5

Factors that Initiate and Terminate Critical Periods

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Abstract

During development, neural circuitry can be profoundly shaped by experience at well-defined periods of time. Using amblyopia as a model of postnatal synaptic plasticity, this chapter reviews the "triggers" and "brakes" that determine the onset and offset of these critical periods. Consideration is given to the molecular constraints that act on plasticity as well as to the physical and sensory environmental factors that impact function and cortical circuit plasticity. Reactivation of plasticity in primary visual cortex suggests that critical periods are not limited to early postnatal development. The extent to which the amblyopia model will generalize at a mechanistic level is discussed. Genetic diversity in mice and humans may provide insight into individual variability and the timing of critical periods and should be pursued. To permit comparison of developmental trajectories more readily across species and disease states, the call is made for better models of critical period plasticity and the identification of biochemical and electrophysiological correlates of these windows.

Introduction

It is well appreciated that defined windows in early life exist when neural circuitry can be robustly restructured in response to experience. These time-limited critical periods have been demonstrated for diverse 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 relative stability in cortical circuitry that follows the critical period may also allow for conservation of energy/resources. With age, however, enhanced stability also inhibits large-scale adaptations to changes in input during adulthood. Utilizing the power of molecular, genetic, and imaging tools, recent advances with mouse models are beginning to unravel the network, cellular, and molecular mechanisms controlling the onset and closure of critical periods of plasticity in primary sensory areas (Figure 5.1). A pivotal

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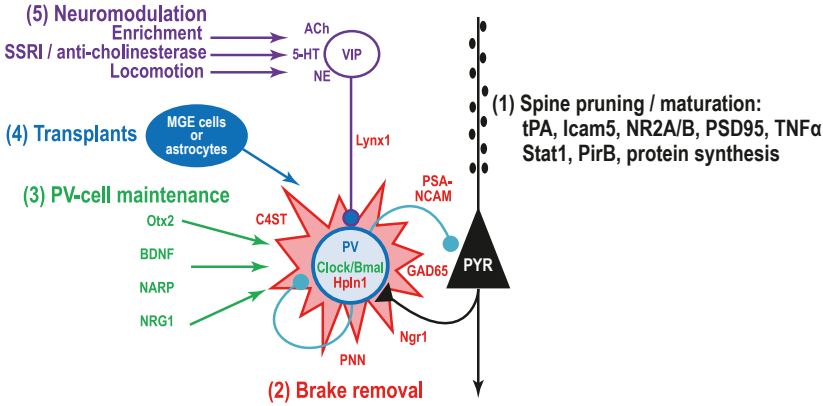

Figure 5.1 Five sites of critical period regulation: (1) Pruning and maturation of excitatory synapses onto dendritic spines involves proteases (tPA) and their cell-adhesion targets (Icam5), NMDA receptors (NR2A/B), and their postsynaptic partners (PSD95) which unsilence them, homeostatic factors (TNFα, Stat1), immune genes (PirB), and new protein synthesis. (2) Removal of brake-like factors on parvalbumin (PV)-positive basket cells enables plasticity outside the critical period, including GABA synthesis (GAD65) or cell-adhesion factors (PSA-NCAM) that control perisomatic inhibitory output, and perineuronal net (PNN) components (C4ST, Hpln1) or receptors (Ngr1) enwrapping their synaptic inputs. (3) Direct manipulation of cell-extrinsic PV-cell maintenance factors (Otx2, BDNF, NARP, NRG1) or intrinsic circadian gene regulation (Clock, Bmal) shifts plasticity onset. (4) Transplantation of immature inhibitory cell precursors (MGE cells) or astrocytes restores plasticity to the mature cortex. (5) Engaging upper layer inhibitory neurons (VIP cells) by neuromodulatory input (ACh, 5-HT, NE) through behavior or drugs disinhibits the core PV-pyramidal (PYR) circuit driving plasticity, and is actively counteracted by other brake-like factors (e.g., Lynx1 on ACh signaling) in adulthood.

player is the fast-spiking, parvalbumin (PV)-positive inhibitory neuron, which matures in register with these windows. Further evidence suggests that mechanisms enabling plasticity in juveniles are not simply lost with age, but rather that plasticity is actively constrained by the developmental upregulation of molecular "brakes." Lifting these brakes enhances plasticity in the adult visual cortex, which can be harnessed to promote recovery of function. Notably, most of the identified brake-like factors converge again upon the PV-positive interneuron, which is well-poised to generate rhythmic oscillations. Here, we discuss recent insights into the neurobiology of critical periods, and how our increasingly mechanistic understanding of these pathways can be leveraged toward improved clinical treatments.

