CHAPTER

Mechanisms of Plasticity in the Developing and Adult Visual Cortex

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Abstract

The visual cortex provides powerful evidence for experience-dependent plasticity during development, and for stimulus and reinforcement-dependent plasticity in adulthood. The synaptic and circuit mechanisms underlying such plasticity are being progressively understood. Increasing evidence supports the hypothesis that plasticity in both the developing and adult visual cortex is initiated by a transient reduction of inhibitory drive, and implemented by persistent changes at excitatory synapses. Developmental plasticity may be induced by alterations in the balance of activity from the two eyes and is implemented by a cascade of signals that lead to feedforward and feedback changes at synapses. Adult plasticity is imposed on mature synapses and requires additional neurotransmitter-dependent mechanisms that alter inhibition and subsequently response gain.

Keywords

circuits, sensory cortex, ocular dominance plasticity, reinforcement learning, inhibition, excitatory synapses, glutamate receptors, parvalbumin neurons

The visual system is a powerful model system for analyzing how sensory experience and electrical activity regulate the development of synapses and neuronal circuits in a processing pathway. In particular, the primary visual cortex, or V1, has been a proving ground for revealing both the phenomena and mechanisms of developmental plasticity in the mammalian cerebral cortex. The visual cortex exhibits profound plasticity during development: for example, an alteration in visual drive induced by even a brief eyelid closure of one eye, which induces unbalanced inputs from the two eyes, results in weakening of V1 neuron responses to the deprived (closed) eye while strengthening the responses to the nondeprived (open) eye (Gordon and Stryker, 1996; Hubel and Wiesel, 1970). The mechanisms underlying developmental

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plasticity in the visual cortex have been the subject of intense study (Espinosa and Stryker, 2012; Nagakura et al., 2013).

The visual cortex also exhibits prominent plasticity in adulthood, as revealed by systematic changes in neuronal responses due to prolonged visual stimulation (Dragoi et al., 2000) or by pairing visual stimuli with neuromodulatory inputs (Chen et al., 2012). While it is generally accepted that adult V1 is less susceptible to passive experience-driven changes and therefore exhibits less plasticity than during the critical period, considerable plasticity can be induced in V1 and other sensory cortex by reinforcement-dependent associative learning; however, the mechanisms of adult plasticity are less understood. In this review, we suggest that both developmental and adult plasticity share common features related to initiating and maintaining changes in neuronal responses. Specific mechanisms by which response plasticity is maintained may differ in the developing and adult cortex, as would specific mechanisms by which plasticity is initiated, but the conceptual similarities point to important principles underlying experience and stimulation-dependent plasticity of neuronal responses and representations in cortical circuits.

1 VISUAL CORTEX PLASTICITY DURING DEVELOPMENT

One of the most extensively studied forms of plasticity in the developing brain relates to changes induced in V1 by brief closure of one eye, or monocular deprivation (MD). Whereas neuronal responses in V1 are normally driven by each of the two eyes in some combination, responses after MD are dominated by the open eye. Such ocular dominance plasticity (ODP) is prominent during a developmental "critical period" (Gordon and Stryker, 1996; but see Frenkel and Bear, 2004), which refers to a particularly sensitive phase of development during which even a brief alteration in visual experience induces significant changes in cortical circuits.

Considerable attention has been devoted to excitatory glutamatergic synapses in V1 and their downstream signaling mechanisms as sites for implementing and maintaining ODP. Glutamate receptors include *N*-methyl-D-aspartate receptors (NMDARs), alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPARs), and metabotropic glutamate receptors (mGluRs). Several lines of evidence suggest that the composition of NR2A subunits (which have reduced calcium influx, and thus reduce plasticity) and NR2B subunits (which have high calcium permeability, and thus enhance plasticity) of NMDARs changes through visual experience during postnatal development (Flint et al., 1997). The NR2A/NR2B ratio increases during normal development, allowing less plasticity toward adulthood (Quinlan et al., 1999). Rearing rodents in the dark from birth, however, leads to reduction in the ratio of NR2A/NR2B subunits (Chen and Bear, 2007), which likely allows ODP to take place even during adulthood (He et al., 2006). MD also induces dephosphorylation and internalization of the GluA1 subunit of AMPARs, which corresponds to synaptic depression induced by MD (Heynen et al., 2003). The mGluRs

are known to be required for plasticity in the visual cortex layer 6, but it appears not in the layer 2/3 nor 5 (Daw et al., 1999; Rao and Daw, 2004).

