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Critical periods in amblyopia

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Abstract

The shift in ocular dominance (OD) of binocular neurons induced by monocular deprivation is the canonical model of synaptic plasticity confined to a postnatal critical period. Developmental constraints on this plasticity not only lend stability to the mature visual cortical circuitry but also impede the ability to recover from amblyopia beyond an early window. Advances with mouse models utilizing the power of molecular, genetic, and imaging tools are beginning to unravel the circuit, cellular, and molecular mechanisms controlling the onset and closure of the critical periods of plasticity in the primary visual cortex (V1). Emerging evidence suggests that mechanisms enabling plasticity in juveniles are not simply lost with age but rather that plasticity is actively constrained by the developmental up-regulation of molecular 'brakes'. Lifting these brakes enhances plasticity in the adult visual cortex, and can be harnessed to promote recovery from amblyopia. The reactivation of plasticity by experimental manipulations has revised the idea that robust OD plasticity is limited to early postnatal development. Here, we discuss recent insights into the neurobiology of the initiation and termination of critical periods and how our increasingly mechanistic understanding of these processes can be leveraged toward improved clinical treatment of adult amblyopia.

Keywords

GABA; Parvalbumin; Perineuronal net; Dark exposure; Acetylcholine; PSD-95; HDAC

It is well appreciated that there are defined windows in early life when neural circuitry can be robustly restructured in response to experience. These time-limited critical periods have been demonstrated for many brain functions across many brain regions and are thought to allow developing neural circuits to establish an individualized, optimal neural representation of a highly variable environment. The enhanced plasticity corresponds to the peak phases of physical growth and may, therefore, allow for constant perception during expansion of the body surface. For example, visual receptive fields must repeatedly remap as the distance between the two eyes increases. Indeed, experience-dependent matching of stimulus selectivity of the visual input from the two eyes occurs during the critical period (Wang et al., 2010).

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The relative stability that follows the critical period may be advantageous in adult circuits, and also allow for conservation of energy/resources. However, the enhanced stability with age also inhibits large-scale adaptations to changes in the input during adulthood. Nonetheless the adult cortex retains the ability to express some forms of synaptic plasticity, but the mechanisms for the induction and expression of plasticity differ from those utilized during the critical period. In this context, it is important to bear in mind that many measures are in current use to study 'ocular dominance (OD) plasticity.' Originally defined as a change in the eye preference of the spiking output of V1 neurons (Wiesel & Hubel, 1963), current methods include visually evoked synaptic potentials, intrinsic hemodynamic signals, immediate early gene activation, thalamocortical axon or dendritic spine morphology and motility, and calcium responses in genetically identified cell types. Each of these methods yields different resolutions and may be variably sensitive to subthreshold inputs (Morishita & Hensch, 2008), which are important considerations when informing therapies for recovery of the visual function in both amblyopic children and adults.

During the critical period, an asymmetry in the quality of the visual input across the two eyes leads to reduced visual acuity and a visually evoked spiking response through the affected eye with no obvious pathology in the eye, thalamus, or cortex. The severity of amblyopia depends on the age at initiation and the type of asymmetry, which can be caused by unequal alignment (strabismus), unequal refractive error (anisometropia), or form deprivation (e.g., cataract). The critical period for developing amblyopia in children extends to 8 years and is relatively easy to correct until that age by improving the quality of visual input in the affected eye (reviewed in Daw, 1998; Mitchell & MacKinnon, 2002; Simons, 2005) but becomes increasingly resistant to reversal with age.

In animal models, amblyopia is most often induced by monocular deprivation (MD)—an eyelid suture which significantly occludes the patterned visual input to one eye. Across various species, MD unleashes a sequence of functional and structural changes in V1 that shifts the OD of binocular neurons away from the deprived eye and toward the open eye, resulting in a reduction in deprived-eye acuity (Wiesel & Hubel, 1963, 1970; Olson & Freeman, 1975; Hubel et al., 1977; Movshon & Dürsteler, 1977; Blakemore et al., 1978; LeVay et al., 1978; Shatz & Stryker, 1978; Antonini & Stryker, 1993; Fagiolini et al., 1994; Gordon & Stryker, 1996; Hensch et al., 1998; Trachtenberg & Stryker, 2001; Mataga et al., 2002; Taha & Stryker, 2002; Prusky & Douglas, 2003; Frenkel & Bear, 2004; Sato & Stryker, 2008).

