Multiple Roles for Nogo Receptor 1 in Visual System Plasticity

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Abstract

During the developmental critical period for visual plasticity, discordant vision alters the responsiveness of neurons in visual cortex. The subsequent closure of the critical period not only consolidates neural function but also limits recovery of acuity from preceding abnormal visual experience. Despite species-specific differences in circuitry of the visual system, these characteristics are conserved. The *nogo-66 receptor 1* (*ngr1*) is one of only a small number of genes identified thus far that is essential to closing the critical period. Mice lacking a functional *ngr1* gene retain developmental visual plasticity as adults and their visual acuity spontaneously improves after prolonged visual deprivation. Experiments employing conditional mouse genetics have revealed that *ngr1* restricts plasticity within distinct circuits for ocular dominance and visual acuity. However, the mechanisms by which NgR1 limits plasticity have not been elucidated, in part because the subcellular localization and signal transduction of the protein are only partially understood. Here we explore potential mechanisms for NgR1 function in relation to manipulations that reactivate visual plasticity in adults and propose lines of investigation to address relevant gaps in knowledge.

Keywords

amblyopia, critical period, dendritic spines, mouse, myelin, ocular dominance, visual acuity, visual cortex, visual plasticity

Introduction

Life experience perpetually refines circuitry and function in the mammalian brain. Understanding when, where, and how, experience modifies synaptic connectivity within the dense architecture of the central nervous system (CNS) to affect future sensation and behavior remains one of the great challenges of neuroscience.

The general view of CNS development is that the flexibility of neural circuitry, or plasticity, diminishes with maturation. Brain circuitry is most pliable during development as neurons first wire together into new and more complex circuits. These immature circuits are then sculpted by patterns of neuronal activity during a brief interval of heightened sensitivity to experience, or "critical period." Thereafter, plasticity diminishes as many circuits become resistant to the same experience that was so impactful during the critical period. Although some plasticity is sustained in the adult, these mechanisms are often less robust than those present during development. Weaker adult plasticity is often suspected to contribute to the limited restitution of function following CNS injury.

The visual system is a premier model for observing this developmental progression but in the context of abnormal experience and maladaptive plasticity. Decades of clinical observations document that temporarily depriving one eye of vision has consequences of significantly different magnitude and permanence depending on the age of onset and duration of deprivation (Webber and Wood 2005). For example, on removing congenital unilateral cataracts, infants and young children can exhibit severe disuse of the affected eye, whereas similar cataracts yield a less substantive but permanent deficit in older children, while in adults only temporary visual impairments are expected (Lloyd and others 2007). This impoverished visual performance is diagnosed as deprivation amblyopia, a visual disorder that cannot be explained by alterations in retinal function of the affected eye (Lepard 1975). Amblyopia results in a number of deficits in spatial vision, including lower visual acuity and depth perception (Levi and Li 2009). While patching the nonaffected eye remains standard of care for improving function of the affected eye, this approach is less effective after the critical period

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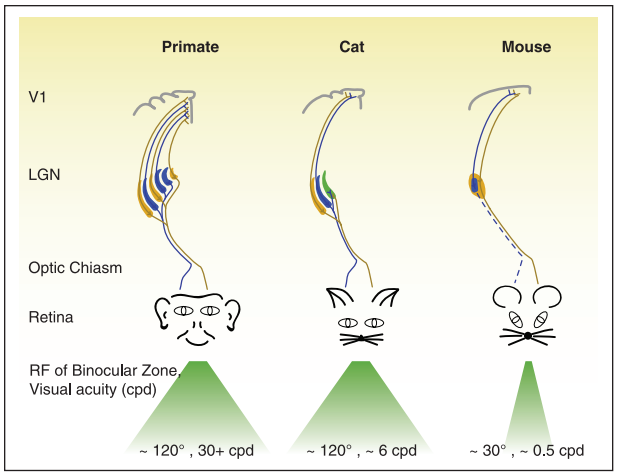

Figure 1. Aspects of visual system circuitry are conserved among mammals. Axons from projection neurons in the retina with receptive fields within the binocular zone (green) converge on the optic chiasm (blue and yellow lines) and then target the lateral geniculate nucleus (LGN) in each hemisphere. In mouse, the majority of axons cross the chiasm and the ipsilateral projection (blue dashed line) is smaller than in predatory mammals such as primates and cats. Within the LGN, axons from each eye innervate distinct domains. These domains comprise six layers in primate and three layers in cat, whereas the ipsilateral eye targets a smaller patch nestled within a larger domain of the contralateral eye in mouse. The axons from the neurons in LGN then project to primary visual cortex (V1).

which closes at around 12 years of age. Over the past 50 years, analogous findings on the effects of early deprivation on visual acuity have been reported for cats, primates, and more recently for mice, consistent with the general conservation in the organization of visual circuitry across mammals (Hensch 2005). A major goal of this field of research is to understand the regulation and mechanisms of visual plasticity sufficiently to devise therapeutics that can improve clinical care for amblyopia and other visual disorders.

Despite significant differences in the organization and performance of the visual system between species, many important similarities remain (Fig. 1). Visual information is first encoded by the retina. Axons from retinal ganglion cells (RGCs) project to a subcortical target, the lateral geniculate nucleus (LGN) or visual thalamus. A fraction of these axons cross the midline at the optic chiasm to innervate the thalamus in the contralateral hemisphere, while others remain ipsilateral. The axons from each eye innervate segregated layers in the thalamus. Axons from these layers project to primary visual cortex (V1), the first substrate within the visual circuit where input from the two eyes converges. In predatory mammals, such as primates and cats, V1 receives equal input from each eye. In mice, the eyes are positioned more laterally and provide a broader "hemi-panoramic" field of vision, yet they retain a defined binocular zone (Dräger 1975). Although the great majority of projections from the retina cross the midline to the contralateral thalamus in mice, the inputs from each eye also remain separate until converging in V1. Importantly, mice also exhibit a critical period of sensitivity to visual deprivation similar to both cats and primates (Gordon and Stryker 1996). Consequently, the mouse has become a predominant model for investigating the genes and mechanisms of visual plasticity because of the available genetic resources and continually improving array of molecular biology tools.

The first gene identified to restrict developmental plasticity to the critical period is the *nogo-66 receptor* (*ngr1*/*rtn4r*). Mice lacking a functional version of this gene retain critical-period visual plasticity as adults (McGee and others 2005). Only a handful of genes have since been identified that also inhibit visual plasticity in adult mice (Levelt and Hübener 2012). In our recent work, we have employed the *ngr1* gene as a tool to disentangle components of developmental visual plasticity. Dissecting how these separable facets of visual plasticity and function are limited by *ngr1* may provide insight not only into how the quality of vision refines the circuitry and performance of the visual system, but how experience sculpts the development and function of the cerebral cortex in general.

