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Lifelong learning: ocular dominance plasticity in mouse visual cortex

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Ocular dominance plasticity has long served as a successful model for examining how cortical circuits are shaped by experience. In this paradigm, altered retinal activity caused by unilateral eye-lid closure leads to dramatic shifts in the binocular response properties of neurons in the visual cortex. Much of the recent progress in identifying the cellular and molecular mechanisms underlying ocular dominance plasticity has been achieved by using the mouse as a model system. In this species, monocular deprivation initiated in adulthood also causes robust ocular dominance shifts. Research on ocular dominance plasticity in the mouse is starting to provide insight into which factors mediate and influence cortical plasticity in juvenile and adult animals.

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Introduction

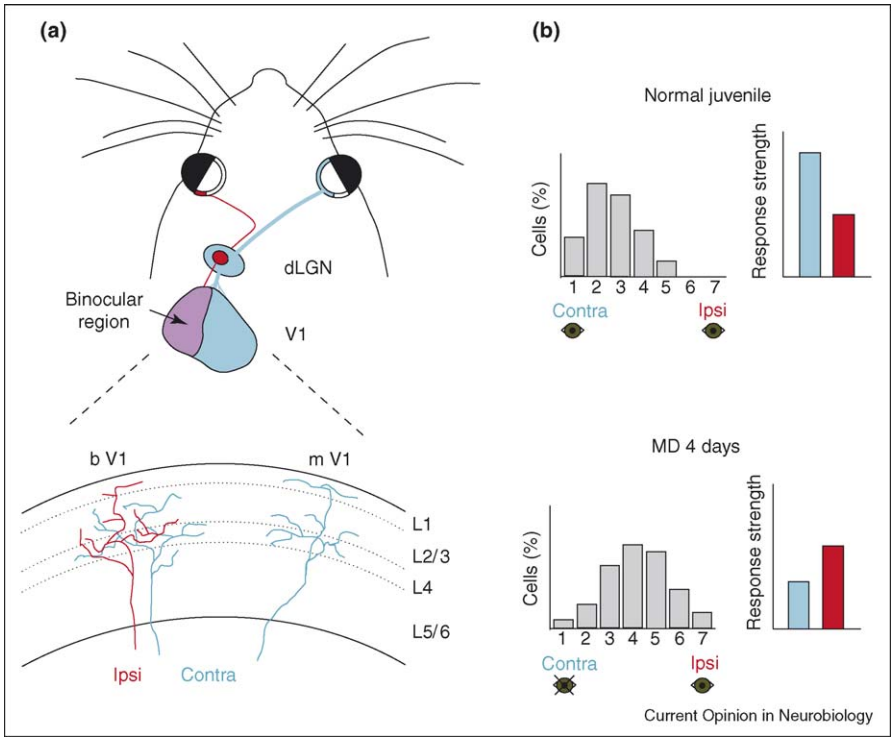
Since the 1960s, when Wiesel and Hubel [1] discovered that the binocular representation in primary visual cortex is particularly susceptible to changes in visual experience, ocular dominance (OD) has served as an important model system for exploring the cellular and molecular mechanisms underlying the plasticity of cortical circuits. Their groundbreaking studies in kittens demonstrated fast and strong adaptive changes of neuronal circuits in response to the imbalanced binocular input caused by transient lid closure of one eye (referred to as monocular deprivation, MD), leading to a shift in the preference of cortical neurons for the eye that remained open [1]. This shift in OD is associated with degraded vision through the deprived eye after reopening [2].

Although the phenomenology of OD shifts has been described in detail in several species [3–5], the underlying cellular and molecular mechanisms are still largely unresolved and merit further study. In this context, the mouse, which shows OD shifts that are comparable to those of higher mammals [4,6], has emerged as a valuable experimental model because of its amenability to genetic manipulation. In this review we summarise the relevant, and at times contradictory, findings on OD plasticity from the past few years, focusing on the underlying mechanisms and the recent discovery of plasticity in the visual cortex of adult mice.

