments and clinical practice; whereas the animals never received any

binocular visual exposure during the period of patching, in clinical practice it happens every day no matter how strict the instruction might be for patching to be continuous. Binocular input occurs before the patch is applied each day, during the night, and with every period of non-compliance. In part because daily binocular exposure nearly always occurs and also for theoretical reasons, systematic explorations (Mitchell *et al.* 1986; Mitchell 1991) were carried out on the effectiveness of part-time patching. For these experiments, occlusion of the NE could not be performed by eyelid suture owing to their short daily duration. Instead, kittens wore the same neoprene foam masks described earlier to cover the NE for part of each day that was restricted to 7 hours of visual input. The masks were removed to allow a daily period of binocular visual exposure. The animals were housed in total darkness with their mother and littermates for the remaining 17 hours.

The initial studies (Mitchell *et al.* 1986) were conducted on kittens that were monocularly deprived by eyelid suture to six weeks after which various regimens of part-time occlusion of the NE were imposed for the next six weeks. The animals were fully trained on the jumping stand prior to the start of part-time patching, so that the change in the vision of the DE could be monitored longitudinally both during and after patching. Improvement of the vision of the DE occurred in all cases during the six-week period of part-time occlusion to a degree that was proportional to the amount of daily occlusion. Of course, with increasing daily occlusion of the NE, the vision of this eye was also reduced proportionally with the greatest effect (apparent blindness) observed with full-time patching. Of far greater interest, however, were the events that followed termination of six weeks part-time patching with the most impressive results being exhibited by animals that received either 3.5 (50%) or 5 (70%) hours patching each day. During the six weeks of part-time patching, the acuity of the DE improved while that of the other eye declined with both effects greater for animals patched for 5 hours than 3.5 hours. However, after part-time patching was discontinued, the acuity of the initially DE continued to improve accompanied by a slower increase in the acuity of the other (recently patched) eye such that the acuity of both eyes achieved normal levels after five weeks. Thus, it appeared as if the six weeks of part-time patching was sufficient to set in place a substrate that permitted further improvement in the vision of both eyes after it was terminated. Perhaps the daily periods of binocular input during part-time patching fostered the establishment of connections with the two eyes of increasingly similar strength with time. The strength of these (binocular) connections with the two eyes might be anticipated to increase even more during the subsequent period of exclusive binocular input leading eventually to the development of equal and normal vision in both eyes. Subsequently, the effects of part-time occlusion were examined on animals that had been monocularly deprived to 8 and 10 weeks of age (Mitchell 1991). In both cases, the only condition of part-time patching that led to a beneficial outcome, namely the eventual achievement of normal acuity in

both eyes, was 5 hours (70%) of daily patching. Patching conditions that resulted in equal grating acuity in the two eyes also resulted in no measurable deficits, in contrast in sensitivity functions or vernier acuity (Mitchell 1991).

An interesting contrast between the results obtained in these studies as compared with those described earlier on prevention of amblyopia was the differing requirement for concordant visual input during the daily period of BE. Whereas it was necessary for binocular input to be concordant for prevention, the same amount of prismatic dissociation of the visual input to the two eyes during the BE portion of part-time patching did not impede recovery (Mitchell 1991). This different outcome may be due to the very different degree of strength of connections from the two eyes in the two situations; for animals in the part-time patching study the DE begins with poor connections to the cortex and possibly receptive fields having larger dimensions that could tolerate a greater degree of prismatic misalignment than those of the animals in the prevention study.

Of course the elimination of measurable deficits in visual acuity in the two eyes does not necessarily mean that vision is normal as it leaves open the question of the status of binocular vision and of stereoscopic vision in particular. Formal investigation was made using two different approaches of the depth perception of monocularly deprived kittens that had recovered normal grating acuity after part-time patching (Mitchell *et al.* 1994). The first and indirect approach was to compare monocular and binocular depth thresholds (Mitchell *et al.* 1979) using real objects displayed in such a way as to reduce monocular depth cues as much as possible. Superior performance using two eyes implies but does not prove the existence of a uniquely binocular depth cue such as stereopsis. To prove the existence of stereopsis, it is necessary to demonstrate directly that the animal can perceive depth on the basis of retinal disparity cues alone. The second method used anaglyphic presentation of red and green random dot stereograms that were viewed by the cats through red and green filters mounted upon scleral contact lenses (Ptito *et al.* 1991).

Of the five cats that had recovered normal grating acuity in both eyes, three exhibited substantial (7.2- to 9.4-fold) superiority of binocular over monocular performance on depth judgements. The magnitude of the binocular superiority as well as the absolute magnitude of their depth thresholds were similar to those observed in normal cats and were consistent with the conclusion that they had acquired local stereopsis. The other two cats that showed only a small binocular superiority (1.4–2.1) had worn masks that held prisms before each eye during the daily period of binocular exposure that either had the same (base up) or had opposite orientation for the two eyes to produce, respectively, concordant or discordant binocular input. Notably, both cats achieved normal visual acuity in each eye yet the lack of a large binocular superiority in depth judgements implied that they did not possess stereopsis. Small differences in the concordance of binocular input, while not having an impact on the ability of the DE to recover visual acuity, nevertheless

did prevent the development of binocular interactions sufficient to support stereopsis for these two animals.

In order to establish whether the animals that exhibited substantial superior binocular performance of the jumping stand truly possessed stereoscopic vision, two animals were administered additional tests to determine whether they possessed global stereopsis as reflected by an ability to perceive depth in random dot stereograms (the appearance of a virtual horizontal rectangle imaged with a retinal disparity of 40 min of arc). Neither cat was able to reach criterion performance in 1000 trials (25 sessions, each of 40 trials per day), suggesting that they had not acquired global stereopsis, a form of stereoscopic vision that requires the neural computation of numerous local disparities in order to perceive a hidden global form.

Although there appears to be a less strict requirement for concordant visual input during the daily period of BE for successful recovery of visual acuity in amblyopic animals as opposed to that required for prevention of amblyopia, the residual deficits in stereopsis in the former situation reveal that nonetheless recovery is incomplete. The greater importance of daily concordant binocular input for the prevention of amblyopia may reflect the high degree of match between the strength of connections from the two eyes with cortical cells at the outset of the period of mixed visual input. By contrast, for the amblyopic animals in the studies of recovery, connections of cortical cells with the DE would probably be weaker and have lower spatial resolution than those from the other eye at the onset of patching and hence may permit some degree of discordance of visual input.

While this review concentrates on the deficits in acuity and binocular vision associated with amblyopia, there are of course other visual functions that are affected, particularly in primates (for a review see Kiorpes 2006). For example, amblyopic monkeys display deficits in the detection of motion at fine spatial scales and slow speeds that go beyond what could be expected on the basis of their deficits in spatial resolution (Kiorpes *et al.* 2006). Deficits have also been observed in terms of contour integration; in some animals, these can even be seen in the fellow eye as well as in the amblyopic eye (Kozma & Kiorpes 2003). Neurophysiological deficits in early (primary) visual cortex are generally insufficient to explain these losses, suggesting additional deficits at higher levels of the visual pathways (Kiorpes & McKee 1999). This point is reinforced by observations of deficits of global form perception (Hess *et al.* 1999; Lewis *et al.* 2002; Jeffrey *et al.* 2004; Wang *et al.* 2007) and holistic processing of faces in human amblyopes (Le Grand *et al.* 2004).

5. ISSUES TO EXPLORE IN THE FUTURE

- (i) Are the results of mixed early visual input explained in terms of a match to a pre-existing anatomical substrate or do they reflect an intrinsic bias for matched binocular input?

The preference demonstrated for concordant binocular visual input has been discussed above in relation

to its match with the relatively mature binocular anatomical substrate that existed in V1 when mixed daily visual input was initiated. However, it is equally possible that our results reflect a bias towards whatever substrate exists at four weeks of age, not just the binocular substrate that normally exists then. One way to test this would be to apply mixed visual input to animals with an abnormal cortex at four weeks. Such an abnormal cortex could be produced by monocular deprivation initiated at eye-opening and extended to four weeks. Thus, at the time that daily mixed visual input starts, ME that matches the experience during the first four weeks may be the preferred input, so that short daily periods of such ME that effectively perpetuate the original deprivation may offset *longer* daily periods of BE. However, it is possible that binocular input may be still preferred even after it has been altered by a prior period of deprivation.

- (ii) Other benefits of daily periods of BE—does it potentiate recovery afterwards?

Our experiments examined only the immediate effects of the month-long period of mixed visual input, so that we may have missed the potential benefits of suboptimal daily periods of BE that were too short to allow the development of normal vision after four weeks of mixed visual input. For example, kittens from the 7 hours cohort that received only 1 hour of BE each day, although exhibiting an acuity in the DE approximately half of that of the fellow eye, may show substantial improvement in vision to normal levels in subsequent weeks. Preliminary data indicate that this may indeed be the case.

6. THE PRESENT AND POTENTIAL FUTURE IMPACT OF WORK ON ANIMAL MODELS FOR TREATMENT OF AMBLYOPIA

- (i) Current attempts to establish optimum times for intervention and length and nature of occlusion therapy as well as attempt to measure and improve compliance

Numerous animal studies on the anatomical, physiological and behavioural effects of reverse occlusion have shown that full-time patching of the fellow eye in order to ameliorate vision in an amblyopic eye does not (or only rarely) result in long-term restoration of normal cortical function and normal visual acuity in both eyes.

However, two alternative strategies provide for a better outcome, at least in cats. First, simply reopening the initially DE, without closing the other eye, and allowing binocular vision for some time results in substantial recovery of visual acuity (Mitchell & Gingras 1998; Mitchell *et al.* 2001) as well as in near-normal cortical responses to stimulation of the previously DE (Kind *et al.* 2002). This recovery critically depends on normal alignment of the visual axes of the two eyes during the binocular vision period. If the fellow eye is made strabismic after the reopening of the DE, recovery is much more limited (Kind *et al.* 2002).

In contrast to cats, monocularly deprived monkeys exhibit little or no recovery of vision upon reopening of the closed eye (Hubel *et al.* 1977; Blakemore *et al.* 1981), which may be due to a higher incidence of strabismus in the post-deprivation period in monkeys (Quick *et al.* 1989) and a greater susceptibility of V1 neurons to small misalignments (Kind *et al.* 2002). However, the finding of poor recovery from an early episode of deprivation in monkeys is at odds with the substantial recovery of vision observed under comparable conditions in humans with early monocular form deprivation (Jacobson *et al.* 1981).

The second approach to improved recovery from early form deprivation is to alternate periods of patching of the previously NE with periods of (concordant) binocular viewing on a daily basis. As summarized in greater detail earlier, success critically depends on the duration of the original period of deprivation and on the exact regimen of part-time reverse occlusion; the best outcomes in both eyes are obtained when the initially NE is patched for 3.5–5 hours a day (Mitchell 1991). These results are in good agreement with our more recent finding, reviewed above in more detail, that amblyopia as a consequence of monocular deprivation is avoided if the patch is removed for approximately 2 hours per day (Mitchell *et al.* 2003, 2006).

These studies have a direct bearing on current attempts to establish the optimal strategy for the treatment of amblyopia (of any aetiology) in children and adolescents. The first point of note is that lasting improvement in terms of the acuity of the amblyopic eye can be achieved in approximately a quarter of patients with either anisometropic and strabismic amblyopia through optimal refractive correction alone (Stewart *et al.* 2004a; Cotter & Pediatric Eye Disease Investigator Group 2006; Cotter *et al.* 2007). Presumably, the underlying cause of the success of this treatment is a restoration of concordant binocular visual input, which we have shown to be critical for recovery from the effects of monocular deprivation (Kind *et al.* 2002). Moreover, based on data from both cats and monkeys, it is possible that if 30 per cent of the visual input each day of children with anisometropia is made binocular and concordant by refractive correction then amblyopia might be prevented.

The conventional treatment of amblyopia involves full- or part-time patching of the good eye in order to force the use of the amblyopic eye. Owing to the risk to the fellow eye, full-time patching is rarely employed nowadays. Since the critical period in humans is generally thought to end at 7–8 years of age, it is not surprising that the outcome of occlusion treatment is better in younger children than in those older than 6 years (Stewart *et al.* 2004b). However, full-time occlusion has been reported as successful in children aged 9–14 years (Park *et al.* 2004), and part-time occlusion (with patching of 2–6 hours per day) in children aged 7–17 years (Scheiman *et al.* 2005); in most children aged 7–12 years, the improvement in acuity persists for at least a year after termination of patching (Hertle *et al.* 2007). Even patients aged 13–17 years may still respond positively to part-time patching if they have not been treated previously, although it is

not yet known whether their visual acuity improvement is permanent (Scheiman *et al.* 2005).

Since the greatest threat to successful patching treatment of amblyopia in childhood is lack of compliance, the assessment of what constitutes the optimal patching regimen and the comparison with the results from animal studies must be based on actual, not prescribed occlusion times. Using objective monitoring of occlusion times by means of an occlusion dose monitor (Fielder *et al.* 1995), Stewart and colleagues have recently designed a study that combines refractive adaptation with monitored part-time patching (Stewart *et al.* 2002). They reported a steady increase in the gain in visual acuity with the total number of hours of occlusion of the non-amblyopic eye ('occlusion dose') up to approximately 400 hours, with most improvement occurring in the first six weeks of patching, as well as an increase in visual acuity gain with the dose rate, i.e. the number of hours of occlusion per day, up to a rate of 2–3 hours (Stewart *et al.* 2004b). Children receiving 3–6 hours of occlusion a day improved by as much as those receiving longer periods, but those with dose rates of under 3 hours a day fared significantly worse (Stewart *et al.* 2007). Moreover, children under the age of 4 required a lower dose rate than older children (Stewart *et al.* 2007). The critical importance of a certain minimum dose rate to achieving the best possible visual outcome is fully in line with the conclusions drawn from animal studies (Mitchell 1991; Mitchell *et al.* 2003; Schwarzkopf *et al.* 2007).

- (ii) The role of specific training therapies: the potential importance of active concordant binocular stimulation (stereo displays)

In addition to the patching of the fellow eye, treatment of amblyopia has for over a century included various training strategies designed to improve the vision of the amblyopic eye, to reduce suppression of this eye when both eyes are open and/or to train fusion and binocular vision. A growing recognition of residual plasticity in the visual cortex of adult animals has inspired application of various perceptual training procedures to the amblyopic eye of adults, where it was thought that motivation would be higher than in young children. Indeed, considerable success in improving visual acuity has been reported in recent years from the use of various perceptual training paradigms on both juveniles and adult amblyopes. Whereas the earliest attempts, such as training on vernier alignment (Levi & Polat 1996), showed only limited generalization beyond the specific trained target orientation, later attempts to ameliorate the deficient spatial interactions in low-level vision in amblyopia by perceptual training led to improvement of other aspects of vision such as Snellen acuity, counting and contrast sensitivity (e.g. Polat *et al.* 2004; Levi 2005; Zhou *et al.* 2006; Li *et al.* 2007; see also Levi & Li 2009).

Important as monocular perceptual training may be, a clear implication of our animal work is that rehabilitation of amblyopia would receive an additional boost from specific training designed to enhance binocular connections in general and of stereoscopic vision in particular. Such specific training of binocular

functions may increase either or both the rate or extent of the amelioration of amblyopia. Further support for therapy directed at the development of stereopsis lies in the finding of McKee *et al.* (2003), that amblyopes with poor or absent stereopsis exhibit the greatest severity of amblyopia. Therapies directed towards both the reduction of the severity of amblyopia and the enhancement of binocular vision may be more successful than procedures designed just to reduce amblyopia. Encouragement for the design and use of therapies directed towards binocular function receives strong support from animal work, which demonstrates retention of binocular connections even after two months of monocular deprivation (Freeman & Ohzawa 1988). A recent treatment study as yet published only in abstract form (Mansouri *et al.* 2008) that employed binocular coherent motion stimuli revealed intact binocular interactions in eight amblyopic subjects when the information content of the stimuli presented to the fellow eye was reduced by an appropriate amount that was titrated individually for each subject. Moreover, a pilot study of binocular training with such specifically matched dichoptic stimuli produced *both* a significant improvement of the visual acuity of the amblyopic eye and of binocular vision.

Another important component of recovery from deprivation appears to be active exploration of the environment which in animal experiments can be encouraged by enrichment (Sale *et al.* 2007). These findings have important implications for the refinement of treatment for human patients. The first is that certain visual activities may be beneficial in terms of the extent of acuity improvement. The American Pediatric Eye Disease Investigator Group (PEDIG), for example, found that amblyopic children prescribed near-vision activities during a daily 2 hours patching regimen exhibited slightly greater improvement in amblyopic eye visual acuity than those assigned to non-near activities (Holmes & Pediatric Eye Disease Investigator Group 2005). Second, conventional patching treatment suffers from two major disadvantages: patching frequently fails to achieve good improvement in acuity owing to a lack of compliance and patching by its nature cannot improve binocular cooperation. A recently developed virtual-reality-based display system aims at the treatment of amblyopia by stimulating both eyes simultaneously, using interactive three-dimensional games and videos which are shown to the patient via a stereo display (Eastgate *et al.* 2005). Preliminary results with this system from a group of six children aged 5 to 7 years demonstrated an improvement in acuity in five children after just a few hours of treatment (Waddingham *et al.* 2005). Approaches such as this will have a far better acceptance among children, but the case study results will have to be followed up by a controlled trial to establish their significance and to assess whether binocular function is also improved.

The potential potency of specific therapy designed to enhance binocular function in adults has received considerable attention from the lyrical descriptions of the emergence of stereoscopic vision in an adult neurobiologist, popularized by Oliver Sacks as Stereo Sue (Barry & Mims 2006; Sacks 2006). Although diagnosed with a strabismus when only a few months

old, surgical intervention at 2 and 7 years of age produced cosmetic alignment of the two eyes but left her without stereoscopic vision. Nevertheless, following binocular therapy initiated in her 40s she has acquired stereopsis.

(iii) Potential promise from rodent studies

In recent years, mice and rats have increasingly been used for studies of the visual system, including models of visual cortical plasticity. They offer the advantage of a short life cycle and, in particular, in the case of mice, the possibility of studying visual cortical plasticity at a molecular level due to the availability of transgenic animals. The binocular segment of the primary visual cortex in mice and rats exhibits a similar response to monocular deprivation as carnivores and primates in terms of an overall shift in ocular dominance towards the open eye (for a review see Hübener 2003), and this is accompanied by a moderate reduction in visual acuity, assessed either directly in behavioural tests or indirectly via visual evoked potentials.

A number of recent studies have suggested novel approaches to how visual cortical plasticity might be enhanced, at least in rodents, and these may have implications for the future treatment of amblyopia. One important finding is that prior experience of a particular type of visual input can enhance plasticity in response to the same visual input later on in life, and even in adulthood. Specifically, mice that had experienced brief periods of monocular deprivation, causing but a transient shift in ocular dominance, earlier in life, were much more susceptible to subsequent deprivation many weeks later. This effect was specific to repeated deprivation of the *same* eye (Hofer *et al.* 2006). This sort of conditioning of the capacity for plasticity in the visual cortex may be useful in the design of visual training paradigms for the treatment of amblyopia.

