Advances in Understanding Visual Cortex Plasticity

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Summary of recent advances

Visual cortical plasticity can be either rapid, occurring in response to abrupt changes in neural activity, or slow, occurring over days as a homeostatic process for adapting neuronal responsiveness. Recent advances have shown that the magnitude and polarity of rapid synaptic modifications are regulated by neuromodulators, while homeostatic modifications can occur through regulation of cytokine actions or NMDA receptor subunit composition. Synaptic and homeostatic plasticity together produce the normal physiological response to monocular impairments. *In vivo* studies have now overturned the dogma that robust plasticity is limited to an early critical period. Indeed, rapid physiological plasticity in the adult can be enabled by prior, experience-driven anatomical rearrangements or through pharmacological manipulations of the epigenome.

Introduction

Coordinated, experience-driven changes in synaptic efficacy are required for the proper development of brain networks. This plasticity has been well-studied in the visual cortex, as a brief period of monocular deprivation produces amblyopia (loss of vision) as a consequence of reduced synaptic inputs to the cortex. The weakening of the deprived-eye response is often followed by a delayed enhancement of the open-eye response [1]. These modifications occur through input-specific strengthening and weakening of synapses, which have been studied in the forms of long-term depression (LTD) and long-term potentiation (LTP). Importantly, the molecular and physiological signatures of *in vitro* plasticity mirror those that occur naturally [2]. LTD and LTP can be rapidly induced by varying the stimulation frequency of presynaptic

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Conflicts of Interest
None.

inputs (frequency-dependent plasticity) or the relative timing between the presynaptic and postsynaptic firing of action potentials (spike timing-dependent plasticity; STDP).

LTD- and LTP- like processes may not be sufficient to fully describe naturally occurring plasticity observed *in vivo*. Homeostatic changes in synaptic efficacy may also be required to fully account for the development of synapses and their modification by experience. In this paradigm, prolonged changes in neural activity produce a cell-wide compensation, either by globally altering synaptic strength [3••] or shifting the threshold for the subsequent induction of LTD/LTP [4].

Researchers have passionately sought the mechanisms underlying frequency-dependent, spike timing-dependent, and homeostatic forms of plasticity. Insights into these mechanisms are expected to guide clinical therapies to prevent or reverse visual derangements such as amblyopia, or may be more generalized to treating disorders of the synapse. In this review we highlight recent advances in our understanding of the signaling mechanisms implicated in visual cortical plasticity. We will briefly discuss (i) the importance of neuromodulation, (ii) the homeostatic contributions to experience-dependent modeling of cortical microcircuits, (iii) plasticity in the mature visual cortex, and (iv) the emerging appreciation of epigenetic influences.

Neuromodulation of synaptic plasticity

The neuromodulators acetylcholine (ACh) and norepinephrine (NE) enhance visual cortex plasticity observed *in vivo* following monocular deprivation [5,6]. Several *in vitro* studies have shown that ACh and NE can cause the induction or enhancement of synaptic plasticity. However, the results of these studies have often appeared contradictory. Such discrepancies have likely arisen because multiple receptor subtypes and their signaling cascades can be engaged by these neuromodulators. Recent studies have taken advantage of more selective pharmacologic and genetic manipulations to address this issue. These studies demonstrate that either muscarinic ACh or α_1-adrenergic receptors coupled to phospholipase C signaling pathways induce or enhance LTD ([7–10••]; but see [11]). In contrast, activation of muscarinic ACh or β-adrenergic receptors coupled to adenylyl cyclase can enhance or induce LTP [9, 12]. Thus, the same neuromodulator can both strengthen and weaken synaptic connections, and the valence of the plasticity is dictated by the precise receptor subtype and signaling pathway enlisted (Figure 1).

