Review

Amblyopia: Background to the Special Issue on Stroke Recovery

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ABSTRACT: *In this introductory article, we summarize the evidence from humans and animal models on the shaping of postnatal visual development by focused binocular input. When balanced input is missing during a sensitive period, deficits emerge, including seemingly permanent impairments in visual acuity that are labeled amblyopia. Rodent models have identified neurochemical changes that control the onset of such sensitive periods and molecular and structural brakes that lead to the diminution of the plasticity thereafter. Both animal and human studies of amblyopia have recently identified exciting ways to remediate vision in adulthood that bear some similarity to the interventions that have proved successful in promoting recovery from stroke. © 2012 Wiley Periodicals, Inc.* Dev Psychobiol 54: 224–238, 2012.

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INTRODUCTION

Human infants are born with very immature vision: their visual acuity is 40 times worse than that of adults with normal eyes, they require a log unit more contrast to see even large objects, they have no binocular vision or sensitivity to direction of motion, and there are serious limitations on their perception of objects and faces (reviewed in Braddick & Atkinson, 2011; Maurer, Mondloch, & Lewis, 2007b). Visual perception improves dramatically over the first 6 months with a sixfold improvement in acuity, the onset of binocular vision and rapid improvements in stereoacuity, and the emergence of motion perception and all object and face processing skills, at least in rudimentary form. Subsequent refinements last until age 7 for low-level vision (acuity, contrast sensitivity, local motion, peripheral vision) but continue into adolescence for some higher-level aspects of motion, object, and face perception (e.g., Hadad, Maurer, & Lewis, 2010; Kovács, 2000; Lewis et al., 2004; Mondloch, Le Grand, & Maurer, 2002; Robbins, Shergill, Maurer, & Lewis, 2011).

Visual input is instrumental in shaping these postnatal changes. The classic work of Hubel and Wiesel with visually deprived cats and monkeys revealed that normal visual development depends on normal visual input during an early critical period. When such input was missing during the critical period, neurons in the visual cortex of the adult cat and monkey had abnormally large receptive fields, poor spatial resolution, and limited binocularity (Hubel & Wiesel, 1970; Wiesel & Hubel, 1963, 1965). Behavioral tests revealed parallel defects in visual acuity (Mitchell & Timney, 1982). A later period of abnormal visual input had no such effect, thereby defining an end to the critical period for damage. Later research indicated a tapering off of the adverse effects of deprivation rather than an abrupt end to plasticity, and the terminology was changed from critical to sensitive period.

Similar to the effects of visual deprivation in animals, abnormal early visual input in humans leads to a condition called amblyopia (from the Greek roots *amblyos* [blunt] and *opia* [vision]). Amblyopia refers to a seemingly permanent reduction in visual acuity secondary to abnormal early visual input caused by a peripheral abnormality that prevented coordinated binocular input to the visual cortex. A similar perturbation later in life has no adverse effects, a pattern confirming

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that there is a sensitive period early in life when visual input is necessary for normal visual development. After that period, the system appears to be sufficiently hardwired to no longer be vulnerable. A common assumption is that after the sensitive period, the visual system is also no longer sufficiently plastic for any therapeutic intervention to be effective. However, recent success in promoting recovery from cortical damage caused by stroke in adulthood suggests that the adult cortex retains some potential for plasticity. In this special issue, six experts on stroke recovery describe the current understanding of the mechanisms underlying recovery from stroke. The five commentaries consider the implications of that adult plasticity for understanding developmental changes in plasticity more generally and its specific implications for promoting plasticity in the adult brain. A particular case motivating this special issue is amblyopia and the possibility that lessons from stroke recovery may provide clues to its effective treatment in adulthood. This introductory article provides background on amblyopia, the sensitive periods during which the human visual system is vulnerable to damage, and the stabilization that makes it more resistant to change. It also summarizes a mouse model of amblyopia that has revealed the mechanisms of plasticity and stabilization and that provides clues about how to restore plasticity after the end of the sensitive period.

BACKGROUND ON AMBLYOPIA

Amblyopia occurs in humans because of abnormal visual input during a sensitive period that begins shortly after birth. Normal visual input can be prevented during this sensitive period because it is blocked by cataracts or a closed eyelid (ptosis), because the eyes are misaligned, or because the two eyes focus at different distances. The peripheral problem can be fixed by removing the cataracts, tightening the eyelid, aligning the eyes, or correcting the refractive error. Nevertheless, subsequent visual development is often abnormal, leading to amblyopia. The three types of amblyopia refer to the cause of the original abnormal visual input:

(a) Deprivation amblyopia when the deficits occur after early cataract or ptosis.
(b) Strabismic amblyopia when the deficits occur after early eye misalignment.
(c) Anisometropic amblyopia when the deficits occur after an early period with unequal refractive errors.

Although the initial problem was peripheral and corrected, amblyopia arises at the cortical level: abnormal early visual input leads to abnormal tuning of cortical circuits. The deficits extend beyond acuity to other aspects of both low-level vision (e.g., contrast sensitivity, peripheral vision, binocular vision) and higher-level integrative vision (e.g., perception of global motion, global form, faces), with the exact pattern of deficits differing across the three types of amblyopia (McKee, Levi, & Movshon, 2003). In adult amblyopes, there is no abnormality in the eye that can account for the deficits and no prescription for glasses that can fix them.

