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Critical Period Mechanisms in Developing Visual Cortex

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Binocular vision is shaped by experience during a critical period of early postnatal life. Loss of visual acuity following monocular deprivation is mediated by a shift of spiking output from the primary visual cortex. Both synaptic and network explanations have been offered for this heightened brain plasticity. Direct experimental control over its timing, duration, and closure has now been achieved through a consideration of balanced local circuit excitation-inhibition. Notably, canonical models of homosynaptic plasticity at excitatory synapses alone (LTP/LTD) fail to produce predictable manipulations of the critical period *in vivo*. Instead, a late functional maturation of intracortical inhibition is the driving force, with one subtype in particular standing out.

Parvalbumin-positive large basket cells that innervate target cell bodies with synapses containing the α1-subunit of $GABA_A$ receptors appear to be critical. With age, these cells are preferentially enwrapped in peri-neuronal nets of extracellular matrix molecules, whose disruption by chondroitinase treatment reactivates ocular dominance plasticity in adulthood. In fact, critical period plasticity is best viewed as a continuum of local circuit computations ending in structural consolidation of inputs. Monocular deprivation induces an increase of endogenous proteolytic (tPA-plasmin) activity and consequently motility of spines followed by their pruning, then re-growth. These early morphological events faithfully reflect competition

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only during the critical period and lie downstream of excitatory-inhibitory balance on a timescale (of days) consistent with the physiological loss of deprived-eye responses *in vivo*. Ultimately, thalamic afferents retract or expand accordingly to hardwire the rapid functional changes in connectivity.

Competition detected by local inhibitory circuits then implemented at an extracellular locus by proteases represents a novel, cellular understanding of the critical period mechanism. It is hoped that this paradigm shift will lead to novel therapies and training strategies for rehabilitation, recovery from injury, and lifelong learning in adulthood.

I. Introduction

For over 40 years the primary visual cortex has stood as the premier model of critical period plasticity (Wiesel and Hubel, 1963). During a brief postnatal period (of weeks to years) proportional to the expected lifespan of the species (Berardi *et al.*, 2000; Daw, 1995), the closure of one eye (but not both) yields a loss of visual acuity. Amblyopia occurs even though there is no damage to the retina or visual thalamus (dorsal lateral geniculate nucleus [dLGN]) and is determined in the neocortex (V1), where the inputs of the two eyes first converge and compete for space (Wiesel and Hubel, 1963). Mouse models are now yielding with greater resolution the molecular, cellular, and structural events underlying experience-dependent circuit refinement. A general understanding of the neural basis for ''critical'' or ''sensitive'' windows of brain development is anticipated to inform classrooms and educational policy, drug design, clinical therapy, and strategies for improved learning into adulthood.

Most impressively, only during the critical period can the seemingly innocuous act of covering an eye profoundly alter the physical structure of the brain. Columnar architecture is the fundamental unit of neocortical organization across mammalian species. Morphological clusters of thalamocortical axon terminals serving the right or left eye tile layer 4 of the mature cortex in alternating ''ocular dominance'' domains (Hubel *et al.*, 1976; Shatz and Stryker, 1978). Monocular occlusion produces an expansion of open eye columns at the expense of deprived-eye afferents, which become reduced in size and complexity (Antonini and Stryker, 1996; Antonini *et al.*, 1999). This physical manifestation of early postnatal experience is preceded by more rapid changes (Trachtenberg and Stryker, 2001; Trachtenberg *et al.*, 2000) of intracortical circuits outside layer 4 that instruct the hardwiring of inputs into an anatomical fingerprint unique to the individual. This chapter considers experience-dependent circuit refinement during the critical period as a cascade of cellular and molecular events linking functional to structural plasticity (Fig. 1).

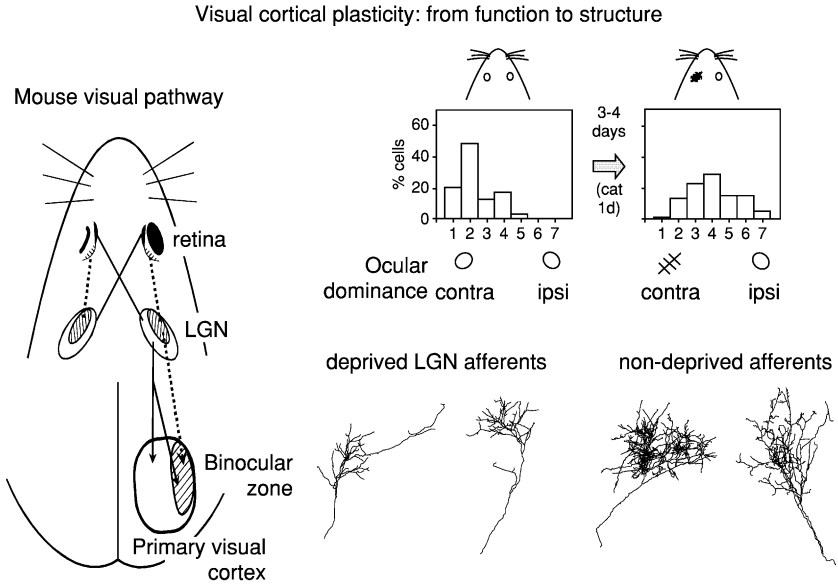

Figure 1 From functional to structural change during the critical period. Visual cortical plasticity begins as a functional shift of spiking response within a few days of monocular deprivation (MD). It first produces a loss of deprived-eye response and gain of open-eye input, as measured by neuronal discharge of single units from mouse visual cortex (Gordon and Stryker, 1996). The ocular dominance of cells rated on a seven-point scale indicates a typical bias toward the contralateral eye (groups 1–3) in the rodent. After 3 or more days of MD, the distribution shifts toward the open, ipsilateral eye (groups >4). Only gradually is this translated into an anatomical shrinkage then expansion of thalamic axons serving the closed or open eye, respectively, in cortical layer 4 (Antonini *et al.*, 1999).

II. Synaptic Mechanisms (LTP/LTD)

What appears essential for vision is the proper communication of output from the primary visual cortex to higher areas. Thus, amblyopia due to monocular deprivation (MD) is faithfully reflected in the relative inability of V1 neurons to fire action potentials through the originally closed eye (ocular dominance; Fig. 1) (Daw, 1995; Prusky and Douglas, 2003). Sensory-evoked field potential amplitudes or the expression of molecular markers (immediate early genes) may remain modifiable beyond the critical period (Pham *et al.*, 2004; Sawtell *et al.*, 2003; Tagawa *et al.*, 2005). However, these largely subthreshold changes in synaptic activity bear little lasting impact on spatial acuity, as perceptual behavior observes a strict critical period that matches single-unit response in V1 (Gordon and Stryker, 1996; Prusky and Douglas, 2003). It is tempting to speculate, nevertheless, that the loss or gain

of visual responsiveness represents a homosynaptic long-term depression (LTD) or potentiation (LTP) of synaptic strength somewhere in the visual circuit. Indeed, these *in vitro* models are coregulated by age and sensory experience and are believed to share mechanisms with the hippocampus (Kirkwood *et al.*, 1993, 1995), where a wealth of molecular understanding is already available (Sanes and Lichtman, 1999).

Activation of postsynaptic NMDA-type glutamate receptors is, for example, thought to be a specific mediator of LTP/LTD, and hence experience-dependent plasticity. In particular, it has been proposed that the progressive shortening of NMDA receptor currents by 2A subunit (NR2A) insertion ends the critical period in visual cortex by truncating calcium influx (Nase *et al.*, 1999; Quinlan *et al.*, 1999; Philpot *et al.*, 2001). Surprisingly, mice engineered to maintain prolonged NMDA responses by targeted deletion of NR2A exhibit weaker ocular dominance shifts that are nevertheless restricted to a typical critical period and are delayed normally by dark-rearing from birth (Fagiolini *et al.*, 2003). Postnatal increase of NR2A subunit interactions with specific LTP induction proteins, as in the hippocampus (Liu *et al.*, 2004; Tang *et al.*, 1999), is unnecessary for visual cortical plasticity *in vivo,* since NR2A knockout mice are rescued without re-introducing NR2A itself (Fagiolini *et al.*, 2003).

Synaptic depression is thought to underlie the loss of cortical responsiveness to an eye deprived of vision during the critical period (Frenkel and Bear, 2004). Type 2 metabotropic glutamate receptors (mGluR2) play a fundamental role in visual cortical LTD (Renger *et al.*, 2002). Direct mGluR2 activation by the selective agonist DCG-IV persistently depresses layer 2/3 field potentials in slices of mouse binocular zone, which occludes conventional LTD by low-frequency stimulation (LFS), indicating shared downstream events. In contrast, Schaeffer collateral synapses do not exhibit this chemical LTD, revealing hippocampal area CA1 (naturally devoid of mGluR2) to be an inappropriate model for neocortical plasticity. Antagonists or gene-targeted disruption of mGluR2 prevents LTD induction in visual cortex by electrical LFS to layer 4. However, monocular deprivation remains effective in mice lacking mGluR2 (Renger *et al.*, 2002), and receptor expression levels are unchanged during the critical period in wild-type mice, indicating that experience-dependent plasticity is independent of LTD induction in visual cortex.

Repeated LFS saturates LTD at a weaker level contralateral to an eye deprived for 24 hr when compared to the opposite (ipsilateral) hemisphere (Heynen *et al.*, 2003). This ‘‘occlusion’’ has been viewed as evidence for LTD as a mechanism of ocular dominance plasticity. Multiple, spaced stimuli, however, typically engage protein synthesis and additional molecular machinery in order to convert early synaptic plasticity into longer-lasting forms (Frey *et al.*, 1993). Again, distinct from that found in hippocampal

area CA1, this late LTD in neocortex involves the *zif268* immediate early gene, transcription, and translation to saturate LTD in an input- and frequency-specific manner (Atapour *et al.*, unpublished data). Suturing one eye for 24 hr (a time period too short to produce ocular dominance shifts *in vivo*; Gordon and Stryker, 1996) yields a well-known activity-dependent decrease of *zif268* expression, which then impairs LTD saturation contralateral to the deprived eye in a gene dose-dependent manner (Atapour *et al.*, unpublished data). But notably, *zif268* is entirely unnecessary for visual plasticity *in vivo* (Mataga *et al.*, 2001), dissociating it from LTD saturation. Moreover, early depression by a single LFS is not occluded by 1 day of MD (Heynen *et al.*, 2003), and these early forms of LTP/LTD that persist in the presence of protein synthesis inhibitors (Frey *et al.*, 1993) are insufficient to shift ocular dominance *in vivo* (Taha and Stryker, 2002).

Phosphorylation state and membrane trafficking of AMPA receptor subunits are signature events of LTP/LTD at a variety of central synapses that have also been observed after natural sensory experience *in vivo* (Barry and Ziff, 2002; Takahashi *et al.*, 2003). One-day MD produces a constellation of phosphorylation state changes on GluR1 subunits in V1 by protein kinase A (PKA) akin to hippocampal LTD (Heynen *et al.*, 2003). But mimicry need not be causal, since no loss of visual response or acuity occurs until several days of eyelid suture have elapsed (Gordon and Stryker, 1996; Prusky and Douglas, 2003). Phosphorylation of an amino acid residue alone is unlikely to explain the complex functional and structural events that constitute the critical period. Overall, no consistent relationship between the ability to induce homosynaptic plasticity *in vitro* and the capacity for visual plasticity *in vivo* has been found (Bartoletti *et al.*, 2002; Daw, 2004; Hensch, 2003; Fischer *et al.*, 2004; Shimegi *et al.*, 2003). The correlation is not straightforward, as LTP/LTD mechanisms may differ further depending on cortical layer (Daw *et al.*, 2004). Most dramatically, homosynaptic models based on NMDA receptor activation predict that the maturation of inhibition will terminate plasticity (Feldman, 2000; Kirkwood *et al.*, 1995), when in fact quite the opposite is true: GABA function is required to trigger the critical period *in vivo* (Hensch *et al.*, 1998).

III. Network Mechanisms (Excitatory-Inhibitory Balance)

Gross pharmacological perturbations of neuronal activity, such as hyperexcitation (Ramoa *et al.*, 1988; Shaw and Cynader, 1984) or total silencing (Bear *et al.*, 1990; Hata and Stryker, 1994; Reiter and Stryker, 1988; Reiter *et al.*, 1986), not surprisingly disrupt plasticity but fail to inform us about intrinsic network behavior. Even small changes in the relative amounts of excitation and inhibition can dramatically alter information processing

(Hensch and Fagiolini, 2004; Liu, 2004). This exquisite balance is dynamically adjusted by the cortical layer (Desai *et al.*, 2002; Turrigiano and Nelson, 2004), especially because inhibitory connections emerge later than excitation in the pre-critical period for ocular dominance (Del Rio *et al.*, 1994). To dissect the role of local circuit elements, a gentle titration of endogenous neurotransmission through gene-targeted disruption in mice was instrumental.

Fortuitously, GABA is synthesized by glutamic acid decarboxylase made from two distinct genes, GAD65 and GAD67; the former is concentrated in axon terminals and is bound to synaptic vesicles, while the latter is found throughout the cell (Soghomonian and Martin, 1998). Reducing stimulated GABA release by GAD65 deletion (knockout) prevents ocular dominance plasticity until inhibition is acutely restored with diazepam (Hensch *et al.*, 1998). Remarkably, this rescue is possible at any age, indicating that the critical period lies in wait of the proper level of inhibition (Fagiolini and Hensch, 2000). Conversely, critical period onset can be accelerated by prematurely enhancing inhibition by direct infusion of benzodiazepines in immature mice (Fagiolini and Hensch, 2000; Fagiolini *et al.*, 2004; Iwai *et al.*, 2003), as well as transgenic overexpression of brain-derived neurotrophic factor (BDNF) to promote GABAergic maturation (Hanover *et al.*, 1999; Huang *et al.*, 1999).

In the absence of NR2A, the depolarizing action of NMDA currents is prolonged, tipping local circuit equilibrium in favor of excitation (like GAD65 deletion) that disrupts plasticity and is restored by diazepam (Fagiolini *et al.*, 2003). Although it seems counterintuitive from a purely LTP perspective (Feldman, 2000), inhibition is required for plasticity *in vivo* when GABAergic transmission is low or NMDA receptor function is high. Conversely, postsynaptic silencing by either GABA agonist (Hata and Stryker, 1994; Reiter and Stryker, 1988) or NMDA receptor antagonist (Bear *et al.*, 1990) yields a paradoxical loss of open eye input (although LTD is blocked by APV). While maturation of other receptive field properties (e.g., orientation bias) may reflect NR2A signaling pathways more directly (Fagiolini *et al.*, 2003), the yin and yang relationship of excitatory-inhibitory balance is essential for ocular dominance plasticity.

Focus on balanced networks thus offers direct control over the timing of the critical period (Fig. 2), an area in which single-synapse models were wanting. Accelerated plasticity *in vivo* is not predicted by homosynaptic rules, given that diazepam (Wan *et al.*, 2004) or endogenous BDNF blocks LTD induction in the cortex (Jiang *et al.*, 2003). The close interrelationship of GABA, BDNF, and neuronal activity also explains the classic effect of dark-rearing. Raising animals without visual experience from birth naturally reduces GABAergic transmission in the visual cortex (Chen *et al.*, 2001; Morales *et al.*, 2002) and delays the critical period profile into adulthood

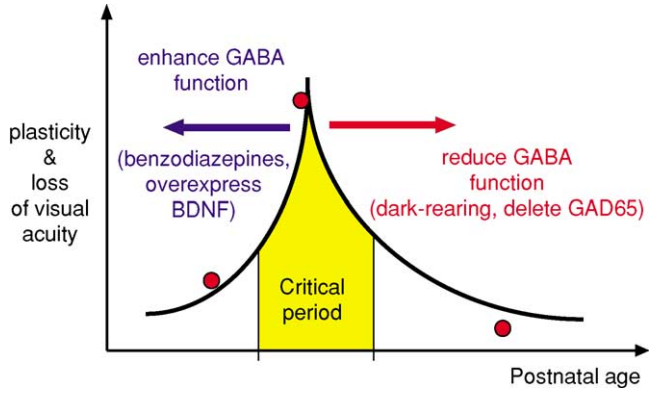

Figure 2 GABAergic control of the critical period. Sensitivity (of spiking response) to monocular deprivation (MD) is restricted to a critical period beginning around 1 week after eye-opening (at P13) and peaking 1 month after birth. Amblyopia as a behavioral consequence is also observed only following MD during the same critical period (red circles). The onset of plasticity can be delayed by directly preventing maturation of GABAergic transmission with gene-targeted deletion of GABA-synthetic enzyme (GAD65) or by dark-rearing from birth (red arrow). Conversely, the critical period may be accelerated by enhancing GABAergic transmission directly with benzodiazepines just after eye-opening or by promoting the rapid maturation of interneurons through excess brain-derived neurotrophic factor (BDNF) expression (blue arrow). See text for references.

(Fagiolini *et al.*, 2003; Iwai *et al.*, 2003; Mower, 1991). Either diazepam infusion (2 days) or BDNF overexpression in complete darkness abolishes the expected delay of plasticity (Gianfranceschi *et al.*, 2003; Iwai *et al.*, 2003). A minimum of 2 days of diazepam treatment at the start of MD that does not need to overlap the deprivation per se is also sufficient to fully activate plasticity in GAD65 knockout mice (Iwai *et al.*, 2003). Thus, tonic signaling through $GABA_A$ receptors rapidly creates a milieu for plasticity within neocortex capable of initiating a critical period for ocular dominance independent of visual experience itself.

IV. Specific GABA Circuits for Plasticity (Large Basket Cells)

Interestingly, not all GABAergic connections are involved in critical period regulation. Several lines of evidence point toward a single class of interneuron with the potential for controlling long-range inhibition and synchrony in visual cortex. Among the large diversity of GABA cells (DeFelipe, 1997; Kawaguchi and Kubota, 1997; Markram *et al.*, 2004), neurochemical markers such as calcium-binding proteins reveal a close correspondence of critical period onset and the emergence of parvalbumin (PV)-positive cells

(Del Rio *et al.*, 1994), both of which are accelerated by BDNF overexpression (Huang *et al.*, 1999). Deletion of a potassium current ($K_v3.1$) that uniquely regulates the fidelity of fast-spiking behavior (and hence GABA release) specifically from PV-positive interneurons (Erisir *et al.*, 1999; Lien and Jonas, 2003; Rudy and McBain, 2001) slows the rate of ocular dominance plasticity (Matsuda *et al.*, unpublished data).

Although widely heterogeneous, GABA cells in the neocortex are remarkably precise in their connectivity (DeFelipe, 1997; Somogyi *et al.*, 1998). Formed largely through molecular cues then refined by neuronal activity (Chattopadhyaya *et al.*, 2004; Di Cristo *et al.*, 2004), PV-positive contacts include axon-ensheathing Chandelier cells and soma-targeting large basket cells. The latter extend a wide-reaching, horizontal axonal plexus, which can span ocular dominance columns in the cat (Buzas *et al.*, 2001). Immuno-electron microscopy indicates that individual $GABA_A$ receptor α-subunits are trafficked to discrete postsynaptic sites on the pyramidal cell axon, soma, and dendrites. For example, α2-subunits are preferentially enriched at the axon initial segment and basket cell synapses innervated by cholecystokinin (CCK)-positive axon terminals (Klausberger *et al.*, 2002). Importantly, the α-subunits determine benzodiazepine binding through a single amino acid residue in their N terminus (Cherubini and Conti, 2001; Sieghart, 1995). Knock-in of a point mutation at this site renders individual $GABA_A$ receptor subtypes insensitive to benzodiazepines in separate lines of mice (Rudolph *et al.*, 2001).

Weak inhibition within visual cortex early in life (like GAD65 deletion) prevents experience-dependent plasticity (Fagiolini and Hensch, 2000; Iwai *et al.*, 2003). Loss of responsiveness to an eye deprived of vision can be initiated prematurely by enhancing GABA-mediated transmission with zolpidem (Fig. 3), a $GABA_A$ α1, 2, 3-selective ligand (Fagiolini *et al.*, 2004). Systematic use of the mouse knock-in mutation further demonstrates that only one of these subtypes controls the critical period. The α1-containing circuits were found to drive cortical plasticity (Fig. 3), whereas α2-enriched connections separately regulated neuronal firing (Fagiolini *et al.*, 2004). This dissociation carries implications not only for models of brain development, but also for the safe design of benzodiazepines for use in human infants (De Negri *et al.*, 1993).

Indeed, the GABA circuit control of visual cortical plasticity in mice may extend to human brain development. In autopsy samples of visual cortex (Murphy *et al.*, 2005), the maturation of NMDA receptor 2A subunits is complete within the first 9 months. In contrast, GAD65 expression and the $GABA_A$ receptor conversion from α3 to α1 exhibits a slower time constant of several years, consistent with the extended length of the critical period for binocular vision (amblyopia) in humans (Berardi *et al.*, 2000; Daw, 1995). Strikingly, the levels of GAD67 and α2-subunits are constant over the same

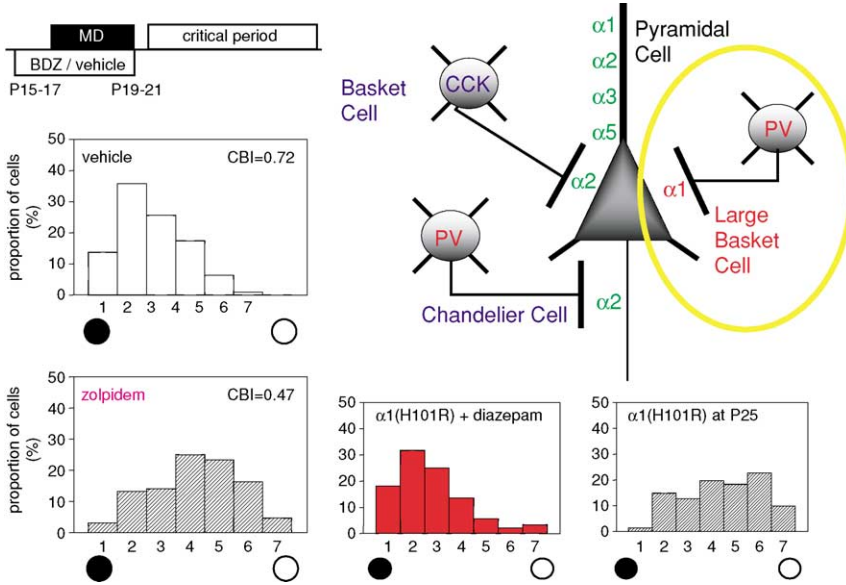

Figure 3 An essential inhibitory subcircuit for critical period plasticity in the visual cortex. Premature ocular dominance plasticity is triggered by the $GABA_A$ receptor α1-subunit-selective benzodiazepine agonist zolpidem. Large parvalbumin (PV)-positive basket cells make somatic synapses that utilize $GABA_A$ receptors containing the α1-subunit. Knock-in of a point mutation rendering only the α1-receptors insensitive to diazepam prevents critical period acceleration by these drugs (red bars). Note that plasticity emerges naturally at the proper time (P25, black bars), since these are still functional GABA receptors. Point mutation of other α-subunits does not interfere with drug-induced premature plasticity. Basket cells extend a wide, horizontal axonal plexus across ocular dominance columns in cats ideally suited for comparing input from the two eyes (Buzas *et al.*, 2001).

early postnatal time period, in agreement with no role in plasticity in animal studies (Fagiolini *et al.*, 2004). Pharmaceutical development of α2-selective ligands would avoid the rapid, premature induction of critical period plasticity through α1-containing receptors. Moreover, the contribution of kinases to ocular dominance plasticity (traditionally viewed from an LTP perspective) must be re-evaluated with regard to their actions upon $GABA_A$ receptors incorporating the α1-subunit (Fischer *et al.*, 2004; Hinkle and Macdonald, 2003).

The $GABA_A$ α1-receptors are preferentially sent to receive PV-positive (but not CCK-positive) synapses upon the soma (Klausberger *et al.*, 2002), further implicating these large basket cell circuits. With age, large PV cells are preferentially enwrapped by peri-neuronal nets of extracellular matrix (ECM) molecules and sugars (Härtig *et al.*, 1999). When these are disrupted,

peri-somatic inhibition is reduced (Saghatelyan *et al.*, 2001), and MD is once again able to induce ocular dominance shifts even in adulthood (Pizzorusso *et al.*, 2002), perhaps by resetting and tapping its original GABAergic trigger (Fig. 4, left) (Fagiolini and Hensch, 2000). Peri-neuronal nets likely control the extracellular ionic milieu (e.g., potassium/GABA concentration; Härtig *et al.*, 1999) surrounding PV cells to establish their firing efficiency (Erisir *et al.*, 1999; Lien and Jonas, 2003; Rudy and McBain, 2001), or may otherwise sequester molecular regulators of PV cell maturation.

V. From Functional to Structural Rewiring (Extracellular Matrix)

The ECM is increasingly emerging as a major site for critical period plasticity (Berardi *et al.*, 2004). Sensory experience physically rewires the brain in early postnatal life through unknown mechanisms. To convert physiological events (altered input) into structural refinements, connections must

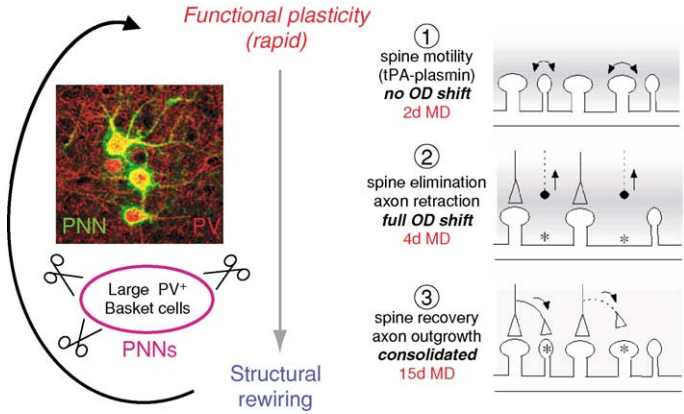

Figure 4 Structural consolidation during the critical period. The structural events that link the functional detection of imbalanced sensory input by GABAergic circuits to anatomical rewiring. A three-step process of increased spine motility (Oray *et al.*, 2004), transient elimination, then regrowth (Mataga *et al.*, 2004) is mediated by a biochemical increase of proteolytic activity (tPA-plasmin; gray background) between 2 and 7 days of monocular deprivation (MD) (Mataga *et al.*, 2002). Spine pruning is the first anatomical correlate of the rapid physiological shifts in ocular dominance (OD) by brief MD. Taking this structural view, plasticity is successfully restored to adult visual cortex only by loosening up the extracellular matrix (ECM) by infusion of chondroitinases (left; Pizzorusso *et al.*, 2002). Interestingly, this treatment (unlike tPA) degrades peri-neuronal net (PNN) structures, which preferentially enwrap the large PV-positive basket cells believed to be the endogenous trigger for the critical period (see text).

ultimately be broken and neuronal wiring rerouted. Proteases are ideally suited to clear the way for growing neurites (Liu *et al.*, 1994). Tissue-type plasminogen activator (tPA) is the major serine protease in the postnatal mammalian brain (Shiosaka and Yoshida, 2000). Originally identified as an immediate early gene upon hippocampal seizures (Qian *et al.*, 1993), tPA activity is gradually upregulated in visual cortex by 2 days of MD during the critical period (gray background, Fig. 4, right), but not in adults or GAD65 knockout mice (Mataga *et al.*, 2002). Conversely, a minimum of 2 days of diazepam treatment is required to rescue plasticity in the absence of GAD65 (Iwai *et al.*, 2003). Functional ocular dominance plasticity is impaired when tPA action is blocked and is rescued by exogenous tPA (but not diazepam) (Mataga *et al.*, 2002; Müller and Griesinger, 1998).

Permissive amounts of tPA may, thus, couple functional changes to structural changes downstream of the excitatory-inhibitory balance that triggers visual cortical plasticity. Second messenger systems recruited in the process (reviewed in Berardi *et al.*, 2003) lie satisfyingly along a molecular cascade linking neuronal activity to tPA release (Fig. 5) (Hensch, 2004), the structural consequences of which have recently been clarified. Occluding an eye of vision during development classically trims that input to the neocortex, while thalamic axons serving the open eye progressively expand (Antonini and Stryker, 1996; Antonini *et al.*, 1999). Yet, this process is far too slow to explain the rapid shift of ocular dominance within days of MD (Gordon and Stryker, 1996; Silver and Stryker, 1999). The most immediate and potent cortical plasticity occurs beyond thalamo-recipient layer 4, for which the structural basis remains obscure (Gordon and Stryker, 1996; Trachtenberg *et al.*, 2000). Morphological plasticity is initiated along the apical dendrites of target pyramidal cells in the cerebral cortex, where spines serve as pleiomorphic sites of excitatory synaptic connections (Yuste and Bonhoeffer, 2001).

Spine shape is highly dynamic when viewed by two-photon laser scanning microscopy in living transgenic mice expressing green fluorescent protein (GFP) in a subset of layer 5 cells. Motility of spines decreases with age in the visual cortex (Grutzendler *et al.*, 2002), but can be transiently elevated by 2-day MD only during the critical period (step 1, Fig. 4, right) (Oray *et al.*, 2004). This occludes the motility triggered by direct protease application to brain slices, indicating that tPA-plasmin may be the endogenous mediator. Increased proteolysis after 2-day MD will degrade ECM and cell adhesion proteins before any ocular dominance shift is detectable. Even along the same apical dendrite (Oray *et al.*, 2004), spines are first set in motion by brief MD only in layers 2, 3, and 5, consistent with early extragranular changes instructing later events in layer 4 (Trachtenberg *et al.*, 2000).

The robust anatomical consequence of 4-day MD in layer 2/3 of visual cortex that corresponds to full, functional loss of responsiveness is spine pruning (Mataga *et al.*, 2004). Protrusions on the apical dendrite of

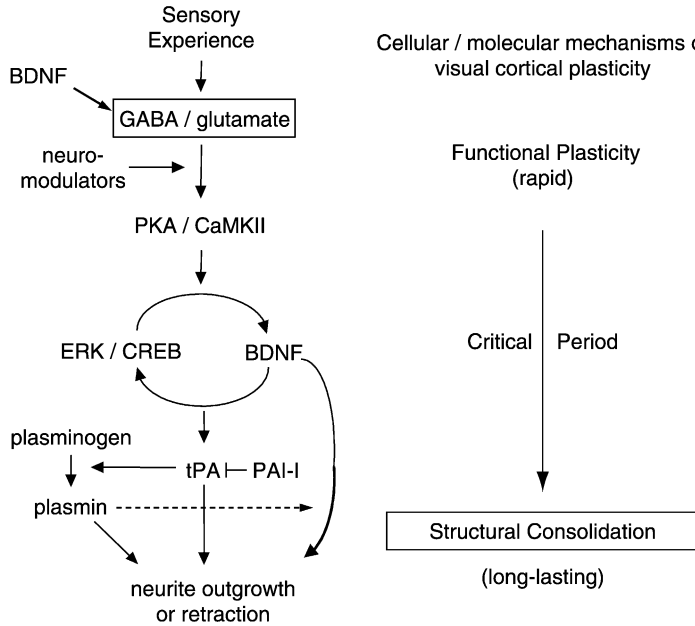

Figure 5 Molecular mechanisms of visual cortical plasticity. Many candidate plasticity factors have been screened in the monocular deprivation paradigm by pharmacology in kittens or gene-targeted disruption in mice (see Berardi *et al.*, 2003). Only a handful of second messenger molecules have been found to play a direct role in plasticity without perturbing global neuronal activity, including protein kinase A (PKA), calcium/calmodulin-dependent protein kinase II (CaMKII), extracellularly regulated kinase (ERK), cyclic AMP response element binding protein (CREB) (Mower *et al.*, 2002; Pham *et al.*, 1999), protein synthesis (Taha and Stryker, 2002), and the plasmin system (tPA-plasmin) regulated by its inhibitors (PAI-1) (Mataga *et al.*, 2002, 2004). Brain-derived neurotrophic factor (BDNF) plays an early role to establish the GABA cells that will later discriminate competing sensory inputs to trigger the critical period (Huang and Reichardt, 2001; Huang *et al.*, 1999). Mature BDNF, produced from the cleavage of pro-BDNF by plasmin (Pang *et al.*, 2004), in turn stimulates expression and release of more tPA (Fiumelli *et al.*, 1999). Both tPA and BDNF can then contribute to the final anatomical rewiring of the cortical circuit by promoting neurite growth through the extracellular matrix (ECM). Plasticity may end when permissive factors are gradually lost or when further growth is actively suppressed by late-emerging inhibitory factors in the ECM (Berardi *et al.*, 2004; Schoop *et al.*, 1997). Gene expression analyses support the view that the critical period offers a unique molecular milieu for plasticity (Ossipow *et al.*, 2004; Prasad *et al.*, 2002), consistent with dendritic spine and axonal rearrangement being limited to this time in life (Antonini and Stryker, 1996; Mataga *et al.*, 2004; Oray *et al.*, 2004).

pyramidal cells increase steadily in number with postnatal age, but are rapidly lost after MD only during the physiological critical period (step 2, Fig. 4, right). Importantly, spine density is not decreased by brief MD in tPA or GAD65 knockout mice, but can be made to decrease pharmacologically with exogenous tPA or diazepam infusion, respectively (Mataga *et al.*, 2004).

Moreover, pruning faithfully reflects competitive interactions between the two eyes, as it fails to occur when both eyes are closed (Majewska and Sur, 2003) or in the adjacent monocular segment receiving input only from the contralateral eye (Mataga *et al.*, 2004). Deletion of the tPA substrate plasminogen mimics the impaired ocular dominance plasticity observed in tPA knockout mice with brief MD. The tPA-plasmin axis may, thus, mediate rapid structural rearrangement underlying experience-dependent plasticity on a timescale (several days) that is more consistent with plasticity *in vivo* than LTP/LTD models (Heynen *et al.*, 2003).

After this postsynaptic pruning, deprived-eye afferents first retract before axonal arbors serving the open eye migrate to spaces cleared away by tPA-plasmin along the dendrite (asterisks, Fig. 4). Ultimately, territory representing the open eye is expanded (step 3, Fig. 4, right). As axons serving the open eye grow, spines emerge to meet them, and spine density largely recovers after prolonged MD (Mataga *et al.*, 2004). Thus, competition detected by an appropriate excitatory-inhibitory balance may gradually be converted into structural changes through a multistep proteolytic action of the secreted tPA-plasmin cascade. This structural model considers an extracellular locus of competition quite distinct from intracellular mechanisms of LTP/LTD. Axons and dendritic spines may be exposed to a permissive growth environment in an activity-dependent manner (Dityatev and Schachner, 2003; Mataga *et al.*, 2002, 2004).

The source and dynamics of tPA-plasmin release in the brain remain unclear due to the lack of specific reagents. Laminar motility of spines (Oray *et al.*, 2004) and their rapid pruning (Mataga *et al.*, 2004) by brief MD could reflect calcium-dependent secretion of proteases (Gualandris *et al.*, 1996; Parmer *et al.*, 1997) from axons of fast-spiking cells themselves, in which PV is a major contributor to presynaptic calcium signals and synaptic integration (Collin *et al.*, 2005). This may explain why spines nearest the soma of layer 2/3 pyramidal cells are most robustly lost (Mataga *et al.*, 2004), as they lie nearest the PV-cell-rich layer (Del Rio *et al.*, 1994). How a competitive outcome arises by uniformly bathing dendrites in proteases also needs to be considered. Cell adhesion and ECM molecules may become insensitive to proteases during high levels of activity (Murase *et al.*, 2002; Tanaka *et al.*, 2000). Less-active synapses would further release fewer endogenous protease inhibitors (Wannier-Morino *et al.*, 2003), tilting the overall balance nearby toward pruning.

VI. Normal Columnar Development

The segregation of columns by normal vision during the critical period is believed to result from the same activity-dependent rules acting upon an initially overlapping continuum of thalamic afferents. This dogma has

recently been challenged by the finding that single thalamic arbors may in part be clustered well before the critical period (Katz and Crowley, 2002). If molecular cues were to establish columnar architecture, a substantial genetic similarity of maps should emerge among siblings, for which there is now some evidence (Kaschube *et al.*, 2002). A significant role for sensory experience is nevertheless predicted to individualize these ocular dominance maps during the critical period.

Even the focal deprivation produced by shadows of blood vessels within an individual eye is embossed as an image of the retinal vasculature onto primary visual cortex (Adams and Horton, 2002). In computational models of self-organization, it is the recipient cortical circuits that largely determine the final spacing of columns (Miller *et al.*, 1989; Willshaw and von der Malsburg, 1976). Overlapping inputs segregate into clusters as "neurons that fire together wire together" through a neocortical organization that spreads excitation locally but is limited at a distance by farther-reaching inhibition. On theoretical grounds, homosynaptic rules of excitatory synaptic plasticity alone are insufficient to produce a competitive outcome (Miller, 1996), requiring other complex mechanisms such as sliding thresholds or metaplasticity. Lateral inhibitory interactions provide a straightforward scaffolding with which to discriminate individual sensory inputs.

By adjusting the canonical "Mexican hat" profile of intracortical activation during development (Fig. 6), lateral inhibition in particular can establish narrow or wide columns *in silico* (Miller *et al.*, 1989). These long-standing theoretical predictions have recently been validated *in vivo* through the direct infusion of benzodiazepines during the critical period in kitten visual cortex (Hensch and Stryker, 2004). Such drugs come in three varieties, including agonists such as diazepam (valium), inverse agonists such as the β-carbolines (e.g., DMCM), and antagonists that block the actions of both (Sieghart, 1995). All are known to act on particular $GABA_A$ receptor subtypes with the opposite effect on chloride flux. Enhancing inhibition with benzodiazepine agonists throughout the critical period leads to a 30% increase in column width, while inverse agonists produce column shrinkage (Fig. 6) (Hensch and Stryker, 2004).

Bidirectional control of columnar architecture is unprecedented and simulated in computer models when long-range (rather than local) inhibition is preferentially altered. Interestingly, increased column spacing is also observed with strabismus following exotropic deviation of the eyes during the critical period (Löwel, 1994). Both enhanced lateral inhibition by direct intracortical infusion of diazepam and decorrelation of visual input by artificial squint are conditions that favor the maximal segregation of ocular dominance. Taken together, local imbalances in neuronal activity influence

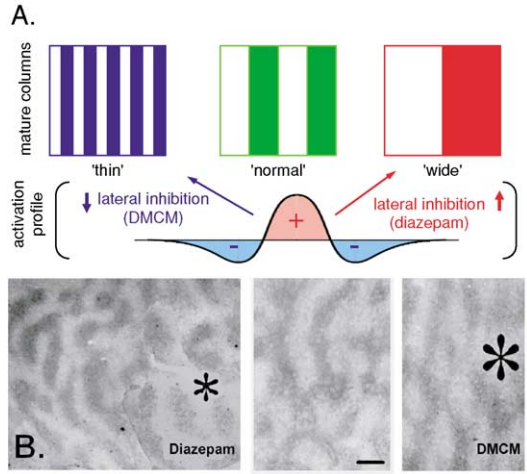

Figure 6 Local circuit control of developing columnar architecture. Activity-dependent models of segregation predict a role for cortical GABAergic circuits in determining final column spacing from an initially overlapping mosaic of afferents (Miller *et al.*, 1989). (A) Neuronal activity from thalamic input serving the right or left eye is spread by local excitatory connections (red cell) within the neocortex but inhibited at farther distances (blue cell). When this "Mexican hat" activation profile is modulated during development by enhancing or reducing horizontal, long-range inhibition preferentially (Hensch and Stryker, 2004), columns emerge that are wider or thinner than normal, respectively. (B) This hypothesis was verified *in vivo* by modulating $GABA_A$ currents with benzodiazepine agonists (diazepam) or inverse agonists (DMCM) throughout the critical period (Hensch and Stryker, 2004). Asterisks, infusion sites; control, middle panel. Scale bar: 1 mm.

column formation during normal development, which cannot be explained solely by genetic instruction.

It is paradoxical to think how inhibition might shape plasticity in the developing brain. Powerful, fast somatic inhibition can edit action potentials that may back-propagate into the dendritic arbor. Spike-timing-dependent models of synaptic plasticity rely upon a precise millisecond time window for such postsynaptic spikes to meet presynaptic input (Bi and Poo, 2001; Song *et al.*, 2000). Sloppy gating by weak inhibition at the soma (DMCM) would reduce competition by allowing spurious coincident activity of overlapping inputs. Contrast enhancement by feed-forward GABA circuits (diazepam) would instead sharpen the edges of emerging columnar borders by suppressing back-propagation of unwanted spikes (Pouille and Scanziani, 2001). This simple circuit relieves the burden of discriminating competitors by homosynaptic mechanisms alone. It entrusts the wide-reaching axons of basket cells receiving input from one eye to inhibit targets of the other eye (Buzas *et al.*, 2001), and thus to sculpt cortical architecture.

VII. Critical Period Reactivation

The critical period, in general, is a time period when the best neural representation of the world is selected from among the many competing inputs that bombard the maturing nervous system. The growth and function of lateral inhibitory circuits offer a rational, cellular substrate that can now be compared and modeled across regions to gain broader insight into brain development and its disorders (Möhler *et al.*, 2004; Rubenstein and Merzenich, 2003).

Critical period closure may reflect sequential locks placed on the molecular pathway as it flows from mature GABA function toward structural consolidation (Fig. 5). In fact, subthreshold, synaptic plasticity is still possible after MD in adulthood (Pham *et al.*, 2004; Sawtell *et al.*, 2003; Tagawa *et al.*, 2005) but has no further impact on spiking output from primary visual cortex or on visuo-spatial acuity (Fagiolini and Hensch, 2000; Gordon and Stryker, 1996; Prusky and Douglas, 2003). To fully reactivate plasticity, it may be necessary to reset the entire cascade from its GABAergic trigger onward (Pizzorusso *et al.*, 2002). Interestingly, cortical lesions or retinal scotomas reconfigure local circuit excitation-inhibition to an immature state (Arckens *et al.*, 2000). This rationalizes the administration of diazepam after acute stroke (to reduce excitotoxicity), which is also used to aid in recovery by triggering plasticity (Lodder *et al.*, 2000).

Conversely, in the somatosensory cortex GABA circuits are formed and reorganized throughout life (Fuchs and Salazar, 1998; Knott *et al.*, 2002; Welker *et al.*, 1989) and are associated with lifelong plasticity (Diamond *et al.*, 1993; Wang *et al.*, 1995). This is also the case in the mammalian olfactory system, where constant neurogenesis is responsible for odor discrimination underlying memory in adulthood (Cecchi *et al.*, 2001; Gheusi *et al.*, 2000). These newly born cells are GABAergic granule cells, whose dual functions include lateral inhibition and synchronization of neuronal activity (Lagier *et al.*, 2004; Yokoi *et al.*, 1995). Would an olfactory critical period emerge in the absence of neurogenesis, or can visual plasticity be maintained at juvenile levels by prolonging cell proliferation in the neocortex? Alternatively, the loss of factors permissive for growth (Mataga *et al.*, 2004) and/or the emergence of active inhibitors of growth (myelin) may terminate structural plasticity (Daw, 1995; Schoop *et al.*, 1997). The true test will be a reliable cure for amblyopia in adulthood.

VIII. Summary

Neuronal circuits in the brain are shaped by experience during "critical periods" of early postnatal life. Surprisingly, it is the functional maturation of local inhibitory connections that triggers this classical activity-dependent

development in primary visual cortex. Among the large diversity of interneurons, a late-developing subset employing specific $GABA_A$ receptors and widespread axons drives plasticity *in vivo* before becoming ensheathed by peri-neuronal nets in adulthood. Ultimately, structural consolidation of competing sensory input is mediated by a proteolytic reorganization of the extracellular matrix only during the critical period. Its reactivation and recovery of impaired function (amblyopia) can now be based on realistic circuit models and may generalize across systems.

References

Adams, D. L., and Horton, J. C. (2002). Shadows cast by retinal blood vessels mapped in primary visual cortex. *Science* **298,** 572–576.

Antonini, A., and Stryker, M. P. (1996). Plasticity of geniculocortical afferents following brief or prolonged monocular occlusion in the cat. *J. Comp. Neurol.* **369,** 64–82.

Antonini, A., Fagiolini, M., and Stryker, M. P. (1999). Anatomical correlates of functional plasticity in mouse visual cortex. *J. Neurosci.* **19,** 4388–4406.

Arckens, L., Schweigart, G., Qu, Y., Wouters, G., Pow, D. V., Vandesande, F., Eysel, U. T., and Orban, G. A. (2000). Cooperative changes in GABA, glutamate and activity levels: The missing link in cortical plasticity. *Eur. J. Neurosci.* **12,** 4222–4232.

Barry, M. F., and Ziff, E. B. (2002). Receptor trafficking and the plasticity of excitatory synapses. *Curr. Opin. Neurobiol.* **12,** 279–286.

Bartoletti, A., *et al*. (2002). Heterozygous knock-out mice for brain-derived neurotrophic factor show a pathway-specific impairment of long-term potentiation but normal critical period for monocular deprivation. *J. Neurosci.* **22,** 10072–10077.

Bear, M. F., Kleinschmidt, A., Gu, Q. A., and Singer, W. (1990). Disruption of experience-dependent synaptic modifications in striate cortex by infusion of an NMDA receptor antagonist. *J. Neurosci.* **10,** 909–925.

Berardi, N., Pizzorusso, T., and Maffei, L. (2000). Critical periods during sensory development. *Curr. Opin. Neurobiol.* **10,** 138–145.

Berardi, N., Pizzorusso, T., Ratto, G. M., and Maffei, L. (2003). Molecular basis of plasticity in the visual cortex. *Trends Neurosci.* **26,** 369–378.

Berardi, N., Pizzorusso, T., and Maffei, L. (2004). Extracellular matrix and visual cortical plasticity; freeing the synapse. *Neuron* **44,** 905–908.

Bi, G., and Poo, M. (2001). Synaptic modification by correlated activity: Hebb's postulate revisited. *Annu. Rev. Neurosci.* **24,** 139–166.

Buzas, P., Eysel, U. T., Adorjan, P., and Kisvarday, Z. F. (2001). Axonal topography of cortical basket cells in relation to orientation, direction, and ocular dominance maps. *J. Comp. Neurol.* **437,** 259–285.

Cecchi, G. A., Petreanu, L. T., Alvarez-Buylla, A., and Magnasco, M. O. (2001). Unsupervised learning and adaptation in a model of adult neurogenesis. *J. Comput. Neurosci.* **11,** 175–182.

Chattopadhyaya, B., *et al*. (2004). Experience and activity-dependent maturation of perisomatic GABAergic innervation in primary visual cortex during a postnatal critical period. *J. Neurosci.* **24,** 9598–9611.

Chen, L., Yang, C., and Mower, G. D. (2001). Developmental changes in the expression of GABA(A) receptor subunits (alpha(1), alpha(2), alpha(3)) in the cat visual cortex and the effects of dark rearing. *Mol. Brain Res.* **88,** 135–143.

Cherubini, E., and Conti, F. (2001). Generating diversity at GABAergic synapses. *Trends Neurosci.* **24,** 155–162.

Collin, T., Chat, M., Lucas, M. G., Moreno, H., Racay, P., Schwaller, B., Marty, A., and Llano, I. (2005). Developmental changes in parvalbumin regulate presynaptic Ca^{2+} signaling. *J. Neurosci.* **25,** 96–107.

Daw, N. (1995). Mechanisms of plasticity in the visual cortex. *In* ''The Visual Neurosciences'' (L. Chalupa and J. S. Werner, Ed.), Vol. 1, pp. 126–145. MIT Press, Cambridge, MA.

Daw, N. (2004). ''Visual Development.'' Plenum, New York.

Daw, N., Rao, Y., Wang, X. F., Fischer, Q., and Yang, Y. (2004). LTP and LTD vary with layer in rodent visual cortex. *Vision Res.* **44,** 3377–3380.

De Negri, M., Baglietto, M. G., and Biancheri, R. (1993). Electrical status epilepticus in childhood: Treatment with short cycles of high dosage benzodiazepine. *Brain Dev.* **15,** 311–312.

DeFelipe, J. (1997). Types of neurons, synaptic connections and chemical characteristics of cells immunoreactive for calbindin-D28K, parvalbumin and calretinin in the neocortex. *J. Chem. Neuroanat.* **14,** 1–19.

Del Rio, J. A., De Lecea, L., Ferrer, I., and Soriano, E. (1994). The development of parvalbumin-immunoreactivity in the neocortex of the mouse. *Dev. Brain Res.* **81,** 247–259.

Desai, N. S., Cudmore, R. H., Nelson, S. B., and Turrigiano, G. G. (2002). Critical periods for experience-dependent synaptic scaling in visual cortex. *Nat. Neurosci.* **5,** 783–789.

Di Cristo, G., Wu, C., Chattopadhyaya, B., Ango, F., Knott, G., Welker, E., Sroboda, K., and Huang, Z. J. (2004). Subcellular domain-restricted GABAergic innervation in primary visual cortex in the absence of sensory and thalamic inputs. *Nat. Neurosci.* **7,** 1184–1186.

Diamond, M. E., Armstrong-James, M., and Ebner, F. F. (1993). Experience-dependent plasticity in adult rat barrel cortex. *Proc. Natl. Acad. Sci. USA* **90,** 2082–2086.

Dityatev, A., and Schachner, M. (2003). Extracellular matrix molecules and synaptic plasticity. *Nat. Rev. Neurosci.* **4,** 456–468.

Erisir, A., Lau, D., Rudy, B., and Leonard, C. S. (1999). Function of specific K(+) channels in sustained high-frequency firing of fast-spiking neocortical interneurons. *J. Neurophysiol.* **82,** 2476–2489.

Fagiolini, M., and Hensch, T. K. (2000). Inhibitory threshold for critical-period activation in primary visual cortex. *Nature* **404,** 183–186.

Fagiolini, M., Katagiri, H., Miyamoto, H., Mori, H., Grant, S. G., Mishina, M., and Hensch, T. K. (2003). Separable features of visual cortical plasticity revealed by N-methyl-D-aspartate receptor 2A signaling. *Proc. Natl. Acad. Sci. USA* **100,** 2854–2859.

Fagiolini, M., Fritschy, J. M., Low, K., Mohler, H., Rudolf, U., and Hensch, T. K. (2004). Specific $GABA_A$ circuits for visual cortical plasticity. *Science* **303,** 1681–1683.

Feldman, D. E. (2000). Inhibition and plasticity. *Nat. Neurosci.* **3,** 303–304.

Fischer, Q. S., Beaver, C. J., Yang, Y., Rao, Y., Jakobsdottir, K. B., Storm, D. R., McKnight, G. S., and Daw, N. W. (2004). Requirement for the RIIβ isoform of PKA, but not calcium-stimulated adenylyl cyclase, in visual cortical plasticity. *J. Neurosci.* **24,** 9049–9058.

Fiumelli, H., Jabaudon, D., Magistretti, P. J., and Martin, J.-L. (1999). BDNF stimulates expression, activity and release of tissue-type plasminogen activator in mouse cortical neurons. *Eur. J. Neurosci.* **11,** 1639–1646.

Frenkel, M. Y., and Bear, M. F. (2004). How monocular deprivation shifts ocular dominance in visual cortex of young mice. *Neuron* **44,** 917–923.

Frey, U., Huang, Y. Y., and Kandel, E. R. (1993). Effects of cAMP simulate a late-stage of LTP in hippocampal CA1 neurons. *Science* **260,** 1661–1664.

Fuchs, J. L., and Salazar, E. (1998). Effects of whisker trimming on GABA(A) receptor binding in the barrel cortex of developing and adult rats. *J. Comp. Neurol.* **395,** 209–216.

Gheusi, G., Cremer, H., McLean, H., Chazal, G., Vincent, J. D., and Lledo, P.-M. (2000). Importance of newly generated neurons in the adult olfactory bulb for odor discrimination. *Proc. Natl. Acad. Sci. USA* **97,** 1823–1828.

Gianfranceschi, L., *et al.* (2003). Visual cortex is rescued from the effects of dark rearing by overexpression of BDNF. *Proc. Natl. Acad. Sci. USA* **100,** 12486–12491.

Gordon, J. A., and Stryker, M. P. (1996). Experience-dependent plasticity of binocular responses in the primary visual cortex of the mouse. *J. Neurosci.* **16,** 3274–3286.

Grutzendler, J., Kasthuri, N., and Gan, W. B. (2002). Long-term dendritic spine stability in the adult cortex. *Nature* **420,** 812–816.

Gualandris, A., Jones, T. E., Strickland, S., and Tsirka, S. E. (1996). Membrane depolarization induces calcium-dependent secretion of tissue plasminogen activator. *J. Neurosci.* **16,** 2220–2225.

Hanover, J. L., Huang, Z. J., Tonegawa, S., and Stryker, M. P. (1999). Brain-derived neurotrophic factor overexpression induces precocious critical period in mouse visual cortex. *J. Neurosci.* **19,** RC40.

Härtig, W., Deroniche, A., Welt, K., Broner, K., Grosche, J., Mader, M., Reichenbach, A., and Bruckner, G. (1999). Cortical neurons immunoreactive for the potassium channel $K_v3.1b$ subunit are predominantly surrounded by perineuronal nets presumed as a buffering system for cations. *Brain Res.* **842,** 15–29.

Hata, Y., and Stryker, M. P. (1994). Control of thalamocortical afferent rearrangement by postsynaptic activity in developing visual cortex. *Science* **265,** 1732–1735.

Hensch, T. K. (2003). Controlling the critical period. *Neurosci. Res.* **47,** 17–22.

Hensch, T. K. (2004). Critical period regulation. *Annu. Rev. Neurosci.* **27,** 549–579.

Hensch, T. K., and Fagiolini, M. (Eds.) (2004). ''Excitatory-Inhibitory Balance: Synapses, Circuits, Systems.'' Kluwer/Plenum, New York.

Hensch, T. K., and Stryker, M. P. (2004). Columnar architecture sculpted by GABA circuits in developing cat visual cortex. *Science* **303,** 1678–1681.

Hensch, T. K., Fagiolini, M., Mataga, N., Stryker, M. P., Baekkeskov, S., and Kash, S. F. (1998). Local GABA circuit control of experience-dependent plasticity in developing visual cortex. *Science* **282,** 1504–1508.

Heynen, A. J., Yoon, B. J., Liu, C. H., Chung, H. J., Hunganir, R. L., and Bear, M. F. (2003). Molecular mechanism for loss of visual cortical responsiveness following brief monocular deprivation. *Nat. Neurosci.* **6,** 854–862.

Hinkle, D. J., and Macdonald, R. L. (2003). Beta subunit phosphorylation selectively increases fast desensitization and prolongs deactivation of $\alpha1\beta1\gamma2L$ and $\alpha1\beta3\gamma2L$ GABA(A). receptor currents. *J. Neurosci.* **23,** 11698–11710.

Huang, E. J., and Reichardt, L. F. (2001). Neurotrophins: Roles in neuronal development and function. *Annu. Rev. Neurosci.* **24,** 677–736.

Huang, Z. J., Kirkwood, A., Pizzorusso, T., Porcïatti, V., Morales, B., Bear, M. F., Mattei, L., and Tonegawa, S. (1999). BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. *Cell* **98,** 739–755.

Hubel, D. H., Wiesel, T. N., and Le Vay, S. (1976). Functional architecture of area 17 in normal and monocularly deprived macaque monkeys. *Cold Spring Harb. Symp. Quant. Biol.* **40,** 581–589.

Iwai, Y., Fagiolini, M., Obata, K., and Hensch, T. K. (2003). Rapid critical period induction by tonic inhibition in visual cortex. *J. Neurosci.* **23,** 6695–6702.

Jiang, B., Akaneya, Y., Hata, Y., and Tsumoto, T. (2003). Long-term depression is not induced by low-frequency stimulation in rat visual cortex *in vivo*: A possible preventing role of endogenous brain-derived neurotrophic factor. *J. Neurosci.* **23,** 3761–3770.

Kaschube, M., Wolf, F., Geisel, T., and Lowel, S. (2002). Genetic influence on quantitative features of neocortical architecture. *J. Neurosci.* **22,** 7206–7217.

Katz, L. C., and Crowley, J. C. (2002). Development of cortical circuits: Lessons from ocular dominance columns. *Nat. Rev. Neurosci.* **3,** 34–42.

Kawaguchi, Y., and Kubota, Y. (1997). GABAergic cell subtypes and their synaptic connections in rat frontal cortex. *Cereb. Cortex* **7,** 476–486.

Kirkwood, A., Dudek, S. M., Gold, J. T., Aizenman, C. D., and Bear, M. F. (1993). Common forms of synaptic plasticity in the hippocampus and neocortex in vitro. *Science* **260,** 1518–1521.

Kirkwood, A., Lee, H. K., and Bear, M. F. (1995). Co-regulation of long-term potentiation and experience-dependent synaptic plasticity in visual cortex by age and experience. *Nature* **375,** 328–331.

Klausberger, T., Roberts, J. D., and Somogyi, P. (2002). Cell type- and input-specific differences in the number and subtypes of synaptic GABA(A) receptors in the hippocampus. *J. Neurosci.* **22,** 2513–2521.

Knott, G. W., Quairiaux, C., Genoud, C., and Welker, E. (2002). Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. *Neuron* **34,** 265–273.

Lagier, S., Carleton, A., and Lledo, P. M. (2004). Interplay between local GABAergic interneurons and relay neurons generates gamma oscillations in the rat olfactory bulb. *J. Neurosci.* **24,** 4382–4392.

Lien, C. C., and Jonas, P. (2003). K_v3 potassium conductance is necessary and kinetically optimized for high-frequency action potential generation in hippocampal interneurons. *J. Neurosci.* **23,** 2058–2068.

Liu, G. (2004). Local structural balance and functional interaction of excitatory and inhibitory synapses in hippocampal dendrites. *Nat. Neurosci.* **7,** 373–379.

Liu, L., Wong, T. P., Pozza, M. F., Lingenhoel, K., Wang, Y., Sheng, M., Auberson, Y. P., and Wang, Y. T. (2004). Role of NMDA receptor subtypes in governing the direction of hippocampal synaptic plasticity. *Science* **304,** 1021–1024.

Liu, Y., Fields, R. D., Fitzgerald, S., Festoff, B. W., and Nelson, P. G. (1994). Proteolytic activity, synapse elimination, and the Hebb synapse. *J. Neurobiol.* **25,** 325–335.

Lodder, J., Luijckx, G., van Raak, L., and Kessels, F. (2000). Diazepam treatment to increase the cerebral GABAergic activity in acute stroke: A feasibility study in 104 patients. *Cerebrovasc. Dis.* **10,** 437–440.

Löwel, S. (1994). Ocular dominance column development: Strabismus changes the spacing of adjacent columns in cat visual cortex. *J. Neurosci.* **14,** 7451–7468.

Majewska, A., and Sur, M. (2003). Motility of dendritic spines in visual cortex in vivo: Changes during the critical period and effects of visual deprivation. *Proc. Natl. Acad. Sci. USA* **100,** 16024–16029.

Markram, H., Toledo-Rodriguez, M., Wang, Y., Gupta, A., Silberberg, G., and Wu, C. (2004). Interneurons of the neocortical inhibitory system. *Nat. Rev. Neurosci.* **5,** 793–807.

Mataga, N., Fujishima, S., Condie, B. G., and Hensch, T. K. (2001). Experience-dependent plasticity of mouse visual cortex in the absence of the neuronal activity-dependent marker egr1/zif268. *J. Neurosci.* **21,** 9724–9732.

Mataga, N., Mizuguchi, Y., and Hensch, T. K. (2004). Experience-dependent pruning of dendritic spines in visual cortex by tissue plasminogen activator. *Neuron* **44,** 1031–1041.

Mataga, N., Nagai, N., and Hensch, T. K. (2002). Permissive proteolytic activity for visual cortical plasticity. *Proc. