Neuron 52, 577–585, November 22, 2006 ©2006 Elsevier Inc. DOI 10.1016/j.neuron.2006.11.001

Experience-Dependent Plasticity in Adult Visual Cortex

Review

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Experience-dependent plasticity is a prominent feature of the mammalian visual cortex. Although such neural changes are most evident during development, adult cortical circuits can be modified by a variety of manipulations, such as perceptual learning and visual deprivation. Elucidating the underlying mechanisms at the cellular and synaptic levels is an essential step in understanding neural plasticity in the mature animal. Although developmental and adult plasticity share many common features, notable differences may be attributed to developmental cortical changes at multiple levels. These range from shifts in the molecular profiles of cortical neurons to changes in the spatiotemporal dynamics of network activity. In this review, we will discuss recent progress and remaining challenges in understanding adult visual plasticity, focusing on the primary visual cortex.

Introduction

As we experience the world around us, each piece of information we take in may affect how we interpret future sensations, as sensory stimuli can modify the structure and function of neural circuits over various timescales. Such experience-dependent plasticity is widespread in the nervous system, and it plays a crucial role in normal brain functions. Although neural plasticity is most evident during development, experience can shape information processing throughout an animal's lifetime. For example, psychophysical studies of perceptual learning show that our ability to discriminate between similar stimuli can be improved by repeated exposure to them in adulthood. Although the functional advantage of such adaptability is obvious, the underlying neural mechanisms remain to be elucidated.

There are notable differences between developmental and adult neural plasticity. For a developing organism, although the general structure of its nervous system is in place at birth, extensive experience-dependent refinement is essential for the normal maturation of its neural circuits. In an adult animal, however, plasticity should be more restricted. Drastic neural remodeling may be detrimental unless it is in response to severe alterations of sensory inputs such as those caused by peripheral lesions. A classic example of plasticity in the visual cortex is ocular dominance (OD) plasticity, in which the relative sensitivity of cortical neurons to inputs from the two eyes can be profoundly altered by visual manipulations within a critical period of development. As the animal matures, the degree of OD plasticity appears to diminish. How much of it remains in adulthood and under what conditions such plasticity is manifest are still under investigation.

The differences between juvenile and adult plasticity in both function and extent are likely to be accompanied by differences in their underlying mechanisms. Modifications of neural circuits depend not only on the pattern of sensory inputs but also on the network of neurons that receives them. Significant changes in cortical networks take place over development, including those in the level of inhibition, the excitability of individual neurons, and the complexity of synaptic connectivity. The molecular composition of both the intracellular machinery and extracellular matrix also changes over time, which directly affects the functional and structural stability of the neurons.

In this review, we will discuss recent progress in our understanding of adult plasticity in the visual cortex, focusing on the primary visual cortex. We will begin by describing the visual manipulation paradigms that can induce cortical modifications, followed by some of the underlying cellular mechanisms. We will then examine the differences between developmental and adult cortical plasticity and discuss the important unresolved issues that may influence future studies.

Experience-Dependent Plasticity in Adult V1

Perceptual Learning

Studies in both humans and animals have shown that training over days to weeks can cause robust and lasting improvement in various aspects of visual perception (Fahle and Poggio, 2002). However, a major challenge is to ascertain where in the visual system the neuronal changes that underlie these perceptual effects take place. In psychophysical experiments, the specificity of the learning effect provides a useful clue to the location of neural modification. For example, if training through one eye can induce perceptual improvement tested through the untrained eye (interocular transfer), the underlying changes are likely to occur in the cortex, after inputs from the two eyes converge. If the perceptual learning is specific to the trained retinal position and orientation (e.g., Fiorentini and Berardi, 1980; Karni and Sagi, 1991), it is likely to take place in early cortical areas, where neurons have small receptive fields and sharp orientation tuning. Unfortunately, measurements at the psychophysical level alone are usually not sufficient to definitively localize the brain regions involved.

Recent studies using functional magnetic resonance imaging (fMRI) and transcranial magnetic stimulation (TMS) have provided more direct evidence that at least some forms of improved visual discrimination involve changes in early circuits such as V1. Furmanski et al. (2004) found that after subjects are trained to detect low-contrast oriented stimuli, a specific improvement in detection at the trained orientation and location is accompanied by an increase in the fMRI signals from V1. Changes in signals localized to V1 were also found after training on the more complex task of illusory contour detection (Maertens and Pollmann, 2005). In addition to

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measuring brain activity with fMRI, TMS has been used to disrupt activity either broadly in all visual areas or specifically in the primary visual cortex. While TMS impaired initial performance in line orientation discrimination, training on this task significantly reduced its disruptive effects, suggesting that perceptual learning strengthened processing in the early visual regions (Neary et al., 2005).

Despite this recent progress in localizing the visual areas involved in perceptual learning, elucidation of the mechanisms at the cellular level remains a challenge. Several possibilities have been proposed. For example, the responses of the neurons involved in processing the trained stimulus could be potentiated (Figure 1A), leading to a more reliable neural representation of that stimulus. A second possibility, found in the auditory (Recanzone et al., 1993) and somatosensory (Recanzone et al., 1992) cortex, is that the number of neurons representing the learned stimulus increases after training (Figure 1B). However, when Schoups et al. (2001) examined changes in V1 orientation tuning accompanying improved performance in orientation discrimination in adult monkeys, they found no increase in the proportion of neurons tuned to the trained orientation. Instead, there was an increase in the slope of the tuning curve at the trained orientation for neurons whose preferred orientations were 10°–20° from the trained one (Figure 1C). The authors suggested that since the firing rates of these neurons are most sensitive to small changes near the trained orientation, they may be the most relevant for the learned discrimination task.

In contrast, a similar study by Ghose et al. (2002) found that perceptual learning caused little change in the response properties of V1 and V2 neurons, aside from a small reduction in the response amplitude of the cells tuned to the trained orientation. They suggest that the psychophysical change is accomplished by a decoding strategy specifically optimized for the trained task, instead of an improved neural representation of orientation in early visual areas. The differences between these two studies at the physiological level could be related to their differences at the psychophysical level. For example, it has been shown that the difficulty of the visual task can affect the extent of V1 involvement in learning (Ahissar and Hochstein, 1997). Thus, differences in the exact task design could lead to differences in the underlying visual areas. Notably, the learning observed by Schoups et al. (2001) was eye and location specific, which is consistent with a neural change in early visual cortex. In contrast, Ghose et al. (2002) found transfer of the perceptual improvement between eyes and across retinotopic locations. Thus, their results do not necessarily argue against V1 as the locus for spatially specific perceptual learning.

Another form of perceptual learning was found to be associated with changes in the contextual modulation of V1 responses (Crist et al., 2001; Li et al., 2004). After training in a three-line bisection or vernier task, monkeys showed significant improvement in determining the location of the middle test line relative to the reference lines. Similar to the case of orientation discrimination (Schoups et al., 2001; Ghose et al., 2002), the perceptual improvement was not accompanied by any obvious change in basic V1 receptive field properties such as

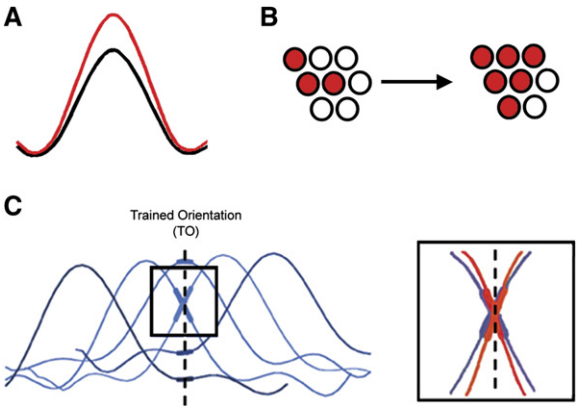

Figure 1. Possible Neural Mechanisms Underlying Perceptual Learning

(A) Increase in response magnitude. Learning may potentiate the responses of neurons responding to the trained stimulus. Shown is an example tuning curve before (black) and after (red) training.

(B) Increased cortical representation. Learning may increase the number of cells in the cortical population that respond to the trained stimulus (red filled circles).

(C) Changes in tuning curve shape, as shown in Schoups et al. (2001). The blue curves (left) represent orientation tuning of a population of neurons. The thick line sections indicate the slope of the tuning curves measured at the trained orientation (TO, dashed vertical line). The black box shows a magnified view of the tuning curves of neurons 2 and 3 before (blue) and after (red) perceptual training. Neurons tuned to orientations 10°–20° from the TO show steeper slopes to their tuning curves after training (adapted from Schoups et al., 2001, with permission from Macmillan Publishers Ltd [Nature]).

location, size, or preferred orientation. Instead, there was a significant change in contextual modulation. The responses of the neurons near the trained retinal location showed higher sensitivity to the positions of the line stimuli outside of the classical receptive field, and this effect existed only when the monkey was performing the relevant task. This shows that perceptual learning can alter the nonclassical receptive field properties of V1 neurons and that the effect is dependent on the task performed as opposed to being hardwired.