Amblyopia is usually unilateral—the eye that had the cataract or that did not fixate because of the misalignment or refractive error will develop poor acuity, while the fellow eye, which fixated focused input during development, will develop (almost) normally. The fact that there are subtle deficits in the fellow eye, even when there has been no patching indicates that normal development requires not only visual input to each eye, but also coordinated binocular signals. Indeed, in the cat, small periods of binocular input can offset the adverse effects of longer periods of monocular deprivation (Mitchell, Kind, Sengpiel, & Murphy, 2003). In rarer cases, congenital cataracts in both eyes lead to bilateral deprivation amblyopia.

It is difficult to find an accurate estimate of the incidence of amblyopia, in part because it varies with the swiftness of diagnosis and treatment during childhood and because an unbiased estimate requires assessment of a large representative sample of the population, not just those who are hospitalized, seen at an eye clinic, or report for military service. An incidence of just over 3% was found in two large scale studies of Australian adults, studies that were successful in sampling almost all adults over a specific age (40 and 49, respectively) in two different geographic regions (Attebo et al., 1998; Brown et al., 2000). In both samples, there were more cases of anisometropic than of strabismic amblyopia and very few cases of deprivation amblyopia.

The standard clinical treatment for amblyopia in young children is to fix any peripheral problem (e.g., prescribe the right glasses, surgically align the two eyes) and, in unilateral cases, patch the ''good eye'' to encourage usage of the previously deprived eye. This treatment regimen parallels the findings from animal models that the adverse effects of eye lid suture on visual cortical neurons is worse after monocular deprivation than after binocular deprivation, and that the adverse effects after monocular deprivation can be mitigated or even eliminated by reverse suture, that is, by shutting the ''good eye'' at the same time the originally deprived eye is opened (e.g., Wiesel & Hubel, 1965). In human treatment, to avoid damage to the good eye, the amount of patching is adjusted by frequent monitoring of its acuity. Patching is usually tapered off around age 7, the age when children with normal

eyes achieve adult-like acuity and, traditionally, the presumed end of the sensitive period.

MULTIPLE SENSITIVE PERIODS FOR DAMAGE

When there was complete deprivation before treatment (e.g., dense bilateral cataracts), the child's initial acuity after treatment is like that of newborns but an accelerated recovery process begins immediately so that the deficit compared to normal slowly diminishes (Maurer, Lewis, Brent, & Levin, 1999). However, the child later fails to keep up with the normal pace of development so that adult acuity is abnormal. Such eventual deficits allow us to assess the sensitive period for damage, that is, the period when abnormal input will lead to later seemingly permanent deficits.

The duration of the sensitive period for damage differs for different visual capabilities, with a pattern for low-level vision largely following the Detroit principle (last hired, first fired) that late maturing functions are more vulnerable (Levi, 2005). Thus, in humans, early visual deprivation from bilateral cataracts causes later deficits in sensitivity to slow rates of flicker and high spatial frequencies (small stripes), both of which emerge postnatally and then mature relatively slowly. It spares (or causes smaller deficits in) sensitivity to high rates of flicker and low spatial frequencies (large stripes), both of which are present at birth and mature to adult levels relatively quickly (Ellemberg, Lewis, Maurer, Lui, & Brent, 1999). In both cases, as well, the outcome is worse after monocular than after binocular deprivation from birth, unless treatment was relatively early (before 2 months) and followed by aggressive patching of the fellow eye in monocular cases (Birch, Stager, Leffler, & Weakley, 1998; Ellemberg, Lewis, Maurer, & Brent, 2000). With such patching, the outcome after monocular deprivation from birth is as good as that after binocular deprivation of the same duration. Those patterns indicate that there are adverse effects from both deprivation and from uneven competition between the eyes for cortical connections, at least for those mediating low-level vision (but the pattern can be different for high level vision (Ellemberg, Lewis, Maurer, Brar, & Brent, 2002)). Although the outcome is better if treatment for bilateral congenital cataract occurs earlier within the first 2 months of life, even those treated by 1 month of age almost always later have deficits (Birch, Cheng, Stager, Weakley, & Stager, 2009).

Despite the fact that visually normal babies are not yet sensitive to high spatial frequencies or low contrast during the first 1–2 months of life, visual deprivation during that period prevents those abilities from developing later. These are examples of sleeper effects (Maurer et al., 2007b): visual input is necessary early in life in order for development to occur at a later age, perhaps because that early visual input sets up, or preserves, the requisite neural architecture. Sleeper effects also occur for higher-level visual integration: early visual deprivation prevents the normal development of sensitivity to global motion, global form, and configural face processing (Ellemberg et al., 2002; Le Grand, Mondloch, Maurer, & Brent, 2001, 2004; Lewis et al., 2002) despite the postnatal emergence of these capabilities in babies with normal eyes. Ostrovsky and colleagues (Ostrovsky, Andalman, & Sinha, 2006; Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009) did find surprising evidence for slow recovery of basic form and face perception (threshold sensitivity was not measured) in four patients despite very late treatment for eye disorders that compromised visual input during infancy and childhood, although some patterned visual input was received in at least some of these cases. Note, however, that as we found for children with well-documented and shorter binocular deprivation from birth, acuity did not recover fully. There is similar evidence for high-level deficits in strabismic amblyopia (Hess, Mcllhagga, & Field, 1997; Hess, Wang, Demanins, Wilkinson, & Wilson, 1999; Sharma, Levi, & Klein, 2000).