Ocular dominance plasticity in juvenile animals

In cats, ferrets and primates, thalamic afferents from eye-specific layers in the lateral geniculate nucleus (LGN) segregate in the visual cortex during early development, giving rise to OD columns of neurons that are driven more strongly by the left or the right eye [7,8]. In rodents, the binocular region of the primary visual cortex lacks clear OD columns but contains mostly binocular cells that on average have a preference for the contralateral eye (Figure 1) [6,9,10]. In higher mammals, strong OD shifts following eye closure have only been reported during a limited postnatal period, the so-called 'critical period' [11]. Although recent studies revealed pronounced plasticity in mouse visual cortex throughout life (see below), the binocular representation still seems to be most sensitive to experiential changes early in life, at around postnatal day 28 [6]. In general, this early sensitive period is not a fixed developmental phase but rather is influenced by molecular and external cues - its onset can be accelerated or delayed, as demonstrated by overexpressing brain-derived neurotrophic factor (BDNF) or by rearing animals in the dark, respectively [12,13]. These manipulations affect the maturation of inhibitory circuits in the visual cortex [12,14], which appears to be the key determinant for initiation of the sensitive period. A certain level of local inhibition seems to be the crucial trigger, because mice deficient in the minor gamma-aminobutiric acid (GABA) synthesizing enzyme glutamic acid decarboxylase 65 (GAD65) display a relatively mild phenotype of weaker GABA release upon stimulation, and do not exhibit OD shifts after short-term MD, presumably because they fail to enter the sensitive period [15]. Enhancing inhibitory transmission pharmacologically at any time restores normal OD plasticity in GAD65 knockout mice, and can also precociously trigger critical period onset in normal mice [15,16]. Specifically, OD plasticity might only become possible when the mature balance of

Figure 1



Ocular dominance (OD) plasticity in juvenile mouse visual cortex. **(a)** An illustration of the mouse visual system. The major part of the primary visual cortex (V1) receives input only from the contralateral retina (turquoise projections). The lateral third of V1 is innervated additionally by ipsilateral projections (red). Although neurons in the binocular region are dominated by contralateral eye input, most neurons respond to both eyes. Thalamocortical axons from the dorsal lateral geniculate nucleus (dLGN) arborise not only within layer 4 (L4) but also in superficial layers (L1-3). **(b)** Four days of MD in juvenile mice (around P28) lead to strong changes in binocular cortical responses. The OD distribution of cortical neurons shifts towards the eye that remained open (ipsilateral eye), as can be seen when comparing the two histograms (grey). Ocular dominance classes from 1–7 indicate relative responsiveness of neurons to contralateral and ipsilateral eye stimulation (1 or 7, cells respond only to the contralateral or ipsilateral eye, respectively; 4, equal response to both eyes). The OD shifts are caused by a strong weakening of deprived eye responsiveness (compare turquoise bars) and a partial strengthening of non-deprived eye responsiveness (compare red bars), as indicated by measurements of population response strength with visually-evoked potentials and intrinsic signal imaging. Abbreviations: bV1, binocular V1; mV1, monocular V1.

excitation and inhibition in cortical networks arises through the activity of fast-spiking basket cells providing input onto pyramidal neuron synapses that contain the α1 subunit of the $GABA_A$ receptor [17••].

Mechanisms of ocular dominance plasticity

Whereas a mature inhibitory network is important for enabling OD plasticity, most studies addressing the mechanisms of OD plasticity have concentrated on changes at excitatory synapses. Early, long-favoured theories postulated that inputs from the eyes concurrently compete for postsynaptic space on, and resources from, target neurons, such as neurotrophic factors [18,19]. However, as yet no evidence has been provided for such direct competition in the binocular cortex. In fact, in rodents, modifications in the monocular zone of the visual cortex (where no competition can occur) that resemble those taking place in the binocular region have been demonstrated after contralateral MD [20,21]. Hence, in the past decade, the focus of discussion has shifted towards alternative, homosynaptic mechanisms of OD plasticity, whereby inputs from the two eyes are affected separately by MD [22]. In support of this idea, eye closure in young animals causes first a weakening of deprived eye connections and only later a strengthening of inputs from the eye that remained open [23,24••,25].