While in the nonhuman primate the neural substrates for perceptual learning appear to be highly task dependent, in rodents the relationship between learning and visual cortical changes may be more straightforward. Frenkel et al. (2006) found that repeated exposure of awake mice to stimuli of a certain orientation induced a specific potentiation of the V1 response to the trained orientation. The improvement occurred in adults as well as juveniles, was specific to the trained eye, and developed only across multiple days of training. This is consistent with the cortical change expected of perceptual learning (Figure 1A), although no performance of any task was required for the effect. Interestingly, such cortical change observed in the mouse is more similar to the training-induced increase in fMRI response in the human visual cortex (i.e., Furmanski et al., 2004) than to the effects measured with single-unit recordings in monkey V1. In addition to changes in their visual responses, cortical neurons may also develop sensitivity to nonvisual inputs that are paired with visual stimuli in a learning task. After training freely moving rats in a task that associates different reward times with visual stimuli to

the two eyes, a significant proportion of visual cortical neurons developed firing patterns that are correlated with the expected reward time (Shuler and Bear, 2006).

A common observation from the studies in both primates and rodents is that perceptual learning in the visual system appears to be mediated primarily by changes in the response strength or tuning of individual neurons (Figures 1A and 1C) rather than large-scale spatial reorganization of the cortical network (Figure 1B) found in the auditory and somatosensory systems. Whether such a difference in cortical modification is due to differences in the perceptual training paradigm or in the cortical circuitry across different modalities remains to be investigated.

Visual Deprivation

While the cortical modifications mediating perceptual learning appear to be induced by increased exposure to certain visual stimuli, significant changes can also be caused by deprivation of inputs in part or all of the visual field. Although it is induced by abnormal visual experience, the capacity of the adult cortex for such reorganization is functionally advantageous, since it allows the neuronal machinery rendered inactive by peripheral injury to be reused for processing other inputs. This could in turn facilitate functional recovery of perception.

One form of visual deprivation is caused by lesion of a region of the retina (scotoma). Binocular retinal lesions initially silence the visual cortical region retinotopically mapped to the scotoma (Figure 2A). Within several months, however, cells in this region become responsive to visual stimuli, as their receptive fields shift or expand into nearby retinal regions (Figure 2B; Kaas et al., 1990; Heinen and Skavenski, 1991; Gilbert and Wiesel, 1992; Chino et al., 1995; Darian-Smith and Gilbert, 1995; Calford et al., 2003). Such functional reorganization is accompanied by intracortical axonal sprouting (Darian-Smith and Gilbert, 1994), suggesting structural modification as an underlying mechanism. However, both the extent and the time course of the functional reorganization in V1 remain controversial. Unlike the experiments using single-unit recordings, measurements based on cytochrome oxidase activity (Horton and Hocking, 1998) and primate fMRI (Smirnakis et al., 2005) revealed little V1 reorganization after months of retinal lesion. Since in these studies cortical reorganization is measured by different physiological parameters using different techniques, future studies combining multiple techniques in the same experiment may be necessary to narrow down the range of potential explanations for the discrepancy (see Calford et al., 2005, and Smirnakis et al., 2005, for technical discussions).

Another form of deprivation-related plasticity is OD plasticity, which was initially characterized in the developing visual cortex (Figure 3Ai; Wiesel and Hubel, 1963). During the critical period of OD plasticity, lid suture of one eye for as little as a few days in mammals can cause a dramatic shift in the preference of V1 neurons to the open eye and a degradation of vision through the closed eye. This functional modification is accompanied by a rapid withdrawal of the thalamocortical axonal arbors representing the closed eye (Antonini and Stryker, 1993). Initial experiments in cats and monkeys suggested that after the critical period closes, the visual cortex is no longer susceptible to monocular deprivation (e.g., Hubel and Wiesel, 1970). However, recent studies in rodents suggest that their critical period may be relative rather than absolute (Figure 3B; Sawtell et al., 2003; Tagawa et al., 2005; Hofer et al., 2006a; He et al., 2006). In adult mice, a longer period of monocular deprivation can cause a shift in cortical ocular dominance (Sawtell et al., 2003; Hofer et al., 2006a), and the effect may be enhanced by a prior OD shift (Hofer et al., 2006a). In adult rats, a prolonged period of binocular deprivation facilitates ocular dominance plasticity (Guire et al., 1999), possibly by reactivating juvenile-like mechanisms (He et al., 2006). In later sections we will further discuss the relationship between adult and developmental OD plasticity.

