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Visual experience and plasticity of the visual cortex: a role for epigenetic mechanisms

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1. ABSTRACT

Plasticity of cortical circuits is maximal during critical periods of postnatal development. Ocular dominance plasticity is a classical model to understand the role of experience in development of the visual cortex. Recent studies are beginning to unravel the synaptic mechanisms underlying this form of plasticity and to elucidate the different plasticity of juvenile and adult animals at mechanistic and molecular level. These investigations indicate that this form of plasticity is regulated by factors located at extracellular and intracellular level. The molecular composition of the extracellular environment in which synaptic plasticity occurs changes during development becoming less permissive for plasticity. In addition, visual experience activates epigenetic mechanisms of regulation of gene transcription that becomes downregulated in adult animals.

2. OCULAR DOMINANCE PLASTICITY

Neocortical circuits are extremely sensitive to manipulations of the sensory environment during restricted temporal windows of postnatal development called critical periods (CPs). Monocular deprivation (MD) is a classical paradigm of experience-dependent plasticity that is highly effective during development and acts by depriving patterned vision through one eye. The resulting imbalance of the electrical activity driven by the two eyes triggers a cortical plastic response [ocular dominance plasticity (ODP)] that consists of anatomical and physiological modifications that eventually impair the animal's behaviour by reducing visual acuity of the deprived eye and affecting stereoscopic vision. The most striking physiological effect of MD on visual cortical neurons is a shift in the ocular preference of the responses of binocular neurons in favour of the non-deprived eye (1). This is accompanied by

modifications of the spatial properties of the receptive field that, together with the decreased number of cells driven by the deprived eye, are thought to underlie the poor spatial vision of the deprived eye (2). An imbalance in binocular vision during childhood affects visual acuity also in humans leading to a pathological condition designated amblyopia or "lazy eye".

2.1. Ocular dominance plasticity: synaptic mechanisms

The shift in ocular preference observed in the binocular zone of the primary visual cortex after MD has been originally thought to be the outcome of a process of activity-dependent competition between the synaptic terminals driven by the two eyes for connection with the postsynaptic neuron. Recent data suggest that, in agreement with the Bienenstock-Cooper-Munro (BCM) theory (3,4), the ocular dominance shift of visual cortical neurons is the result of two forms of synaptic plasticity involving the synaptic pathways driven by the two eyes separately: an initial depression of responsiveness to stimulation of the deprived eye followed by potentiation of responsiveness to stimulation of the non-deprived eye (5).

Several lines of evidence indicate that the loss of responsiveness to the deprived eye is the result of an active phenomenon of homosynaptic depression. Since long-term depression (LTD) is activity-dependent, it is suggested that the spontaneous activity coming from the deprived eye should contribute to the active depression of responsiveness to stimulation of that eye. Indeed, lid suturing is more effective in shifting the ocular preference towards the non-deprived eye than retinal silencing with intravitreal tetrodotoxin (6). In particular, retinal silencing prevents depression of responsiveness to the closed eye but enhances potentiation of responsiveness to the open eye (5). Moreover, brief MD at the peak of the critical period sets in motion the same phosphorylation pattern of glutamate receptor 1 (GluR1) subunit that occurs after LTD induction *in vitro* and is accompanied by AMPA receptor internalization. Brief MD occluded further LTD, causally involving LTD-like mechanisms in the loss of responsiveness observed after MD (7). Since LTD occlusion and AMPA receptor modifications are not observed in adult animals subjected to MD, it was concluded that the capability to depress a deprived input is developmentally regulated. Other data are at odds with the view that MD effects during the CP are solely due to LTD-like mechanisms. Indeed, glutamic acid decarboxylase 65 (GAD 65) KO mice, which are never sensitive to MD, does not show a selective impairment of LTD inducibility *in vitro* (8), although LTD impairments have been reported by a different group in different conditions (9). In addition, LTD mediated by metabotropic glutamate receptors type 2 does not play a role in ODP-related depression of responsiveness of the closed eye (10). Furthermore, ODP is blocked by overexpression of the protein phosphatase calcineurin but LTD appears normal in these animals (11). In summary, the *in vivo* data demonstrate that MD causes a depression of the cortical responses to the deprived eye, however it is still unclear whether this phenomenon is adequately modeled by LTD.

Other lines of evidence suggest that synaptic potentiation of the synapses driven by the open eye are involved in ODP. First, alphaCaMKII activity is required for both long-term potentiation (LTP) *in vitro* and ODP *in vivo* (12,13). Second, one form of LTP (white matter-layer 2/3) in the visual cortex is developmentally regulated with a decline over time that mirrors that of the critical period. This decline of white matter-layer 2/3 LTP is delayed by DR and can be reinstated after critical period end by putting the antagonist of GABA-A receptors bicuculline in the recording pipette, in accordance with the view that the developmental maturation of inhibition is crucially involved in critical period closure. Other forms of NMDA-dependent LTP (layer 4- layer 2/3) are present in visual cortical slices of adult rat. This raised the hypothesis that the developmental maturation of an "inhibitory gate" in layer 4 could be responsible for the developmental decline of white matter-layer 2/3 LTP and of ODP *in vivo* (14). Third, the capability of use-dependent potentiation remains relatively intact in the adult visual cortex, as shown by the fact potentiation of visually driven responses has been described *in vivo* in the adult rodent visual cortex after tetanic stimulation of the visual thalamus (15). Of relevance, an experience- and NMDA- dependent form of synaptic potentiation has been described in the adult mouse visual cortex *in vivo* (16).