Recently, researchers have tried to gain insight into the cellular and molecular mechanisms underlying the strengthening and weakening of inputs from the eyes by relating them to those involved in long term potentiation (LTP) and long term depression (LTD) at central synapses. Although the electrical induction of synaptic plasticity *in vitro* cannot be directly compared with the complex experience-dependent changes of neuronal circuits in an intact animal, such studies are nonetheless helpful in exposing the molecular pathways that potentially contribute to plasticity *in vivo*. Indeed, the very early phase of MD-induced plasticity in the visual cortex resembles N-methyl-D-aspartate (NMDA)

receptor-dependent LTD or at least employs similar mechanisms [20]. Likewise, the signalling pathway through specific isoforms of cAMP-dependent protein kinase A (PKA) is required for OD plasticity as well as for different forms of synaptic plasticity in the visual cortex *in vitro* [26,27]. By contrast, synaptic depression mediated by metabotropic glutamate receptor type 2 (mGluR2) does not seem to play a role [28].

Some recent data in mice are at odds with the view that homosynaptic LTD at excitatory synapses is the sole mediator of OD shifts during the first days of deprivation. Alpha calcium calmodulin kinase II (α-CaMKII) activity, which is mainly associated with synaptic LTP *in vitro*, plays a role in short-term OD plasticity [29]. Furthermore, OD plasticity is blocked after overexpression of the protein phosphatase calcineurin [30], which is important for LTD [31]. However, enhanced activity of this enzyme is not expected to affect the weakening of deprived eye inputs, especially because visual cortex LTD appears normal in mice overexpressing calcineurin [30]. In addition, further downstream in the potential signalling pathways, the activation of kinases and transcriptional regulators, such as Erk kinase and cAMP response element binding protein (CREB), respectively, and changes in gene expression have been implicated in OD shifts [32,33,34,35•]. Taken together, these results indicate that OD plasticity is not mediated by a straightforward signalling cascade, but rather involves several interacting processes that might act differentially on different cell types. It should be noted that, although the initial weakening of the deprived eye synapses might be caused by LTD, evidence pointing to a role of LTP in the strengthening of non-deprived eye synapses in juvenile animals is still lacking.

It is also well established that the shift in functional connectivity that occurs during MD is followed by substantial reorganisation of thalamocortical axon arbors [25]. In the mouse, however, notable axonal remodelling takes several weeks of deprivation [10]. This finding is perhaps not surprising considering that axons subserving the left and the right eye are strongly intermingled in this species and provide input to many cells in the binocular visual cortex, and, therefore, reorganisation during the early phase of MD is only expected to occur on a local scale. Indeed, OD plasticity correlates with considerably more rapid structural changes in mouse visual cortex at the level of dendritic spines, which bear the majority of excitatory synapses in the brain. Two days of MD increased the motility of spines, hinting at a destabilization of functional connections [36]. Four days of MD, which induced saturating OD shifts in juvenile mice [6,37••], led to significant spine loss on apical dendrites of layer 2/3 pyramidal neurons, consistent with the initial, strong reduction of cortical responsiveness to deprived eye stimulation [38••]. Formation of new connections from spared eye inputs might occur only after longer deprivation periods [38••], consistent with the subsequent strengthening of the representation of the open eye.

Tissue plasminogen activator (tPA) could provide an important link between the early stages of synaptic plasticity and the structural changes following MD, because in tPA knockout mice neither functional OD shifts nor structural changes occur after MD [36,38••,39]. This secreted protease presumably enables or promotes synapse destabilization and spine pruning by cleavage of cell adhesion molecules and other extracellular matrix proteins [40]. Alternatively, tPA might also function indirectly, for instance via activation of BDNF [41], a molecule associated with synaptic plasticity *in vitro* and OD shifts *in vivo* [42].