The results summarized so far all involve comparisons of visual outcome for different visual capabilities when the deprivation began at birth. To estimate sensitive periods, it is necessary to compare cases in which deprivation of comparable duration began at different postnatal ages. In the monkey, early monocular deprivation leads to deficits in the deprived eye in scotopic sensitivity (sensitivity at low light levels that stimulate the rods), photopic spectral sensitivity (sensitivity of different cone types at higher light levels), spatial contrast sensitivity (sensitivity to different spatial frequencies at low contrast), and binocular summation (better contrast sensitivity with binocular viewing, a measure that correlates with stereopsis) (Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986b). The deficits can be avoided if deprivation begins postnatally, but the age at which the sensitive period for damage ends varies with the visual capability: 3 months for scotopic sensitivity, 6 months for photopic spectral sensitivity, 18–24 months for spatial contrast sensitivity, and after 24 months for binocular vision. These findings establish that there is not just one visual sensitive period for a species but rather that there are different sensitive periods during which different aspects of vision can be damaged.

In humans, the effects on visual deprivation on low-level vision largely follow the Detroit principle (Lewis

& Maurer, 2005): more slowly developing visual functions have longer sensitive periods during which they can be damaged. Thus, optokinetic nystagmus (OKN, a repetitive jerky eye movement elicited by a moving pattern) is initially asymmetrical in young infants when they are tested monocularly: it is elicited readily by stripes moving from the temporal visual field toward the nasal visual field (e.g., right to left for the right eye) but poorly, if at all, for stripes moving in the opposite direction (Lewis, Maurer, Chung, Holmes-Shannon, & Van, 2000). For wide, high contrast stripes, OKN becomes increasingly symmetrical over the first 3 months of life, but the asymmetry persists forever in patients who developed cataracts in both eyes any time during the first 18 months of life, regardless of the duration of the subsequent deprivation (Lewis, Maurer, & Brent, 1989). Visual acuity has a longer developmental trajectory—it improves until age 7 in children with normal eyes—and a longer sensitive period for damage from congenital cataracts—until about age 10 (Maurer, Mondloch, & Lewis, 2007a). Sensitivity to light in the mid-periphery has an even longer developmental trajectory—past age 7—and an even longer sensitive period for damage—until at least age 13 (Bowering, Maurer, Lewis, & Brent, 1993, 1997). In all of these cases, visual input is necessary to drive the entire period of normal development and for a period thereafter. In other words, visual input remains necessary for a period after adult function is achieved, presumably to stabilize the connections. When visual input is missing during that period, there is what Worth called amblyopia of extinction—deficits arising because connections have been extinguished.

Surprisingly, the only higher-level visual function for which the duration of the sensitive period has been investigated does not fit the Detroit principle: sensitivity to global motion (the overall direction of movement of disparate local motion trajectories) emerges postnatally and is refined over the next 14 years (Hadad, Maurer, & Lewis, 2011). Binocular deprivation from birth causes permanent large deficits. However, monocular deprivation from birth causes only small deficits in the previously deprived eye and monocular or binocular deprivation beginning postnatally from as early as 6 months of age causes no deficits at all, despite damaging acuity if it began anytime before about age 10 (Ellemberg et al., 2002). Thus, the sensitive period for damage to global motion ends by 6 months of age and the damage is greater after binocular than after monocular deprivation. Perhaps there is relative sparing after monocular deprivation because of the convergence of input across the visual field and between eyes that occurs at higher levels of the visual pathway. That convergence may allow input from one eye near birth to be sufficient to establish nearly normal neural architecture that can benefit the other eye once it is treated. Consistent with this interpretation, adults with strabismic amblyopia show no interocular transfer of low level motion aftereffects: after the good eye is adapted to one direction of motion, there is no impact on the perception of motion by the amblyopic eye, as would be expected if motion-sensitive cells in primary visual cortex do not have normal binocularity. However, they show completely normal transfer of global motion aftereffects mediated at higher levels of the visual pathway (McColl & Mitchell, 1998), a result suggesting that normal input from the nondeviating eye was sufficient to tune motion-sensitive cells in higher levels of the visual pathway and that connections to those cells remain from the initially misaligned eye.

The sensitive period for damage to binocular vision from eye misalignment appears to begin postnatally. In children with normal eyes, the first evidence of stereopsis emerges abruptly around 3 months of age, stereoacuity improves rapidly until around 1 year of age, and then gradual improvement continues until around age 3 (Birch, Gwiazda, & Held, 1982; Birch & Petrig, 1996). Studies of children with congenital esotropia (misalignment in which one eye turns in) that began in the first few postnatal months and that was corrected by surgical eye alignment at different postnatal ages indicate that the system becomes vulnerable around 2.5–3 months of age, with no evidence of damage to binocular vision from misalignment during the first 2 months of life. Beginning from 3 months of age, the damage is greater the longer the misalignment lasted (Banks, Aslin, & Letson, 1975; Birch, Stager, Wright, & Beck, 1998; Fawcett, Wang, & Birch, 2005). As a result, children with later treatment for congenital esotropia are less likely to develop stereopsis or any other sign of binocular vision. For children with onset of esotropia after early infancy, usually caused by difficulty focusing on near objects because of farsightedness, the sensitive period for damage to binocular vision does not begin until about 11 months of age, peaks at about 20 months, and then tails off to near zero around 6 years of age (Fawcett et al., 2005). Note that in both congenital and late onset esotropia, the sensitive period for damage begins postnatally, consistent with electrophysiological evidence that 2 weeks of eye misalignment in the monkey causes a greater reduction in the sensitivity of neurons in the primary visual cortex to binocular cues if it began at 6 weeks of age than if it began at 2 weeks of age (Kumagami, Zhang, Smith, & Chino, 2000). Like the damage to acuity from visual deprivation, the sensitive period for damage to binocular vision continues past the age when normal development is complete (i.e., 6 vs. 3 years). That pattern suggests that

visual input between ages 3 and 6 is necessary to stabilize binocular connections.