The Amblyopia Model

The shift in ocular dominance of binocular neurons and blunted acuity (amblyopia) induced by discordant vision through the two eyes ("lazy eye") is

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the canonical model for synaptic plasticity confined to a postnatal critical period. The enhanced plasticity corresponds to 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 visual input from the two eyes occurs during the critical period (Wang et al. 2010). An asymmetry in the quality of visual input across the two eyes at this time leads to reduced visual acuity and 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 eight years, and is relatively easy to correct until that age by improving the quality of visual input in the affected eye (reviewed by Daw 1998; Mitchell and MacKinnon 2002; Simons 2005) but becomes increasingly resistant to reversal with age. Developmental constraints on this plasticity lend stability to mature visual cortical circuitry but also impede the ability to recover from amblyopia beyond an early window.

In animal models, amblyopia is most often induced by monocular deprivation (MD)—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 ocular dominance of binocular neurons away from the deprived eye and toward the open eye, resulting in a reduction in deprived-eye acuity (Wiesel and Hubel 1963, 1970; Olson and Freeman 1975; Hubel et al. 1977; Movshon and Dürsteler 1977; Blakemore et al. 1978; LeVay et al. 1978; Shatz and Stryker 1978; Antonini and Stryker 1993; Fagiolini et al. 1994; Gordon and Stryker 1996; Hensch et al. 1998; Trachtenberg and Stryker 2001; Mataga et al. 2002; Taha and Stryker 2002; Prusky and Douglas 2003; Frenkel and Bear 2004; Sato and Stryker 2008).

While ocular dominance plasticity peaks during the postnatal critical period, it generally persists at some level in many species, including rodents and cats, beyond sexual maturity. For example, the adult cortex may retain the ability to express some forms of synaptic plasticity, which may be expressed differently 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 plasticity*. Originally defined as a change in the eye preference of spiking output of V1 neurons (Wiesel and Hubel 1963), it has grown to encompass visually evoked synaptic potentials, intrinsic hemodynamic signals, immediate early gene activation, thalamocortical axon or dendritic spine morphology and motility, and calcium responses in individual cell types. Each of these methods yields different resolution and may be variably sensitive to subthreshold

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inputs (Morishita and Hensch 2008), which are important considerations when informing therapies for recovery of visual function.

Pruning Connections

The initial response to MD during the critical period is a reduction in functional strength and selectivity of deprived eye visual responses (Gordon and Stryker 1996; Hensch et al. 1998; Trachtenberg et al. 2000; Frenkel and Bear 2004). Depression of deprived-eye responses may occur by synaptic depression at both thalamocortical and intracortical connections. Notably, the most rapid shifts in visual response are seen in PV-expressing inhibitory interneurons which may enable further functional changes within V1 (Yazaki-Sugiyama et al. 2009; Aton et al. 2013; Kuhlman et al. 2013). Depression is then followed by a relatively slower, homeostatic strengthening of open eye responses (Sawtell et al. 2003; Frenkel and 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, and that this may destabilize the cytoskeleton and promote plasticity (Duffy and Livingstone 2005; Duffy et al. 2007; Duffy and Mitchell 2013). Brief MD during the critical period alters spine density on pyramidal neurons (Mataga et al. 2004; Tropea et al. 2010; Yu et al. 2011a; Djurisic et al. 2013) and induces a transient decrease in the density of synapses formed by thalamocortical axons originating from the lateral geniculate nucleus (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 and Stryker 1978; Antonini et al. 1999) as well as a significant reduction in dendritic spine density (Montey and 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. The residual plasticity that persists in adult visual cortex, however, appears to differ from the plasticity during the critical period in several important ways:

- The shift in ocular dominance in adults is slower and smaller and may require a longer duration of deprivation to engage.
- It may not require depression of deprived eye responses for subsequent strengthening of responses to the nondeprived eye.

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- It may be restricted to synapses in supragranular and infragranular lamina, as plasticity in layer IV has been shown to be constrained early in postnatal development.
- 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 ocular dominance 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 adult layer I after MD (Hofer et al. 2009).

Inhibition and Critical Period Induction

Powerful new tools in neuroscience, especially those which enable molecular genetic control in mice, are beginning to elucidate the cellular and molecular mechanisms that may 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 and Hensch 2000; Iwai et al. 2003; Fagiolini et al. 2004). Premature initiation of the critical period can be induced if early maturation of the specific class of inhibitory interneurons containing the calcium-binding protein PV is promoted by increasing levels of growth factors, BDNF (Hanover et al. 1999; Huang et al. 1999) and 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).

The perisomatic inhibition mediated by these fast-spiking PV interneurons exerts powerful control over the excitability and plasticity of downstream pyramidal neurons, potentially sharpening the spike timing required for 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 (NARP: Gu et al. 2013; NRG1: Gu et al. 2016; Sun et al. 2016). Accordingly, NARP-deficient mice fail to initiate a critical period unless rescued by enhancing the strength of inhibitory output or excitatory drive onto PV interneurons (Gu et al. 2013, 2016). The dynamic balance of excitation–inhibition within PV networks also drives oscillatory activity in the

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gamma-frequency (30–80 Hz) range (Bartos et al. 2007), which may shift dramatically over development and disease states.

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 (Harauzov et al. 2010) or 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 fast-spiking interneurons may explain the requirement for longer durations of MD with age (Kameyama et al. 2010). Together, these studies indicate that PV inhibitory cells exert bidirectional control over ocular dominance plasticity (van Versendaal and 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 I 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 and Stryker 2010) and promotes adult plasticity by increasing inhibition onto other interneuron subtypes that target pyramidal neurons (Fu et al. 2014, 2015). Similarly, reinforcement signals (reward and punishment) during the performance of an auditory discrimination task activate VIP neurons in auditory cortex, which increase the gain of a functional subpopulation of pyramidal neurons by disinhibition (Pi et al. 2013). Thus, disinhibitory circuits that transiently suppress other inhibitory interneurons may be a general mechanism for enabling plasticity in the adult cortex.

Molecular Constraints on Critical Period Plasticity

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 downregulate expression of genes that promote plasticity over development. HDAC inhibition then enhances plasticity in adult V1, allowing for recovery from amblyopia (Putignano et al. 2007; Silingardi et al. 2010). 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

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period closure, which would dampen 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 enables 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 ocular dominance 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 MD, and its 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, 2006; Carulli et al. 2010) or the molecules which bind to it (Otx2: Beurdeley et al. 2012) enables ocular dominance plasticity and recovery from amblyopia in adults. Consistent with this, mice lacking (globally or only from PV cells) 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 morphological plasticity of dendritic spines on layer V pyramidal neurons in adults (Bochner et al. 2014).

One recently identified 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 resting membrane potential. In contrast, the immediate early gene *Arc* promotes removal of AMPA receptors from cortical synapses and precludes visual plasticity when deleted (McCurry et al. 2010). Genetic reduction of PSD-95 in adulthood increases the number of silent synapses and reactivates the juvenile form of ocular dominance 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

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mechanism to constrain plasticity across brain regions (Greifzu et al. 2013; 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 ocular dominance plasticity. Robust ocular dominance plasticity persists into adulthood when mice are raised in large complex cages with multisensory and motor enrichment (Sale et al. 2007; Greifzu et al. 2013). 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. 2013).

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 and Quinlan 2011; Duffy and Mitchell 2013; Stodieck et al. 2014; Eaton et al. 2016; Mitchell et al. 2016). Several mechanisms, engaged by dark exposure, have been predicted to lower the threshold for synaptic plasticity in pyramidal neurons (Cooper and Bear 2012). For example, the composition of the NMDA type glutamate receptors is reset to a "juvenile" form (containing the NR2B subunit) which exhibits enhanced temporal summation (Yashiro et al. 2005; He et al. 2006). In addition, synaptic plasticity typically limited to juveniles is re-expressed (Huang et al. 2010; Montey et al. 2013), spines on pyramidal neurons are shifted toward 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 (He et al. 2006; Goel and Lee 2007; Guo et al. 2012).

Dark exposure also decreases the excitability of PV interneurons, and the reactivated plasticity can then be reversed by increasing the strength of excitatory synaptic input onto them (Gu et al. 2016). A loss of specific neurofilament protein associated with cytoskeletal stability is observed in the lateral geniculate nucleus following dark exposure, which may further contribute to the reactivation of structural ocular dominance plasticity beyond the peak of the critical period (O'Leary et al. 2012; Duffy et al. 2016). Thus, the seemingly opposite interventions of environmental enrichment and dark exposure may ultimately enhance cellular plasticity through the removal of functional and