Another potentially significant observation is that environmental enrichment can accelerate visual system development (Cancedda *et al.* 2004) and that environmental enrichment in adult rats that have been long-term monocularly deprived can restore normal visual acuity and cortical ocular dominance; this recovery is due to reduced GABAergic inhibition in the visual cortex (Sale *et al.* 2007). However, it should be noted that such recovery does not occur by simply reopening of the DE but requires reverse lid suture, i.e. closure of the fellow eye. Even more remarkable is a recent report that the effects of long-term monocular deprivation can be reversed in adult rats if they are placed in a dark room for 10 days prior to reopening of the DE and reverse lid suture (He *et al.* 2007). The beneficial effect of dark rearing has been attributed to a relative decrease in the expression of GABA_A receptors relative to excitatory AMPA receptors and a return to the juvenile form of NMDA receptors (He *et al.* 2006). The benefits of diverse manipulations such as dark rearing or environmental enrichment in adulthood have also been attributed to a reset of the balance of excitatory–inhibitory cortical circuits to a juvenile state (Morishita & Hensch 2008).

Finally, studies on rodents indicate possible avenues for treating amblyopia at the cellular or molecular level.

These interventions are based on an identification of factors that lead to the closure of the critical period and of strategies to reverse that closure. It has become evident that neuronal plasticity is inhibited, for example, by the aggregation of extracellular matrix molecules such as chondroitin sulphate proteoglycans (CSPGs; Berardi *et al.* 2003) and by myelin-associated proteins such as Nogo-A, whose recognition by the Nogo receptor NgR activates a cascade of intracellular events, which inhibits axonal growth (Niederöst *et al.* 2002). Enzymatic digestion of CSPGs has been shown to restore visual cortical plasticity in adult rats (Pizzorusso *et al.* 2002) and to reverse the effects of long-term monocular deprivation in combination with reverse occlusion (Pizzorusso *et al.* 2006). In NgR^{-/-} knockout mice, the critical period is extended into adulthood (McGee *et al.* 2005), implying that blockade of the Nogo/NgR pathway may be a way to enhance visual cortical plasticity into adulthood.

Although a number of studies on rodents point at avenues for future treatment of amblyopia, some caveats need to be considered carefully. First, the potential for experience-dependent modification of the visual cortex in adulthood seems generally greater in rodents than in carnivores or primates (Sawtell *et al.* 2003; Pham *et al.* 2004; Fischer *et al.* 2007). Second, as an animal model of human amblyopia, rodents cannot be employed without reservations, since even long-term form deprivation causes only moderate reductions in acuity of only an octave (logMAR 0.3) or less (Pizzorusso *et al.* 2006). Finally, all studies thus far that have reported recovery from monocular deprivation in adult rats have required lid suture of the fellow eye. As discussed above, a regimen of full-time patching would be problematic in cats or primates.

All experimental procedures were approved by local ethical review and carried out under licence from the appropriate British, Canadian and German government authorities.

We wish to thank our colleagues (Drs K. Murphy, P. Kind, D. S. Schwarzkopf and V. Vorobyov) and technicians (Marc Jones and Jan Kennie) for their contributions to some of the studies described in this review. Our work has been supported by grants from NSERC, the McDonnell Foundation and by the UK Medical Research Council.

REFERENCES

- Barry, S. R. & Mims, J. L. 2006 Correspondence: followup on: Sacks O. Regaining binocular stereoscopic vision in adulthood. A case report. A neurologist's notebook: Stereo Sue. Why two eyes are better than one. *Binoc. Vis. Strab. Quart.* **21**, 199–202.
- Bear, M. F. 2003 Bidirectional synaptic plasticity: from theory to reality. *Phil. Trans. R. Soc. B* **358**, 649–655. (doi:10.1098/rstb.2002.1255)
- Berardi, N., Pizzorusso, T., Ratto, G. M. & Maffei, L. 2003 Molecular basis of plasticity in the visual cortex. *Trends Neurosci.* **26**, 369–378. (doi:10.1016/S0166-2236(03)00168-1)
- Birch, E. E. & Stager, D. R. 1996 The critical period for surgical treatment of dense congenital unilateral cataract. *Invest Ophthalmol. Vis. Sci.* **37**, 1532–1538.
- Blakemore, C. & Van Sluyters, R. C. 1974 Reversal of the physiological effects of monocular deprivation in kittens:

- further evidence for a sensitive period. *J. Physiol.* **237**, 195–216.
- Blakemore, C., Garey, L. J. & Vital-Durand, F. 1978 The physiological effects of monocular deprivation and their reversal in the monkey's visual cortex. *J. Physiol.* **283**, 223–262.
- Blakemore, C., Vital-Durand, F. & Garey, L. J. 1981 Recovery from monocular deprivation in the monkey. I. Reversal of physiological effects in the visual cortex. *Proc. R. Soc. B* **213**, 399–423. (doi:10.1098/rspb.1981.0072)
- Bonhoeffer, T. & Grinvald, A. 1996 Optical imaging based on intrinsic signals. The methodology. In *Brain mapping: the methods* (eds A. W. Toga & J. C. Mazziotta), pp. 55–97. London, UK: Academic Press.
- Cancedda, L., Putignano, E., Sale, A., Viegi, A., Berardi, N. & Maffei, L. 2004 Acceleration of visual system development by environmental enrichment. *J. Neurosci.* **24**, 4840–4848. (doi:10.1523/JNEUROSCI.0845-04.2004)
- Chino, Y. M., Smith III, E. L., Yoshida, K., Cheng, H. & Hamamoto, J. 1994 Binocular interactions in striate cortical neurons of cats reared with discordant visual inputs. *J. Neurosci.* **14**, 5050–5067.
- Cotter, S. A. & Pediatric Eye Disease Investigator Group 2006 Treatment of anisometropic amblyopia in children with refractive correction. *Ophthalmology* **113**, 895–903. (doi:10.1016/j.ophtha.2006.01.068)
- Cotter, S. A. *et al.* 2007 Treatment of strabismic amblyopia with refractive correction. *Am. J. Ophthalmol.* **143**, 1060–1063. (doi:10.1016/j.ajo.2007.02.029)
- Crair, M. C., Gillespie, D. C. & Stryker, M. P. 1998 The role of visual experience in the development of columns in cat visual cortex. *Science* **279**, 566–570. (doi:10.1126/science.279.5350.566)
- Crowley, J. C. & Katz, L. C. 2000 Early development of ocular dominance columns. *Science* **290**, 1321–1324. (doi:10.1126/science.290.5495.1321)
- Crowley, J. C. & Katz, L. C. 2002 Ocular dominance development revisited. *Curr. Opin. Neurobiol.* **12**, 104–109. (doi:10.1016/S0959-4388(02)00297-0)
- Daw, N. W. 1998 Critical periods and amblyopia. *Arch. Ophthalmol.* **116**, 502–505.
- Daw, N. W. 2002 *Visual development*, 2nd edn. New York, NY: Springer.
- Daw, N. W. 2003 Critical periods in the visual system. In *Neurobiology of infant vision* (eds B. Hopkins & S. P. Johnson), pp. 43–103. Westport, CT: Praeger.
- Daw, N. W., Fox, K., Sato, H. & Czepita, D. 1992 Critical period for monocular deprivation in the cat visual cortex. *J. Neurophysiol.* **67**, 197–202.
- Eastgate, R. M. *et al.* 2005 Modified virtual reality technology for treatment of amblyopia. *Eye* **20**, 370–374. (doi:10.1038/sj.eye.6701882)
- Epelbaum, M., Milleret, C., Buisseret, P. & Dufier, J. L. 1993 The sensitive period for strabismic amblyopia in humans. *Ophthalmology* **100**, 323–327.
- Fawcett, S. L., Wang, Y. Z. & Birch, E. E. 2005 The critical period for susceptibility of human stereopsis. *Invest Ophthalmol. Vis. Sci.* **46**, 521–525. (doi:10.1167/iov.04-0175)
- Fielder, A. R., Irwin, M., Auld, R., Cocker, K. D., Jones, H. S. & Moseley, M. J. 1995 Compliance in amblyopia therapy: objective monitoring of occlusion. *Br. J. Ophthalmol.* **79**, 585–589. (doi:10.1136/bjo.79.6.585)
- Fischer, Q. S., Graves, A., Evans, S., Lickey, M. E. & Pham, T. A. 2007 Monocular deprivation in adult mice alters visual acuity and single-unit activity. *Learn. Mem.* **14**, 277–286. (doi:10.1101/lm.392107)
- Freeman, R. D. & Ohzawa, I. 1988 Monocularly deprived cats: binocular tests of cortical cells reveal functional connections from the deprived eye. *J. Neurosci.* **8**, 2491–2506.
- Giffin, F. & Mitchell, D. E. 1978 The rate of recovery of vision after early monocular deprivation in kittens. *J. Physiol.* **274**, 511–537.
- Gingras, G., Mitchell, D. E. & Hess, R. F. 2005 The spatial localization deficit in visually deprived kittens. *Vision Res.* **45**, 975–989. (doi:10.1016/j.visres.2004.10.021)
- He, H. Y., Hodos, W. & Quinlan, E. M. 2006 Visual deprivation reactivates rapid ocular dominance plasticity in adult visual cortex. *J. Neurosci.* **26**, 2951–2955. (doi:10.1523/JNEUROSCI.5554-05.2006)
- He, H. Y., Ray, B., Dennis, K. & Quinlan, E. M. 2007 Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nat. Neurosci.* **10**, 1134–1136. (doi:10.1038/nn1965)
- Hensch, T. K. 2005 Critical period plasticity in local cortical circuits. *Nat. Rev. Neurosci.* **6**, 877–888. (doi:10.1038/nrn1787)
- Hertle, R. W., Scheiman, M. M., Beck, R. W., Chandler, D. L. & Pediatric eye disease investigator group 2007 Stability of visual acuity improvement following discontinuation of amblyopia treatment in children aged 7 to 12 years. *Arch. Ophthalmol.* **125**, 655–659. (doi:10.1001/archophth.125.5.655)
- Hess, R. F. & Holliday, I. E. 1992 The spatial localization deficit in amblyopia. *Vis. Res.* **32**, 1319–1339. (doi:10.1016/0042-6989(92)90225-8)
- Hess, R. F., Wang, Y. Z., Demanins, R., Wilkinson, F. & Wilson, H. R. 1999 A deficit in strabismic amblyopia for global shape detection. *Vision Res.* **39**, 901–914. (doi:10.1016/S0042-6989(98)00157-6)
- Hofer, S. B., Mrcic-Flogel, T. D., Bonhoeffer, T. & Hübener, M. 2006 Prior experience enhances plasticity in adult visual cortex. *Nat. Neurosci.* **9**, 127–132. (doi:10.1038/nn1610)
- Holmes, J. M. & Clarke, M. P. 2006 Amblyopia. *Lancet* **367**, 1343–1351. (doi:10.1016/S0140-6736(06)68581-4)
- Holmes, J. M. & Pediatric Eye Disease Investigator Group 2005 A randomized pilot study of near activities versus non-near activities during patching therapy for amblyopia. *J. Am. Assoc. Ped. Ophthalmol. Strabismus* **9**, 129–136. (doi:10.1016/j.jaapos.2004.12.014)
- Hooks, B. M. & Chen, C. 2007 Critical periods in the visual system: changing views for a model of experience-dependent plasticity. *Neuron* **56**, 312–326. (doi:10.1016/j.neuron.2007.10.003)
- Horton, J. C. & Hocking, D. R. 1996 An adult-like pattern of ocular dominance columns in striate cortex of newborn monkeys prior to visual experience. *J. Neurosci.* **16**, 1791–1807.
- Hubel, D. H. & Wiesel, T. N. 1963 Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *J. Neurophysiol.* **26**, 994–1002.
- Hubel, D. H. & Wiesel, T. N. 1965 Binocular interaction in striate cortex of kittens reared with artificial squint. *J. Neurophysiol.* **28**, 1041–1059.
- Hubel, D. H. & Wiesel, T. N. 1968 Receptive fields and functional architecture of monkey striate cortex. *J. Physiol.* **195**, 215–243.
- Hubel, D. H. & Wiesel, T. N. 1970 The period of susceptibility to the physiological effects of unilateral eye closure in kittens. *J. Physiol.* **206**, 419–436.
- Hubel, D. H. & Wiesel, T. N. 2004 *Brain and visual perception*. New York, NY: Oxford University Press.