The ability of neuromodulators to alter the valence of synaptic plasticity is particularly salient in STDP. Two critical components for determining the magnitude and direction of changes in synaptic strength are the relative timing (within ~50 ms window) and the temporal order of the pre- and post-synaptic action potentials. However, information encoded by the temporal order of action potential firing is dependent upon which signaling pathways are activated. Kirkwood and colleagues [10••] elegantly showed that neuromodulators can dictate the outcome of STDP through the signaling pathways they engage. When adenylyl cyclase signaling pathways are stimulated through β-adrenergic receptors, LTP is induced regardless of the temporal order in which the presynaptic and postsynaptic action potentials occurred. In contrast, activation of phospholipase C through M1 muscarinic ACh or α_1-adrenergic receptors causes the induction of LTD and prevents the induction of LTP across timing intervals. Thus, to enable the temporal relevance of spike timing to induce both LTD and LTP, both phospholipase C and adenylyl cyclase neuromodulatory pathways are necessary. The unique downstream targets of these pathways are currently unknown, although some evidence suggests that the pathways differentially phosphorylate glutamate receptor subunits and thereby alter their function [10••]. These data indicate that, equally important to the exact timing

of presynaptic and postsynaptic events, interactions amongst neuromodulatory inputs are necessary to produce the full range of timing-dependent plasticities.

These studies show a clear importance of neuromodulators, and their different signaling pathways, to the induction of synaptic plasticity. Future studies may be able to take advantage of neuromodulatory systems when attempting to reinstate plasticity that is diminished through age or disease. In support of this idea, a classic study has demonstrated that infusions of NE into the adult cortex can restore ocular dominance plasticity [6].

Homeostatic synaptic plasticity

The development and modification of neuronal properties in visual cortex cannot be described by a model that simply employs the rapid, activity-dependent induction of LTD and LTP. For example, it is difficult to account for the delayed increase in the open-eye response following monocular deprivation with a strict LTD/LTP model, as this increase occurs days after the more immediate loss of responsiveness to the deprived eye [1]. This delayed response to monocular deprivation is thought to be necessary for maintaining neuronal responsiveness within an optimal range. Such plasticity can be explained by two proposed homeostatic mechanisms: synaptic scaling and a sliding threshold of synaptic plasticity (a form of metaplasticity). In synaptic scaling, a decrease (or increase) in neuronal firing is compensated for by a global scaling up (or down) of excitatory synaptic strength [3••]. In metaplasticity, diminished neuronal activity produces a global reduction in the threshold for synaptic potentiation, making it more likely that synapses will be potentiated, while heightened neuronal activity raises this threshold [13].

There is now clear evidence that synaptic scaling can occur both *in vitro* and *in vivo*. *In vitro*, reductions in neuronal firing by tetrodotoxin (TTX) treatment produce a robust and reliable scaling up of synaptic strengths [3••]. *In vivo*, monocular deprivation by intraocular injection of TTX or binocular deprivation with dark-rearing can produce synaptic scaling in layer 4 and layers 2/3 [14,15]. An exciting observation is that there is a clear developmental shift in the expression of synaptic scaling. Synaptic scaling of excitatory synapses is first observed in layer 4 and then in layers 2/3. Unlike layer 4, synaptic scaling appears to be maintained throughout life in layers 2/3 [15], mirroring the maintenance of LTD/LTP in these superficial layers [16]. Interestingly, the qualities of synaptic scaling shift with age so that multiplicative scaling is no longer observed in more mature animals [15].

Does synaptic scaling contribute to the observed physiological response to monocular deprivation? The recent finding that the cytokine TNFα is required for synaptic scaling has now allowed this question to be addressed [17•]. The genetic or molecular knockdown of TNFα, and hence synaptic scaling, did not prevent the loss of the deprived eye response in the visual cortex following monocular deprivation [17•]. However, the delayed increase in the open eye response was prevented, suggesting a critical role for synaptic scaling. These data indicate that both rapid Hebbian plasticity and slower homeostatic processes combine to produce the full physiological response to changes in sensory experience.

Metaplasticity, another prominent model of homeostatic plasticity, incorporates an experience-dependent sliding threshold for LTD/LTP induction. Together with LTD and LTP, the sliding threshold for synaptic modifications was integrated into a theoretical model that could account for the experimentally observed consequences of sensory deprivation [4]. Unlike the synaptic scaling model, a sliding plasticity threshold has the additional advantage of being able to account for the acquisition of stimulus-selective properties (e.g. orientation selectivity). Evidence for a sliding threshold comes from the observation that dark-rearing lowers the LTP induction threshold recorded *ex vivo*, while visual experience increases this threshold [18]. The lowering of the LTP threshold is paralleled by a reduction in the ratio of NMDA receptors

containing the NR2A subunit compared to the NR2B subunit [19]. Consistent with the idea that the NR2A/NR2B ratio adjusts the threshold for synaptic modifications, experience-dependent metaplasticity is absent in mice that lack NR2A [20].

Two lines of evidence suggest that metaplasticity can account for the acquisition of stimulus-selective neuronal properties and experience-dependent modifications. First, as predicted from theoretical models, mice lacking metaplasticity due to the genetic deletion of NR2A exhibit broad orientation selectivity [21]. This suggests that homeostatic adjustment of the plasticity threshold facilitates the acquisition of stimulus selectivity in neurons. Second, genetic deletion of NR2A impairs the biphasic response to monocular deprivation. While wildtype mice exhibit a rapid depression of the deprived eye response and a delayed (~5 days) potentiation of the open eye response after monocular deprivation, NR2A knockout mice instead exhibit only a rapid (~1 day) open eye potentiation [22]. Coupled to the observation that a reduction in NR2A/NR2B normally precedes the delayed potentiation of the open eye response in wildtype mice, these data indicate that a change in NMDA receptor subunit composition is a naturally occurring event for reducing the threshold for synaptic potentiation.

Whether synaptic scaling or a sliding threshold of plasticity is physiologically employed has been a contentious issue, but the distinction between the two may be an artifact of the complexity and heterogeneity of the neocortex. By analogy, the mechanisms of cortical LTD and LTP were originally thought to be homologous to those occurring in the CA1 region of the hippocampus, however recent studies have revealed the incredible diversity of plasticity mechanisms across development and the various cortical microcircuits [14,16,23,24]. Homeostatic mechanisms may exhibit a similar heterogeneity. In support of this idea, the homeostatic response to monocular deprivation can vary tremendously with the manner of deprivation [25]. Specifically, monocular TTX treatment leads to a scaling up of excitatory connections and a scaling down of inhibitory connections onto layer 2/3 neurons. In contrast, monocular lid suture fails to induce the predicted synaptic scaling, but instead maintains responsiveness of layer 2/3 neurons by changing their intrinsic membrane properties.

We propose that synaptic scaling and metaplasticity are non-mutually exclusive homeostatic mechanisms that are both required for the full repertoire of physiological modifications by sensory experience. Future studies using mutant mice that lack synaptic scaling or metaplasticity may be used to parse the relative contributions of each process, and to test the possibility that these processes may even engage overlapping mechanisms.

Adult plasticity

The classic work of Hubel and Wiesel instilled the idea that visual cortex plasticity was limited to a critical period of early life [26]. However, elegant work in mice has revealed a remarkable capacity for the adult visual cortex to reorganize following monocular deprivation [27,28••]. Although the net effect of monocular deprivation in juveniles and adults is to reduce the response of the deprived eye relative to the open eye, the adult plasticity is qualitatively unique. Specifically, adult mice fail to undergo the rapid reduction in the deprived eye response that is observed in juvenile mice, but instead only exhibit the delayed potentiation of the open eye response [1,28••].