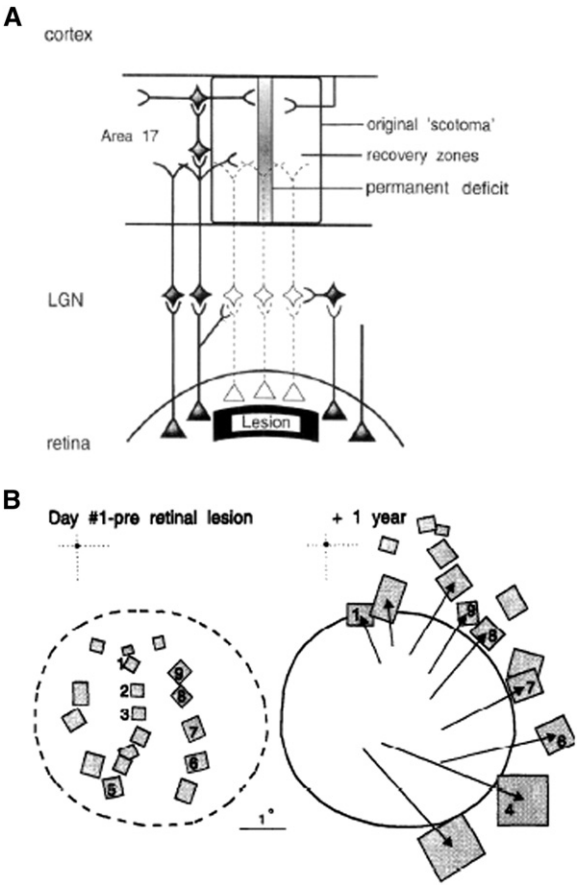

Figure 2. Receptive Field Plasticity in V1 after Retinal Lesion (Scotoma)

(A) Diagram of the effects of retinal lesion (scotoma) on the cortical circuit. Dashed lines indicate neural pathways deprived of visual input.

(B) Remapping of receptive fields after scotoma in monkey V1. Left side shows the receptive fields of a number of neurons prior to lesion. Arrows on the right indicate the direction of remapping of the same recording sites 1 year after injury.

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Synaptic Correlates of Adult Cortical Plasticity

A natural candidate for the cellular mechanism of cortical plasticity is activity-dependent synaptic modification, including both long-term potentiation (LTP) and

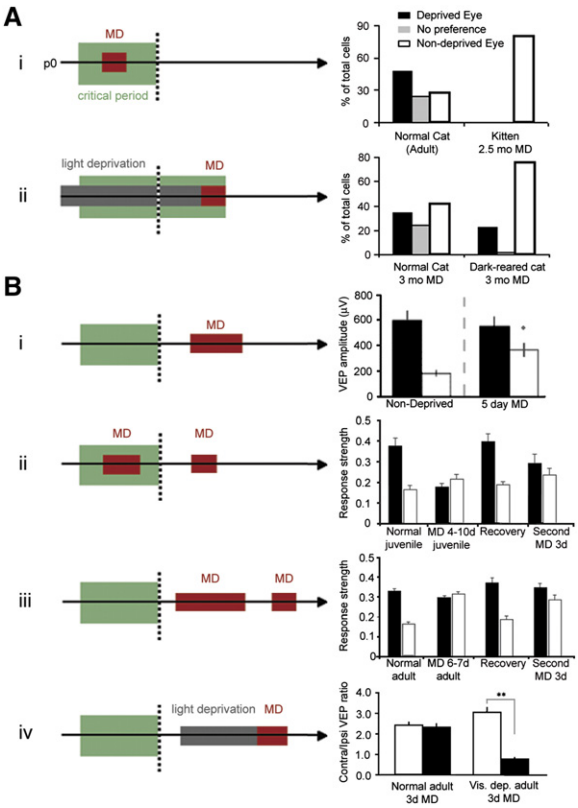

Figure 3. Ocular Dominance Plasticity in Developing and Adult Visual Cortex

(A) Studies of OD plasticity with monocular deprivation (MD) in cat visual cortex. Timelines of experimental manipulations shown on the left. Duration of the critical period is indicated in green; dashed black vertical line indicates the end of critical period in normal animals. Histograms on the right indicate the percentage of recorded cells that show preference for the deprived (black) or nondeprived (white) eye. Neurons with no preference indicated in gray. (Ai) Classical monocular deprivation (red box) in kitten during the critical period causes a decrease in preference to the deprived eye and an increase in preference to the nondeprived eye (adapted from Wiesel and Hubel, 1963; reproduced with permission of the American Physiological Society). (Aii) OD shift similar to that in kittens is successfully induced in adult 8-month-old cats after light deprivation (gray) from birth (adapted from Cynader and Mitchell, 1980; reproduced with permission of the American Physiological Society). (B) Studies of OD plasticity in adult rodents. Bar graphs on the right indicate strength of field potential evoked by visual stimulation of the deprived (black) or nondeprived (white) eye. (Bi) Extended (5 day) periods of MD cause adult-type OD shifts, with an increase in the response to the nondeprived eye, but no change in response to the deprived eye (adapted from Sawtell et al., 2003). (Bii) Monocular deprivation during the critical period facilitates juvenile-type OD shifts after only 3 days of deprivation in adults. (Biii) Prior MD in adulthood allows for later rapid induction of adult-type OD shift (with [Bii], adapted from Hofer et al., 2006a; adapted/reproduced by permission from Macmillan Publishers Ltd. [Nature Neuroscience]). (Biv) Visual deprivation for 10 days in adult rats facilitates expression of juvenile-type OD shifts after only 3 days of MD. Results are reported as the ratio of VEP amplitude evoked by stimulation of the eye contralateral (C) and ipsilateral (I) to the recorded location; white bars represent the C/I ratio measured from nondeprived cortex, black bars from deprived cortex (adapted from He et al., 2006; reproduced/adapted with permission from the Society for Neuroscience, copyright 2006).

depression (LTD). During development, altered visual experience can also cause drastic changes in axonal and dendritic structures. Recent studies have investigated the synaptic and structural basis for adult plasticity.

Hebbian Synaptic Plasticity

Given the difficulty in identifying the cellular mechanisms underlying learning- and deprivation-induced cortical modifications, an alternative approach is to start with known forms of synaptic plasticity characterized in vitro and explore their functional consequences in vivo. A central hypothesis guiding this line of research is Hebb's rule (Hebb, 1949), in which the correlation between pre- and postsynaptic activity plays a crucial role in synaptic modification. Hebb's rule has been used in theoretical studies to explain ocular dominance plasticity (e.g., Miller et al., 1989; Clothiaux et al., 1991), and there is strong experimental evidence for Hebbian synaptic plasticity in adult visual cortex.

In a series of studies, synchronous visual stimulation and iontophoretic cortical activation were shown to induce rapid modification of orientation tuning (Fregnac et al., 1988, 1992) and ocular dominance (Fregnac et al., 1988; Shulz and Fregnac, 1992) of cat V1 neurons. Pairing the activation of cortical neurons and the presentation of stimuli through a particular eye or at a certain orientation causes a long-term enhancement of the cortical response to the paired stimulus, whereas suppression of cortical activity during visual stimulation reduced the responses to the paired stimulus. In another experiment, synchronous visual stimulation of the classical receptive field and an unresponsive surround region caused a long-lasting expansion of the receptive field into the unresponsive region, which is presumably due to the enhancement of subthreshold inputs from this region (Eysel et al., 1998). These experiments suggest that the temporal covariation of pre- and postsynaptic activity plays a critical role in cortical modification, consistent with Hebb's rule of synaptic modification.

In addition to the temporal proximity, the sequence of pre- and postsynaptic spiking also plays a key role in synaptic modification. In spike timing-dependent plasticity (STDP), presynaptic spiking before postsynaptic spiking leads to long-term potentiation, whereas the opposite order leads to depression (Levy and Steward, 1983; Markram et al., 1997; Debanne et al., 1998; Bi and Poo, 1998). Similar timing-dependent receptive field plasticity has been demonstrated in vivo in developing primary visual cortex (Schuett et al., 2001; Meliza and Dan, 2006). In several recent studies, the effect of stimulus sequence on cortical modification was tested in V1 of adult cat. Asynchronous visual stimuli flashed in two adjacent retinal regions (Fu et al., 2002) or at two orientations (Yao and Dan, 2001; Yao et al., 2004) were found to induce rapid shifts in receptive field location or orientation tuning, respectively. The dependence of the receptive field modifications on the sequence and interval of the paired flashes is consistent with the requirements of STDP measured in visual cortical slices (Froemke and Dan, 2002; Sjostrom et al., 2001). In addition to these changes observed in anesthetized cat V1, similar visual conditioning induced corresponding perceptual shifts in human subjects (Fu et al., 2002; Yao and Dan, 2001; Yao et al., 2004), suggesting a functional relevance for the cortical modifications.

An open question is whether the timing-dependent form of plasticity is related to learning- or deprivation-induced functional modifications of the visual cortex. Their time courses are quite different; the induction of timing-dependent receptive field and perceptual changes occurs in minutes and their expression in some cases lasts for only tens of minutes (Yao and Dan, 2001; Fu et al., 2002). It will be important to determine whether this rapid form of modification represents the first phase of a long-term effect and whether prolonged exposure to the stimulus patterns (as in perceptual learning and visual deprivation) can convert the transient cortical modification into a more permanent reorganization.

Other Forms of Long-Term Synaptic Plasticity

In addition to timing-dependent Hebbian modifications, other types of LTP and LTD may also be involved in adult functional visual cortical plasticity. For example, the potentiation of mouse cortical responses induced by repeated exposure to oriented stimuli (Frenkel et al., 2006) depends on both NMDA receptor activation and AMPA receptor trafficking, consistent with the properties of LTP. In humans, a visual tetanus of rapid stimulus presentation enhances a component of visually evoked event-related potentials (Teyler et al., 2005), which is reminiscent of synaptic LTP induced by tetanic presynaptic stimulation. In a study in the rat visual pathway, the strength of the thalamocortical connection was measured by the local field potential in cortical layer 4 evoked by extracellular stimulation in the lateral geniculate nucleus (LGN; Heynen and Bear, 2001). A theta burst stimulation (TBS), commonly used for LTP induction, caused a long-lasting, NMDA receptor-dependent enhancement of the cortical responses not only to the thalamic stimulation but also to visual stimuli. This suggests that potentiation of the thalamocortical connection directly enhances the visual response of cortical neurons. A similar TBS-induced field potentiation has been observed in cortical layer 2/3 (Dringenberg et al., 2006).