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structural constraints that normally accumulate over development to stabilize 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 and Stryker 2014; Greifzu et al. 2016). This suggests that environmental reopening of plasticity in adulthood is a two-stage process that requires (a) the reactivation of plasticity machinery (permissive step) and (b) focused sensory experience to stimulate perceptual learning (instructive step). One of the challenges, therefore, is to identify the optimal sensory stimulation to drive change. In addition, prolonged plasticity by environmental enrichment in mice raises the question whether complex environments better mimic those of primates including humans. At a minimum, it 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 primary visual cortex has revised the idea that critical periods are strictly limited to early postnatal development (Bavelier et al. 2010; Takesian and Hensch 2013; Sengpiel 2014). As described above, early in the visual pathway, MD induces significant structural rearrangements in V1, including pruning of thalamocortical inputs that serve the deprived eye (Wiesel and Hubel 1963; Hubel et al. 1977; Shatz and Stryker 1978). Long-term MD yields a near complete loss of stimulus selectivity for input coming in through the chronically deprived eye (Montey and 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.

Based on mechanistic studies (above), novel therapies with translational potential to reverse the developmental constraints have been identified. 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 (SSRIs) (Maya Vetencourt et al. 2008), could be repurposed to rescue adult amblyopic patients. Interestingly, reduced PV interneuron function may be a mechanism common to several of these interventions. The SSRI antidepressant fluoxetine reduces 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). The use of action video games or vagal nerve stimulation, to recruit neuromodulatory pathways that engage attention and motivation (Mitchell and Duffy 2014; Hess and Thompson 2015; Levi et

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al. 2015; Murphy et al. 2015), may also be effective in treating sensory abnormalities (Hess and Thompson 2015; Tsirlin et al. 2015).

Beyond Ocular Dominance

One now must wonder to what extent the amblyopia model will generalize at a mechanistic level. Multiple critical periods are reported across a variety of modalities (for a review, see Hensch 2005). Armed with the molecular markers of critical period initiation and termination from the visual cortex, we can expect a "golden age" of critical period research across brain regions. For example, novel windows of plasticity for higher cognitive functions such as multisensory integration in the insular cortex (Gogolla et al. 2014) or the acquisition of preference behaviors in the medial prefrontal cortex (Yang et al. 2012) have been shown to observe common principles of PV cell maturation and reversibility by HDAC/Nogo receptor inhibitors, respectively. Of greatest interest is the potential to monitor electrophysiological signatures of shifting excitatory–inhibitory balance indicative of critical period timing which can be translated noninvasively to the human.

Even in the visual domain, the primary aspects of visual system function assessed in animal studies of amblyopia are ocular dominance and spatial acuity. Amblyopia, however, 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). Furthermore, separable neuronal response properties of individual V1 neurons have distinct, overlapping critical periods (reviewed in Kiorpes 2015). For example, in kittens, direction selectivity precedes ocular dominance (Daw and Wyatt 1976), and 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). 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 mouse visual cortex without impacting the development or plasticity of ocular dominance in juveniles (Fagiolini et al. 2003).

Moreover, 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 indicate 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 have been described in amblyopic monkeys (Kiorpes et al. 2006) partly explained by

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aberrant development of extrastriate area MT/V5. Higher brain areas and neuromodulatory pathways are also potential targets to facilitate visual responses and plasticity within V1 of amblyopic adults (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. Future primate studies, ideally with tools to monitor, activate or silence specific neural circuits, will also be essential to examine plasticity within higher-order visual regions.

Concluding Remarks and Outlook

During developmental "critical periods," neural circuitry can be potently shaped by experience. Although the brain retains the capacity to rewire beyond early life, adult forms of plasticity may utilize distinct underlying mechanisms. Understanding the differences between developmental and adult plasticity, including differences in how they are measured, will provide key insights into novel therapies for recovery of visual function from amblyopia in both children and adults.

Importantly, 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 is instead actively constrained beyond the 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; that is, biologically inspired clinical studies for functional recovery.

Future work should include the development of better models for critical period plasticity across animal species and humans. Several molecules implicated in regulating the timing of the critical period, including the constraints on adult plasticity, are known risk factors for neurodevelopmental disorders such as schizophrenia (e.g., redox imbalance, HDAC and NRG1) (Rico and Marín 2011; Penzes et al. 2013; Do et al. 2015). Curiously, male schizophrenics are two times less likely to have refractive errors (Caspi et al. 2009). Capitalizing on genetic diversity in mice and humans will provide insight into the individual variability that influences the timing of critical periods. Identifying biochemical and electrophysiological correlates of these windows will allow us to compare developmental trajectories more readily across species and disease states.

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