While OD plasticity peaks during the postnatal critical period, it (Lehmann and Lowel, 2008) persists beyond sexual maturity at some level in many species, including rats, mice and cats. The age at initiation and duration of MD then strongly impacts the severity of the subsequent amblyopia, as well as the potential for recovery (Liao et al., 2004; Eaton et al., 2016). Accordingly, short durations of MD within the critical period induce a shift in OD and a reduction in the deprived eye visual acuity that are rapidly corrected by restoring normal vision (Schwarzkopf et al., 2007). In contrast, long-term MD initiated early and persisting through the end of the critical period induces a shift in OD and a loss of visual acuity that is highly resistant to reversal.

The initial response to MD during the critical period is a reduction in functional strength and selectivity of the deprived eye visual responses (Gordon & Stryker, 1996; Hensch et al., 1998; Trachtenberg et al., 2000; Frenkel & Bear, 2004) and disrupts the balance of excitatory ad inhibitory inputs to individual binocular neurons (Saiepour et al., 2015). Depression of deprived-eye responses may occur by synaptic depression at both thalamocortical and intracortical connections. Notably, rapid shifts in the visual response of parvalbumin (PV)-expressing inhibitory interneurons may enable these first functional changes within V1 (Yazaki-Sugiyama et al., 2009; Aton, Broussard et al., 2013; Kuhlman et al., 2013). Depression is then followed by a relatively slow, strengthening of open eye responses (Sawtell et al., 2003; Frenkel & Bear, 2004; Kaneko et al., 2008).

Robust morphological plasticity is also induced by MD during the critical period. An initial degradation of the extracellular matrix by the upregulation of proteases occurs within the first 2 days after MD in the mouse and may elevate spine motility (Mataga et al., 2004; Oray et al., 2004). Studies in cats, monkeys, and humans suggest that structural plasticity is facilitated by a reduction in the neurofilament-light protein within V1, which may de-stabilize the cytoskeleton and promote plasticity (Duffy & Livingstone, 2005; Duffy et al., 2007; Duffy & Mitchell, 2013). Brief MD during the critical period alters the spine density on pyramidal neurons (Mataga et al., 2004; Tropea et al., 2010; Yu et al., 2011; Djurisic et al., 2013) and induces a transient decrease in the density of synapses formed by thalamocortical axons originating from the lateral geniculate nucleus (LGN) (Coleman et al., 2010). Long-term MD yields enduring alterations in the length and extent of thalamocortical arbors serving the two eyes (Hubel et al., 1977; Shatz & Stryker, 1978; Antonini et al., 1999) and a significant reduction in dendritic spine density (Montey & Quinlan, 2011).

Studies from humans and nonhuman primates suggest a protracted decline in visual plasticity that extends into adulthood rather than an abrupt closure of the critical period. However, the residual plasticity that persists in the adult visual cortex appears to differ from the plasticity during the critical period in several important ways: (1) the shift in OD in adults is slower and smaller and may require a longer duration of deprivation to engage; (2) it may not require depression of deprived eye responses for the subsequent strengthening of responses to the nondeprived eye; (3) it may be restricted to synapses in the supragranular and infragranular lamina, as plasticity in layer 4 has been shown to be constrained early in postnatal development; (4) it may be restricted by saturated synapses, setting limits on the amount of recovery of visual function that can be accomplished using this pathway. Additionally, MD in adults does not elicit the robust structural alterations that accompany OD plasticity during the critical period such as increased spine motility and pruning (Mataga et al., 2004; Oray et al., 2004; Lee et al., 2006). Indeed, a general decline in structural plasticity is one of the hallmarks of the termination of the critical period. However, residual increases in the rate of formation and stability of dendritic spines may persist in the adult layer I after MD (Hofer et al., 2009).

Inhibition and critical period induction

Powerful new tools in neuroscience, especially the molecular genetic control available in mice, are beginning to elucidate the cellular and molecular mechanisms that initiate and

terminate critical periods. Ocular dominance plasticity peaks during the third postnatal week in rodents, demonstrating that elevated plasticity is not the initial state of immature circuits. Indeed, the maturation of specific inhibitory circuitry is necessary to initiate the critical period, which can be accelerated by activating inhibitory $GABA_A$ receptors with allosteric modulators such as benzodiazepines (Hensch et al., 1998; Fagiolini & Hensch, 2000; Iwai et al., 2003; Fagiolini et al., 2004). Promoting early maturation of a specific class of inhibitory interneurons that express the calcium binding protein parvalbumin (PV) by increasing the levels of growth factors (Huang et al., 1999; Hanover et al., 1999; *Otx2*: Sugiyama et al., 2008; Spatazza et al., 2013) or by removing cell adhesion (PSA: Di Cristo et al., 2007) or DNA binding proteins (MeCP2: Durand et al., 2012; Krishnan et al., 2015) can induce premature initiation of the critical period.