Since monocular deprivation-induced ocular dominance shifts in the adult rat also depend on NMDA receptor activation (Sawtell et al., 2003), one can further speculate that OD plasticity may share common mechanisms with the theta burst-induced field LTP. However, whether the observed change arose from direct potentiation of the thalamocortical connection is unclear. Yoshimura et al. (2003) found that the field LTP induced by TBS may be due to LTD of inhibition. They also showed that LTD of inhibitory synapses persists throughout the animal's lifetime, although LTP and LTD of excitatory synapses rarely occur in adulthood (Yoshimura et al., 2003; Dudek and Friedlander, 1996). Furthermore, several studies have indicated that not all forms of LTP or LTD are required for experience-dependent cortical plasticity (Hensch et al., 1998b; Renger et al., 2002; Fischer et al., 2004).

Along with changes in the strengths of specific synaptic connections, visual deprivation may also cause global modifications of cortical circuits through homeostatic plasticity. Long-term changes in the level of network activity (over days) have been shown to regulate several intrinsic and synaptic properties of cortical and hippocampal neurons in a manner that helps to restore network activity to some set point (Turrigiano and Nelson, 2004; Mody, 2005). In the juvenile rat, visual deprivation was found to induce shifts in the intrinsic excitability of layer 4 neurons in the visual cortex (Maffei et al., 2004), although the extent to which this and other forms of homeostatic plasticity persist in the adult animal remains unclear (Desai et al., 2002, but see Karmarkar and Buonomano, 2006). In general, the input-specific synaptic plasticity and network-wide homeostatic plasticity may both operate under visual deprivation. Studying their interactions could help explain some puzzling observations that are difficult to understand based on each mechanism alone.

Structural Plasticity

In addition to changes in the strength of existing synaptic connections, some cortical modifications may involve structural remodeling of neuronal processes. In adult cats, retinal lesions induce axonal sprouting and an increased density of axonal boutons of cortical neurons in the area corresponding to the scotoma (Darian-Smith and Gilbert, 1994). Cortical plasticity may also be mediated by postsynaptic changes. In adult rodent barrel cortex, Trachtenberg et al. (2002) found that portions of the cortex deprived of sensory input showed an increase in the ratio between mobile and stable dendritic spines, implying that adult cortical reorganization was achieved through the elimination of existing synapses and formation of new ones. However, two recent studies in adult visual cortex indicate that monocular deprivation causes no change in the number of dendritic protrusions in layer 2/3 (Mataga et al., 2004) and a slight decrease in spine motility in layer 5 (Oray et al., 2004), suggesting a lack of postsynaptic structural remodeling. It would be interesting to know whether monocular deprivation causes any change in either the structure or the motility of the presynaptic axons, as suggested by the study of retinal scotoma (Darian-Smith and Gilbert, 1994).

Compared to the glutamatergic pyramidal neurons, the dendrites of GABAergic interneurons appear much more dynamic in adult rat V1 (Lee et al., 2006). This is consistent with the observation that LTD of inhibitory responses persists well into adulthood (Yoshimura et al., 2003), and it suggests an important role for inhibitory synapses in functional visual cortical plasticity.

Mechanistic Differences between Adult and Developmental Plasticity

Since the adult cortex consists of fully functioning circuits, a certain level of structural and functional stability would be advantageous. Indeed, compared to developing visual cortex, experience-dependent modification of adult cortex is in general less drastic. The cellular mechanisms underlying the differences between adult and juvenile plasticity are just beginning to be elucidated.

Morphologically, adult cortical neurons appear much more stable. In mouse somatosensory cortex, while some spine motility remains in adulthood, the dynamics are much slower than in young animals (Holtmaat et al., 2005). In the visual cortex of adult mice, nearly all spines of layer 5 pyramidal neurons appear stable (Grutzendler et al., 2002), and the dendritic arbors of layer 2/3 pyramidal neurons exhibit little change over 3–10 weeks (Lee et al., 2006). In adult monkey V1, the primary branches of axons are also stable, although there is some motility of smaller branches and turnover of synaptic boutons

(Stettler et al., 2006). At the molecular level, activation of the signaling pathway mediated by Nogo receptors, which inhibits axonal growth (McGee et al., 2005), and an increase in the density of extracellular matrix (ECM) scaffolding around neurons (Pizzorusso et al., 2002) significantly reduce the extent of structural remodeling in the adult cortex. Degradation of the ECM in mature animals allows not only an increase in spine motility (Oray et al., 2004) but also the late induction of OD shifts (Pizzorusso et al., 2002). Mutation of the Nogo-66 receptor also markedly prolongs the critical period for OD plasticity (McGee et al., 2005).