The role of other forms of plasticity in ODP has begun to be investigated only recently: *in vivo* calcium imaging recordings (17) and electrophysiological data in slices (18) indicate that visual deprivation also activates mechanisms of homeostatic plasticity that could participate to mediate the effects of MD. Recent studies have addressed the importance of the temporal order of pre- and postsynaptic spiking in eliciting long-term synaptic depression or potentiation (19). This form of synaptic plasticity has been designated spike-timing dependent synaptic plasticity (STDP) and has been shown to be involved in experience-dependent plasticity of sensory cortices (20,21). Its role in ODP, however, is still unexplored.

Several studies have proven that an optimal level of maturation of intracortical inhibitory networks is crucial in promoting plasticity of the visual cortex (8,22-25). Notwithstanding this, the mechanistic role of rearrangements of intracortical inhibition in the expression of ODP is still to be fully understood. Indeed, both depression of responsiveness to the deprived eye and potentiation of responsiveness to the open eye could in principle be explained by a potentiation or inhibition of the inhibitory transmission driven by the respective eyes. Single unit recordings in kittens showed that only a small portion of neurons changes the ocular preference after iontophoresis with GABA antagonists. Thus, it remains unknown if depression of responsiveness to the deprived eye observed during the CP is attributable to an increase of the inhibitory neurotransmission driven by the deprived eye (26).

3. DEVELOPMENTAL REGULATION OF AMBLYOPIC EFFECTS OF MONOCULAR DEPRIVATION

In all mammals tested so far a developmental decline of ODP has been described to accompany the functional maturation of the visual system. Classical experiments in monkeys and kittens have shown little or no effects of MD in adult animals. However the importance of transgenic animals for mechanistic studies has prompted an analysis of ODP and its CP in mice. Behavioral tests have shown that MD in adult mice does not induce amblyopia of the deprived eye, and that an eye made amblyopic by MD during the critical period does not recover its normal visual acuity if the deprived eye is reopened in the adult (27). In adult rats, behavioral studies have shown that MD does not affect visual acuity (28) Interestingly, experiments on rats have shown that MD causes a moderate increase of visual acuity in the non deprived eye (29). In mice, adult MD improves the spatial resolution of the optokinetic response selectively through the nondeprived eye in the monocular visual field. This improvement is prevented by the block or the removal of the visual cortex suggesting a permissive role for cortical activity in this form of plasticity (30).

Recent studies of cortical responses in adult mice reported significant shifts of ocular dominance as a consequence of MD during adulthood. This has been shown by visually evoked potentials recordings, intrinsic signals imaging, and using the activity reporter gene Arc (16,31,32). Some, but not all, laboratories have reported adult mouse ODP using extracellular unit recordings (8,31,33-36). The effects elicited by MD in the adult seems to be variable depending on the anesthesia used for recordings, on the type of imaging used (e.g. flavoprotein fluorescence signal vs. intrinsic signals) (31,37,38), and whether the ipsilateral or the contralateral projection is examined. Two differences between the adult and juvenile ODP observed in mice have to be stressed. First, the ODP shift measured in adult mice is smaller (38) and requires longer deprivation times to be observed as compared to juvenile animals. Second, most of the effect of MD in the adult seems to be due to potentiation of open eye responsiveness suggesting that a different mechanism could be involved in these forms of plasticity (16). A depression of responsiveness to the deprived eye after adult MD has also been described, but only for the ipsilateral pathway (31,32). Thus, like in the barrel cortex of rodents (39), the capability to depress unused synaptic pathways could be developmentally downregulated. Overall, the available data show that ODP is qualitatively different and quantitatively less compared to juvenile animals. Thus, despite these recent acquisitions, the potential for experience-dependent plasticity of the adult visual cortex seems to be maximal during development also in the mouse.

Interestingly, previous or ongoing experience seems to be another factor regulating adult ODP. For instance, the critical period is lengthened when animals never experience natural vision from birth [dark rearing (DR)]. On the other hand, a complete visual deprivation is able of reinstating ODP and to promote recovery form early MD effects even when performed in adult rats (40,41). Of relevance, recent data show that the potential for ODP during adulthood depend on the level of experience-dependent plasticity exhibited during the CP. A saturating shift of ocular preference during the CP is enough to leave adult mice susceptible to the effects of a brief MD episode that would have been otherwise ineffective in animals that never experienced ODP during the CP. This "priming" effect was eye-specific, showing that a prior plastic modification of a synaptic pathway during development leaves a permanent trace in the adult visual cortex and reinforces the potential for map cortical plasticity during adulthood (31). Finally, the plasticity levels of the adult visual cortex are also influenced by the modalities of rearing of animals. Indeed, amblyopic adult rats are able to recover electrophysiologically and behaviorally from amblyopia when the deprived eye is reopened and the formerly open eye is sutured (a procedure called reverse suture), if the animals are reared in enriched environment (42).