All of the data on the adverse effects of visual deprivation and eye misalignment indicate that there is an age at which the system is sufficiently stable that a period of abnormal input does not cause any permanent damage. Although the age of stability varies across visual functions, the implication is that eventually each neural pathway becomes ''hard-wired'' and resistant to change. This has traditionally been thought of as the end of neural plasticity: not only the end of vulnerability but also, it was thought, the end of the period during which visual experience can refine the vision of the child with normal eyes or allow recovery in the child with amblyopia. For that reason, patching is traditionally discontinued in children with unilateral eye problems around age 7–8, the age when acuity becomes adult-like in children with normal eyes. The loss of plasticity is usually conceptualized as a systemic change, likely neurochemical, in the malleability of synaptic connections. However, as we show in ''Multiple Sensitive Periods for Damage'' Section, a mouse model of amblyopia indicates that the end of the sensitive period for damage results from the stabilizing of the system by both structural and neurochemical changes that keep it tuned to the environment in which it developed. That framework is useful for understanding the challenge of reinstating plasticity in the adult brain affected by stroke or amblyopia. It provides clues to manipulations that may be effective in removing the brakes in order to allow recovery from amblyopia after the sensitive period for damage or to allow recovery from cortical lesions induced by stroke. In ''Mouse Model of Amblyopia'' Section and ''Restoration of Plasticity in the Rodent Model'' Section, we give examples of successful interventions for amblyopia in the adult rodent and human, respectively, and discuss how they may be related to this framework. In ''Effective Late Treatments for Human Amblyopia'' Section, we discuss the relevance of the work on stroke.

MOUSE MODEL OF AMBLYOPIA

For a number of reasons, the mouse is a useful model system with which to dissect the neurochemical and structural determinants of critical periods for amblyopia. First, the effects of monocular deprivation on the development of its acuity are very tightly timed. In the visually normal mouse, acuity develops over the first postnatal month. Similar to humans, a brief period of monocular deprivation can cause an enduring loss of acuity, but only within a limited postnatal period. Thus, between postnatal days 20 (P20) and 40 (P40), just 4 days of monocular deprivation is sufficient to cause an enduring loss of acuity. As in humans, visual input is necessary for a short period even after acuity reaches adult functional levels (day 30), presumably for the crystallization of connections. Nevertheless, monocular deprivation just after eye opening (at 12 days) until P20 or after P40 has no appreciable effect on the normal development of acuity (Prusky & Douglas, 2003). Second, neural correlates for the loss of acuity can be examined directly in the binocular portion of mouse primary visual cortex (V1b). Unlike the case for humans, the critical period for damage does not begin at birth but only some time after eye opening at Day 12—and hence one can investigate the brain changes responsible for the onset of the critical period. During the critical period from P20 to P40, a short period of monocular deprivation (4 days) is sufficient to cause a shift in ocular dominance (Gordon & Stryker, 1996) and pruning of dendritic spines (Mataga, Mizuguchi, & Hensch, 2004), such that neurons in V1b lose their typical bias toward the contralateral eye in favor of the nondeprived, ipsilateral eye. Further deprivation eventually leads to altered thalmocortical afferents from the lateral geniculate nucleus into V1b (Antonini, Fagiolini, & Stryker, 1999). Third, as demonstrated below, the tremendous toolbox of mouse genetics allows one to manipulate candidate factors and to test hypothesized mechanisms.

The pivotal determinant of the onset of the visual critical period in the mouse appears to be an increase in inhibitory influences that balance the initial excitatory dominance (Hensch, 2005). Specifically, a postnatal increase in GABA synthesis triggers the sensitivity of acuity to monocular deprivation. When GABA synthesis is prevented by gene-targeted deletion of the synaptic isoform of glutamic acid decarboxylase (GAD65), brief monocular deprivation has no effect throughout life on ocular dominance, spine pruning, or acuity. The critical period can also be delayed by dark rearing (Cynader & Mitchell, 1980), which prevents the maturation of perisomatic GABA synapses (Katagirl, Fagiolini, & Hensch, 2007). Plasticity can be restored in the GAD65 knockout or dark-reared wild-type mouse by increasing post-synaptic sensitivity to GABA via administration of benzodiazepines—at any age (Fagiolini & Hensch, 2000; Iwai, Fagiolini, Obata, & Hensch, 2003). Conversely, the onset of the natural critical period can be accelerated by administration of benzodiazepines (Fagiolini et al., 2004), by prematurely boosting brain-derived neurotropic factor (BDNF) levels (Hanover, Huang, Tonegawa, & Stryker, 1999), or by particular homeoprotein transcription factors (Otx2), all of which accelerate the maturation of specific GABA circuits, the perisomatic, large basket cell (Sugiyama et al., 2008).

GABAergic inhibition may be important because it controls the structural changes underlying ocular dominance shifts, namely the secretion of extracellular proteases for spine elimination and the retraction of axons from thalamic neurons responding to the deprived eye (Antonini et al., 1999; Mataga et al., 2004). This is followed by axon outgrowth from thalamic neurons responding to the nondeprived eye and spine recovery once protease levels naturally return to baseline. It is noteworthy that the amblyopia model (induced by monocular deprivation) was the first to identify a physiological role for tissue-type plasminogen activator (tPA) in this type of rewiring of neural circuits in the brain (Mataga et al., 2004). This is in sharp contrast to the excitotoxic effects of tPA influx into the brain from the blood supply associated with stroke. Curiously, none of the dynamic anatomical events are seen following monocular deprivation in the adult rodent (Oray, Majewska, & Sur, 2004).