- Hubel, D. H., Wiesel, T. N. & LeVay, S. 1977 Plasticity of ocular dominance columns in monkey striate cortex. *Phil. Trans. R. Soc. B* **278**, 377–409. (doi:10.1098/rstb.1977.0050)
- Hübener, M. 2003 Mouse visual cortex. *Curr. Opin. Neurobiol.* **13**, 413–420. (doi:10.1016/S0959-4388(03)00102-8)
- Jacobson, S. G., Mohindra, I. & Held, R. 1981 Development of visual acuity in infants with congenital cataracts. *Br. J. Ophthalmol.* **65**, 727–735. (doi:10.1136/bjo.65.10.727)
- Jeffrey, B. G., Wang, Y. Z. & Birch, E. E. 2004 Altered global shape discrimination in deprivation amblyopia. *Vision Res.* **44**, 167–177. (doi:10.1016/j.visres.2003.09.009)
- Kind, P. C., Mitchell, D. E., Ahmed, B., Blakemore, C., Bonhoeffer, T. & Sengpiel, F. 2002 Correlated binocular activity guides recovery from monocular deprivation. *Nature* **416**, 430–433. (doi:10.1038/416430a)
- Kiorpes, L. 2006 Visual processing in amblyopia: animal studies. *Strabismus* **14**, 3–10. (doi:10.1080/09273970500536193)
- Kiorpes, L. & Mckee, S. P. 1999 Neural mechanisms underlying amblyopia. *Curr. Opin. Neurobiol.* **9**, 480–486. (doi:10.1016/S0959-4388(99)80072-5)
- Kiorpes, L., Tang, C. & Movshon, J. A. 2006 Sensitivity to visual motion in amblyopic macaque monkeys. *Vis. Neurosci.* **23**, 247–256. (doi:10.1017/S0952523806232097)
- Kozma, P. & Kiorpes, L. 2003 Contour integration in amblyopic monkeys. *Vis. Neurosci.* **20**, 577–588. (doi:10.1017/S0952523803205113)
- Le Grand, R., Mondloch, C. J., Maurer, D. & Brent, H. P. 2004 Impairment in holistic face processing following early visual deprivation. *Psychol. Sci.* **15**, 762–768. (doi:10.1111/j.0956-7976.2004.00753.x)
- LeVay, S., Wiesel, T. N. & Hubel, D. H. 1980 The development of ocular dominance columns in normal and visually deprived monkeys. *J. Comp. Neurol.* **191**, 1–51. (doi:10.1002/cne.901910102)
- Levi, D. M. 2005 Perceptual learning in adults with amblyopia: a reevaluation of critical periods in human vision. *Dev. Psychobiol.* **46**, 222–232. (doi:10.1002/dev.20050)
- Levi, D. M. & Li, R. W. 2009 Improving the performance of the amblyopic visual system. *Phil. Trans. R. Soc. B* **364**, 399–407. (doi:10.1098/rstb.2008.0203)
- Lewis, T. L. & Maurer, D. 2005 Multiple sensitive periods in human visual development: evidence from visually deprived children. *Dev. Psychobiol.* **46**, 163–183. (doi:10.1002/dev.20055)
- Levi, D. M. & Polat, U. 1996 Neural plasticity in adults with amblyopia. *Proc. Natl Acad. Sci. USA* **93**, 6830–6834. (doi:10.1073/pnas.93.13.6830)
- Lewis, T. L., Ellemberg, D., Maurer, D., Wilkinson, F., Wilson, H. R., Dirks, M. & Brent, H. P. 2002 Sensitivity to global form in Glass patterns after early visual deprivation in humans. *Vision Res.* **42**, 939–948. (doi:10.1016/S0042-6989(02)00041-X)
- Li, R. W., Provost, A. & Levi, D. M. 2007 Extended perceptual learning results in substantial recovery of positional acuity and visual acuity in juvenile amblyopia. *Invest Ophthalmol. Vis. Sci.* **48**, 5046–5051. (doi:10.1167/iovs.07-0324)
- Loudon, S. E. & Simonsz, H. J. 2005 The history of the treatment of amblyopia. *Strabismus* **13**, 93–106. (doi:10.1080/0927397050949818)
- Mansouri, B., Thompson, B. & Hess, R. F. 2008 Intact binocular interaction in amblyopia: a new gateway to treatment of amblyopia. *Invest Ophthalmol. Vis. Sci.* **49**, 2594.
- McGee, A. W., Yang, Y., Fischer, Q. S., Daw, N. W. & Strittmatter, S. M. 2005 Experience-driven plasticity of visual cortex limited by myelin and nogo receptor. *Science* **309**, 2222–2226. (doi:10.1126/science.1114362)
- McKee, S. P., Levi, D. M. & Movshon, J. A. 2003 The pattern of visual deficits in amblyopia. *J. Vis.* **3**, 380–405. (doi:10.1167/3.5.5)
- Mitchell, D. E. 1988 Animal models of human strabismic amblyopia: some observations concerning the interpretation of the effects of surgically and optically induced strabismus in cats and monkeys. In *Advances in neural and behavioral development* (ed. P. G. Shinkman), pp. 209–269. Norwood, NJ: Ablex Publishing Corp.
- Mitchell, D. E. 1991 The long-term effectiveness of different regimens of occlusion on recovery from early monocular deprivation in kittens. *Phil. Trans. R. Soc. B* **333**, 51–79. (doi:10.1098/rstb.1991.0060)
- Mitchell, D. E. & Gingras, G. 1998 Visual recovery after monocular deprivation is driven by absolute, rather than relative, visually evoked activity levels. *Curr. Biol.* **8**, 1179–1182. (doi:10.1016/S0960-9822(07)00489-7)
- Mitchell, D. E. & MacKinnon, S. 2002 The present and potential impact of research on animal models for clinical treatment of stimulus deprivation amblyopia. *Clin. Exp. Optom.* **85**, 5–18.
- Mitchell, D. E. & Timney, B. 1984 Postnatal development of function in the mammalian visual system. In *Handbook of physiology: sec. I. The nervous system* (ed. I. Darian-Smith), pp. 507–555. Bethesda, MD: American Physiological Society.
- Mitchell, D. E., Giffin, F. & Timney, B. 1977 A behavioural technique for the rapid assessment of the visual capabilities of kittens. *Perception* **6**, 181–193. (doi:10.1068/p060181)
- Mitchell, D. E., Kaye, M. & Timney, B. N. 1979 Assessment of depth perception in cats. *Perception* **8**, 389–396. (doi:10.1068/p080389)
- Mitchell, D. E., Murphy, K. M. & Kaye, M. G. 1984a Labile nature of the visual recovery promoted by reverse occlusion in monocularly deprived kittens. *Proc. Natl Acad. Sci. USA* **81**, 286–288. (doi:10.1073/pnas.81.1.286)
- Mitchell, D. E., Murphy, K. M. & Kaye, M. G. 1984b The permanence of the visual recovery that follows reverse occlusion of monocularly deprived kittens. *Invest Ophthalmol. Vis. Sci.* **25**, 908–917.
- Mitchell, D. E., Murphy, K. M., Dzioba, H. A. & Horne, J. A. 1986 Optimization of visual recovery from early monocular deprivation in kittens: implications for occlusion therapy in the treatment of amblyopia. *Clin. Vision. Sci.* **1**, 173–177.
- Mitchell, D. E., Ptito, M. & Lepore, F. 1994 Depth perception in monocularly deprived cats following part-time reverse occlusion. *Eur. J. Neurosci.* **6**, 967–972. (doi:10.1111/j.1460-9568.1994.tb00591.x)
- Mitchell, D. E., Gingras, G. & Kind, P. C. 2001 Initial recovery of vision after early monocular deprivation in kittens is faster when both eyes are open. *Proc. Natl Acad. Sci. USA* **98**, 11 662–11 667. (doi:10.1073/pnas.201392698)
- Mitchell, D. E., Kind, P. C., Sengpiel, F. & Murphy, K. 2003 Brief daily periods of binocular vision prevent deprivation-induced acuity loss. *Curr. Biol.* **13**, 1704–1708. (doi:10.1016/j.cub.2003.09.026)
- Mitchell, D. E., Wynberg, J., Sengpiel, F., Kennie, J., Murphy, K. & Kind, P. 2005 Prevention of deprivation-induced acuity loss is determined by the proportion of daily visual exposure that is binocular. *Soc. Neurosci.* **2005**, 37 013.