4. MOLECULAR CONTROL OF VISUAL CORTICAL PLASTICITY

What are the molecular mechanisms that trigger and eventually execute the plasticity program mediating experience-dependent plasticity of the visual cortex? Is there a difference between the mechanism at work during the CP and in adulthood? Starting from the initial experiments on neurotrophins and NMDA receptors, a flurry of studies have tried to answer these questions analyzing the role of different neurotransmitter systems, neurotrophic factors and intracellular signaling pathways in mediating the action of experience on plasticity of the visual cortex. These results have been already reviewed elsewhere and they will not be further discussed here (43-45). However, two new molecular mechanisms have recently emerged. First, it has been found that some important factors of the plasticity program are present in the extracellular environment (35,46-49). Second, it has been shown that there is a strong link between visual experience and control of gene transcription that comprises activation of transcription factors and post-translational modifications of histones (50).

4.1. Extracellular environment

Several experiments have indicated that the extracellular and pericellular microenvironment contains important regulators of visual cortical plasticity. First, genetic and pharmacological interference with the extracellular protease tissue plasminogen activator (tPA) has been shown to hinder the effects of MD during the CP indicating that extracellular proteolytic activity is necessary for ocular dominance plasticity in juvenile animals (51). This work extended the results of previous work showing that tPA was necessary for reverse suture plasticity in kittens (52). Further work indicated that the increase of tPA that occurs after MD is needed for structural plasticity of dendritic spines (49). The authors found that MD leads to a transient decrease of dendritic spine density, presumably due to retraction of terminals corresponding to the deprived eye followed by a regrowth of nondeprived eye terminals.

These effects of MD did not occur in mice with genetic deletion of tPA. These data appeared simultaneously with evidence showing that tPA applied on the developing visual cortex increases dendritic spine dynamics (48). Summarizing this series of experiments it is clear that factors present in the extracellular environment need to be proteolytically removed for visual cortical plasticity to occur.

A second series of experiments have outlined the role of chondroitin sulphate proteoglycans (CSPGs), a class of molecules representing a major component of brain extracellular matrix. The first evidence that extracellular matrix (ECM) molecules are present in the synaptic microenvironment came from studies that showed the presence of adhesion molecules in subsets of cerebellar and hippocampal synapses, and from work of Susan Hockfield documenting activity-dependent expression of CSPGs in lateral geniculate nucleus, visual cortex and spinal cord (53-55). In the adult brain most of the CSPGs condensate around the soma and dendrites of parvalbumin positive interneurons in a multimolecular, specialized form of ECM called perineuronal nets (PNNs). Further studies showed that the developmental increase of PNNs correlated with the end of the classical CP and that DR, a rearing condition that delays the end of CP, delays the formation of PNNs in the visual cortex (47). The inhibitory role of CSPGs on adult visual cortical plasticity was shown by inducing enzymatic degradation of CSPGs with chondroitinase ABC (ChABC) in the adult visual cortex of rats. CSPG removal resulted in CP-like plasticity in adult rats without modifying the main functional response properties of visual cortical neurons (47). This same treatment promoted a full recovery from the effects of a prolonged MD initiated during CP in adult rats on ocular dominance and on behaviorally and electrophysiologically measured visual acuity (46). Finally, an anatomical correlate of this recovery effect was found, as ChABC treatment coupled with reverse suture increased spine density on basal dendrites of layer 2/3 pyramids after long-term MD (46). Interestingly, the level of CSPGs can be also modulated in the adult by rearing protocols that promote adult plasticity. Indeed, environmental enrichment that facilitates recovery from amblyopia induced by long-term MD, also diminishes the number of visual cortical PNNs (42). The activity-dependent regulation of CSPGs by endogenous mechanisms suggest that CSPGs could not only be targets for treatments with exogenous factors aimed at increasing plasticity, but that their regulation could also be an intrinsic mechanism of control of cortical plasticity.

Finally, a third series of experiments have shown that mice with genetic deletion of the Nogo receptors do not show a closure of the critical period (35). Since Nogo receptor signaling is thought to be activated by myelin-derived Nogo, myelin-associated glycoprotein (MAG) and oligodendrocyte-myelin glycoprotein (OMgp), these experiments involve myelinization in the mechanisms that could contribute to the cessation of the classical critical period. This finding could be exploited by analyzing whether inhibiting Nogo receptor in adult animals could induce CP-like plasticity

4.2. Experience-dependent regulation of gene transcription and visual cortex plasticity

Long-term modifications of neural circuits is thought to require mechanisms that link neural activity with gene transcription. For instance, studies on the molecular mechanisms of learning and memory have shown that new protein synthesis and new mRNA transcription is required for long term consolidation of memories (56). These mechanisms are probably at work also in mediating the action of visual experience on the development of the visual cortex. Indeed, inhibition of the synthesis of new proteins inhibits the effects of MD on ocular dominance of visual cortical neurons (57), and many studies have shown dramatic changes in gene transcription in visual cortical neurons in response to visual stimulation or visual deprivation (58-62). Interestingly, this approach led to the demonstration that monocular deprivation (MD) increases the expression of IGF-1 binding protein and affects several genes in the IGF-1 pathway. The functional relevance of these findings was confirmed by the result that exogenous application of IGF-1 prevents the physiological effect of MD on ocular dominance (58) and by further studies demonstrating that IGF-1 mediates the effects of enriched environment on visual acuity development (63).