A major goal in the field has been to reinstate juvenile-like plasticity in the adult visual cortex using pharmacologic and genetic interventions, with the expectation that this will guide therapies for amblyopia. Successful enhancement of adult plasticity has been achieved by altering (i) the excitation to inhibition balance [29,30], (ii) extracellular matrices [31], (iii) neuromodulation [6,30], (iv) inhibitory influences from myelin [32], and (v) growth factor

functions [33]. In each case, the recovery of plasticity most likely requires complex changes to the local cellular milieu.

Despite the discovery of multiple manipulations that can successfully enhance adult plasticity, none of these have been translated into therapies for amblyopia. An exciting new development is the possibility that behavioral manipulations can be used to enhance adult visual cortex plasticity, as these non-invasive approaches may be more rapidly translated to clinical therapies. Environmental enrichment has been used to facilitate the recovery from amblyopia in adult rodents, through a reduction in GABA-mediated inhibition [34]. Late-onset visual deprivation can also facilitate the recovery from amblyopia [35•], likely through reductions in GABAergic inhibition and the NR2A/NR2B ratio [36]. Additionally, prior monocular deprivation can enable a subsequent rapid ocular dominance shift in adults, akin to that observed during the critical period [27]. Collectively these observations provide compelling evidence that behavioral manipulations can powerfully alter the induction of plasticity in the adult cortex.

Recent observations demonstrate that the re-expression of rapid experience-dependent plasticity in the adult cortex is preceded by profound anatomical changes [37••]. An initial monocular deprivation in the adult cortex, which produces an ocular dominance shift that emerges slowly over ~8 days, is accompanied by a dramatic and persistent increase in the density of dendritic spines in layer 5 neurons in binocular cortex [37••]. A subsequent monocular deprivation fails to further increase spine density, but now the ocular dominance shift occurs much more rapidly (within ~3 days), similar to that observed during the critical period. This suggests that anatomical restructuring provides a substrate upon which subsequent physiological modifications may rapidly occur.

While adult plasticity is clearly observed in rodents, several outstanding issues remain. First, is adult visual cortex plasticity limited to rodents, or can robust plasticity be introduced in higher primates, as suggested by a recent human study showing that amblyopic deficits can be transiently ameliorated [38]? Second, does the reintroduction of adult plasticity occur through common signaling mechanisms, or are there multiple pathways for achieving the same end result? Third, is there a causal relationship between the anatomical changes observed in layer 5 and the recovery of rapid ocular dominance plasticity, and if so, do other cell types engage this same mechanism?

Epigenetic mechanisms for visual cortical synaptic plasticity

During the critical period, even a relatively brief monocular deprivation can lead to a lasting change in ocular dominance. The neural mechanisms for such enduring modifications are still unclear, although the plasticity is undoubtedly activated and maintained through the differential expression of so-called "plasticity genes" that have particularly salient expression during the critical period [39,40]. It seems likely that experience-driven changes in transcription of these plasticity genes act to gate visual cortex plasticity.

Gene transcription can be regulated through chromatin remodeling such as DNA methylation and histone modifications. Chromatin structure likely serves as a platform for relaying and integrating information from numerous experience-driven signaling pathways. In support of this idea, chromatin remodeling complexes are thought to regulate synaptic strength and memory storage via orchestrated alterations in DNA methylation and histone acetylation [41, 42].

Can changes in visual experience (e.g. light) modify the properties of synaptic plasticity by triggering downstream changes to chromatin structure? The answer appears to be an emphatic "yes." For instance, light stimulates phosphorylation and acetylation of histone H3 in the

suprachiasmatic nucleus [43,44]. In the visual cortex, light induces phosphorylation and acetylation of histone H3 during the critical period [45•]. Such long-lasting epigenetic changes could alter the activity-dependent strengthening or weakening of synapses, or even trigger homeostatic plasticity, by regulating gene transcription.