Interestingly, no spine loss was observed in the monocular portion of mouse visual cortex after short-term MD [38••], even though brief deprivation induces LTD-like changes in this region [20]. Because LTD is associated with spine pruning [43,44], these findings necessitate a more complex explanation of how MD affects individual neurons. In monocular neurons subserving the deprived eye, it is conceivable that intrinsic, compensatory mechanisms prevent the total loss of connectivity that might have emerged from Hebbian plasticity alone. Indeed, in neural preparations with globally manipulated activity levels, there is growing evidence supporting the existence of homeostatic processes acting to alter the overall synaptic strength or intrinsic excitability [45,46], or to modify the threshold for synaptic plasticity [47,48]. For instance, a flexible modification threshold, as outlined in the Bienenstock-Cooper-Munro (BCM) model [47,48], could regulate the strength and direction of plasticity at individual synapses during MD, depending on the overall strength of activation of the neuron. The higher firing rates of binocular neurons, which also receive non-deprived eye inputs, would thereby promote synaptic depression of the weak, deprived-eye inputs, whereas in neurons only receiving inputs from the deprived eye, the low post-synaptic activity would inhibit further weakening of synaptic transmission. This idea of an indirect interaction of eye inputs according to the BCM theory is supported by the finding that complete silencing of one eye by tetrodotoxin (TTX) injections seems to prevent weakening of deprived-eye inputs, but accelerates strengthening of open-eye inputs in visual cortex [24••,49].

Although the cellular and molecular mechanisms of OD plasticity have recently attracted much attention and debate, a more basic problem remains unexplored, namely which features of the altered sensory input initiate the synaptic modifications. Do the changes induced by MD simply arise from the weaker drive at deprived eye synapses or are OD shifts instead mediated by changes in the temporal structure of the inputs? The

precise millisecond timing of pre- and post-synaptic activity can determine the direction of synaptic plasticity *in vitro* [50,51]. Such spike timing dependent plasticity (STDP) also leads to changes in response properties of neurons in visual cortex *in vivo* [52,53]. In the somatosensory cortex, the timing of stimulation-evoked spiking is altered strongly after whisker deprivation [54•]. It will, therefore, be important to investigate whether in visual cortex MD also alters the relative timing of arrival of inputs from the eyes and whether STDP shifts OD. This could explain why the maturation of the inhibitory circuitry is important for OD plasticity, enabling more precise timing of postsynaptic activity by fast inhibition [17••].

Although it is commonly believed that it is the level or pattern of activity reaching the cortex that determines the extent and direction of cortical plasticity, recent data point to another potential mechanism [55]: in rats, MD was found to decrease the levels of BDNF in the deprived retina, and replenishing retinal BDNF by exogenous application counteracted the MD effect in the cortex. Moreover, it was also shown that BDNF is transported from the retina to the LGN. These results suggest that there might be an additional signal that informs the cortex of an altered sensory input, namely the anterograde transport of molecular factors.

Ocular dominance plasticity in adult visual cortex

In contrast to the classic notion of a critical period for experience-dependent plasticity [11], several studies have recently reported that OD shifts in mice can also be induced in adulthood [37••,56,57,58•]. Strong OD plasticity was demonstrated after MD in adult mice with several methods, including extracellular microelectrode recordings [37••], intrinsic signal imaging [37••] and visually evoked potentials (VEPs) [56] under different anaesthetic regimes and importantly also in awake animals [56] (Figure 2). A study using the activity reporter gene Arc to assess functional eye representation in mouse visual cortex additionally showed MD effects prior to, and after, the traditional 'critical' period [58•] (Figure 2). Given these results, the concept of a strict 'critical' period for OD plasticity seems, at least in the mouse, not to hold true. Nevertheless, the binocular cortical representation is still more sensitive in juvenile mice, as in adults OD shifts require longer MD durations and are generally somewhat smaller [37••,56,57].