The analyses of visually regulated gene transcription showed that the ensemble of activated genes was specific for the different type of manipulation of visual experience, and for the age at which the deprivation was performed. For example, different sets of genes were activated by DR and MD, and while some genes were activated by MD at all ages, other genes were activated only when MD was performed during the critical period (61). The mechanisms by which modifications of visual experience are able to induce this selective regulation of gene transcription are central for molecular regulation of visual cortical plasticity. Signalling molecules such as alphaCaMKII, calcineurin, PKA and ERK are involved in experience-dependent gene expression and have been found to be necessary for ODP (11,43). In particular, the kinase ERK is strongly activated by visual experience both at the cell soma and at synaptic level (64,65). ERK action is necessary to mediate the effects of visual experience on the transcription of several genes (61) and its inhibition prevents synaptic plasticity as well as the effects of MD on ODP in the developing visual cortex (36,64,66,67). To regulate gene transcription, ERK should act on downstream molecules able to bind DNA and modify transcriptional activation of specific genes. Indeed, visual stimulation is also effective in inducing phosphorylation of the CREB kinase MSK, the transcription factor CREB, and CREB-mediated gene transcription as well (50). All these events were blocked by ERK inhibition. These data indicate a central role for CREB in mediating the action of visual experience. Further studies in which CREB activity was increased or decreased showed a corresponding increase or decrease in various forms of visual cortical plasticity (36,68,69).

Recent results suggest that activation of specific transcription factors like CREB is not the only mechanism

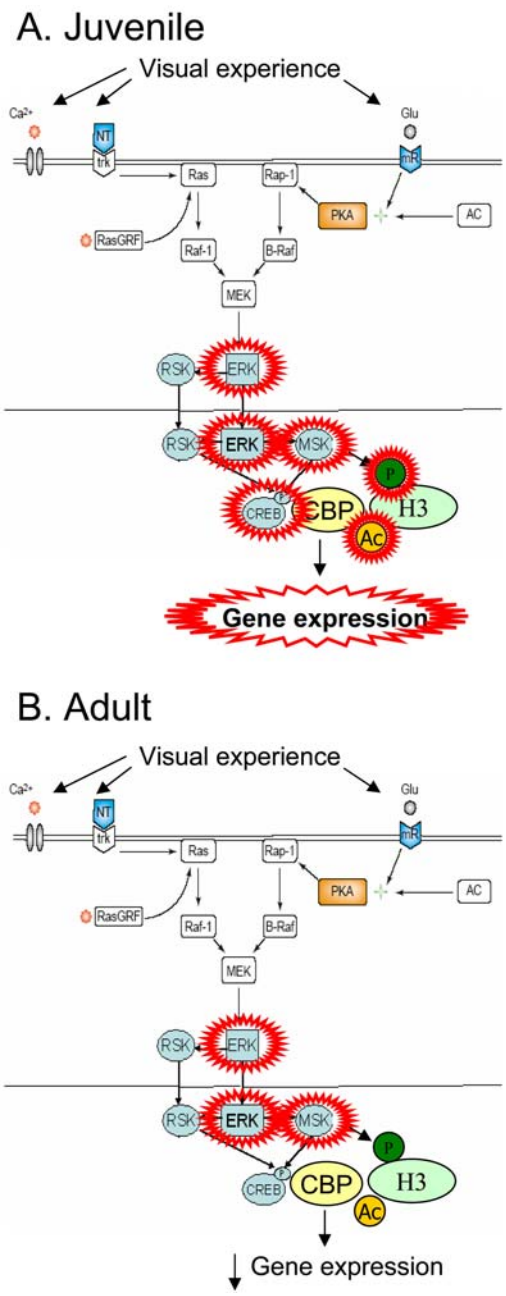

Figure 1. In the juvenile visual cortex (A) visual experience leads to activation of ERK and MSK that are followed by histone phosphoacetylation and CREB mediated gene expression. In the adult (B), ERK and MSK are still activated by visual experience but downstream actions on CREB and histones are limited, resulting in downregulation of CREB-mediated gene transcription. ERK: extracellular regulated kinase, CREB: Calcium-responsive element binding protein, MSK: Mitogen and stress-activated kinase, CBP: CREB-binding protein, H3: histone H3, RSK: ribosomal S6 kinase, Ras: rat sarcoma protein, Rap1: Ras related p21 protein, NT: neurotrophins, trk: tyrosine kinase receptor, RasGRF: Ras guanine release factor; PKA: protein kinase A, AC: adenylate cyclase, B-raf: v-raf murine sarcoma viral oncogene homolog B1, Raf-1: v-raf murine leukemia viral oncogene homolog 1.

mediating the action of visual experience on gene transcription. Molecular studies have shown that gene transcription requires not only activation of transcription factors, but also recruitment of other factors that stimulate or repress transcription (70). This epigenetic regulation of gene transcription could be due to the induction of dynamic changes in the organization of chromatin directing gene expression. For instance, histone acetylation in a region of active transcription is necessary for high levels of transcription (71,72) suggesting that acetylated histones participate to the activation of gene transcription. Histone acetylation can exert its effects on transcription either by physical remodeling of chromatin structure or by further recruitment of signaling complexes (73,74). Histones can undergo many different post-translational modifications in addition to acetylation, including methylation, phosphorylation and SUMOylation and it is thought that the combinatorial presence of different type of histone post-translational modifications on the upstream sequences of a given gene could regulate its transcriptional activity.

Recent work shows that neuronal cells are able to regulate these post-translational modifications of histones dynamically in response to cell electrical activity. Indeed, stimuli that reset the circadian rhythms induce phosphorylation of H3 in the suprachiasmatic nucleus (75), and acetylation of H3 and H4 during the transcriptional activation phase of the circadian rhythm has been described (76); histone phosphoacetylation in the striatum is involved in cocaine-induced neural and behavioral plasticity (77); and histone acetylation, together with DNA methylation, is involved in mediating the influence of postnatal environment on brain response to stress (78). Histone acetylation also controls transcription of genes required for consolidation of long-term memory and LTP (79,80).

Histone phosphoacetylation has been recently shown to be involved also in visual cortical plasticity (50). Indeed, these modifications are triggered in visual cortex of juvenile animals within minutes from visual stimulation. A mediator of the action of visual experience seems to be the kinase ERK because its block inhibits visually induced histone phosphoacetylation. The molecular mechanisms used by ERK to induce histone acetylation are still unclear, while its action on histone phosphorylation might be mediated by MSK. Intriguingly, visually induced phosphoacetylation seems to developmentally downregulated in correlation with the downregulation of plasticity occurring after the CP. In the adult mouse visual cortex, visual stimulation was able to induce ERK and MSK activation at levels comparable to those observed in juvenile animals, but induction of histone phosphoacetylation and CREB-mediated gene expression were much lower in adult than in juvenile animals (Figure 1). The mechanisms uncoupling experience-dependent ERK and MSK activation from histone phosphoacetylation and CREB-mediated gene expression in the adult visual cortex are still obscure, however they could be important in reducing ODP in the adult. Indeed, pharmacological increase of histone acetylation in adult mice by means of trichostatin was able to promote ODP in response to three days of MD, indicating that trichostatin reinstated CP-like

ODP in the adult. The observation that agents that induce histone acetylation do not induce a generalized increase of transcription, but specifically activate a subset of genes (79,81,82), suggests that experience dependent regulation of histone acetylation could be a way to regulate specific sets of genes important to consolidate plastic changes. Increasing histone acetylation in the adult could reactivate the regulation of these transcripts resulting in increased ODP.

Pharmacological increase of histone acetylation is able to promote plasticity not only in the adult visual cortex, but also in other regions of the brain. This could be of practical relevance for the design of therapeutic strategies ameliorating the cognitive deficits present in neurodegenerative diseases or in genetic diseases displaying mental retardation. Indeed, treatments that increase histone acetylation are effective in rescuing learning and memory deficits in models of Rubinstein-Taybi syndrome (83,84), and in a model of Alzheimer-like neurodegeneration caused by conditional expression of p25 (85).