The perisomatic inhibition mediated by these fast-spiking PV interneurons exerts powerful control over the excitability and plasticity of downstream pyramidal neurons, regulating many forms of downstream synaptic plasticity (Katagiri et al., 2007; Kuhlman et al., 2013; Toyoizumi et al., 2013). Several proteins that regulate synaptic strength and/or number are highly enriched at excitatory synapses onto PV interneurons and impact the timing of the critical period and NRG1 (NARP: Chang et al., 2010; Gu et al., 2013, Pelkey et al., 2015; Gu et al., 2016; kaplan et al., 2016; Sun et al., 2016). Accordingly, NARP-deficient mice fail to initiate a critical period unless rescued by enhancing the strength of the inhibitory output or excitatory drive onto PV interneurons (Gu et al., 2013; Gu et al., 2016).

A further increase in perisomatic inhibition is thought to terminate the critical period. Hence, the critical period can be reopened in adulthood by pharmacological reduction of inhibition (Harazouv et al., 2010) or by the knockdown of *Otx2* (Beurdeley et al., 2012; Spatazza et al., 2013). Treatment with an NRG1 peptide induces a precocious termination of the critical period, while inhibition of the activity of the NRG receptor (ErbB) reactivates the critical period in adults (Gu et al., 2016). Indeed, a developmental reduction of plasticity at excitatory synapses onto FS interneurons may explain the requirement for longer durations of MD with age (Kameyama et al., 2010). Together, these studies indicate that PV inhibitory neurons exert bidirectional control over OD plasticity (van Versendaal & Levelt, 2016).

Other classes of inhibitory neurons may influence the expression of plasticity, either independently or through the regulation of PV neurons. Interestingly, inhibitory neurons in layer 1 (L1) of the visual cortex and those expressing vasoactive intestinal peptide (VIP) are strongly activated during certain behavioral states and exert cortical effects by disinhibition of pyramidal neurons (Letzkus et al., 2011; Donato et al., 2013; Pfeffer et al., 2013; Pi et al., 2013; Fu et al., 2015). Locomotion activates VIP interneurons, which enhances neural activity in V1 (Niell & Stryker, 2010) and promotes adult plasticity by increasing inhibition onto other interneuron subtypes that target pyramidal neurons (Fu et al., 2014; Fu et al., 2015). Similarly, reinforcement signals (reward and punishment) during the performance of an auditory discrimination task activate VIP neurons in the auditory cortex, which increase the gain of a functional subpopulation of pyramidal neurons by disinhibition (Pi et al., 2013). Thus, disinhibitory circuits which transiently suppress other inhibitory interneurons may be a general mechanism for enabling plasticity in the adult cortex.

Molecular reactivation of critical period in adulthood

Increasing evidence demonstrates that removing molecular ‘brakes’ in adulthood can enhance plasticity and promote recovery from amblyopia. For example, epigenetic mechanisms, such as histone deacetylase (HDAC) activity, may down regulate the expression of genes that promote plasticity over development. Accordingly, HDAC inhibition enhances plasticity in adult V1, allowing for recovery from amblyopia (Putignano et al., 2007; Silingardi et al., 2010; Baroncelli et al., 2016). However, the downstream targets of histone acetylation at specific stages of development remain to be identified.

Alternatively, increased expression of specific genes over development can actively limit rewiring. The expression of *Lynx1*, an endogenous inhibitor of nicotinic acetylcholine receptors, emerges in V1 coincident with critical period closure, which would dampen the neuromodulatory actions of acetylcholine (Miwa et al., 1999; Morishita et al., 2010). Both genetic deletion of *lynx1* and administration of acetylcholinesterase inhibitors enhance spine motility and the morphological plasticity induced by MD (Sajo et al., 2016) and enable recovery of visual acuity following MD throughout life (Morishita et al., 2010). The major histocompatibility complex class I (MHCI) receptor, PirB, is another molecular brake. Disruption of PirB signaling enhances OD plasticity throughout life and facilitates recovery from amblyopia in adults (Syken et al., 2006; Bochner et al., 2014). Another immune system molecule, Stat1, restricts the increase of open eye responses following monocular deprivation, while genetic deletion enhances this component of plasticity (Nagakura et al., 2014). The identification of specific molecules that actively suppress plasticity in the adult visual cortex may inform strategies for pharmacological interventions to reopen the critical period.