Classic Vision Studies

Visual plasticity is best understood in relation to the pioneering studies in kittens. The experimental paradigm and parlance of visual plasticity originated with the seminal work by Drs. David Hubel, Torsten Wiesel, and their contemporaries in the 1960s and 1970s. At the time, advances in the design and fabrication of microelectrodes provided a new opportunity to perform "single-unit" recordings throughout the depth of cerebral cortex (Hubel 1957). Studies employed this technique to examine if and how perturbing concordant vision altered the responses of neurons in developing cat visual system to subsequent visual stimuli. These efforts discovered that briefly occluding one eye (monocular deprivation [MD]) in kittens, but not older cats, dramatically altered eye dominance as measured by the firing of neurons in visual cortex to the same visual stimulus provided to each eye independently (Blakemore and van Sluyters 1974; Hubel and Wiesel 1965, 1970; Wiesel and Hubel 1963). Closing one eye during this early sensitive, or "critical," period for longer than a few days perturbed the normal binocular responsiveness, whereas depriving one eye of vision thereafter had little consequence. These classic studies

revealed that disruptions of normal eye dominance (ocular dominance [OD]) preceded deficits in visual acuity. These findings are the basis of a circuit model for the pathophysiology of the prevalent childhood visual disorder amblyopia (Fig. 2).

In initial studies, deprivation amblyopia was induced in kittens by limiting patterned vision to one eye from the time of natural eye opening for a period of 3 months (Wiesel and Hubel 1963). Kittens exhibited behavioral blindness through the deprived eye once normal vision was restored that gradually improved over 3 to 18 months (Wiesel and Hubel 1965). The critical period for ocular dominance overlaps with the maturation of acuity; both conclude around approximately 3 months of age in kittens (Daw 1998; Ikeda 1980). Subsequent studies demonstrated that even durations of deprivation as short as brief as 6 days during the zenith of the critical period (4-6 weeks of age) impair visual acuity through the deprived eye (Mitchell and Gingras 1998; Mitchell and others 2001). Interestingly, when vision is restored at this point, acuity partially improves to a level comparable to that of the non-deprived eye at the age of initial deprivation. However, longer durations of MD spanning the critical period not only result in sustained deficits in visual acuity but also increase the branching and extension of thalamocortical axons representing the nondeprived eye at the expense of corresponding axons from the deprived eye (Antonini and Stryker 1993). This redistribution of axon fibers carrying visual information for each eye from the thalamus can be visualized with metabolic labeling techniques. These "ocular dominance columns" expand for the nonaffected eye within primary visual cortex (Shatz and Stryker 1978).

Mice also exhibit alterations in OD plasticity as well as impaired vision following monocular deprivation, albeit with smaller magnitude (Dräger 1978; Gordon and Stryker 1996; Priebe and McGee 2014; Prusky and Douglas 2003). Similar to cats, mice display a critical period for eye dominance shortly after eye opening. The critical period lasts around 2 weeks, from approximately P19 to P32 (Gordon and Stryker 1996). Interestingly, this is also when visual acuity matures (Huang and others 1999; Stephany and others 2014). However, whereas a week of deprivation has a profound impact on visual function in kittens, relatively longer durations of MD yield more modest deficits in mice. Four days of MD is required for saturating OD plasticity and the magnitude of the resulting shift in eye dominance is less than that observed in cats or primates (Fig. 2) (LeVay and others 1980; Wiesel and Hubel 1963). Likewise, although a week of MD within the critical period for kittens halves visual acuity, reduced behavioral acuity in mice has only been reported following long-term deprivation (LTMD) that spans the duration of the critical period (Fig. 2) (Prusky and Douglas 2003). In contrast to cats and primates, the smaller mouse brain lacks surface convolutions and mice do not possess detectable ocular dominance columns, although the branching pattern and length of individual axons from the visual thalamus subserving the deprived and nondeprived eye appear to diverge following LTMD (Antonini and others 1999). Mice also possess several characteristics of visual circuitry first discovered in carnivores, including linear versus nonlinear spatial summation, contrast-invariant tuning, and selectivity for stimulus parameters such as orientation and spatial frequency (Niell and Stryker 2008).

The prevalent model supported by this substantive body of evidence is (1) OD plasticity drives functional changes that are (2) consolidated with subsequent anatomical rearrangements of synaptic connectivity by thalamocortical afferents and (3) that these alterations in visual circuitry are irreversible with the closure of the critical period. Thus, "reopening" the critical period is considered a first and essential step in reversing deficits associated with amblyopia.

NgR1 Governs Multiple Facets of Developmental Visual Plasticity through Distinct Circuits

Adult *ngr1* constitutive "knock-out" mutant (*ngr1*−/−) mice retain OD plasticity typically confined to the critical period (McGee and others 2005). This plasticity was identified with single-unit recordings under barbiturate anesthesia, conditions that discriminate plasticity during the critical period from plasticity resident in the mature brain (Pham and others 2004). This approach compares the relative firing rate of neurons to the same visual stimulus presented independently to each eye and is similar to preceding experiments performed in kittens. Thus, it provides the most direct comparison to classic studies. However, other approaches can also be employed to measure OD plasticity, including visually evoked potentials (VEPs), distribution of activity-dependent gene transcription, and optical imaging of intrinsic signals (Cang and others 2005; Sawtell and others 2003; Tagawa and others 2005). These techniques have advantages, including repeated measures and compatibility with experiments on alert mice, and also disadvantages, particularly that these techniques reflect a combination of subtheshold (synaptic) activity and superthreshold (spiking) output, which may not reliably reflect spiking activity accurately (Morishita and Hensch 2008).

Several manipulations that reinstate developmental OD plasticity after the critical period also yield recovery of visual acuity following LTMD (Levelt and Hübener 2012). These studies employ VEPs to estimate visual acuity. Environmental manipulations, including environmental

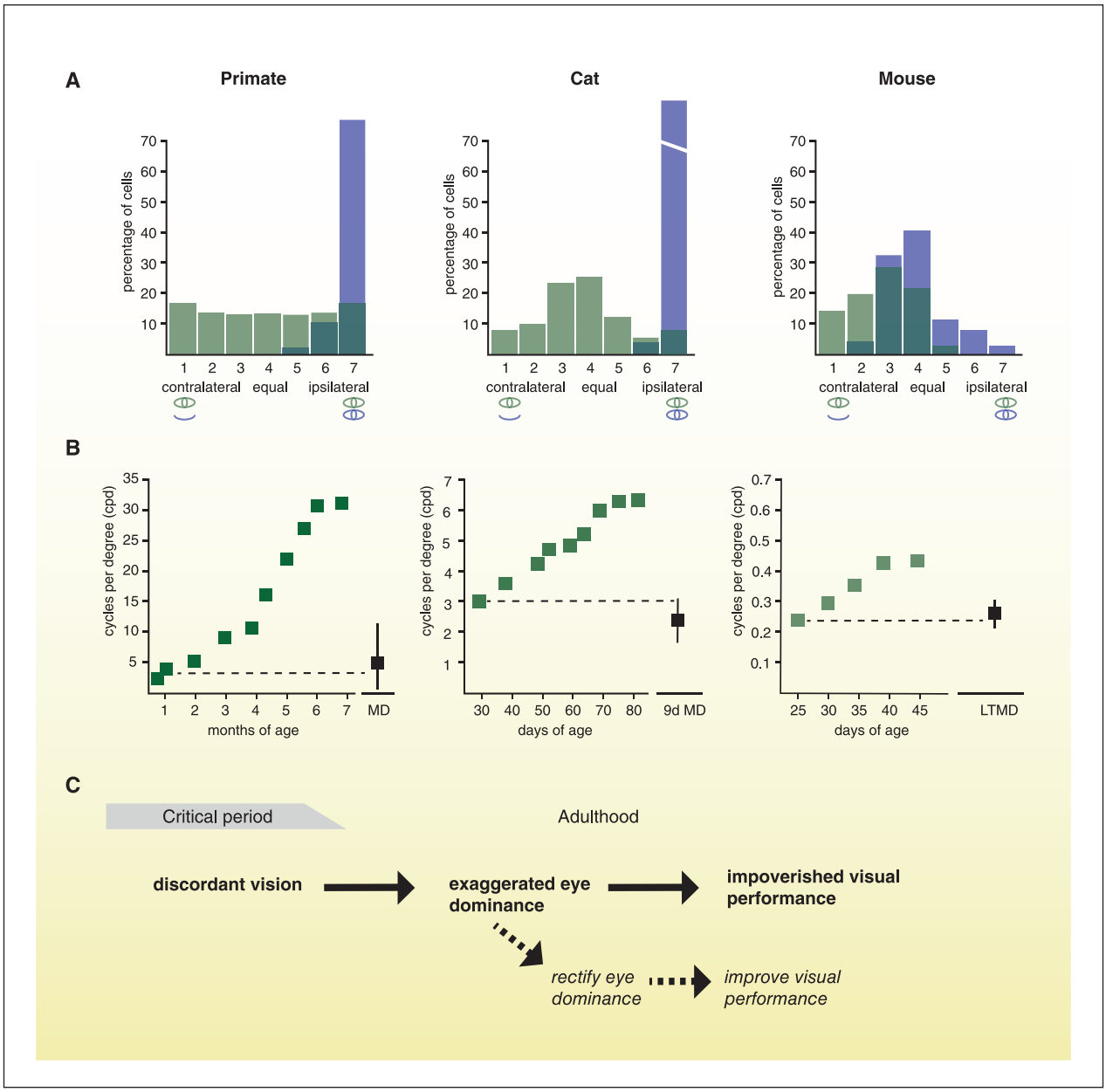

Figure 2. Aspects of visual system plasticity are conserved among mammals. (A) Monocular deprivation (MD) during the critical period disrupts eye dominance. Ocular dominance (OD) histograms plot the distribution of relative responsiveness of neurons in V1 to a visual stimulus presented independently to each eye. Neurons increasingly more responsive to the contralateral eye are categorized with lower numbers (3, 2, 1) while those with increasing preference for the ipsilateral eye are binned into higher number categories (5, 6, 7). Neurons with equal responsiveness to each eye are categorized as "4." In primates and cats with normal vision (green bars and eye symbols below) this distribution is binocular. In mouse, normal vision is biased to the contralateral eye. Closing the contralateral eye for as briefly as a few days (purple bars and eye symbols below) shifts eye dominance toward the nondeprived ipsilateral eye. This plasticity is conserved between species although the magnitude of the OD shift varies. (B) Visual acuity increases during the critical period (green squares) and closing one eye during this maturation permanently impairs visual acuity. The resulting acuity following MD is similar to the acuity at the age of deprivation (black square), although these results are more variable in primate studies. In mice, deprivation for the duration of the critical period (long-term deprivation, LTMD) is required to impair acuity. (C) One model for how MD impairs visual performance in mammals. Discordant vision, such as deprivation or strabismus, first exaggerates eye dominance as in (A), diminishing responsiveness to the affected eye in visual cortex. This limited representation of the affected eye prevents the normal maturation of visual circuits subserving performance, such as acuity as in (B). After the critical period, these mechanisms of plasticity are no longer accessible. "Reactivating" developmental visual plasticity otherwise confined to the critical period is one strategy for rectifying eye dominance and potentially improving vision through the affected eye.

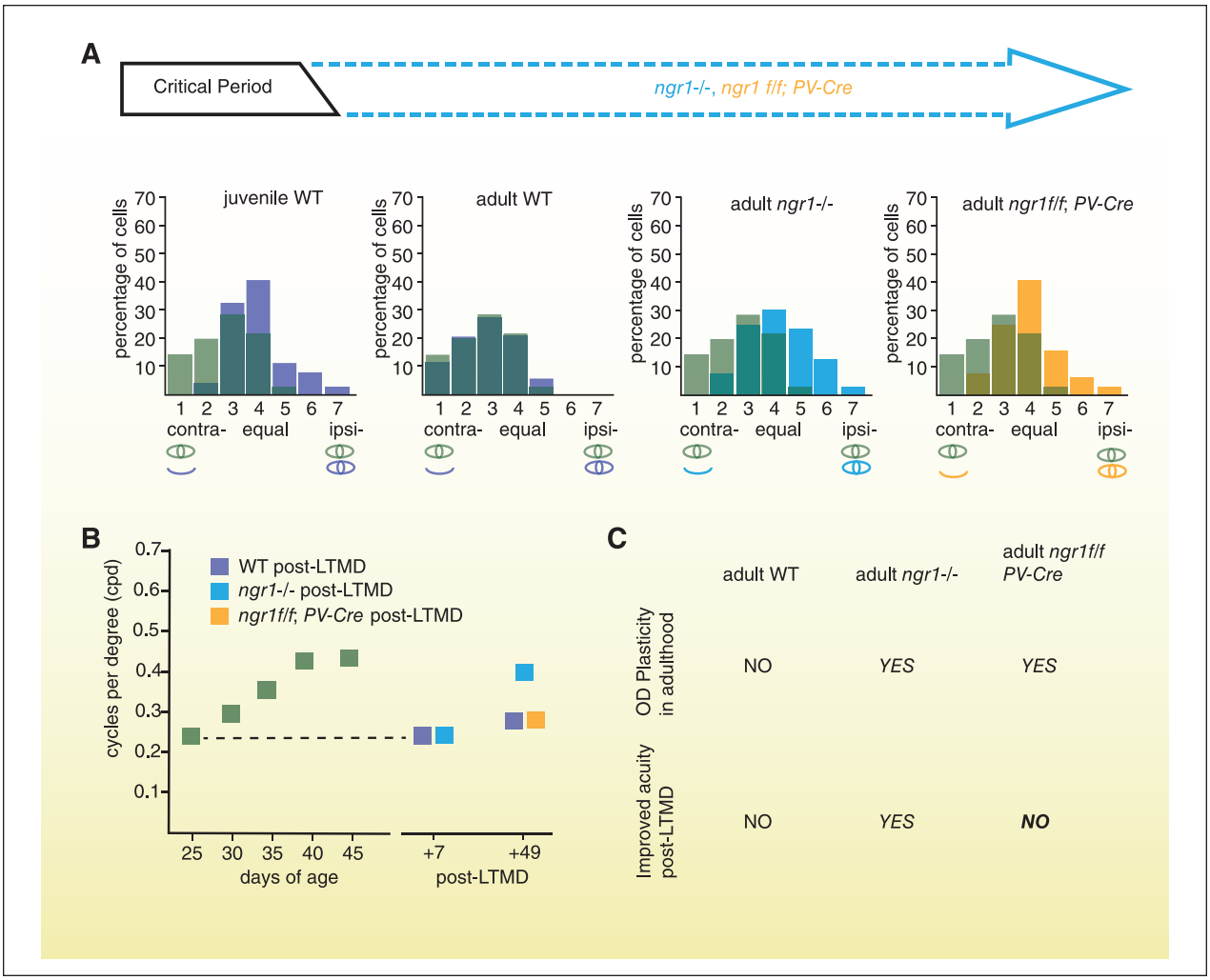

Figure 3. The *ngr1* functions in neurons within distinct circuits to limit ocular dominance (OD) plasticity and improvement in acuity. (A) Mice lacking *ngr1* constitutively (*ngr1−/−*), or selectively in PV interneurons (*ngr1 f/f;PV-Cre*), retain developmental visual plasticity as adults. During the critical period, 4-days of MD (purple bars and eye symbols below) shifts the distribution of neuronal eye dominance (green bars and eye symbols below). This is not observed in adult WT mice. In contrast, in adult *ngr1−/−* mice or *ngr1 f/f;PV-Cre* mice, 4 days of MD continues to shift ocular dominance. (B) Adult *ngr1−/−* mice spontaneously recover visual acuity over 7 weeks following long-term deprivation (LTMD), but WT and *ngr1 f/f;PV-Cre* mice do not. (C) A comparison of the facets of visual plasticity present in different genotypes of mice. This genetic dissection of the expression of *ngr1* reveals that OD plasticity is not sufficient to improve visual acuity.

enrichment and dark exposure, may decrease inhibitory transmission to reactivate OD plasticity and increase visual acuity following LTMD (Baroncelli and others 2010; H.-Y. He and others 2006; H.-Y. He and others 2007; Lloyd and others 2007; Sale and others 2007). Rodents injected with fluoxetine, the serotonin-specific reuptake inhibitor, or chondroitinase ABC, an enzyme that degrades specific sugar polymers in perineuronal nets, display juvenile-like OD plasticity as adults and higher visual acuity following LTMD (Maya Vetencourt and others 2008; Pizzorusso and others 2002; Wiesel and Hubel 1965). Each of these treatments has been reported to yield a rapid development of cortical responses to higher spatial frequency visual stimuli. Unfortunately, acuity estimated with VEPs does not always register with acuity measured behaviourally (H.-Y. He and others 2007). Nonetheless, these data correlate OD plasticity with greater visual acuity following LTMD.

Consistent with a potential role for OD plasticity in recovery from amblyopia, *ngr1−/−* mice also display a spontaneous although gradual recovery of visual acuity by the affected eye following LTMD (Stephany and others 2014) (Fig. 3). In these experiments, acuity is estimated from performance in a vision discrimination assay, the visual water task (Prusky and others 2000). In mice, closing one eye for the duration of the critical period impairs visual acuity for that eye permanently (Prusky

and Douglas 2003). These behavioral measurements are similar regardless of whether they are performed 2, 3, or 6 months following reopening of the closed eye. In contrast to environmental and pharmacologic approaches to enhancing visual plasticity, acuity slowly increases in *ngr1*−/− mice. Several weeks of normal vision following LTMD are required to see improvement (Fig. 3). At present, *ngr1* is the only gene demonstrated to limit improvement of performance on the visual water task in this murine model of amblyopia.

However, selective deletion of the *ngr1* gene with conditional mouse genetics reveals that the circuitry underlying OD plasticity and recovery of visual acuity are separable (Fig. 3). Whereas *ngr1*−/− mice exhibit OD plasticity as adults and recovery of visual acuity (Frantz and others 2015; McGee and others 2005; Stephany and others 2014), mice in which deletion of *ngr1* is restricted to parvalbumin-positive (PV) inhibitory neurons (*ngr1 flx/flx; PV-Cre*) only retain OD plasticity beyond the critical period. They do not recover visual acuity following LTMD. Thus, *ngr1* operates within PV interneurons to confine OD plasticity to the critical period but functions more broadly within visual circuitry to limit improvement of acuity. This genetic dissection of *ngr1* provides the first genetic evidence that OD plasticity and the mechanisms of plasticity governing visual acuity are dissociable and may occur in distinct cortical circuits. Whether deleting *ngr1* in an a subset of neurons within the visual system can permit improvement of acuity following LTMD and whether the plasticity mediating improved visual performance is accompanied by OD plasticity are not yet known.

Elucidating how *ngr1* limits these facets of visual plasticity remains a challenge because the molecular function of NgR1 is poorly understood and the nature of experience-dependent plasticity in the visual system is only partially characterized.

NgR1 Molecular Signaling

NgR1 is the founding member of a family of three neuronal receptors (Baldwin and Giger 2015). Each comprises several leucine-rich repeats (LRRs) followed by a unique "stalk" signaling domain and a glycosyl-phosphatidylinositol (GPI) lipid anchor. NgR1 binds to a number of unrelated ligands expressed by both neurons and oligodendrocytes (Fig. 4).

NgR1 was first characterized as a surface protein that bound to an isolated 66-amino acid fragment of the reticulon protein Rtn4a/Nogo-A (Fournier and others 2001). Nogo-A is one of several proteins enriched in membranes of CNS myelin that inhibit the extension of axons by primary neurons *in vitro* (Z. He and Koprivica 2004). Subsequently, NgR1 was reported to bind two additional