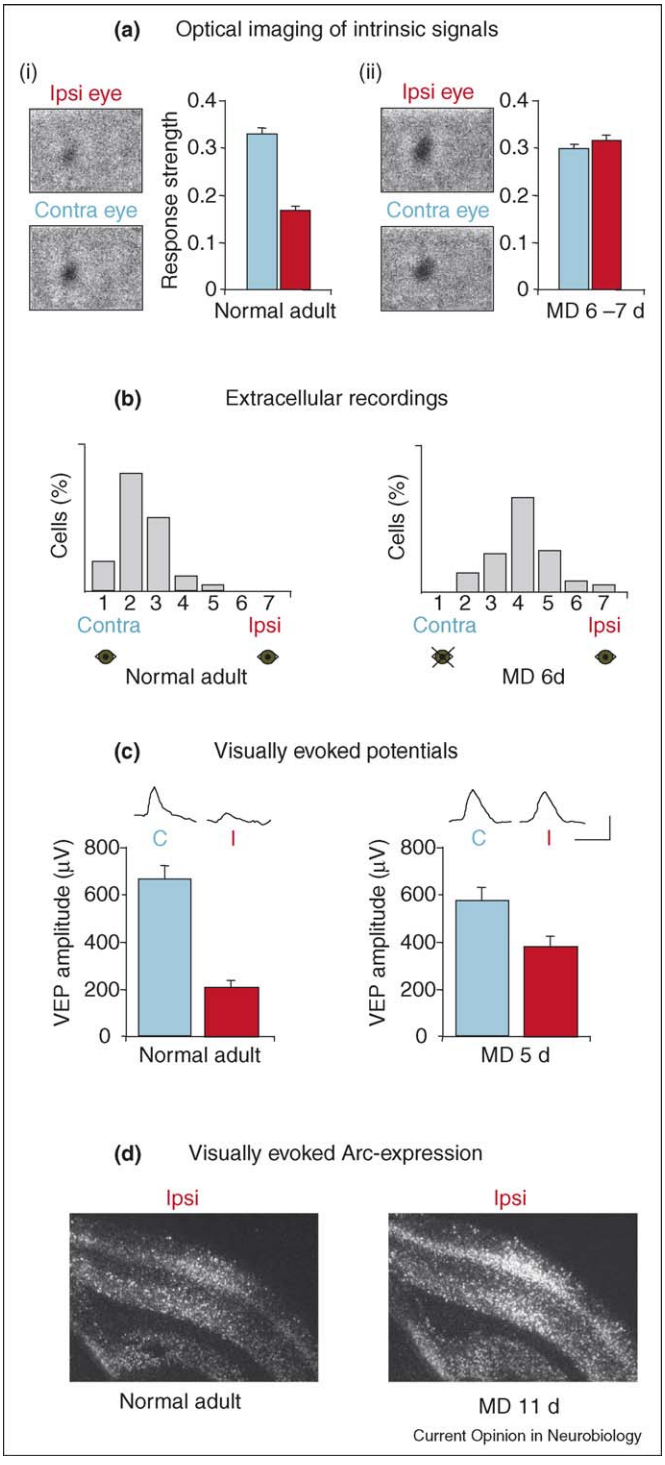
Previous studies failing to detect adult plasticity used barbiturate anesthesia [16], which seems to specifically mask the OD shift in adult mice [59•]. Interestingly, the differential effect of barbiturates in juvenile and adult mice suggests that mechanisms of OD plasticity might change with age, which is also apparent from other studies. Whereas in juvenile mice both initial weakening of deprived eye responses and subsequent strengthening of open eye responses contribute to the shift in OD [24••], in adults the MD effect might be due to NMDA receptor-dependent strengthening of open-eye inputs, as found when testing the hemisphere contralateral to the deprived eye [56]. The absence of the fast loss of input from the contralateral eye after deprivation probably explains why short periods of MD ($\leq$3 days) are insufficient to induce OD shifts in older mice, because even in juvenile animals strengthening of the open-eye representation is delayed and takes longer to develop [24••]. In general, however, depression of inputs is still possible in adult visual cortex. The innately weaker, ipsilateral eye representation undergoes further weakening after ipsilateral eye closure in adult mice [37••,58•], and, therefore, seems to remain particularly susceptible to altered experience in adulthood.