Molecular brakes can also present physical barriers to morphological plasticity. Perineuronal nets are highly enriched around PV neurons and reach maturity at the end of the critical period. Disrupting the molecular latticework of this extracellular matrix (Pizzorusso et al., 2002; Pizzorusso et al., 2006; Carulli et al., 2010) or the molecules which bind to it (i.e., Otx2: Beurdeley et al., 2012) enables OD plasticity and recovery from amblyopia in adults. Consistent with this, mice lacking the Nogo receptor (Ngr1), a bimodal receptor for chondroitin sulfate proteoglycans and myelin-derived inhibitory factors (Dickendesher et al., 2012), also retain critical period plasticity into adulthood and spontaneously recover visual acuity following long-term MD (McGee et al., 2005; Stephany et al., 2014). Interestingly, PirB may act in concert with Ngr1 (Atwal et al., 2008) to dampen the morphological plasticity of dendritic spines on layer 5 pyramidal neurons in adults (Bochner et al., 2014) (Fig. 1).

Interestingly, one recently discovered molecular brake may lie within the dendritic spine itself. Postsynaptic density protein 95 (PSD-95), an intracellular scaffold highly enriched at excitatory synapses, is thought to accelerate maturation of excitatory synapses. PSD-95 promotes the incorporation of AMPA-type glutamate receptors into synapses containing only NMDA receptors, which are normally functionally “silent” at the resting membrane potential. In contrast, the immediate early gene *Arc* promotes removal of AMPA receptors from cortical synapses and deletion precludes visual plasticity (McCurry et al., 2010).

Genetic reduction of PSD-95 in adulthood increases the number of silent synapses and reactivates the juvenile form of OD plasticity, characterized by a rapid and robust deprived-eye depression (Huang et al., 2015). Notably, no changes in GABAergic or NMDA receptor currents are observed, suggesting that the reactivation of plasticity by PSD-95 deletion lies downstream of the regulation of inhibitory circuitry. A conversion of 'silent' to functional synapses has been proposed as a general mechanism to constrain plasticity across brain regions (Greifzu et al., 2014; Huang et al., 2015).

Environmental reactivation of critical period in adulthood

Characteristics of the physical or sensory environment strongly impact the function and plasticity of cortical circuits. Remarkably, adding social, sensory, or motor enrichment to the typically impoverished environment of the laboratory rodent influences the expression and time course of OD plasticity. Robust OD plasticity persists into adulthood when mice are raised in large complex cages with multisensory and motor enrichment (Sale et al., 2007; Scali et al., 2012; Greifzu et al., 2014). In fact, enriched rearing may better reflect the sensorimotor environment of primates including humans. At a molecular level, exposure to enriched environments in adulthood increases H3 acetylation (Baroncelli et al., 2016), reduces the expression of PV and GAD67 within inhibitory neurons of the visual cortex, weakens GABA signaling, and fosters plasticity in both the cortex and hippocampus (Sale et al., 2007; Donato et al., 2013; Greifzu et al., 2014).

In this regard, it is intriguing that total visual deprivation also reactivates robust plasticity in adult V1 and promotes recovery from chronic MD (He et al., 2007; Montey & Quinlan, 2011; Duffy & Mitchell, 2013; Stodieck et al., 2014; Eaton et al., 2016; Mitchell et al., 2016). The BCM theory of a sliding synaptic modification threshold forecasted that dark exposure would enhance plasticity and indeed several mechanisms are engaged by the dark exposure that are predicted to lower the threshold for synaptic plasticity in pyramidal neurons (Cooper & Bear, 2012). For example, the composition of the NMDA type glutamate receptors is reset to a "juvenile" form (containing the NR2B subunit; Quinlan et al., 1999) which exhibit enhanced temporal summation (Yashiro et al., 2005; He et al., 2006). In addition, forms of synaptic plasticity typically limited to juveniles are re-expressed (Huang et al., 2010; Montey & Quinlan, 2011), spines on pyramidal neurons are shifted toward an immature structure and dynamics (Tropea et al., 2010), and immature excitatory synapses on pyramidal neurons are strengthened, thereby increasing excitability and expanding the integration window for spike-timing dependent plasticity (Goel & Lee, 2007; He et al., 2007; Guo et al., 2012).

In contrast, dark exposure decreases the excitability of PV interneurons, and the reactivated plasticity can be reversed by increasing the strength of their excitatory synaptic inputs (Gu et al., 2016). A loss of specific neurofilament protein associated with cytoskeletal stability is observed in the LGN following dark exposure, which may further contribute to the reactivation of structural OD plasticity (O'Leary et al., 2012; Duffy et al., 2016). Importantly, dark exposure restores a period of susceptibility to MD and also promotes the recovery of visual function in adults with amblyopia, as has been demonstrated in rats, mice, and cats (He et al., 2006; He et al., 2007; Duffy & Mitchell, 2013; Stodieck et al., 2014;

Duffy et al., 2016). The reactivation of plasticity by dark exposure has also been shown to strengthen the thalamic input to the cortex (Montey & Quinlan, 2011). Thus, the seemingly opposite interventions of environmental enrichment and dark exposure may both enhance cellular plasticity by the removal of functional and structural constraints that normally accumulate over development to stabilize the V1 circuitry.