The signaling initiated by glutamate and its receptors is conveyed inside a neuron into a cascade of downstream signaling. The cAMP-dependent protein kinase (protein kinase A or PKA) regulates glutamate receptor-mediated synaptic plasticity by phosphorylating GluA1 and regulating glutamate receptor complexes (Heynen et al., 2003; Kameyama et al., 1998). Moreover, PKA translocates into the nucleus for downstream cAMP response element (CRE)-mediated gene expression together with extracellular signal-regulated kinase 1,2 (ERK) (Cancedda et al., 2003). Both PKA and ERK are required for ODP (Beaver et al., 2001; Di Cristo et al., 2001), likely through CRE-mediated gene expression (Fig. 1).

Gene expression analysis in the primary visual cortex during the critical period and following visual deprivation provides a comprehensive view of cortical changes during normal development and experience-dependent plasticity. The critical period in mice is accompanied by a distinct transcriptional profile that includes genes

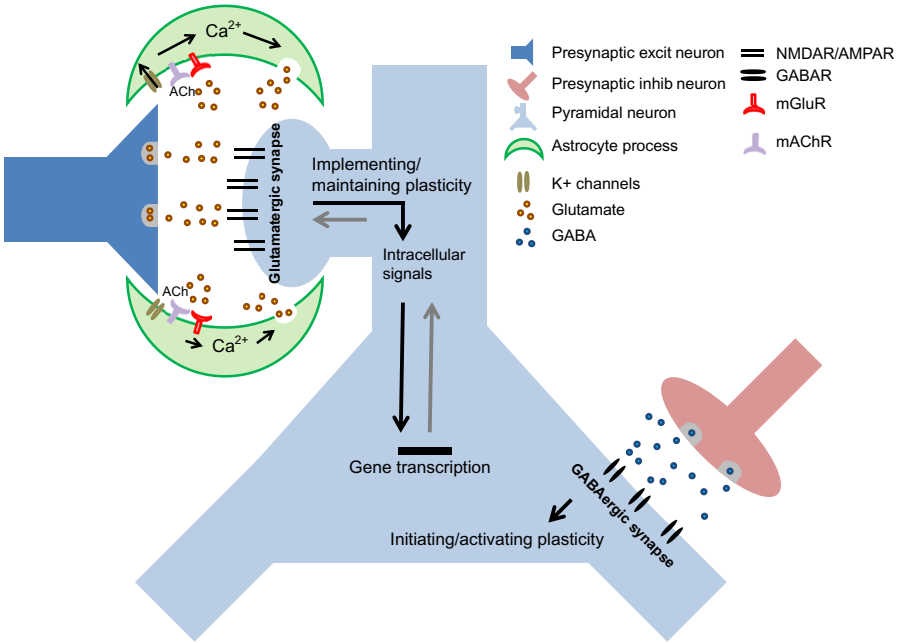

FIGURE 1

Schematic of a cortical pyramidal neuron with an excitatory synapse (top left) and inhibitory synapse (bottom right). Symbols are explained in the key (top right). Increasing evidence supports the hypothesis that plasticity in the developing and adult cortex is initiated by a transient reduction of inhibitory drive, and implemented by persistent changes at excitatory synapses. See text for details.

related to the actin cytoskeleton, G protein signaling, transcription and myelination, and MD during the critical period reverses the expression pattern of the majority of these genes (Lyckman et al., 2008). In particular, MD activates sets of genes that comprise molecular pathways related to growth factors and neuronal degeneration (Tropea et al., 2006). Expression of a binding protein of insulin-like growth factor-1 (IGF1) is highly upregulated after MD, which downregulates IGF1 and its downstream phosphatidylinositol 3-kinase/Akt signaling pathway; exogenous application of IGF1 upregulates these signals and prevents ODP (Tropea et al., 2006). Taken together, signaling initiated by the release of glutamate leads to significant changes in the postsynaptic response, which leads to subsequent physiological changes that are important components of implementing ODP.