The molecular mechanisms underlying LTP and LTD of excitatory synapses may also be regulated developmentally. For example, the induction of several forms of LTP and LTD depends on Ca^{2+} influx through the NMDA receptors (Malenka and Bear, 2004). The molecular composition of NMDA receptors is known to change during development, with an increase in the ratio of NR2A to NR2B subunits (Monyer et al., 1994; Sheng et al., 1994; Yoshimura et al., 2003). The shifted ratio changes the kinetics of the NMDA receptor, causing a more rapid decay of the Ca^{2+} response (Carmignoto and Vicini, 1992; Flint et al., 1997; Nase et al., 1999). However, the role of this NMDA receptor subunit change in the developmental regulation of OD plasticity remains controversial (e.g., Yoshimura et al., 2003; Quinlan et al., 1999; He et al., 2006, but also see Roberts and Ramoa, 1999). In addition, expression of the protein CREB, which is involved in the consolidation of synaptic modification, also declines with age. Increasing CREB expression in adult visual cortex helps to stabilize ocular dominance shifts (Pham et al., 2004). It should be noted that here we have only highlighted a few molecular mechanisms that are known to differ between developing and adult animals rather than summarizing all the cellular processes involved in cortical plasticity (see Hofer et al., 2006b, for a comprehensive review on the molecular mechanisms of OD plasticity).

In contrast to excitatory neurons, the dendrites of GABAergic neurons are dynamically modified in adult rat V1, which could allow large-scale changes in the inhibitory network (Lee et al., 2006). As described above, long-term depression of inhibitory responses persists into adulthood (Yoshimura et al., 2003), which may underlie some forms of functional plasticity. The importance of inhibitory circuits in cortical plasticity is highlighted by a series of studies in mouse visual cortex showing that timing of the critical period for OD plasticity is controlled by the developmental state of the inhibitory network (Fagiolini and Hensch, 2000). Appearance of GABAergic transmission seems to play an important role in ocular dominance plasticity (Hensch et al., 1998a), and when inhibition increases above a certain threshold, the animal becomes insensitive to short periods of monocular deprivation. Together, these studies raise the possibility that while plasticity of the excitatory circuit plays a major role in developmental plasticity, with maturation the inhibitory network gradually replaces the excitatory network as the main mediator for cortical plasticity in older animals.

In summary, multiple cellular and molecular differences between the developing and adult visual cortex may contribute to the difference in their functional plasticity. Elucidation of the roles of these factors in circuit modification will also help us understand why certain forms of plasticity are restricted to developing animals while others persist into adulthood.

Manipulations that Awaken Adult Plasticity

In addition to the smaller magnitude of adult cortical reorganization, changes are also likely to be induced under more restricted conditions, i.e., only visual stimuli that are most relevant for the organism will be effective in cortical modification. This restriction may be implemented in various ways, from the duration and frequency of the stimuli to the activation of neuromodulatory circuits that could serve as an overall gate for cortical plasticity.

Pattern and Duration of Visual Stimuli

As discussed earlier, the 2–3 days of monocular deprivation effective in juveniles must be extended to at least 5 days in order to induce ocular dominance shifts in adult mouse V1 (Figure 3Bi; Sawtell et al., 2003; Tagawa et al., 2005), and even longer deprivation may be required for adult rats (Guire et al., 1999). While developmental OD plasticity involves a rapid reduction of responses to the deprived inputs followed by a later enhancement of the nondeprived inputs (Frenkel and Bear, 2004), adult OD shifts in mice are primarily accounted for by increased responses to the nondeprived eye (Figure 3Bi; Sawtell et al., 2003; Tagawa et al., 2005). Evidence from adult rats suggests that this increase could be due to a reduction of inhibition rather than a potentiation of the excitatory synapses (Yoshimura et al., 2003). Thus, the slower induction of adult OD shifts may be partly attributed to the absence of a form of rapid plasticity of excitatory synapses that only operates during development, and this distinction could apply to other forms of cortical plasticity as well.