It is important to note that dark exposure alone does not impact visual acuity or neuronal stimulus selectivity, which is regained only after repetitive visual experience (Montey et al., 2013; Eaton et al., 2016). Likewise, enrichment or locomotion alone does not strengthen visual performance (Kaneko & Stryker, 2014; Greifzu et al., 2016). This suggests that the recovery from amblyopia in adulthood is a two-stage process that requires (1) the reactivation of plasticity in the adult amblyopic cortex (permissive step) and (2) focused visual experience to stimulate perceptual learning (instructive step). One of the challenges, therefore, is to identify the optimal visual stimulation to drive recovery of the function, which may differ based on age and depth of amblyopia (Montey & Quinlan, 2011; Eaton et al., 2016). However, prolonged plasticity by environmental enrichment makes it unclear if complex environments better mimic those of primates including humans. At a minimum, these experiments provides a valuable condition with which to better understand the biological basis of critical period closure.

Reactivating plasticity to enhance recovery

The reactivation of plasticity in the primary visual cortex has revised the idea that critical periods are strictly limited to early postnatal development (Bavelier et al., 2010; Takesian & Hensch, 2013; Sengpiel, 2014). However, the mechanisms that engage the cortical plasticity necessary to treat amblyopia may be very different from the plasticity that enables the cortex to regain sensitivity to MD. Indeed, it has long been known that the critical period for plasticity in response to MD differs from the critical period for recovery of the binocularity and orientation selectivity by removing the MD (Liao et al., 2004). Although initially assumed to overlap with the critical period for susceptibility to amblyopia, it is now clear that the treatment window for the reversal of amblyopia in humans may extend beyond early life (reviewed in Daw, 1998). It is, therefore, important that key molecular effectors be tested in their ability to recover (not induce) amblyopia in adults.

Mechanistic studies performed primarily in mice, have identified novel therapies with translational potential to reverse the developmental constraints on recovery from amblyopia. Several commonly prescribed drugs, such as cholinesterase inhibitors (Morishita et al., 2010), valproate (Gervain et al., 2013; Lennartsson et al., 2015), or selective serotonin reuptake inhibitors (Maya Vetencourt et al., 2008), could be repurposed to reactivate plasticity in adult amblyopic patients. Interestingly, a reduction in PV interneuron function may be a mechanism common to several of these interventions. The SSRI antidepressant fluoxetine reduces the basal levels of extracellular GABA (Maya Vetencourt et al., 2008) and the number of PV interneurons surrounded by dense perineuronal nets (Guirado et al., 2014). Similarly, dark exposure may rejuvenate intracortical inhibition by reducing the excitatory drive onto PV neurons (Gu et al., 2016) (Fig. 2).

Future work that explores noninvasive ways to tap into these mechanisms to trigger plasticity may generate novel amblyopia treatments for adults. It will also be important to learn if the success of behavioral manipulations, such as dark rearing, environmental enrichment and exercise, promotes the recovery from amblyopia in rodents by reversing molecular brakes or engaging residual plasticity mechanisms that are normally expressed in the adult cortex (Sale et al., 2007; He et al., 2007; Duffy & Mitchell, 2013; Eaton et al., 2016). Such biological insights gleaned from animal model systems have provided the foundation for a number of promising ongoing clinical trials aimed at improving vision in amblyopic patients (Stryker & Löwel, this volume).

In addition, it is important to keep in mind that while robust OD plasticity is lost with age, the adult visual cortex does retain the ability to learn. This is reflected in the success of visual training (repetitive visual task performance, visual perceptual learning) to promote enhancement of acuity and recovery of stereoscopic vision in both amblyopic humans and experimental animals (Levi & Li, 2009; Bonaccorsi et al., 2014; Kawato et al., 2014; Sengpiel, 2014). Recent approaches to visual training include dichoptic visual stimulation (in humans and cats) to normalize the quality of visual input across the strong and weak eye, and the use of action video games, to recruit neuromodulatory pathways that engage attention and motivation (Stryker & Löwel, this volume; Mitchell & Duffy, 2014; Hess & Thompson, 2015; Murphy et al., 2015; Levi et al., 2015). However, the improvements in visual acuity achieved with these methods in humans have been relatively modest to date (Tsirlin et al., 2015, but see; Hess & Thompson, 2015).

Expanding the focus beyond ocular dominance

The primary aspects of visual system function assessed in animal studies of amblyopia are OD and spatial acuity. However, amblyopia is associated with a range of visual deficits, including loss of stereoscopic depth perception, crowding, impairments in shape discrimination, deficits in motion and direction perception, and object tracking (reviewed in Daw, 2013). Some of these impairments, such as the loss of stereoscopic depth perception and visual crowding, may greatly impact the quality of the life of the amblyopic patient (Levi et al., 2015). Expanding the focus of animal studies of amblyopia beyond the recovery of OD will broaden the ability of this work to inform clinical strategies.