ODP was described as arising from "binocular competition" (Hubel and Wiesel, 1970), which is now considered to involve two separable processes: a feedforward or Hebbian component in which closed eye responses are reduced, and a feedback or homeostatic component in which open eye responses are enhanced (Sato and Stryker, 2008; Tropea et al., 2009). In mice, these two processes are sequential in time: short-term MD, of ~1–4 days duration, leads to reduction of closed eye responses, whereas longer MD, of ~5 or more days, reveals open eye enhancement. In ferrets, however, the enhancement of open eye responses is evident nearly synchronously with reduction of closed eye responses (Yu et al., 2011), suggesting that the mechanisms of feedforward and feedback changes may themselves be dynamically regulated. Distinct mechanisms have been proposed for these changes. In addition to the molecules mentioned previously, most of which affect the reduction of closed eye responses after MD and hence the feedforward component of ODP, many microRNAs are abundantly expressed in V1 and are affected by MD (Mellios et al., 2011). Expression of miR-132 is significantly reduced by short-term MD, and inhibition of miR-132 prevents the reduction of closed eye responses after brief MD.

Other molecules affect the feedback component of MD. Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that is released by glial cells and acts on neurons through its receptor TNFR1 (Stellwagen and Malenka, 2006; Stellwagen et al., 2005). In mice lacking TNF-α, no homeostatic increase is observed in open eye responses while closed eye responses are left intact (Kaneko et al., 2008). These mice show normal LTP in the visual cortex but lack synaptic amplitude regulation induced by activity blockade, suggesting a role for synaptic scaling in this component of plasticity. Separate molecules negatively regulate feedback plasticity. In mice lacking STAT1 (a member of the Signal Transducers and Activators of Transcription family of transcription factors), there is an accelerated increase of open eye responses after short-term MD along with normal decrease of closed eye responses (Nagakura et al., 2011). Interestingly, the accelerated enhancement of open eye responses is accompanied by increased AMPAR expression and function. A single molecule that appears to coregulate both feedforward and feedback plasticity is the immediately-early gene Arc (Arg3.1). Arc has a role in synaptic plasticity through regulation of AMPAR trafficking (Shepherd and Bear, 2011), and mice lacking Arc show impairments in both closed and open eye responses after MD (McCurry et al., 2010).

Arc is coexpressed with the synaptic molecule CaMKIIα in pyramidal neurons; a novel FRET probe reveals that activated CaMKIIα is upregulated in individual closed eye synapses/spines of ferret V1 after brief MD and thus has a role in preserving spines from being lost (Mower et al., 2011).

While changes in glutamatergic, excitatory synaptic transmission are crucial for implementing ODP, growing evidence points to the role of gamma-aminobutyric acid (GABA) receptor-mediated inhibition in initiating ODP and regulating the critical period (Fig. 1). Mice with genetic deletion of the GABA-synthetic enzyme GAD65 show lack of ODP induced by MD (Hensch et al., 1998), while accelerating GABA circuit function triggers premature plasticity prior to the critical period (Di Cristo et al., 2007; Sugiyama et al., 2008). Brain-derived neurotrophic factor (BDNF) is a key neurotrophin that triggers maturation of inhibitory circuits, and overexpression of BDNF leads to a precocious termination of the critical period for ODP (Huang et al., 1999). Parvalbumin (PV)-expressing basket cells, which comprise the largest class (up to 50%) of inhibitory interneurons in the mouse visual cortex (Gonchar et al., 2007), appear to regulate ODP via synaptic inputs to $GABA_A$ receptor-α1 subunits in excitatory neurons (Fagiolini et al., 2004). Maturation of PV cells is controlled by molecules such as BDNF and the embryonic homeoprotein Otx2 (Huang et al., 1999; Sugiyama et al., 2008). Additional mechanisms of regulating inhibition include Lynx1, which binds to the nicotinic acetylcholine (ACh) receptor and maintains the balance between excitation and inhibition through cholinergic inhibition; without Lynx1, plasticity is extended into adulthood (Morishita et al., 2010). Transient reduction of PV-mediated inhibition appears to have a crucial role in triggering ODP (Kuhlman et al., 2013): direct recordings from PV interneurons in mouse V1 reveal a reduction in their closed eye (and even open eye) responses after 1 day of MD, which leads to a rapid restoration of visual drive to pyramidal neurons. Enhancing GABAergic inhibition blocks ODP, while reducing the spike activity of PV neurons extends the critical period.