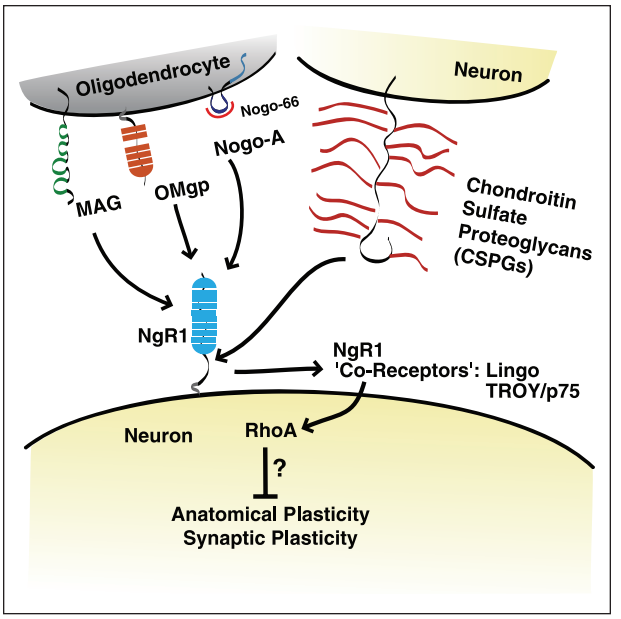

Figure 4. Several disparate extracellular ligands bind NgR1. Myelin-associated glycoprotein (MAG), oligodendrocyte-myelin glycoprotein (OMgp), and the Nogo-66 region of Nogo-A are ligands for NgR1. These proteins each bind the leucine-rich repeat (LRR) domain of NgR1. Several members of the family of chondroitin sulfate proteogylcans (CSPGs) also bind to NgR1. The sugar chains on these molecules interact with the stalk region of the receptor. As NgR1 is attached to the plasma membrane by a lipid anchor, NgR1 is proposed to transduce a signal from these ligands through one or more transmembrane "co-receptors" such as Lingo, TROY and p75, to activate the small GTPase RhoA. How this signal may limit anatomical plasticity and/or synaptic plasticity remains unclear.

myelin-associated inhibitors (MAIs) of neurite outgrowth expressed by oligodendrocytes, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp) (McGee and Strittmatter 2003). Each of these disparate proteins binds to overlapping locations within the LRR domain (Hu and others 2005). NgR1 also binds the membrane-bound form of amyloid precursor protein (APP), the soluble fibroblast growth factors 1 and 2 (FGF1, FGF2) and the secreted protein leucine-rich glioma inactivated (LGI1) (Lee and others 2008; J. H. Park and others 2006; Thomas and others 2010). Interestingly, the glycosaminoglycan (GAG) moiety of chondroitin sulfate proteoglycans (CSPGs) also interacts with NgR1 (Dickendesher and others 2012). These sugar chains on CSPGs decorate the length of the extracellular domains for several families of proteins, many of which are enriched in perineuronal nets (Siebert and others 2014). In contrast to MAIs, CSPGs bind the stalk domain of NgR1 (Dickendesher and others 2012).

As NgR1 lacks a transmembrane domain, it is likely associated with a signal-transducing co-receptor. Several

transmembrane proteins have been proposed as co-receptors although they share little homology. NgR1 is reported to form a tripartite signaling complex with LRR and immunoglobulin domain-containing Nogo receptor interacting protein (Lingo-1), the low affinity neurotrophin receptor p75, and/or tumor necrosis factor receptor 19 (Tnfr19/TAJ/TROY) (Mi and others 2004; J. B. Park and others 2005; K. C. Wang and others 2002). TROY and p75 are proposed to be functional homologs that transduce the intracellular signal of NgR1 although these proteins share only modest conservation of primary amino acid sequence. Experimental support for these proteins as co-receptors derives from experiments in which neutralizing signaling by TROY or genetic deletion of p75 in cultured dorsal root ganglion (DRG) neurons alleviates the inhibition of neurite outgrowth by MAIs in vitro (J. B. Park and others 2005; K. C. Wang and others 2002). Lingo-1 is proposed to serve as an adaptor in the signaling complex. When NgR1 binds MAIs in the presence of p75/TROY and LINGO, this is reported to activate the intracellular signaling molecule RhoA to transduce an inhibitory signal (Mi and others 2004). By comparison, NgR1 signaling following binding of CSPGs does not require p75 (Dickendesher and others 2012). Thus, while there may be functional overlap in the effects of these different ligands on neurite outgrowth in vitro, the intracellular signaling by NgR1 on binding distinct ligands may differ. The functions of these ligands and putative co-receptors are predominantly inferred from binding and neurite outgrowth experiments in vitro and there is little physiologic evidence for the obligatory role for these ligands or proposed co-receptors in mediating the physiological functions of NgR1. Overall, the information available on the molecular role of NgR1 provides few clues as to how it may function to limit visual plasticity.

Potential Mechanisms of NgR1 Function in Visual Plasticity

Several compatible mechanisms may contribute to the critical-period plasticity observed in adult *ngr1*−/− mice. NgR1 may function by restricting anatomical changes to local circuitry, impeding maturation of the balance of excitatory and inhibitory neurotransmission (E/I balance), or by transducing signals from inhibitory factors in the extracellular environment. Each of these mechanisms contributes to regulating plasticity in the visual system (Morishita and Hensch 2008).

Anatomical Plasticity

NgR1 is expressed throughout the visual system, including the retina, LGN, and V1 (Barrette and others 2007; Dickendesher and others 2012). However, the subcellular localization of NgR1 is unclear, as the receptor has been reported in similar experiments to localize almost exclusively to axons and presynaptic terminals, or to be enriched in the somatodendritic compartment and dendritic spines, or to be distributed throughout the neuron (X. Wang and others 2002; Wills and others 2012; Zemmar and others 2014). NgR1 is abundant in subcellular fractions that are enriched for postsynaptic proteins (synaptosomes) (Akbik and others 2013; Lee and others 2008). Unfortunately, these experiments must be interpreted with caution because these purification conditions, specifically fractionation of low-density membranes and insolubility in nonionic detergents, are biochemical characteristics of GPI-linked cell surface proteins in general (Brown and Rose 1992; Carlin and others 1980). In cultures of murine primary cortical neurons, immunocytochemistry with antibodies specific for NgR1 reveal staining in the soma and dendrites but it does not appear to exclusively overlap with the staining pattern for postsynaptic density 95kD (PSD-95), a common marker of synapses (Wills and others 2012).

The role of NgR1 in neurite outgrowth in vitro motivated the prediction that NgR1 may restrict plasticity by regulating the formation and stability of new synaptic connections (McGee and Strittmatter 2003). Recent studies have examined if NgR1 limits the formation, stability, and loss of dendritic spines and axonal boutons in neocortex. Unfortunately, the results of these studies do not support a unifying conclusion. In transfected hippocampal organotypic slice cultures, reducing expression of NgR1 with shRNAs increases dendritic spine density whereas overexpressing NgR1 reduces spine density by half (Wills and others 2012). In contrast, spine density is normal in *ngr1*−/− mice and in vivo overexpression of NgR1 in cerebral cortex does not alter spine density (Karlén and others 2009; Lee and others 2008; Wills and others 2012). A study examining the formation and loss of dendritic spines on the apical arbors of layer 5 (L5) pyramidal neurons in somatosensory cortex with repeated two-photon in vivo imaging reported that both constitutive and acute deletion of *ngr1* in mice induces spine turnover at a rate almost 3 times higher than wild-type (WT) controls. This represents the largest increase in spine dynamics reported for age-matched mice for any genetic, pharmacologic, or environmental manipulation. We have performed similar, in some cases nearly identical, two-photon in vivo imaging experiments with the same strains of *ngr1* mutant mice, but are unable to reproduce these findings (Fig. 5). We measured spine formation and loss among more spines per group for more imaging intervals but we observed that *ngr1* mutant mice exhibit normal spine dynamics (J. I. Park and others 2014). While this mix of results from different studies does not support a role for *ngr1* as a prominent regulator of dendritic spine turnover,