Furthermore, separable neuronal response properties of individual V1 neurons have distinct, overlapping critical periods (reviewed in Kiorpes, 2015). For example, it has long been known that the critical period for direction selectivity in kittens precedes the critical period for OD (Daw & Wyatt, 1976). In the primate visual system, critical periods for basic spectral sensitivities end relatively early (6 months), whereas those for complex representations such as contrast sensitivity and binocularity extend much later (25 months; Harwerth et al., 1986). There is also evidence that some manipulations may globally reinstate V1 plasticity across these distinct visual functions. For example, dark exposure in adulthood, which reactivates plasticity for the recovery of normal OD in amblyopic rats, mice, and kittens (He et al., 2007; Montey & Quinlan, 2011; Duffy & Mitchell, 2013; Stodieck et al., 2014; Eaton et al., 2016; Mitchell et al., 2016) promotes the recovery of stimulus selectivity and visual response strength (Montey et al., 2013). As critical periods for different visual functions may

depend on separate underlying mechanisms, some manipulations may restore only selective features of V1 responses. For example, a genetic deletion of PSD-95 disrupts the development of orientation preference in the mouse visual cortex, without impacting the development or plasticity of OD in juveniles (Fagiolini et al., 2003).

It is particularly important to ask if the interventions that promote the recovery of OD and/or visual acuity also promote the visual functions that underlie stereopsis, such as retinal disparity tuning and/or binocular matching of stimulus preference. Binocular integration in the primary visual cortex is an important first step in the perception of depth from retinal disparity (Scholl et al., 2013). It has been demonstrated that shortly after eye opening, V1 neurons exhibit orientation tuning and respond to visual stimulation of either eye; however, the orientation preference through each eye, which is initially mismatched, becomes tuned to similar orientations during the critical period (Wang et al., 2010). Indeed, manipulations that prolong V1 plasticity, such as environmental enrichment, accelerate binocular matching of the stimulus selectivity in the developing mouse primary visual cortex (Gu et al., 2016). In contrast, manipulations that accelerate plasticity in the cortex, such as heterozygous loss of *Mecp2*, prevent the acquisition of matched stimulus selectivity (Krishnan et al., 2015). Recovery of stereopsis in rodents can be assessed through behavioral measures such as visual cliff or SLAG performance (Gil-Pagés et al., 2013). Incorporation of physiological and psychophysical assessments that examine contrast sensitivity, direction selectivity, and stereoscopy would greatly improve assessement of the treatment efficacy across multiple aspects of vision in patients with amblyopia.

Expanding the focus beyond primary visual cortex

The majority of animal work on amblyopia has focused on regions early in the visual pathway, as MD induces significant structural re-arrangements in V1, including pruning of thalamocortical inputs that serve the deprived eye (Wiesel & Hubel, 1963; Hubel et al., 1977; Shatz & Stryker, 1978). Long-term MD induces a near complete loss of stimulus selectivity for input coming in through the chronically deprived eye (Montey & Quinlan, 2011). Given these severe structural and functional deficits in V1, it is even more remarkable that full recovery of visual acuity has been demonstrated with some interventions.

However, the magnitude of compromised vision observed in psychophysical experiments is often not mirrored by changes in the function of V1 neurons, suggesting that physiological changes may be propagated and amplified in higher cortical areas (Shooner et al., 2015). Indeed, psychophysical and neural recording data suggest that amblyopia is also associated with abnormalities in extrastriate regions (reviewed in Kiorpes, 2015). For example, deficits in higher order visual functions, such as motion perception, which have been described in amblyopic monkeys (Kiorpes et al., 2006) may be partly explained by aberrant development of the extrastriate area MT/V5. Here neurons driven by the amblyopic eye exhibit reduced sensitivity to coherent motion and reduced ability to integrate motion information over time (El-Shamayleh et al., 2010).

Higher brain areas and neuromodulatory pathways are also potential targets to facilitate visual responses and plasticity within V1 of amblyopic adults. For example, children with

macular degeneration show large regions of V1 that are unresponsive during passive viewing of the visual stimuli, but can be activated by engaging the subjects in a stimulus-related task, suggesting a powerful role of top-down influences. Remarkably, the same visual task-related responses are not observed in simulated lesion zones in normal binocular subjects, suggesting that macular degeneration may potentiate or unmask feedback signals (Masuda et al., 2008).