- Mitchell, D. E., Kind, P. C., Sengpiel, F. & Murphy, K. 2006 Short periods of concordant binocular vision prevent the development of deprivation amblyopia. *Eur. J. Neurosci.* **23**, 2458–2466. (doi:10.1111/j.1460-9568.2006.04755.x)
- Morgan, M. J. 1977 *Molyneux's question*. Cambridge, UK: Cambridge University Press.
- Morishita, H. & Hensch, T. K. 2008 Critical period revisited: impact on vision. *Curr. Opin. Neurobiol.* **18**, 101–107. (doi:10.1016/j.conb.2008.05.009)
- Movshon, J. A. 1976a Reversal of the physiological effects of monocular deprivation in the kitten's visual cortex. *J. Physiol.* **261**, 125–174.
- Movshon, J. A. 1976b Reversal of the behavioural effects of monocular deprivation in the kitten. *J. Physiol.* **261**, 175–187.
- Movshon, J. A. & Kiorpes, L. 1990 The role of experience in visual development. In *Development of sensory systems in mammals* (ed. J. R. Coleman), pp. 155–202. New York, NY: Wiley.
- Murphy, K. M. & Mitchell, D. E. 1987 Reduced visual acuity in both eyes of monocularly deprived kittens following a short or long period of reverse occlusion. *J. Neurosci.* **7**, 1526–1536.
- Movshon, J. A. & Van Sluyters, R. C. 1981 Visual neural development. *Annu. Rev. Psychol.* **32**, 477–522. (doi:10.1146/annurev.ps.32.020181.002401)
- Murphy, K. M. & Mitchell, D. E. 1991 Vernier acuity of normal and visually deprived cats. *Vision Res.* **31**, 253–266. (doi:10.1016/0042-6989(91)90116-M)
- Niederöst, B., Oertle, T., Fritsche, J., McKinney, R. A. & Bandtlow, C. E. 2002 Nogo-a and myelin-associated glycoprotein mediate neurite growth inhibition by antagonistic regulation of RhoA and Rac1. *J. Neurosci.* **22**, 10 368–10 376.
- Olson, C. R. & Freeman, R. D. 1980 Profile of the sensitive period for monocular deprivation in kittens. *Exp. Brain Res.* **39**, 17–21. (doi:10.1007/BF00237065)
- Park, K. H., Hwang, J.-M. & Ahn, J. K. 2004 Efficacy of amblyopia therapy initiated after 9 years of age. *Eye* **18**, 571–574. (doi:10.1038/sj.eye.6700671)
- Pham, T. A., Graham, S. J., Suzuki, S., Barco, A., Kandel, E. R., Gordon, B. & Lickey, M. E. 2004 A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB. *Learn. Mem.* **11**, 738–747. (doi:10.1101/lm.75304)
- Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Fawcett, J. W. & Maffei, L. 2002 Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* **298**, 1248–1251. (doi:10.1126/science.1072699)
- Pizzorusso, T., Medini, P., Landi, S., Baldini, S., Berardi, N. & Maffei, L. 2006 Structural and functional recovery from early monocular deprivation in adult rats. *Proc. Natl Acad. Sci. USA* **103**, 8517–8522. (doi:10.1073/pnas.06026 57103)
- Polat, U., Ma-Naim, T., Belkin, M. & Sagi, D. 2004 Improving vision in adult amblyopia by perceptual learning. *Proc. Natl Acad. Sci. USA* **101**, 6692–6697. (doi:10.1073/pnas.0401200101)
- Ptito, M., Lepore, F. & Guillemot, J. P. 1991 Stereopsis in the cat: behavioural demonstration and underlying mechanisms. *Neuropsychologia* **29**, 443–464. (doi:10.1016/0028-3932(91)90004-R)
- Quick, M. W., Tigges, M., Gammon, J. A. & Boothe, R. G. 1989 Early abnormal visual experience induces strabismus in infant monkeys. *Invest Ophthalmol. Vis. Sci.* **30**, 1012–1017.
- Rathjen, S. & Lowel, S. 2000 Early postnatal development of functional ocular dominance columns in cat visual cortex. *Neuroreport* **11**, 2363–2367. (doi:10.1097/00001 756-200008030-00006)
- Rauschecker, J. P. 1991 Mechanisms of visual plasticity: Hebb synapses, NMDA receptors and beyond. *Physiol. Rev.* **71**, 587–615.
- Sacks, O. 2006 A neurologist's notebook. Stereo Sue. *The New Yorker*, 19 June 2006, pp. 64–75.
- Sakai, E., Bi, H., Maruko, I., Zhang, B., Zheng, J., Wensveen, J., Harwerth, R. S., Smith III, E. L. & Chino, Y. M. 2006 Cortical effects of brief daily periods of unrestricted vision during early monocular form deprivation. *J. Neurophysiol.* **95**, 2856–2865. (doi:10.1152/jn.01265.2005)
- Sale, A., Vetencourt, J. F. M., Medini, P., Cenni, M. C., Baroncelli, L., De Pasquale, R. & Maffei, L. 2007 Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat. Neurosci.* **10**, 679–681. (doi:10.1038/nn1899)
- Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S. & Bear, M. F. 2003 NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* **38**, 977–985. (doi:10.1016/S0896-6273(03)00323-4)
- Scheiman, M. M., Hertle, R. W., Beck, R. W., Edwards, A. R., Birch, E. E. & Pediatric Eye Disease Investigator Group 2005 Randomized trial of treatment of amblyopia in children aged 7 to 17 years. *Arch. Ophthalmol.* **123**, 437–447. (doi:10.1001/archophth.123.4.437)
- Schwarzkopf, D. S. 2007 The weighting of binocular experience in visual cortical development. PhD dissertation, Cardiff University.
- Schwarzkopf, D. S., Vorobyov, V., Mitchell, D. E. & Sengpiel, F. 2007 Brief daily binocular vision prevents monocular deprivation effects in visual cortex. *Eur. J. Neurosci.* **25**, 270–280. (doi:10.1111/j.1460-9568.2006.05273.x)
- Sengpiel, F. & Kind, P. C. 2002 The role of activity in development of the visual system. *Curr. Biol.* **12**, R818–R826. (doi:10.1016/S0960-9822(02)01318-0)
- Sengpiel, F., Blakemore, C., Kind, P. C. & Harrad, R. 1994 Interocular suppression in the visual cortex of strabismic cats. *J. Neurosci.* **14**, 6855–6871.
- Sengpiel, F., Jirmann, K. U., Vorobyov, V. & Eysel, U. T. 2006 Strabismic suppression is mediated by inhibitory interactions in the primary visual cortex. *Cereb. Cortex* **16**, 1750–1758. (doi:10.1093/cercor/bhj110)
- Silva, A. J., Kogan, J. H., Frankland, P. W. & Kida, S. 1998 CREB and memory. *Annu. Rev. Neurosci.* **21**, 127–148. (doi:10.1146/annurev.neuro.21.1.127)
- Smith III, E. L., Chino, Y. M., Ni, J. R., Cheng, H., Crawford, M. L. J. & Harwerth, R. S. 1997 Residual binocular interactions in the striate cortex of monkeys reared with abnormal binocular vision. *J. Neurophysiol.* **78**, 1353–1362.
- Stewart, C. E., Fielder, A. R., Stephens, D. A. & Moseley, M. J. 2002 Design of the monitored occlusion treatment of amblyopia study (MOTAS). *Br. J. Ophthalmol.* **86**, 915–919. (doi:10.1136/bjo.86.8.915)
- Stewart, C. E., Moseley, M. J., Fielder, A. R., Stephens, D. A. & MOTAS Cooperative 2004a Refractive adaptation in amblyopia: quantification of effect and implications for practice. *Br. J. Ophthalmol.* **88**, 1552–1556. (doi:10.1136/bjo.2004.044214)
- Stewart, C. E., Moseley, M. J., Stephens, D. A. & Fielder, A. R. 2004b Treatment dose-response in amblyopia therapy: the monitored occlusion treatment of amblyopia study (MOTAS). *Invest Ophthalmol. Vis. Sci.* **45**, 3048–3054. (doi:10.1167/iov.04-0250)
- Stewart, C. E., Stephens, D. A., Fielder, A. R., Moseley, M. J. & ROTAS Cooperative 2007 Objectively monitored patching regimens for treatment of amblyopia: randomised trial. *Br. Med. J.* **335**, 707–713. (doi:10.1136/bmj.39301.460150.55)