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6. REFERENCES

1. TN Wiesel, DH Hubel: Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens. *J Neurophysiol* 28, 1029-1040 (1965)
2. L Kiorpes, DC Kiper, LP O'Keefe, JR Cavanaugh, JA Movshon: Neuronal correlates of amblyopia in the visual cortex of macaque monkeys with experimental strabismus and anisometropia. *J Neurosci* 18, 6411-6424 (1998)
3. BS Blais, HZ Shouval, LN Cooper: The role of presynaptic activity in monocular deprivation: comparison of homosynaptic and heterosynaptic mechanisms. *Proc Natl Acad Sci U S A* 96, 1083-1087 (1999)
4. EL Bienenstock, LN Cooper, PW Munro: Theory for the development of neuron selectivity: orientation specificity and binocular interaction in visual cortex. *J Neurosci* 2, 32-48 (1982)
5. MY Frenkel, MF Bear: How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* 44, 917-923 (2004)
6. CD Rittenhouse, HZ Shouval, MA Paradiso, MF Bear: Monocular deprivation induces homosynaptic long-term depression in visual cortex. *Nature* 397, 347-350 (1999)
7. AJ Heynen, BJ Yoon, CH Liu, HJ Chung, RL Huganir, MF Bear: Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat Neurosci* 6, 854-862 (2003)
8. TK Hensch, M Fagiolini, N Mataga, MP Stryker, S Baekkeskov, SF Kash: Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science* 282, 1504-1508 (1998)
9. SY Choi, B Morales, HK Lee, A Kirkwood: Absence of long-term depression in the visual cortex of glutamic Acid decarboxylase-65 knock-out mice. *J Neurosci* 22, 5271-5276 (2002)
10. JJ Renger, KN Hartman, Y Tsuchimoto, M Yokoi, S Nakanishi, TK Hensch: Experience-dependent plasticity without long-term depression by type 2 metabotropic glutamate receptors in developing visual cortex. *Proc Natl Acad Sci U S A* 99, 1041-1046 (2002)
11. Y Yang, QS Fischer, Y Zhang, K Baumgartel, IM Mansuy, NW Daw: Reversible blockade of experience-dependent plasticity by calcineurin in mouse visual cortex. *Nat Neurosci* 8, 791-796 (2005)
12. A Kirkwood, A Silva, MF Bear: Age-dependent decrease of synaptic plasticity in the neocortex of alphaCaMKII mutant mice. *Proc Natl Acad Sci U S A* 94, 3380-3383 (1997)
13. S Taha, JL Hanover, AJ Silva, MP Stryker: Autophosphorylation of alphaCaMKII is required for ocular dominance plasticity. *Neuron* 36, 483-491 (2002)
14. A Kirkwood, HK Lee, MF Bear: Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature* 375, 328-331 (1995)
15. AJ Heynen, MF Bear: Long-term potentiation of thalamocortical transmission in the adult visual cortex in vivo. *J Neurosci* 21, 9801-9813 (2001)
16. NB Sawtell, MY Frenkel, BD Philpot, K Nakazawa, S Tonegawa, MF Bear: NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* 38, 977-985 (2003)
17. TD Mrsic-Flogel, SB Hofer, K Ohki, RC Reid, T Bonhoeffer, M Hubener: Homeostatic regulation of eye-specific responses in visual cortex during ocular dominance plasticity. *Neuron* 54, 961-972 (2007)
18. A Maffei, SB Nelson, GG Turrigiano: Selective reconfiguration of layer 4 visual cortical circuitry by visual deprivation. *Nat Neurosci* 7, 1353-1359 (2004)
19. Y Dan, MM Poo: Spike timing-dependent plasticity of neural circuits. *Neuron* 44, 23-30 (2004)
20. CD Meliza, Y Dan: Receptive-field modification in rat visual cortex induced by paired visual stimulation and single-cell spiking. *Neuron* 49, 183-189 (2006)
21. T Celikel, VA Szostak, DE Feldman: Modulation of spike timing by sensory deprivation during induction of cortical map plasticity. *Nat Neurosci* 7, 534-541 (2004)
22. M Fagiolini, JM Fritschy, K Low, H Mohler, U Rudolph, TK Hensch: Specific GABAA circuits for visual cortical plasticity. *Science* 303, 1681-1683 (2004)
23. M Fagiolini, TK Hensch: Inhibitory threshold for critical-period activation in primary visual cortex. *Nature* 404, 183-186 (2000)
24. TK Hensch, MP Stryker: Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science* 303, 1678-1681 (2004)
25. H Katagiri, M Fagiolini, TK Hensch: Optimization of somatic inhibition at critical period onset in mouse visual cortex. *Neuron* 53, 805-812 (2007)
26. A Maffei, K Nataraj, SB Nelson, GG Turrigiano: Potentiation of cortical inhibition by visual deprivation. *Nature* 443, 81-84 (2006)
27. GT Prusky, RM Douglas: Developmental plasticity of mouse visual acuity. *Eur J Neurosci* 17, 167-173 (2003)