It remains unknown whether substantial structural rearrangements that accompany functional OD shifts in juvenile animals also occur in the mature cortex during MD. Morphological plasticity of synaptic structures is associated with functional reorganisation after retinal lesions in the visual cortex of adult cats [60]. Moreover, in untreated adult mice, formation and pruning of synapses still occur in visual cortex [61], and in the somatosensory cortex spine turnover is enhanced by sensory deprivation [62]. The spine loss apparent in the juvenile visual cortex after four days of contralateral eye MD was not observed in adult animals [38••], consistent with the absence of significant weakening of deprived-eye inputs in the contralateral hemisphere at older ages [37••,56]. Interestingly, however, there was a weak trend for spine gain, which could correspond to the strengthening of non-deprived eye inputs [38••]. Because in adult visual cortex longer deprivation periods are necessary for saturating OD shifts, it is plausible that longer periods of MD (>6 days) would yield significant synaptic remodelling. As structural plasticity is thought to become more limited in scope as the brain matures [61,63,64], it is possible that OD plasticity in adulthood relies more on other mechanisms - including changes in inhibitory circuitry, as implicated by the masking of adult OD shifts by barbiturates, which mainly augment inhibitory transmission. For instance, the potentiation of the non-deprived, ipsilateral eye responses might actually be caused by a depression of eye-specific inhibitory activity. *In vitro*, the potentiation of field potentials in adult visual cortex has been shown to be entirely due to LTD at inhibitory synapses [65]. The application of barbiturates might, therefore, enhance inhibitory transmission and thereby occlude the 'disinhibition' of the non-deprived eye inputs.

Promoting adult plasticity

The potential for large-scale plasticity in adult primary visual cortex is restricted in most mammals and even in

Figure 2



OD plasticity in adult mouse visual cortex can be demonstrated with different methods. **(a)** Intrinsic signal imaging shows strengthening of responses to non-deprived, ipsilateral eye stimulation after six to seven days of MD [37••]. Bars represent visually-evoked changes of intrinsic signals (population responses) in **(i)** normal adult mice and **(ii)** in those after deprivation of the eye contralateral to the examined hemisphere. **(b)** Extracellular recordings show substantial OD shifts towards the non-deprived eye after adult contralateral MD [37••] (OD classes 1-7, Figure 1). **(c)** The measurement of visually evoked field potential (VEP) amplitudes for both eyes after 5 days of MD in animals older than P36 [56] indicates mostly a strengthening of non-deprived eye responses. Traces above the graphs are typical VEP waveforms for normal and deprived animals. Scale bar: 0.4 mV, 0.2 s. **(d)** In-situ hybridization of Arc mRNA in coronal sections of mouse visual cortex after stimulation of the ipsilateral eye. Arc mRNA expression is substantially stronger after 11 days of contralateral MD than it is in normal adult mice [58].

the mouse it does not match the extent of plasticity found in juvenile animals. Rearing animals in the dark enables strong plasticity in the visual cortex of older animals by retarding the maturation of cortical circuits [66]. Recently, it has also been demonstrated that complete visual deprivation in adult rats re-established a more immature cortical state, leading to enhanced OD plasticity [67]. However, the influence of this sensory deprivation paradigm is short-lasting, because brief periods of vision restore a mature, less plastic status quo in cortical circuits [68]. Two recent studies identified factors that restrict plasticity in the mature visual cortex. Pharmacological degradation of the extracellular matrix (ECM) by cleaving glycosaminoglycan chains reactivated OD plasticity in adult rats [64]. Genetic deletion of the Nogo receptor, which mediates myelin-associated inhibition of neurite outgrowth after nerve injury, equally enhanced adult plasticity [69•]. The maturation of ECM and myelin-associated molecules, therefore, presumably adversely affects OD plasticity by inhibiting the remodelling of synaptic structures.

Although the manipulations described above effectively create an immature environment that is more permissive for plasticity in general, recent experiments indicate that experiences by themselves can specifically expand the capacity of mature circuits for change [37••,70]. Inducing a saturating OD shift by brief eye closure in juvenile or adult mouse visual cortex enabled faster and more persistent OD changes in response to a second MD several weeks later [37••]. Because this enhancement of plasticity was specific to repeated closure of the same eye, it seems that an initial experience of MD, no matter at what age, leaves a lasting trace in the altered cortical connections, even though functionally, normal binocular responses completely recover after re-opening of the deprived eye. Taken together, these examples demonstrate that the scope for adult plasticity can be expanded not only by the removal of plasticity-restricting molecules but also by prior experience.