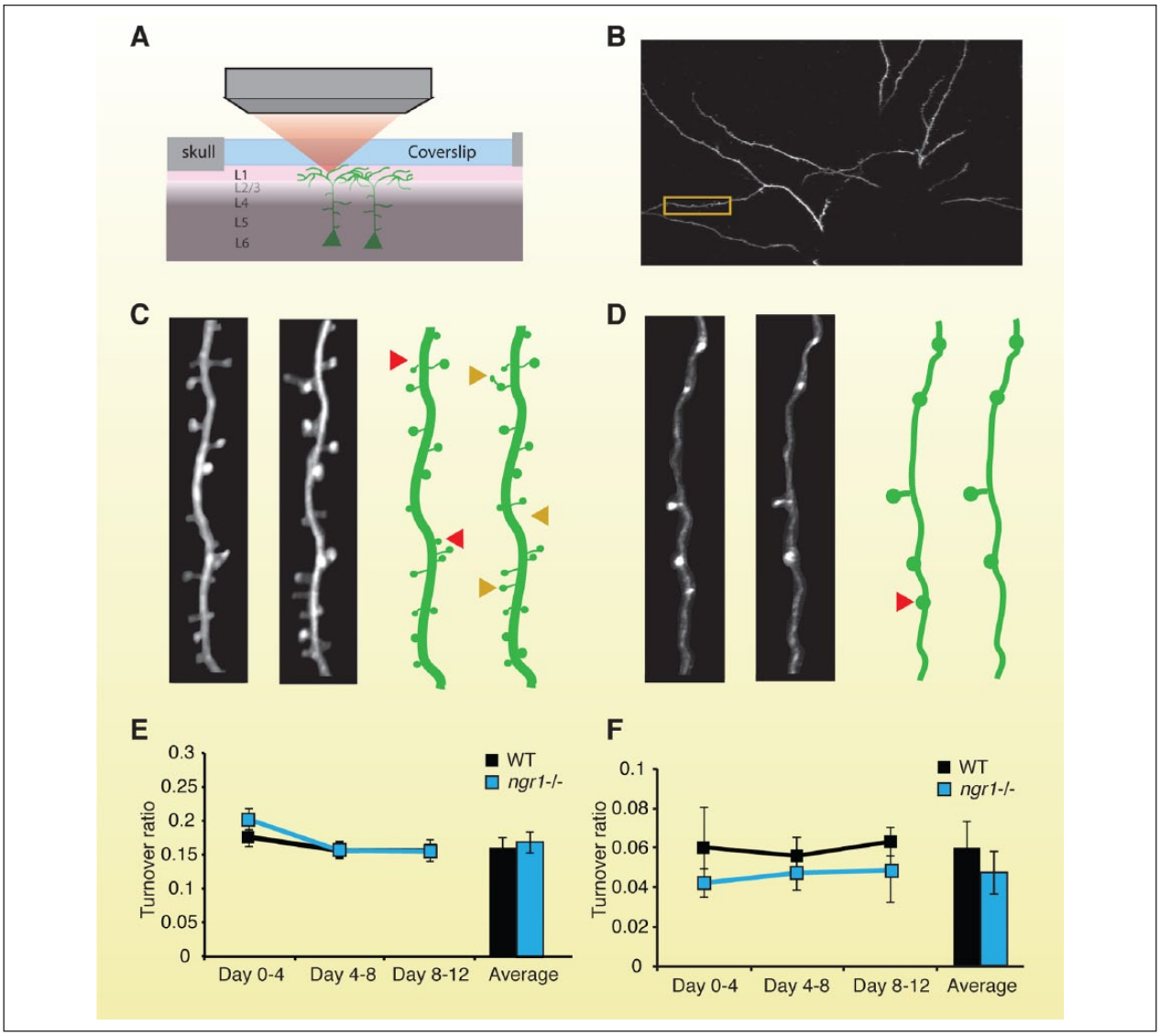

Figure 5. The *ngr1* gene does not determine the set point for synaptic turnover in cerebral cortex. (A) One approach for investigating how specific genes may influence synaptic structural plasticity is in vivo 2-photon laser scanning microscopy (2plsm) through a cranial window, a small coverslip replacing a region of overlying skull. This approach permits repeated imaging of dendrites present in the most superficial layers of cortex, L1 and L2/3, in mice expressing green fluorescent protein (GFP+) in a sparse subset neurons. In this schematic, two GFP+ pyramidal neurons in L5 are shown with their apical dendrite branching in L1. The grey overlay emphasizes that only dendrites present in L1 and L2/3 are visible with this approach. (B) An example of apical dendrites in L1 from two pyramidal neurons. The yellow rectangle is the location of the dendrites presented in panel (C). At left, a segment of dendrite imaged four days apart. At right, a schematic of the locations of spines along the dendrite, including spines lost (red arrowheads) and spines gained (yellow arrowheads). (D) At left, a segment of axon imaged four days apart. At right, a schematic of the positions of boutons along the axon, including a bouton lost (red arrowhead). (E) The turnover ratio for dendritic spines ([percent gained + percent lost]/2) for wild-type (WT) and *ngr1*−/− mice across three consecutive imaging intervals as well as the average ± standard error of the mean (SEM). (F) The turnover ratio for axonal boutons ([percent gained + percent lost]/2) for WT and *ngr1*−/− mice across three consecutive imaging intervals as well as the average ± SEM.

whether visual plasticity in adult *ngr1* mutant mice during MD or following LTMD may also induce greater synaptic structural plasticity remains to be determined.

Alternatively, NgR1 could function presynaptically to inhibit structural plasticity by axons and axonal boutons, thereby limiting visual plasticity. In cats, a week of MD induces a rapid pruning of branches of thalamocortical axons transmitting information from the deprived eye (Antonini and Stryker 1993) and visual deprivation lasting months results in shrinkage of OD columns for the

deprived eye and expansion of OD columns for the non-deprived eye (Shatz and Stryker 1978). Similarly, brief MD in mice is reported to reduce the density of thalamocortical synapses and LTMD yields a trend of more branch points and greater total length for thalamocortical axons from the non-deprived eye (Antonini and others 1999). Much like dendritic spines, a small percentage of axonal boutons are gained and lost in vivo (De Paola and others 2006). Yet whether genes or experience affect turnover of axonal boutons remains relatively understudied. To address whether NgR1 regulated bouton dynamics, we measured the rates of addition or loss of axonal boutons of intracortical layer 2/3 and 5 excitatory neurons of WT or *ngr1*−/− mice prior to and then during 8 days of MD or during LTMD followed by restoration of normal vision. Neither brief MD nor reopening the deprived eye following LTMD altered intracortical bouton dynamics for WT or *ngr1*−/− mice (Frantz and others 2015). Recently developed genetic resources for expressing fluorescent proteins in thalamic axons should permit future studies to examine whether these manipulations of visual experience impact the formation or stability of thalamocortical axons and boutons during the critical period or in adulthood. These imaging studies will be most informative once technical limitations for resolving these small structures in L4 are surmounted.