The end of the critical period may, therefore, arise either from a gradual depletion of factors enabling structural rewiring or from emergence of molecular ''brakes'' on plasticity that make it more difficult for new synapses to form. Evidence is mounting that molecular brakes play a pivotal role in diminishing plasticity at the same time that they serve to stabilize existing connections. One type of brake is the development of perineuronal nets that enwrap the large basket cells (Pizzorusso et al., 2002). Dissolving the perineuronal nets with chondroitinase injections into adult rat V1b renders the system plastic again. Ocular dominance shifts can be re-induced in normal adult rats by combining chondroitinase with monocular deprivation. Moreover, amblyopic rats can recover normal acuity, ocular dominance, and spine density by chronroitinase treatment combined with concurrent reverse suturing of the initially nondeprived eye (Pizzorusso et al., 2006).

A second type of brake on critical period plasticity is myelin-related signaling through the Nogo receptor (McGee, Yang, Fischer, Daw, & Strittmatter, 2005). The myelin sheath that forms around axons is replete with ligands that actively prevent axonal outgrowth. Deleting or blocking the Nogo receptor in adulthood can restore acuity after earlier monocular deprivation (Morishita & Hensch, unpublished data). Similarly, focal demyelination by the administration of lysolecithin or ethidium bromide leaves the adult mouse once again sensitive to monocular deprivation. These findings indicate that the physiological role of Nogo receptor signaling is to limit brain plasticity beyond a critical period. Gene expression changes after stroke are also more extensive in young compared to aged rats and include an up-regulation of both axonal growth-related proteins and the Nogo signaling system, suggesting time windows for therapeutic interventions and optimal training procedures (Li et al., 2010).

RESTORATION OF PLASTICITY IN THE RODENT MODEL

Given that the mechanisms involved in the recovery from stroke are similar to those that operate during normal development, it is conceivable that screens for molecules that contribute to synapse maturation might yield further permissive factors for stroke recovery. Recent studies have described a number of ways to restore visual plasticity in the adult rodent beyond the critical period (Morishita & Hensch, 2008). These successes are all the more surprising because a variety of approaches have been successful, despite the redundant brakes on plasticity that have been documented. For example, a second period of plasticity can be induced in the adult mouse by implanting fetal precursor cells to GABAergic cells (Southwell, Froemke, Alvarez-Buylia, Stryker, & Gandhi, 2010). Plasticity can also be restored by removing either of the structural brakes, that is, perineuronal nets or myelin (see ''Multiple Sensitive Periods for Damage'' Section). The implication is that the brain's default state may be plasticity and multiple checks are needed to keep stable the connections that match the organism's environment.

Importantly, plasticity has recently also been restored to the adult rodent's brain by a variety of less-invasive interventions, all of which may work by reducing intracortical inhibition: putting the animal into the dark (10 days) or into an enriched environment, or chronic administration of fluoxetine. After any of those manipulations, monocular deprivation once again induces shifts in ocular dominance and there is recovery from amblyopia induced earlier in life (He, Hodos, & Quinlan, 2006; He, Ray, Dennis, & Quinlan, 2007; Maya Vetencourt et al., 2008; Sale et al., 2007; Spolidoro, Sale, Berardi, & Maffei, 2009). The plasticity-inducing effects of environmental enrichment or fluoxetine are counteracted if intracortical inhibition is increased by infusion of benzodiazepine or diazepam, respectively (Maya Vetencourt et al., 2008; Sale et al., 2007). Clinical trials for fluoxetine in rescuing amblyopia are currently underway in Finland, India, and New Zealand (L. Maffei, personal communication, http://www.hermopharma.com/news-a-publication/120-first-patients-completed-the-amblyopia-phase-2a-study).

Thus, plasticity may be under constant regulation by top-down influences on excitatory:inhibitory circuit balance. The discovery of a molecular brake, Lynx1, on neuronal nicotinic acetylcholine receptors in adult

mouse V1b suggests that the presence of massive cholinergic innervation maintains the stability of the balance between inhibition and excitation in mature cortical networks (Morishita, Miwa, Heintz, & Hensch, 2010). Lynx1 is expressed at low levels during the critical period but increases dramatically thereafter. Mice lacking Lynx1 are the first animal model found to recover spontaneously from amblyopia. These findings raise the exciting possibility of remediating amblyopia in adulthood through neuromodulation by re-purposing clinically approved drugs that modulate cholinergic innervation. Consistent with this possibility, enhancing cholinergic tone with acetylcholinesterasae inhibitors restores visual acuity to amblyopic wild-type animals.

Following a stroke, the peri-infarct region transiently exhibits heightened tonic forms of inhibition, due to mis-regulation of the GABA transporter, GAT3 (Clarkson, Huang, Macisaac, Mody, & Carmichael, 2010). This may counteract recovery of function by excessive inhibition. Photothrombotic lesion of the somatosensory cortex impairs visual cortical plasticity farther caudally in the ipsi-lateral hemisphere (Greifzu, Schmidt, Schmidt, Kreikemeier, Witte, & Löwel, 2011). This stroke may have global impact by disrupting the cholinergic projections to other cortical regions in the same hemisphere. The noninvasive control of cholinergic neuromodulation might thereby enable learning in heightened states of arousal (like that induced by playing action video games) after stroke or amblyopia.