Consistent with the idea that epigenetic marks can influence synaptic plasticity, pharmacologically enhancing histone acetylation with the histone deacetylase inhibitor (HDACi) trichostatin restores juvenile-like ocular dominance plasticity in the adult visual cortex [45•]. These findings demonstrate that epigenetic modifications are likely a naturally occurring mechanism for gating critical period plasticity. While the recovery of adult cortical plasticity using a broad spectrum HDACi is promising, such global manipulations are likely to have unintended and undesirable side effects. It is clear, however, that the ability to selectively manipulate epigenetic marks hold great promise for recovering adult plasticity.

Given the broad targeting of the HDACi used for recovering visual plasticity, it is difficult to pinpoint which epigenetic events are critical and which genes are undergoing altered transcription. However, there are some indications that epigenetic influences might alter the transcription of genes signaled through an ERK/MSK/CREB signaling pathway (Figure 2). Synaptic plasticity is associated with signaling pathways, including mitogen-activated protein kinase (MAPK) cascades. The MAPK cascade activated by extracellular signal-regulated kinase (ERK) and its downstream neural targets are necessary for experience-dependent plasticity in the visual cortex (Figure 2) [46]. Visual stimulation during cortical maturation induces site-specific phosphorylation of MSK and CREB [45•]. While visual stimulation during the critical period can also induce posttranslational modifications in histones H3 and H4 within the visual cortex, stimulation after the critical period fails to do so. However, the observations that HDACi can restore plasticity in adult visual cortex indicate that some epigenetic events are reversible and flexible even after the critical period.

Conclusions

Nearly a half century has elapsed since the original findings of a critical period for synaptic plasticity in the visual cortex [26]. While our understanding of the mechanisms underlying synaptic plasticity continues to grow at a staggering pace through elegant technological and innovative advances [47–49], a cure for amblyopia has yet to be discovered. We suggest that an increased understanding of the role of neuromodulators, homeostasis, and epigenetic modifications offer particular promise for future attempts at curing amblyopia and other cortically-based visual disorders. Moreover, we must appreciate the remarkable capacity for plasticity that the adult visual cortex maintains, at least in some species, and unlock the mechanisms underlying this competency. Given the fast pace of discovery within the field of visual cortex plasticity, the next half century may well bring a cure for amblyopia and, perhaps, other synaptopathies that can be modeled in the visual cortex [50].