In summary, although initial studies provided encouraging, and in some cases extraordinary, findings that NgR1 may limit synaptic structural plasticity, subsequent experiments do not reaffirm the conclusion that NgR1 governs synaptic turnover in adult cortex. As new results emerge to inform understanding of when, where, and how, visual plasticity alters circuitry within V1, we anticipate that advances in in vivo imaging will facilitate experiments to pinpoint and examine these specific synaptic connections.

Excitatory and Inhibitory Neurotransmission Balance

Understanding the characteristics of circuitry in V1 during the critical period may provide insight into the mechanisms of visual plasticity as well as reveal changes in cortical architecture that diminish plasticity in adults. Several strategies that influence the timing of the critical period are linked to changes in the balance of excitatory and inhibitory neurotransmission (E/I balance) (Levelt and Hübener 2012). Early studies demonstrated that visual experience is necessary to open the critical period as rearing kittens in complete darkness (dark rearing) delayed the onset of the visual plasticity until they were introduced to normal housing conditions (Cynader and Mitchell 1980). Dark rearing also impeded the development of neurotransmission for the γ-aminobutyric acid (GABA) in visual cortex as measured with biochemical assays (Fosse and others 1989). These initial findings have been extended by both pharmacologic and molecular genetic studies in mice. Rearing rodents in the dark also delays maturation of visual function and OD plasticity by reducing GABAergic transmission in V1 (Fagiolini and others 1994; Morales and others 2002). In addition, mutant mice lacking a functional gene for glutamic acid decarboxylase 65Dkd (GAD-65) lack OD plasticity (Hensch 1998). GAD-65 contributes to the synthesis of the GABA at nerve terminals. However, briefly treating *gad65*−/− mice with diazepam, a benzodiazepine, initiates the critical period in both juvenile and adult mice (Fagiolini and Hensch 2000). Thus, a minimum threshold of inhibitory tone is required to open the critical period. Augmenting cortical inhibition in young mice prior to the normal onset of the critical period (P19) with either diazepam, or transgenic overexpression of brain-derived neurotrophic factor (BDNF) also induces visual plasticity (Hanover and others 1999; Huang and others 1999; Iwai and others 2003) (Fig. 6).

In the mouse, cortical inhibition strengthens across the critical period (Morales and others 2002). Interestingly, several manipulations that reduce inhibitory neurotransmission partially reactivate OD plasticity. Introducing adult rodents into an enriched environment with increased visual stimulation decreases local inhibition in V1 and partially restores OD plasticity (Baroncelli and others 2010). Complete deprivation of visual input by sequestering mice in a dark environment for 10 days preceding a period of brief MD also enhances OD plasticity. This manipulation also decreases the ratio of $GABA_A$ receptors to NMDA receptors in comparative immunoblots (H.-Y. He and others 2006). The acute administration of fluoxetine, or 3-mercaptopropionic acid (MPA), an inhibitor of GAD, which both yield a reduction of cortical inhibitory transmission, also promotes OD plasticity in adult rodents (Maya Vetencourt and others 2008; Harauzov and others 2010). *Ngr1*−/− mice and *ngr1 flx/flx; PV-Cre* mice both display a decrease in excitatory drive onto PV interneurons that is accompanied by a reduction in spontaneous inhibitory postsynaptic currents on excitatory pyramidal neurons. These metrics are consistent with a modest reduction in cortical inhibition and elevated E/I balance.

Several recent studies have focused on mechanisms by which PV interneurons may govern experience-dependent plasticity in neocortex. Experiments employing cell-attached recordings *in vivo* and local circuit mapping with laser scanning photostimulation demonstrate that a decrease in excitatory drive onto PV interneurons initiates OD plasticity (Kuhlman and others 2013). This increase in E/I balance may permit synaptic competition between eye inputs. Another study proposes that these