Recovery from monocular deprivation

Another way of exploring visual cortex plasticity is to study the effect of re-establishing binocular vision after MD. In models of OD plasticity based solely on competition, recovery from MD is not expected to occur when the deprived eye is simply re-opened. But, in fact, full recovery of binocular responses after a period of binocular vision has been shown in different species [37••,71,72,73,74]. One might assume that the recovery from MD is simply a reversal of the initial MD effect, but the fact that MD leaves a trace in cortical connections that facilitates plasticity with repeated deprivation suggests otherwise [37••]. Indeed, the induction of OD shifts and their recovery are probably mediated by fundamentally differential processes, as recovery from MD does not require CREB activation or protein synthesis [35,75]. Moreover, in ferrets, the recovery of deprived eye responses has been demonstrated to occur within hours, thus much faster than the initial OD shift, and this rapid recovery is not restricted to the critical period for MD effects [35•,73].

No substantial recovery occurs after early-onset, long-term MD [73,76]. This is not surprising, because depriving one eye of salient input early in postnatal development is likely to prevent correct formation of thalamocortical connections and integration of deprived eye inputs into the cortical network, thus permanently disrupting the visual processing of this eye.

Conclusions

Ocular dominance plasticity in visual cortex has long served as a useful model for examining how cortical circuits are shaped by experience. Altered activity at deprived eye synapses initiates a sequence of cellular and molecular events such that the cortex becomes more responsive to the eye that remained open. Although progress has been made in identifying some of the underlying physiological and biochemical processes, a coherent synthesis of how experience alters cortical circuitry is, as of yet, failing to emerge, and many important questions remain unanswered. For example, which cells and synapses initially detect an imbalance of binocular activity? Does MD lead to differences in the arrival of inputs from the two eyes, thereby enabling STDP to shift OD? To what degree does inhibition play a role in this process, and is there plasticity at inhibitory synapses? Is the intrinsic connectivity of the cortical microcircuit reconfigured so as to enable more efficient processing of the open eye information? Although Hebbian rules of synaptic plasticity can, in principle, explain how binocular cells shift their preference towards the non-deprived eye, it remains to be demonstrated whether homeostatic mechanisms also play a role during OD plasticity.

The mouse will continue to be an effective model for answering some of these questions. The application of *in vivo* two-photon imaging to monitor structural changes at individual synapses during MD will determine how functional shifts in both juvenile and adult cortex are related to remodelling of excitatory synapses. Moreover, monitoring network activity in the visual cortex at the single cell level, for instance with *in vivo* calcium imaging [77], will reveal how each neuron is affected by MD. In the future, mice expressing genetically encoded neuronal activity indicators and other cell-type specific markers will enable long-term observation of both structural and functional changes at the level of individual cells, and even synapses, during visual cortex plasticity. Taken together, these approaches will elucidate the exact sequence of events affecting different cell types in different cortical layers leading to OD shifts after MD and, in general, give insight into how the brain learns and adapts to the environment.

Update

Two recent studies explored how different manipulations of visual environment differentially regulate the expression of genes in mouse visual cortex [78,79]. They exposed a cohort of novel candidate molecules and molecular signalling pathways involved in the adaptive changes of cortical neurons in response to modification of visual experience, including those specifically associated with monocular deprivation.

Acknowledgements

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Using intrinsic signal imaging, the authors show that one episode of MD strongly facilitates subsequent OD plasticity later in life. A few days of MD resulted in a strong shift in OD, which fully recovered after reopening of the deprived eye. Nevertheless, the induction of a second MD several weeks later led to faster and more persistent OD shifts. This conditioning effect was independent of age, but it was specific for the eye that was deprived previously. In addition, substantial OD plasticity in both hemispheres of normal adult mice was observed with intrinsic signal imaging and extracellular recordings.

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