Prior exposure to a particular pattern of inputs can facilitate adult plasticity. In a recent study, mice underwent a period of monocular deprivation during the critical period and were allowed to recover with normal binocular vision. Subsequent brief (3 day) monocular deprivation in the adults caused a significant OD shift, although the mice with no such prior experience did not show similar plasticity (Figure 3Bii; Hofer et al., 2006a). Thus, early experience can leave a lasting trace in the adult cortex. However, the effect of prior experience manipulation is not age dependent. Seven days of monocular deprivation induced an OD shift in naive mice older than p70. After these animals were allowed to recover, only 3 days of deprivation were sufficient to induce an adult form of OD shift (Figure 3Biii), in which the primary change is an increase in response to the nondeprived eye. A similar effect was previously observed in the barn owl optic tectum. A shift in the auditory receptive field map induced by prism wearing in juveniles facilitates induction of the same shift in adults (Knudsen, 1998). The juvenile experience manipulation causes a lasting structural change in the tectum (Linkenhoker et al., 2005), although the physiological contribution of the abnormal connections are masked by inhibition (Zheng and Knudsen, 1999). These functionally dormant connections appear to provide the substrate for rapid readaptation in adulthood. In the adult visual cortex, it will be interesting to determine whether the

effect of prior monocular deprivation is mediated by the same mechanism.

Light Deprivation

Rearing a young animal in complete darkness prior to or at the start of the critical period of OD plasticity is well known to prolong the period that the cortex remains plastic (Figure 3Aii) (Cynader and Mitchell, 1980; Fagiolini et al., 1994; Guire et al., 1999) and to affect the maturation of the inhibitory network (Morales et al., 2002). Interestingly, a recent study in adult rats suggests that extended dark housing (light deprivation) can return these animals to a state of plasticity similar to that in juveniles. Ten days of light deprivation rejuvenated the adult visual cortex, which showed decreases in the ratio of inhibitory to excitatory neurotransmitter receptors and an NMDA receptor subunit composition more like that of young rats. In addition, after dark rearing, only 3 days of MD in the adult were sufficient to induce an OD shift, which involves both a decrease in response to the deprived input and an increase to the nondeprived input (Figure 3Biv; He et al., 2006).

These results raise an intriguing possibility of a reset mechanism in the adult rodent brain that endows some form of plasticity throughout the lifetime of the animal. The above study tests plasticity with a fairly strong stimulus manipulation involving competition between inputs from the two eyes. It would be interesting to know whether the rejuvenated visual cortex also shows increased ability to learn or adapt to more complex and natural stimuli. In addition, adult OD plasticity has been observed primarily in rodents, most strongly in the mouse. Further studies are needed to determine whether it exists in other mammalian species with more refined visual cortical circuits.

Behavioral Contexts and Neuromodulators

While cortical modifications in developing animals appear to depend primarily on the patterns of sensory inputs, recent studies in awake animals have revealed the importance of the behavioral state in adult neural modification. For example, compared to adult barn owls fed with dead mice, birds that hunt live prey showed markedly enhanced tectal map plasticity (Bergan et al., 2005). A more surprising effect was found in the rat barrel cortex. For adult rats living in a home cage, removal of all whiskers surrounding a single spared whisker caused an expansion of the cortical representation of the spared whisker, but the same manipulation had the opposite effect if the rats actively explored the environment away from their home cage (Polley et al., 1999).

It will be important to determine whether behavioral contexts also modulate or even gate adult plasticity in the visual system. Such effects could be mediated by top-down projections from higher cortical areas or by various neuromodulators. The roles of neuromodulators in adult plasticity have been well demonstrated in the auditory cortex (Bao et al., 2001; Kilgard and Merzenich, 1998). Along these lines, new evidence from adult visual cortex indicates that basal forebrain stimulation or direct application of cholinergic agonists facilitates LTP induction by theta burst stimulation (Dringenberg et al., 2006). However, much remains to be learned about their effects on functional cortical modification induced by natural visual inputs.

Conclusion

Recent findings have opened up new avenues for studying adult cortical plasticity, an important feature of the mammalian visual system. While our knowledge of developmental plasticity will no doubt provide valuable clues, it is equally important to elucidate the distinct features of plasticity in adult animals. Neural circuits transform visual inputs into complex spatiotemporal patterns of electrical activity, which then induce cortical modifications; this transformation may change qualitatively with maturation of the circuits. In addition to the changing levels of inhibition that shape network activity, the adult patterns of intracortical connections may cause strongly correlated firing within selected assemblies of cortical neurons both spontaneously and in response to visual stimuli. These correlations may profoundly influence cortical modification through Hebbian synaptic plasticity. Thus, it will be important to extend the study of cortical plasticity from the level of single cells and synapses to populations and networks. Fortunately, recent development in optical imaging and multielectrode recording techniques has greatly expanded our ability to study neuronal populations. Applying these techniques to awake behaving animals will ultimately allow us to understand how adult cortical plasticity operates in natural sensory and behavioral contexts.

Acknowledgments

We would like to thank Natalia Caporale for her helpful comments. This work is supported by NIH grants F32EY016645 (U.R.K.) and R01EY15180 (Y.D.).

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