Acknowledgements

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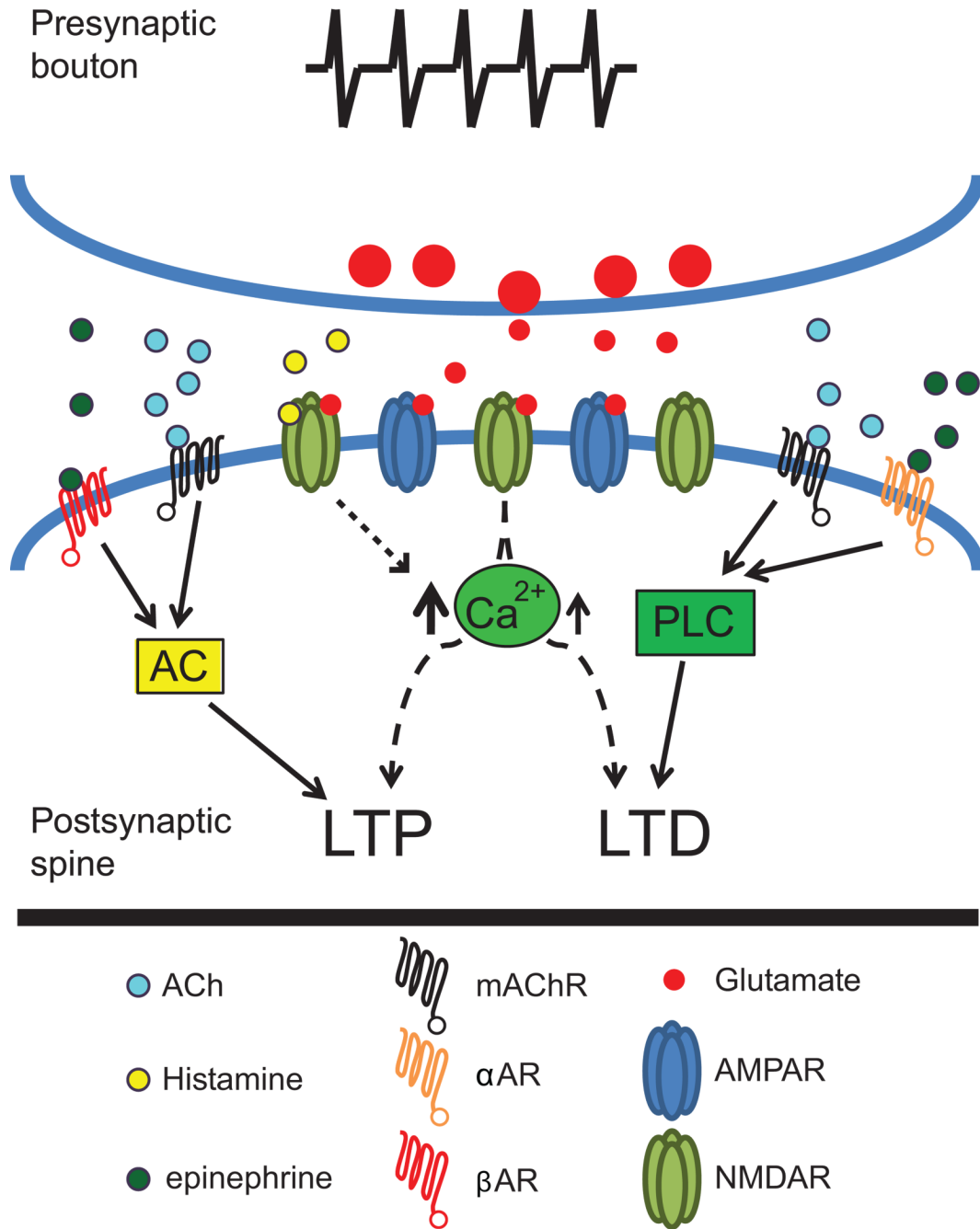
Figure 1. Neuromodulators direct the valence of synaptic plasticity through distinct signaling pathways

mAChR or α_1AR stimulation induces LTD through a PLC-dependant cascade, whereas mAChR or βAR activation of AC induces LTP. Enhancement of NMDAR currents by histamine augments LTP, possibly through increasing intracellular calcium levels. These observations suggest that activation of specific signaling pathways through discrete neuromodulator receptor subtypes dictates the direction of plasticity induced in visual cortex. AC: Adenylyl cyclase; ACh: Acetylcholine; α_1AR: alpha adrenergic receptor; βAR: beta adrenergic receptor; LTD: Long-term depression; LTP: Long-term potentiation; mAChR:

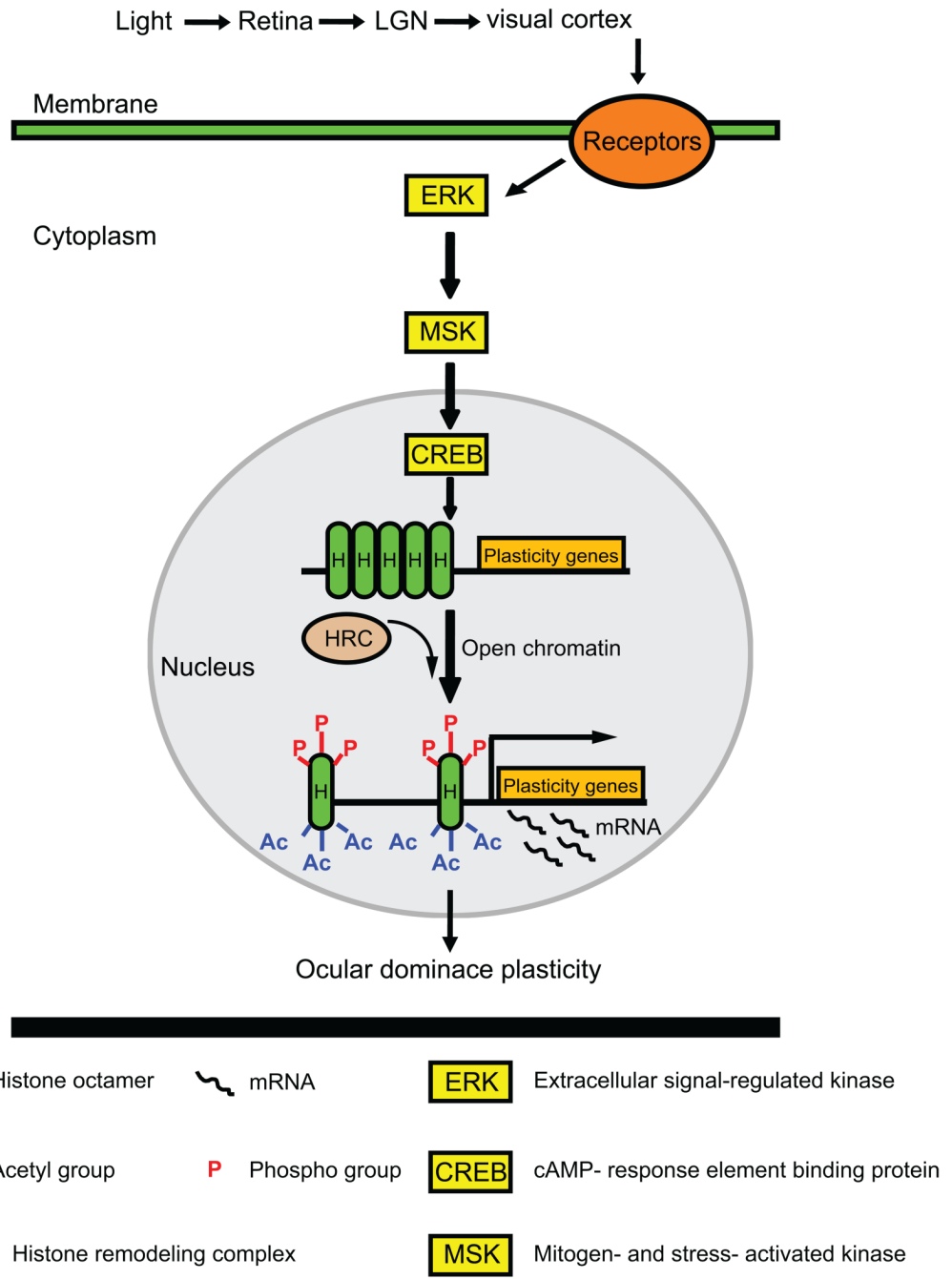Muscarinic acetylcholine receptor; NMDAR: N-methyl d-aspartate receptor; PLC: Phospholipase C.

Figure 2. Epigenetic remodeling of chromatin can enable ocular dominance plasticity through an ERK-mediated cascade

Visual experience (light) can activate ERK and its downstream neural targets, MSK and CREB. CREB-mediated transcription is normally modest, due to a tight chromatin conformation. A histone remodeling complex can open the chromatin conformation through phosphorylation and acetylation of histone H3, thereby increasing the rate of CREB-mediated transcription of plasticity genes. Activation of plasticity gene expression contributes to the ocular dominance plasticity in the visual cortex. LGN: lateral geniculate nucleus; MAPK: mitogen-activated protein kinase; ERK: extracellular signal-regulated kinase; MSK: mitogen-and stress-activated

kinase; CREB: cAMP-response element binding protein; HRC: histone remodeling complex; P: phospho group; Ac: acetyl group; H: histone octamer.