Regions outside of the primary sensory cortices are thought to express late, prolonged windows of plasticity that extend well beyond that of V1. Thus, devising treatments to target these regions may be an effective strategy for recovery of visual function in adulthood that does not require the reactivation of plasticity in V1. Advanced tools enabling the monitoring, activation, or silencing of specific neural circuits in mice or higher species will contribute to our understanding of the top-down influences on plasticity within V1. Future primate studies will also be essential to examine plasticity within higher order visual regions.

Path forward

Rapidly evolving genetic, imaging, and physiological tools have allowed mechanistic insights into how critical period plasticity is regulated, including the identification of molecular ‘triggers’ and ‘brakes’ that control the initiation and termination in V1. Much of this knowledge has been gleaned recently from mouse models, which offer unprecedented experimental control of specific neuronal and synaptic populations, including optogenetic, chemogenetic, and magnetogenetic approaches. However, to better inform amblyopia treatment, mechanistic work should be expanded to additional species, especially those with a columnar organization of ocular preference and neurons tuned for small retinal disparities. The increasing availability of molecular genetic techniques such as CRISPR makes this a likely goal.

In addition, examination of the incidence and expression of amblyopia across human populations may elucidate the impact of environmental and genetic factors on individual differences in visual plasticity. An assessment of OD plasticity across a large number of recombinant inbred mouse strains revealed striking variability in response to MD. Interestingly, there was no correlation between the weakening of deprived eye responses and the strengthening of nondeprived eye responses, suggesting that these two pathways may be regulated by separate genetic factors (Heimel et al., 2008). In addition, several molecules implicated in regulating the timing of the critical period, including the constraints on adult plasticity, are the known risk factors for neurodevelopmental disorders such as schizophrenia. These include HDAC and NRG1 (Rico & Marín, 2011; Penzes et al., 2013). Interestingly, male schizophrenics are two times less likely to have refractive errors (Caspi et al., 2009), raising the possibility that common genetic risk factors contribute generally to the maturation of neuronal circuitry, including the normal development of binocular vision. Further work is necessary to identify human populations that may be at a greater or at a lesser risk for the development of amblyopia.

Capitalizing on these biological insights, one goal is to develop targeted strategies to guide clinical trials by enhancing plasticity in the postcritical period visual cortex in humans. In

addition, such a critical period regulation could also be extended to strabismus, eye movement control disorders, and the restoration of the optimal neural function after damage from a stroke or other traumatic brain injuries.

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Recommendations

- During developmental 'critical periods,' neural circuitry can be potently shaped by experience. Although the brain retains the capacity to re-wire beyond early life, adult forms of plasticity may utilize mechanisms distinct from those available to juveniles. Understanding the differences between developmental and adult plasticity, including differences in how they are typically measured, will provide key insights into novel therapies for recovery of the visual function from amblyopia in both children and adults.
- Evolving tools in neuroscience have shed new light on the 'triggers' and 'brakes' that determine the onset and offset of critical periods. Strikingly, the brain's intrinsic potential for plasticity is not lost with age but instead is actively constrained beyond early critical periods. Indeed, lifting molecular 'brakes' unmasks potent plasticity in adulthood. Ongoing work to determine how the various 'brakes' act within common cellular and circuit networks will lead to targeted therapeutic strategies to promote plasticity and biologically-inspired clinical studies for amblyopia recovery.
- Most animal studies have focused on reinstating a period of susceptibility to MD in adulthood. Yet, the plasticity necessary to recover from amblyopia may be different from that required to recover sensitivity to MD. Thus, future work should emphasize animal studies that specifically examine recovery of the visual function in amblyopic brains.
- Amblyopia is associated with a range of visual impairments beyond acuity, but the majority of studies in mouse models of amblyopia have focused exclusively on OD shifts. Future work should identify other physiological measures and behavioral paradigms to examine widespread visual functions beyond OD, such as contrast sensitivity and stereopsis that can be applied across species.
- Some of the deficits associated with amblyopia may result from abnormalities in regions beyond the primary visual cortex (V1). Moreover, signals from higher brain areas may facilitate visual responses and plasticity within V1. Thus, understanding developmental trajectories and critical period mechanisms throughout the visual system may identify new treatments for the recovery from amblyopia in adulthood.
- Future work should include the development of better models for amblyopia across animal species and humans. Identifying biochemical correlates of plasticity will allow us to compare developmental trajectories more readily across species. Capitalizing on genetic diversity in mice and humans will provide insights into the individual variability that influences the etiology or recovery from amblyopia.