- Tychsen, L. 2005 Can ophthalmologists repair the brain in infantile esotropia? Early surgery, stereopsis, monofixation syndrome, and the legacy of Marshall Parks. *J. Am. Assoc. Pediatric Ophthalmol. Strabismus* **9**, 510–521. (doi:10.1016/j.jaapos.2005.06.007)
- Vaegan & Taylor, D. 1979 Critical period for deprivation amblyopia in children. *Trans. Ophthalmol. Soc. UK* **99**, 432–439.
- von Noorden, G. K. 1985 Idiopathic amblyopia. *Am. J. Ophthalmol.* **100**, 214–217.
- von Noorden, G. K. 1996 *Binocular vision and ocular motility: theory and management of strabismus*, 5th edn. St. Louis, MO: CV Mosby.
- von Noorden, G. K., Campos, E. C. & Keech, R. V. 2002 *Binocular vision and ocular motility: theory and management of strabismus*, pp. 1–672, 6th edn. Louis, MO: CV Mosby.
- Vorobyov, V., Schwarzkopf, D. S., Mitchell, D. E. & Sengpiel, F. 2007 Monocular deprivation reduces reliability of visual cortical responses to binocular disparity stimuli. *Eur. J. Neurosci.* **26**, 3553–3563.
- Waddingham, P. E. *et al.* 2005 Preliminary results from the use of the novel interactive binocular treatment (I-BiT[trade]) system, in the treatment of strabismic and anisometropic amblyopia. *Eye* **20**, 375–378. (doi:10.1038/sj.eye.6701883)
- Wang, J., Ho, C. S. & Giaschi, D. E. 2007 Deficient motion-defined and texture-defined figure-ground segregation in amblyopic children. *J. Pediatr. Ophthalmol. Strabismus* **44**, 363–371.
- Wensveen, J. M., Harwerth, R. S., Hung, L. F., Ramamirtham, R., Kee, C. S. & Smith III, E. L. 2006 Brief daily periods of unrestricted vision can prevent form-deprivation amblyopia. *Invest Ophthalmol. Vis. Sci.* **47**, 2468–2477. (doi:10.1167/iovs.05-0885)
- Wiesel, T. N. & Hubel, D. H. 1963 Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* **26**, 1003–1017.
- Wiesel, T. N. & Hubel, D. H. 1965 Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J. Neurophysiol.* **28**, 1029–1040.
- Worth, C. A. 1929 *Squint: its causes, pathology and treatment*, 6th edn. Philadelphia, PA: Blakiston's Sons & Co.
- Zhang, B., Bi, H., Sakai, E., Maruko, I., Zheng, J., Smith III, E. L. & Chino, Y. M. 2005 Rapid plasticity of binocular connections in developing monkey visual cortex (V1). *Proc. Natl Acad. Sci. USA* **102**, 9026–9031. (doi:10.1073/pnas.0500280102)
- Zhou, Y., Huang, C., Xu, P., Tao, L., Qiu, Z., Li, X. & Lu, Z. L. 2006 Perceptual learning improves contrast sensitivity and visual acuity in adults with anisometropic amblyopia. *Vision Res.* **46**, 739–750. (doi:10.1016/j.visres.2005.07.031)