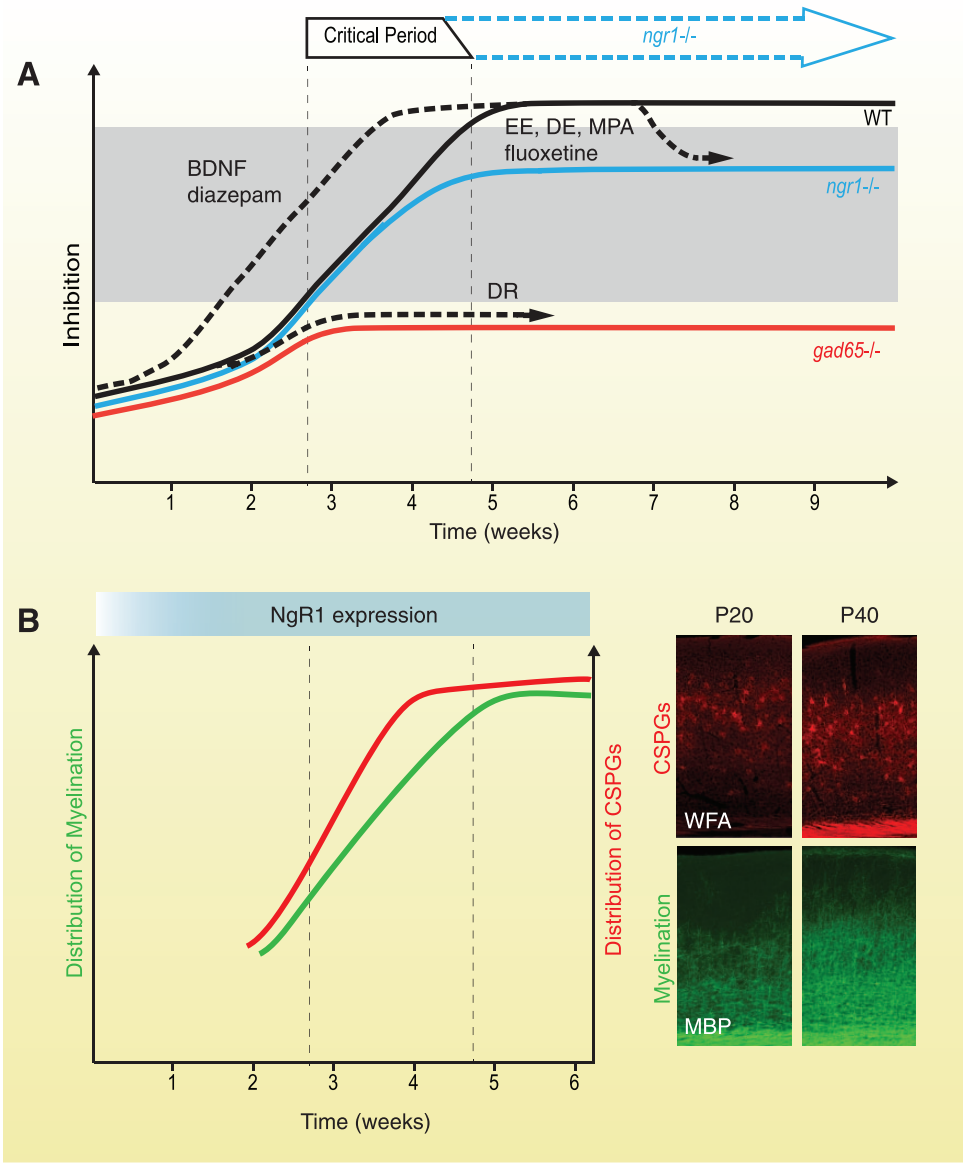

Figure 6. Potential mechanisms of NgR1 function in visual plasticity. (A) *Ngr1* may affect the relative strength of excitatory and inhibitory neurotransmission (E/I balance) in visual cortex. Several manipulations that enhance visual plasticity after the critical period also may increase the E/I ratio. A specified threshold of inhibition is required to open the critical period (gray region), whereas elevated inhibition is associated with the close of the critical period. In normal mice (wild-type [WT]), this threshold to open the critical period is achieved in the third postnatal week and the critical period then closes approximately 2 weeks later (black line). Manipulations that alter E/I balance also affect the timing of the critical period. Treatments that elevate inhibition precociously, such as transgenic expression of brain-derived neurotrophic factor (BDNF) or administration of benzodiazepines (such as diazepam), cross this threshold to critical period plasticity earlier and the critical period subsequently closes sooner (black dashed line). Rearing animals in complete darkness (DR) prevents the opening of the critical period and delays maturation of cortical inhibition (lower black dashed arrow). Likewise, the critical period does not open in *gad65*−/− mice (red line). Distinct environmental (environmental enrichment [EE] and dark environment [DE]) and pharmacologic (3-mercaptopropionic acid [MPA] and fluoxetine) approaches for decreasing cortical inhibition also enhance adult visual plasticity (upper black dashed arrow). *Ngr1*−/− mice also exhibit a modest increase in E/I balance relative to WT mice (blue line). (B) NgR1 may close the critical period by transducing inhibitory signals from extracellular ligands that emerge with cortical maturation. NgR1 is a receptor for both multiple inhibitor factors associated with myelin membranes and chondroitin sulfate proteoglycans (CSPGs). The distributions of both cortical myelination (green line) and CSPGs (red line) increase as the critical period closes. Representative images of the distribution of CSGPs and myelin near the opening (P20) and closing (P40) of the critical period are provided at right. CSPGs are labeled with a lectin, Wisteria floribunda agglutinin (WFA), while myelin is stained with an antibody directed against myelin basic protein (MBP).

inhibitory neurons modulate the expression of PV and GAD-67, another enzyme important for the synthesis of the GABA, to regulate experience-dependent plasticity (Donato and others 2014). Perhaps *ngr1* mutants retain these mechanisms of plasticity within visual circuitry as adults.

Inhibitory Factors in the Extracellular Environment

The extracellular environment surrounding neurons contains several factors inhibitory to neurite outgrowth in vitro. The expression of some of these inhibitors, such as CSPGs and MAIs, increases as the critical period closes. The development of perineuronal nets that encapsulate PV neurons concludes near the end of the critical period (Pizzorusso and others 2002). Likewise, the distribution of myelination increases throughout the critical period and plateaus by P40 (McGee and others 2005). Manipulations that remove these inhibitors in adult visual cortex unmask visual plasticity (Bavelier and others 2010). Injecting chondroitinase ABC into V1 of adult rats reinstates partial OD plasticity while focal demyelination has also been reported to reactivate OD plasticity. In mice lacking neural expression of the gene for cartilage link protein Crtl1 (Hapln1), CSPGs are present in visual cortex but not enriched in perineuronal nets (Carulli and others 2010). These mice also exhibit enhanced visual plasticity. As mentioned previously, NgR1 is a receptor for several MAIs and CSPGs.

Yet how these inhibitors may restrict visual plasticity remains unclear. Do they limit experience-dependent anatomical plasticity? Do they alter E/I balance? CSPGs are enriched in perineuronal nets but are also present throughout the neuropil (Carulli and others 2010). Thus, these factors could limit synaptic structural plasticity. In contrast, MAIs seem poorly positioned to influence the dynamics of dendritic spines and axonal boutons. After the close of the critical period, myelination is more extensive in cortical layers L4, L2/3 and L1, but remains sparse relative to the density of spines (McGee and others 2005) (Fig. 6). Consequently, few dendritic spines would seem proximal to these membrane-bound inhibitors. Injecting chondroitinase ABC in hippocampus reduces the relative expression of PV as evaluated with immunofluorescence (Yamada and others 2014). As lower PV levels are proposed to reflect low GAD-67 levels and reduced inhibition, removal of CSPGs may increase E/I balance as well (Donato and others 2014). By comparison, the axons of a proportion of PV interneurons are myelinated, including PV neurons, but how myelination affects E/I balance is not evident (McGee and others 2005; Somogyi and Soltész 1986). However, these are not the only possible mechanisms nor are they exclusive. Additional studies are required to validate and refine these models.

Directions of Future Research

Understanding how *ngr1* restricts different facets of visual plasticity will require an improved molecular characterization of the NgR1 signaling pathway. There are a number of related questions yet to be answered. Which ligands and putative co-receptors contribute to NgR1 function in cortex? Both CSGPs and Nogo-A have already been implicated as factors contributing to the closure of the critical period (McGee and others 2005; Pizzorusso and others 2002). However, it is unclear which co-receptors are required to close the critical period. What are the cellular mechanisms by which NgR1 limits plasticity? Although *ngr1* does not appear to determine the set point for synaptic structural plasticity, whether it gates the influence of experience on the rate of turnover or stability of new synapses remains unknown. How these mechanisms may contribute to the slightly higher E/I ratio in *ngr1* mutant mice is also unclear. Last, where does NgR1 operate within the circuitry of the visual system to inhibit recovery in the murine model of amblyopia? The receptor is expressed in retina, thalamus, and cortex. Identifying where *ngr1* expression is required to limit improved acuity following LTMD may reveal whether changes in retinal, subcortical, and/or cortical circuitry contribute to impaired visual performance. In addition to sustained critical-period visual plasticity as adults, *ngr1* mutant mice display interesting phenotypes in perceptual learning, motor learning, spatial learning and extinction of fear conditioning (Akbik and others 2013; Karlén and others 2009; J. I. Park and others 2014). Thus, *ngr1* may restrict conserved elements of cortical experience-dependent plasticity, and neutralizing these molecular mechanisms holds therapeutic potential for not only improving vision in amblyopia, but for treating a broad spectrum of neurodevelopmental disorders.

Authors' Note

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