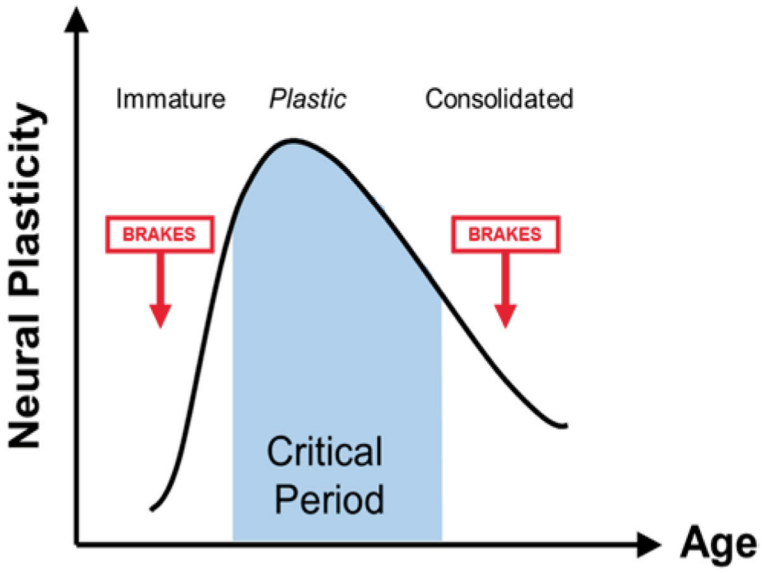

FIG. 1.

Critical period plasticity as a function of age. Initially, immature brain circuits are dominated by excitatory inputs and fail to express plasticity. As inhibitory circuits mature, a highly plastic critical period is induced. Plasticity then declines with age as inhibitory circuits and brake-like factors dominate, harboring the potential for plasticity throughout life. Dynamic changes in the excitatory/inhibitory balance across age are shown below the graph. Figure courtesy of Takao Hensch (Harvard University).

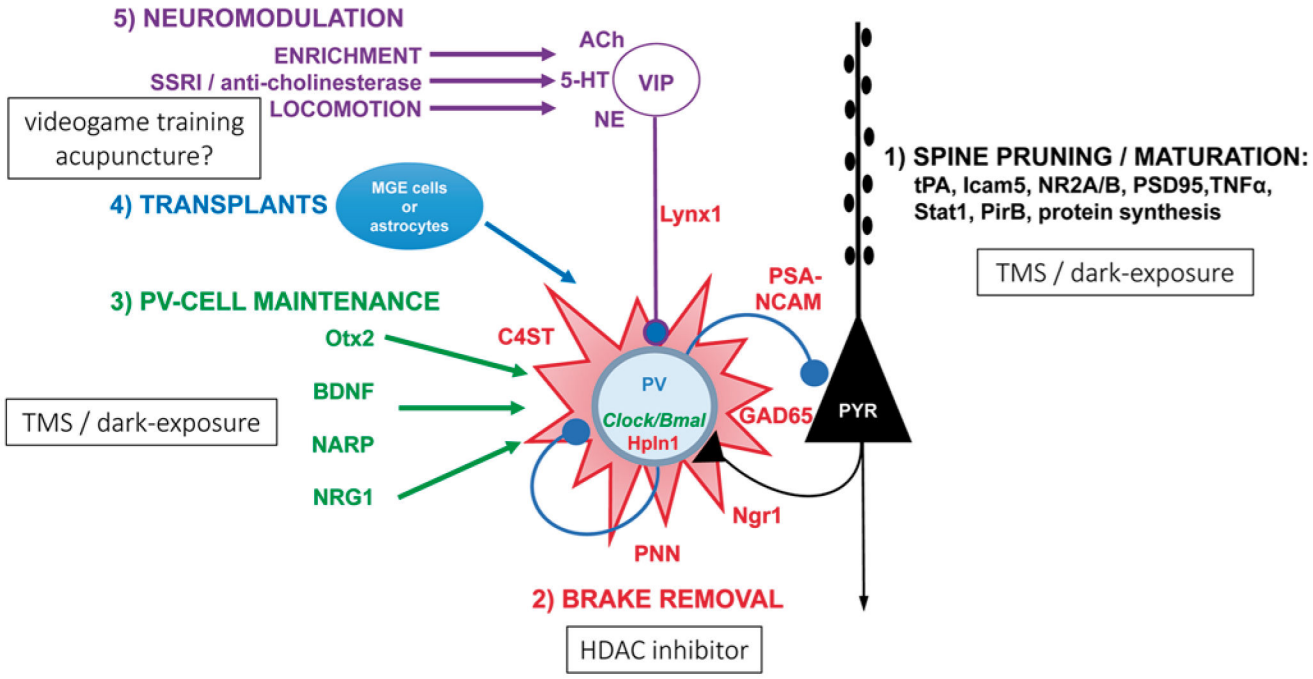

Fig. 2.
Pathways known to enhance plasticity in the adult visual cortex.