EFFECTIVE LATE TREATMENTS FOR HUMAN AMBLYOPIA

In recent years, a number of interventions have been successful in improving the acuity of older human children or adults with unilateral amblyopia caused by earlier misalignment (strabismus) and/or unequal refractive errors (anisometropia). To date, there has been no report of possible late recovery from deprivation amblyopia in humans. Some of the successful treatments for strabismic and anisometropic amblyopia are likely to be effective because they mitigate the unfavorable excitatory:inhibitory balance by reducing the impact of input to the good eye by its loss, patching, transcranial magnetic stimulation (TMS), or a pharmacological manipulation. Behavioral training has also been used effectively, but the mechanism is less clear, although it, too, may induce neurochemical changes that alter the excitatory:inhibitory balance.

Loss of the Good Eye

There are case reports of rapid improvements in the vision of the amblyopic eye of adults with strabismic and/or anisometropic amblyopia after the fellow ''good'' eye was lost to injury or disease—as if the amblyopic eye had formed neural connections that were being inhibited by the fellow eye and/or as if it has some potential to be tuned by visual input even in adulthood once the excitatory:inhibitory balance is more favorable (El Mallah, Chakravarthy, & Hart, 2000; Leonards & Sireteanu, 1993; Rahi et al., 2002; Vereecken & Brabant, 1984; Wilson, 1992). One of the most striking cases involves anisometropic amblyopia in the left eye in a patient whose dominant right eye with normal visual acuity was enucleated 1 day after an accident at 19 years of age (Kaarniranta & Kontkanen, 2003). Over the next 1–2 years, the acuity of the amblyopic left eye progressed from 20/60 to a normal value of 20/20, which was maintained over the next 15 years. Another example comes from a patient with strabismic amblyopia in the right eye whose normal left eye was damaged by a penetrating injury at age 44 that led to retinal detachment, which was treated surgically (Klaeger-Manzanell, Hoyt, & Good, 1994). The acuity of the left eye dropped immediately from a normal 20/20 to counting fingers at 2 m and later to mere light perception. Six weeks after the accident, the acuity of the amblyopic eye had improved from 20/200 to 20/80, where it remained for the next 13 months. When the right eye was subsequently enucleated (because of pain), the acuity of the amblyopic eye improved further to 20/30, a level at which it remained for the ensuing 6 years. Despite these dramatic reports, it is not possible to estimate the commonness of such improvements in humans with amblyopia after removal or damage to the normal fellow eye (cf. Vereecken & Brabant, 1984 vs. El Mallah et al., 2000).

In cats which had been monocularly deprived for a long period of time beginning before eye opening and monkeys raised with strabismus, subsequent enucleation of the fellow eye can lead to improved but not normal acuity and parallel increases in the percentage of cells in the visual cortex that can be driven by the previously deprived eye (Harwerth, Smith, Duncan, Crawford, & von Noorden, 1986a; Smith, 1981), although this is not always the case (Harwerth, Smith, Crawford, & von Norden, 1984).

Late Patching

As described above, treatment for unilateral amblyopia involves fixing the peripheral problem and patching the ''good eye'' to force usage of the amblyopic eye, with patching tapered toward the end of the putative sensitive period, that is around age 7, when children with normal eyes achieve adult-like acuity. However, several studies of children with strabismic and/or

anisometropic amblyopia have found that patching the good eye after age 7 can improve the acuity of the amblyopic eye. In an early meta-analysis of 17 studies, Birnbaum, Koslowe, and Sanet (1977) found that patching improved acuity by at least 4 lines (the patient was able to read letters 4 lines farther on an eye chart) in 55–59% of children whether they were in the group under 7, 7–10, or 11–15 years old. Even in the group over 15, that much improvement occurred in 42% of patients. A subsequent study involved 507 children with strabismic or anisometropic amblyopia at 49 clinical sites (Schelman et al., 2005). There was a gradual and substantial improvement in the acuity of roughly 25% of the amblyopic eyes from merely prescribing the optimal glasses. The success rate was similar for children 7–8, 9–10, 11–12, and 13–17 years old, with even greater improvement if the child had not been treated previously for amblyopia. When up to 6 months of patching, near work, and pharmacological blurring of the good eye were added, the amount of improvement was larger at all ages. Like the earlier meta-analysis, these results suggest that giving the amblyopic eye good visual input (by optical correction) and offsetting the unfavorable excitatory:inhibitory balance (by patching or blurring the good eye) are as effective in older childhood as they are before 7 years of age.

Repetitive Transcranial Magnet Stimulation (rTMS)

Transcranial magnetic stimulation (see Sharma & Cohen, in press) involves the induction of weak electric currents in brain tissue by rapid changes in a magnetic field applied to the scalp. When this is done repeatedly, the effect can last longer than the period of stimulation and, depending on the intensity and frequency of the stimulation, the orientation of the magnetic coil, and the baseline firing level, it can increase or decrease the excitability of neurons beneath the coil. Thus, in normally sighted adults, rTMS over area MT/V5, which plays a role in the perception of global motion, impairs the ability to detect motion (Silvanto, Cattaneo, Battelli, & Pascual-Leone, 2008). However, when performance (and presumably the activity of MT/V5 neurons) is first suppressed by 1-Hz rTMS for 10 min, subsequent rTMS improves performance. This pattern suggests that rTMS can have an inhibitory effect on neurons already in an excitatory state but a paradoxically facilitatory effect on neurons already in a suppressed state. rTMS has been used in stroke to increase neural activity in the affected hemisphere while simultaneously reducing it in the unaffected hemisphere (see Sharma & Cohen, in press).