2 PLASTICITY IN THE ADULT VISUAL CORTEX

V1 neuron responses in the adult brain can be modified by previous visual experience, on timescales ranging from seconds to days. In particular, the orientation tuning curves of neurons can be altered by selective experience with particular orientations. Practicing orientation discrimination for weeks or months can lead to an overrepresentation of the practiced orientation at the expense of other orientations (Schoups et al., 2001). Specific temporal patterns of rapidly presented pairs of stimuli, for tens of minutes, can shift the tuning curve of V1 neurons toward the conditioned orientation (Felsen et al., 2002; Yao and Dan, 2001; Yao et al., 2004). Paired electrical and visual stimulation can induce a similar effect after prolonged pairing (Godde et al., 2002). Physiologically, continuous presentation of a single orientation for several seconds to minutes leads to a reduction of responses to the adapting orientation, and a shift in the tuning curve away from the adapting orientation

(Dragoi et al., 2000, 2001, 2002). Perceptually, the "tilt aftereffect" demonstrates that viewing a tilted contour even briefly causes the perceived orientation of a subsequently viewed contour to be tilted away from the adapting contour (Gibson, 1937; Paradiso et al., 1989; Wenderoth and Johnstone, 1988). These forms of visual plasticity induced by passive exposure are often of short duration, and persistent training-induced plasticity in the adult brain often requires prolonged practice coupled with reinforcement.

Adult plasticity on long time scales induced by reinforced associative learning importantly involves neuromodulatory systems including ACh, norepinephrine, serotonin, dopamine, and histamine. These neuromodulators can alter cellular excitability and induce plasticity through presynaptic and/or postsynaptic mechanisms (Gu, 2002). Among the neuromodulators, the role of ACh in the sensory cortex, including the visual cortex, is best understood. The cortex receives its main source of ACh from cholinergic axons that originates in the nucleus basalis of the basal forebrain (Metherate et al., 1992). When cholinergic activation of the adult cortex is paired with both intracellular depolarization of neurons (Woody et al., 1978) and application of glutamate (Lin and Phillis, 1991; Metherate et al., 1987), prolonged facilitation of neuronal responses is observed. Pairing cholinergic and sensory stimulation in the adult cortex can induce both neuronal and representational plasticity in the adult somatosensory cortex (Donoghue and Carroll, 1987; Howard and Simons, 1994; Lamour et al., 1988; Metherate et al., 1987; Rasmusson and Dykes, 1988; Tremblay et al., 1990a,b), auditory cortex (Bakin and Weinberger, 1996; Dimyan and Weinberger, 1999; Edeline et al., 1994; Kilgard and Merzenich, 1998a,b; Kilgard et al., 2001), and visual cortex (Chen et al., 2012). ACh-induced changes can occur at both single cell and cortical map levels. The former involves neuronal plasticity characterized by potentiation of glutamatergic synapses at pyramidal neurons, while the latter involves representational plasticity as characterized by reorganization of sensory maps that represent and encode specific parameters of sensory stimuli (Bakin and Weinberger, 1996; Bao et al., 2003; Froemke et al., 2007; Kilgard and Merzenich, 1998a; Puckett et al., 2007).

The mechanisms underlying ACh-induced plasticity include direct and indirect pathways, and appear to involve mechanisms for both initiating and implementing plasticity. Activation of M1 muscarinic receptors by ACh can directly potentiate responses in pyramidal neurons through inhibition of postsynaptic SK channels (Buchanan et al., 2011; Giessel and Sabatini, 2010). ACh leads to prolonged but prominent calcium responses in astrocytes *in vitro* (Perea and Araque, 2005), and *in vivo* (Navarrete et al., 2012; Takata et al., 2011), making astrocytes a potential mediator of nucleus basalis-mediated plasticity of cortical responses. Indeed, stimulation of the nucleus basalis directly and strongly activates calcium responses in V1 astrocytes via muscarinic receptors, and mice with conditional knockout of astrocyte-specific IP_3R2 receptors do not have ACh-induced calcium elevation and fail to show neuronal plasticity induced by paired visual and nucleus basalis stimulation (Chen et al., 2012). Astrocytes can induce release of gliotransmitters or regulate extracellular glutamate (Schummers et al., 2008) and potassium

(Seigneur et al., 2006); these mechanisms can lead to increased levels of extracellular glutamate (Fellin et al., 2004) or D-serine (Henneberger et al., 2010) that can activate neuronal NMDARs to implement plasticity at excitatory synapses (Fig. 1).

ACh stimulation also elicits rapid responses in inhibitory neurons (Alitto and Dan, 2012; Kawaguchi, 1997; McCormick and Prince, 1986), including excitatory responses from subsets of inhibitory neurons and inhibitory responses from other subsets (Arroyo et al., 2012). An important correlate of basalis-induced plasticity in the auditory cortex is a transient reduction of inhibition to pyramidal neurons (Froemke et al., 2007), and reinforcement learning in the adult auditory cortex is accompanied by a reduction of PV neuron firing by cholinergic inputs (Letzkus et al., 2011). Since PV neurons provide divisive inhibition and regulate the response gain of their target neurons (Wilson et al., 2012), a reduction in PV neuron firing provides a powerful way to enhance the influence of inputs to pyramidal neurons. Thus, the rapid reduction of PV-mediated inhibition to pyramidal neurons, together with sensory drive, may be a necessary condition for initiating plasticity in the adult sensory cortex.

3 COMMON PRINCIPLES OF DEVELOPMENTAL AND ADULT PLASTICITY

Certain common principles seem to anchor neuronal and circuit plasticity in both the developing and adult sensory cortex. The initiation or activation of plasticity appears to involve a transient reduction of inhibition on pyramidal neurons, likely mediated via a reduction of activity of PV interneurons. This reduction of PV activity is induced by simple and passive manipulations such as MD during the critical period in the developing visual cortex, but in the adult cortex, after excitatory synapses on cortical neurons along with intracortical inhibition have matured, MD no longer suffices to initiate ODP and additional mechanisms are required to affect PV activity. We hypothesize that neuromodulatory inputs have this role; by their selective action on inhibitory neuron types, they transiently reduce PV activity in order to initiate plasticity. A minimal level of excitatory drive to PV neurons seems to be required when the critical period starts, so that these neurons can reflect reduced closed eye responses and thus trigger plasticity. Mature levels of drive to PV neurons appear to close off the critical period for MD-driven changes (via mechanisms that remain to be elucidated), and neuromodulatory systems related to reinforcement or reward are required in conjunction with sensory training signals to activate response changes. An important element of this hypothesis is that neuromodulatory signals should specifically target PV neurons and thus affect PV-pyramidal neuron circuits that also receive feedforward sensory drive. The powerful regulation of response gain in pyramidal neurons by PV input is consistent with the proposal that a reduction of PV activity significantly impacts responses due to correlated (or uncorrelated) sensory inputs. Indeed, methods for reactivating ODP in the adult visual cortex

uniformly require a prominent reduction of intracortical inhibition (reviewed in Espinosa and Stryker, 2012; Nagakura et al., 2013).

The implementation and maintenance of neuronal and circuit plasticity appears to rely importantly on changes at glutamatergic synapses (Fig. 1), though we cannot rule out plasticity at inhibitory synapses as well. Plasticity of glutamatergic synapses is implemented by a host of mechanisms that eventually lead to increased or decreased insertion and function of AMPA (and other) receptors. These changes must be synapse-specific, since closed and open eye inputs, which target separate synapses, seem to be separately regulated, as revealed by feedforward and feedback changes after MD. Whether or not similar mechanisms are also involved in implementing and maintaining adult plasticity remains to be discovered. Regardless of specific details, however, these hypotheses provide a conceptual framework for understanding cortical plasticity that can motivate future experiments.

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