28. GT Prusky, PW West, RM Douglas: Experience-dependent plasticity of visual acuity in rats. *Eur J Neurosci* 12, 3781-3786 (2000)
29. K Iny, AJ Heynen, E Sklar, MF Bear: Bidirectional modifications of visual acuity induced by monocular deprivation in juvenile and adult rats. *J Neurosci* 26, 7368-7374 (2006)
30. GT Prusky, NM Alam, RM Douglas: Enhancement of vision by monocular deprivation in adult mice. *J Neurosci* 26, 11554-11561 (2006)
31. SB Hofer, TD Mrsic-Flogel, T Bonhoeffer, M Hubener: Prior experience enhances plasticity in adult visual cortex. *Nat Neurosci* 9, 127-132 (2006)
32. Y Tagawa, PO Kanold, M Majdan, CJ Shatz: Multiple periods of functional ocular dominance plasticity in mouse visual cortex. *Nat Neurosci* 8, 380-388 (2005)
33. QS Fischer, A Graves, S Evans, ME Lickey, TA Pham: Monocular deprivation in adult mice alters visual acuity and single-unit activity. *Learn Mem* 14, 277-286 (2007)
34. JA Gordon, MP Stryker: Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J Neurosci* 16, 3274-3286 (1996)
35. AW McGee, Y Yang, QS Fischer, NW Daw, SM Strittmatter: Experience-driven plasticity of visual cortex limited by myelin and Nogo receptor. *Science* 309, 2222-2226 (2005)
36. TA Pham, SJ Graham, S Suzuki, A Barco, ER Kandel, B Gordon, ME Lickey: A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CREB. *Learn Mem* 11, 738-747 (2004)
37. M Tohmi, H Kitaura, S Komagata, M Kudoh, K Shibuki: Enduring critical period plasticity visualized by transcranial flavoprotein imaging in mouse primary visual cortex. *J Neurosci* 26, 11775-11785 (2006)
38. JA Heimel, RJ Hartman, JM Hermans, CN Levelt: Screening mouse vision with intrinsic signal optical imaging. *Eur J Neurosci* 25, 795-804 (2007)
39. K Fox, RO Wong: A comparison of experience-dependent plasticity in the visual and somatosensory systems. *Neuron* 48, 465-477 (2005)
40. HY He, B Ray, K Dennis, EM Quinlan: Experience-dependent recovery of vision following chronic deprivation amblyopia. *Nat Neurosci* 10, 1134-1136 (2007)
41. HY He, W Hodos, EM Quinlan: Visual deprivation reactivates rapid ocular dominance plasticity in adult visual cortex. *J Neurosci* 26, 2951-2955 (2006)
42. A Sale, JF Maya Vetencourt, P Medini, MC Cenni, L Baroncelli, R De Pasquale, L Maffei: Environmental enrichment in adulthood promotes amblyopia recovery through a reduction of intracortical inhibition. *Nat Neurosci* 10, 679-681 (2007)
43. N Berardi, T Pizzorusso, GM Ratto, L Maffei: Molecular basis of plasticity in the visual cortex. *Trends Neurosci* 26, 369-378 (2003)
44. TK Hensch: Critical period regulation. *Annu Rev Neurosci* 27, 549-579 (2004)
45. TK Hensch: Critical period plasticity in local cortical circuits. *Nat Rev Neurosci* 6, 877-888 (2005)
46. T Pizzorusso, P Medini, S Landi, S Baldini, N Berardi, L Maffei: Structural and functional recovery from early monocular deprivation in adult rats. *Proc Natl Acad Sci U S A* 103, 8517-8522 (2006)
47. T Pizzorusso, P Medini, N Berardi, S Chierzi, JW Fawcett, L Maffei: Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* 298, 1248-1251 (2002)
48. S Oray, A Majewska, M Sur: Dendritic spine dynamics are regulated by monocular deprivation and extracellular matrix degradation. *Neuron* 44, 1021-1030 (2004)
49. N Mataga, Y Mizuguchi, TK Hensch: Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator. *Neuron* 44, 1031-1041 (2004)
50. E Putignano, G Lonetti, L Cancedda, G Ratto, M Costa, L Maffei, T Pizzorusso: Developmental downregulation of histone posttranslational modifications regulates visual cortical plasticity. *Neuron* 53, 747-759 (2007)
51. N Mataga, N Nagai, TK Hensch: Permissive proteolytic activity for visual cortical plasticity. *Proc Natl Acad Sci U S A* 99, 7717-7721 (2002)
52. CM Muller, CB Griesinger: Tissue plasminogen activator mediates reverse occlusion plasticity in visual cortex. *Nat Neurosci* 1, 47-53 (1998)
53. S Zaremba, A Guimaraes, RG Kalb, S Hockfield: Characterization of an activity-dependent, neuronal surface proteoglycan identified with monoclonal antibody Cat-301. *Neuron* 2, 1207-1219 (1989)
54. S Hockfield, RD McKay: A surface antigen expressed by a subset of neurons in the vertebrate central nervous system. *Proc Natl Acad Sci U S A* 80, 5758-5761 (1983)
55. S Hockfield, RG Kalb, S Zaremba, H Fryer: Expression of neural proteoglycans correlates with the acquisition of mature neuronal properties in the mammalian brain. *Cold Spring Harb Symp Quant Biol* 55, 505-514 (1990)
56. Y Dudai, M Eisenberg: Rites of passage of the engram: reconsolidation and the lingering consolidation hypothesis. *Neuron* 44, 93-100 (2004)
57. S Taha, MP Stryker: Rapid ocular dominance plasticity requires cortical but not geniculate protein synthesis. *Neuron* 34, 425-436 (2002)
58. D Tropea, G Kreiman, A Lyckman, S Mukherjee, H Yu, S Horng, M Sur: Gene expression changes and molecular pathways mediating activity-dependent plasticity in visual cortex. *Nat Neurosci* 9, 660-668 (2006)
59. SS Prasad, LZ Kojic, P Li, DE Mitchell, A Hachisuka, J Sawada, Q Gu, MS Cynader: Gene expression patterns during enhanced periods of visual cortex plasticity. *Neuroscience* 111, 35-45 (2002)
60. V Ossipow, F Pellissier, O Schaad, M Ballivet: Gene expression analysis of the critical period in the visual cortex. *Mol Cell Neurosci* 27, 70-83 (2004)
61. M Majdan, CJ Shatz: Effects of visual experience on activity-dependent gene regulation in cortex. *Nat Neurosci* 9, 650-659 (2006)
62. PE Lachance, A Chaudhuri: Microarray analysis of developmental plasticity in monkey primary visual cortex. *J Neurochem* 88, 1455-1469 (2004)
63. F Ciucci, E Putignano, L Baroncelli, S Landi, N Berardi, L Maffei: Insulin-Like Growth Factor 1 (IGF-1) Mediates the Effects of Enriched Environment (EE) on Visual Cortical Development. *PLoS ONE* 2, e475 (2007)
64. L Cancedda, E Putignano, S Impey, L Maffei, GM Ratto, T Pizzorusso: Patterned vision causes CRE-mediated gene expression in the visual cortex through PKA and ERK. *J Neurosci* 23, 7012-7020 (2003)