Mansouri and colleagues (Thompson, Mansouri, Koski, & Hess, 2008; see also Thompson et al., in press) tested the efficacy of rTMS in promoting recovery in adults with an amblyopic eye. They reasoned that rTMS might stimulate and suppress the activity of neurons receiving input from the amblyopic and fellow eye, respectively, because the latter would be in a more excitable state. Indeed, in six adults with strabismic and/or anisometropic amblyopia, 10-Hz rTMS over the primary visual cortex led to an improvement in contrast sensitivity for a spatial frequency near the individual's acuity limit that was still present 30 min (but not 1 week) later. rTMS over the motor cortex had no effect.

Levodopa

Levodopa, a precursor to dopamine, has been used successfully to improve acuity in adults with strabismic and/or anisometropic amblyopia. Dopamine is plentiful in the normal retina, where it acts as a neurotransmitter; it also likely has more central neuromodulatory effects. One effect of monocular deprivation in the monkey is to reduce dopamine levels in the retina (Iuvone, Tigges, Fernandes, & Tigges, 1989). In human adults with strabismic or anisometropic amblyopia, a single dose of Levodopa is sufficient to induce an improvement in contrast sensitivity and, in some cases acuity, measured 90 min later (Algaze et al., 2005; Gottlob, Charlier, & Reinecke, 1992; Rogers, 2003). Although the mechanism underlying such improvement is unknown, the speed of the improvement suggests that it likely represents the release of existing connections by the rebalancing of excitatory:inhibitory interactions, rather than the formation of new connections.

Eye Exercises

Active eye exercises, such as exercises requiring fixation, tracking, and eye–hand coordination, with feedback, combined with patching of the nonamblyopic eye, have been successful in inducing visual improvements in adult amblyopes. In a pioneering study, Kupfer (1957) hospitalized six strabismic amblyopes with acuity of 20/200 or worse in the amblyopic eye. During the 4-week intervention, the good eye was patched full-time and the patient spent many hours doing fixation exercises with the amblyopic eye that were designed to promote steady foveal fixation. There was some improvement in all cases, with the acuity of four patients improving to the nearly normal range (20/25–20/40), improvements that were maintained on a test 6 months later. We can only speculate about why this therapy may have been effective. One critical ingredient is likely to have been the stimulation of the

amblyopic eye (akin to enriched environments for amblyopic rats) combined with full-time patching of the nonamblyopic eye to minimize adverse inhibitory influences. Once the patching was discontinued, the fixation training may have allowed patients to maintain bifoveal fixation with two eyes with nearly equal acuity and hence for the two eyes to send temporally synchronized signals of nearly equal strength to the visual cortex. In the process of the intervention, existing connections may have been unmasked, or the system may have become sufficiently plastic to allow new connections to form.

A similar explanation may underlie the success of exercises in bifoveal fixation in inducing improvements in binocular vision and stereopsis in an adult who has come to be called StereoSue (Barry, 2009). Because of congenital esotropia, she had several surgeries to realign her eyes and learned to alternate fixation rapidly between the two eyes. That alternation preserved good patterned input to each eye at the expense of any synchronous binocular input. As a result, she did not develop amblyopia (i.e., her visual acuity developed normally in each eye) but she failed to develop any stereoscopic binocular vision. Through vision therapy after age 50, she learned to fixate the same point simultaneously with each eye without suppression of either, and as a result, experienced stereoscopic 3D vision for the first time, albeit not normal stereoacuity. It is not clear whether the binocular fixation unmasked binocular connections that were already present, or whether the binocular input the visual cortex received for the first time after age 50 induced the formation of new connections. Whatever the explanation, this case is another demonstration of the possibility of improving vision in adulthood.

Perceptual Training

Prolonged training on visual tasks, with feedback, can improve the vision even of adults without eye problems (reviewed in Fine & Jacobs, 2002). In adults with amblyopia, training the amblyopic eye, while patching the nonamblyopic eye, also leads to improvements but they often take longer to achieve than in adults with normal vision. Nevertheless, the eventual improvement can be substantial, long lasting, and much larger than the gains after patching alone (Levi, 2005; Levi & Li, 2009; Polat, 2009). Improvements have been achieved with training tasks requiring the detection of low contrast gratings or letters (Chung, Li, & Levi, 2006; Huang, Lu, & Zhou, 2009; Huang, Zhou, & Lu, 2008; Zhou et al., 2006), sometimes with surrounding distractors (Polat, 2008; Polat, Ma-Naim, Belkin, & Sagi, 2004), the detection of small differences in the alignment of visual elements (Levi & Polat, 1996; Levi, Polat, & Hu, 1997; Li, Klein, & Levi, 2008; Li & Levi, 2004; Li, Provost, & Levi, 2007), and the detection of a small difference in spatial frequency (e.g., which grating has wider stripes) (Astle, Webb, & McGraw, 2010). The training in these studies usually involved thousands of trials over many days, with feedback about the accuracy of response, and gradual increases in the difficulty of the task as performance improved. When the training was continued until performance had been stable for 15–20 of the 960-trial sessions, fivefold improvements have been observed in amblyopes with initially severe deficits (Li et al., 2008). Simultaneous (but smaller) improvements in the nontrained nonamblyopic eye are often observed and indicate that the effects occur in the cortex, where inputs are first integrated across the two eyes (that is, at or beyond layers 2 or 3 in the primary visual cortex) (reviewed in Levi & Li, 2009). In some ways, the training effects are highly specific: for example, training to detect small deviations in the alignment of vertically aligned elements does not transfer to horizontally aligned elements (Levi & Polat, 1996; Levi et al., 1997; Li & Levi, 2004) and training with contrast-defined letters does not transfer to luminance-defined letters (Chung et al., 2006). On the other hand, there is usually transfer to improved Snellen letter acuity (reviewed in Levi & Li, 2009), and sometimes improvement on other untrained tasks, namely, stereoacuity, contrast sensitivity, and the accurate counting of the number of briefly flashed visual elements (Astle et al., 2010; Li & Levi, 2004; Polat, 2008). Training near the limits of amblyopic vision appears to be more effective than more widespread training (Zhou et al., 2006) and to generalize better to other stimuli (Astle et al., 2010; Huang et al., 2008). The breadth of generalization is greater for amblyopes than for adults with normal eyes (Astle et al., 2010; Huang et al., 2008).

The mechanism or mechanisms by which perceptual training improves vision in adult amblyopes is unknown, as is how they relate to the mechanisms of stability, or brakes on plasticity, identified in animal models (Bavelier, Levi, Li, Dan, & Hensch, 2010; Hensch, 2005). By examining the effect of added noise on visual accuracy and its consistency, scientists have deduced that some amblyopes improve by becoming more efficient at using visual information, that is, by better weighting of inputs so as to reach a correct decision about the external signal (Huang et al., 2009; Levi, 2005; Li & Levi, 2004; Li et al., 2008; see Wandell & Smirnakis, 2009 for evidence of a similar basis for improvements observed in adults with juvenile macular degeneration). Others improve instead, or in addition, through a reduction in internal noise, which can arise from random firing unrelated to the external signal

or scrambled synaptic connections that distort the normally regular retinotopic mapping between locations in the world and in the visual cortex. Both may be aided by a decrease in inter-ocular and inter-neuronal suppression (Polat, 2008). However, it remains unknown whether these changes occur at the level of inputs to neurons in the primary visual cortex, feedback to those neurons from higher centers, or changes only at higher ''decision stages'' of the visual pathway.

Video Games

Adults with normal eyes who play action video games surpass those who do not on a number of visual measures: they have a larger useful field of view and better contrast sensitivity, process a stream of rapidly presented letters more accurately, can track more moving objects simultaneously, have better central and peripheral acuity, are less affected by peripheral distracters or having to do concurrent central and peripheral tasks, and are better at other tasks requiring selective control of attention. Most of these effects are apparent even when adults without previous gaming experience are randomly assigned to play action video games or a control task for 2–6 weeks in the lab (Buckley, Codina, Bhardwaj, & Pascalis, 2010; Castel, Pratt, & Drummond, 2005; Feng, Spence, & Pratt, 2007; Green & Bavelier, 2003, 2006, 2007; Karle, Watter, & Shedden, 2010; Li, Polat, Makous, & Bavelier, 2009).

Many of the visual tasks that are improved by playing action video games in adults with normal eyes are ones that are impaired in amblyopia. Action video games also seem like a promising therapy because they require the detection and localization of fast moving targets of low contrast and thus skilled allocation of spatial attention and continual reweighting of the inputs on which decisions are made. They also are constantly adjusted to the player's current level of skill, are highly motivating, activate dopaminergic neural circuits (Koepp et al., 1998), and, at least for first person shooters, require ''vision-for-action,'' the integration of visual signals with motor action. In the first study to test these predictions, Li, Ngo, Nguyen, and Levi (2011) found that acuity improved in 17 strabismic and anisometropic amblyopes after they played a first person shooter game (Medal of Honor) for 40 hr while the good eye was patched. The average improvement was 30% and several amblyopes with initially mild impairments achieved normal 20/20 acuity. There was no such improvement when a control group patched the good eye for comparable time without playing a video game. The experimental group also showed improvements in positional acuity (determining the average height of five horizontally dispersed elements), in counting the number of briefly flashed elements, and, for the five anisometropic amblyopes, in stereoacuity. By examining consistency and the effect of added noise, Li and colleagues deduced that, like the results for perceptual learning, the improvement in positional acuity resulted from both improved efficiency in using available visual information and reduced internal noise. How those changes relate to the brakes on plasticity identified in animal models is unclear. One possibility is that there is an increase in the ability of higher level attentional systems to selectively enhance and suppress lower level visual processing, perhaps through the alteration of the excitatory:inhibitory balance (Bavelier et al., 2010). Like the benefits of eye exercises and perceptual training, the process might involve the unmasking of already formed connections and/or the development of new connections.

RELATIONSHIP TO STROKE AND THE SPECIAL ISSUE

The work on amblyopia indicates that there are indeed sensitive periods during which visual experience tunes the visual system. Abnormal visual input during those sensitive periods leads to persistent visual deficits. Animal models indicate that the sensitive periods for damaging the system by abnormal input terminate because of structural and neurochemical mechanisms of stability that make the mature system less malleable. Yet recent animal models and studies of adult amblyopes indicate that interventions can change the mature system. The purpose of this special issue is to gain insights from another domain in which effective interventions can change the mature system: stroke recovery. When the adult brain is damaged by stroke, as with amblyopia, there are significant and seemingly permanent impairments. However, in the last decade there have been major advances in improving the prognosis after stroke. Those advances provide insights about the nature of plasticity in the adult brain and how it differs from plasticity earlier in life. The six core papers in the special issue describe the effective interventions and the more general principles underlying them that can inform us about the nature and limits to adult plasticity. The commentaries present a broader view of the principles differentiating child and adult plasticity and the application of the lessons from stroke to domains like language learning and the treatment for amblyopia. Two themes seem especially relevant to amblyopia: (1) damage to one brain area alters not only that brain area's function, but the function of an entire network spanning both hemispheres to which that brain area is connected and (2) as a consequence, effective therapy

requires establishing conducive excitatory:inhibitory balance within such networks.

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