65. EM Boggio, E Putignano, M Sassoe-Pognetto, T Pizzorusso, M Giustetto: Visual Stimulation Activates ERK in Synaptic and Somatic Compartments of Rat Cortical Neurons with Parallel Kinetics. *PLoS ONE* 2, e604 (2007)
66. B Kaminska, L Kaczmarek, S Zangenehpour, A Chaudhuri: Rapid phosphorylation of Elk-1 transcription factor and activation of MAP kinase signal transduction pathways in response to visual stimulation. *Mol Cell Neurosci* 13, 405-414 (1999)
67. G Di Cristo, N Berardi, L Cancedda, T Pizzorusso, E Putignano, GM Ratto, L Maffei: Requirement of ERK activation for visual cortical plasticity. *Science* 292, 2337-2340 (2001)
68. TA Pham, S Impey, DR Storm, MP Stryker: CRE-mediated gene transcription in neocortical neuronal plasticity during the developmental critical period. *Neuron* 22, 63-72 (1999)
69. AF Mower, DS Liao, EJ Nestler, RL Neve, AS Ramoa: cAMP/Ca2+ response element-binding protein function is essential for ocular dominance plasticity. *J Neurosci* 22, 2237-2245 (2002)
70. MG Rosenfeld, CK Glass: Coregulator codes of transcriptional regulation by nuclear receptors. *J Biol Chem* 276, 36865-36868 (2001)
71. KE Neely, JL Workman: Histone acetylation and chromatin remodeling: which comes first? *Mol Genet Metab* 76, 1-5 (2002)
72. W Fischle, Y Wang, CD Allis: Histone and chromatin cross-talk. *Curr Opin Cell Biol* 15, 172-183 (2003)
73. CL Peterson, MA Laniel: Histones and histone modifications. *Curr Biol* 14, R546-551 (2004)
74. RH Jacobson, AG Ladurner, DS King, R Tjian: Structure and function of a human TAFII250 double bromodomain module. *Science* 288, 1422-1425 (2000)
75. C Crosio, N Cermakian, CD Allis, P Sassone-Corsi: Light induces chromatin modification in cells of the mammalian circadian clock. *Nat Neurosci* 3, 1241-1247 (2000)
76. JP Etchegaray, C Lee, PA Wade, SM Reppert: Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* 421, 177-182 (2003)
77. A Kumar, KH Choi, W Renthal, NM Tsankova, DE Theobald, HT Truong, SJ Russo, Q Laplant, TS Sasaki, KN Whistler, RL Neve, DW Self, EJ Nestler: Chromatin remodeling is a key mechanism underlying cocaine-induced plasticity in striatum. *Neuron* 48, 303-314 (2005)
78. MJ Meaney, M Szyf: Maternal care as a model for experience-dependent chromatin plasticity? *Trends Neurosci* 28, 456-463 (2005)
79. CG Vecsey, JD Hawk, KM Lattal, JM Stein, SA Fabian, MA Attner, SM Cabrera, CB McDonough, PK Brindle, T Abel, MA Wood: Histone deacetylase inhibitors enhance memory and synaptic plasticity via CREB:CBP-dependent transcriptional activation. *J Neurosci* 27, 6128-6140 (2007)
80. JM Levenson, JD Sweatt: Epigenetic mechanisms in memory formation. Nat Rev Neurosci 6, 108-118 (2005)
81. C Van Lint, S Emiliani, E Verdin: The expression of a small fraction of cellular genes is changed in response to histone hyperacetylation. *Gene Expr* 5, 245-253 (1996)
82. DM Fass, JE Butler, RH Goodman: Deacetylase activity is required for cAMP activation of a subset of CREB target genes. *J Biol Chem* 278, 43014-43019 (2003)
83. E Korzus, MG Rosenfeld, M Mayford: CBP histone acetyltransferase activity is a critical component of memory consolidation. *Neuron* 42, 961-972 (2004)
84. JM Alarcon, G Malleret, K Touzani, S Vronskaya, S Ishii, ER Kandel, A Barco: Chromatin acetylation, memory, and LTP are impaired in CBP+/- mice: a model for the cognitive deficit in Rubinstein-Taybi syndrome and its amelioration. *Neuron* 42, 947-959 (2004)
85. A Fischer, F Sananbenesi, X Wang, M Dobbin, LH Tsai: Recovery of learning and memory is associated

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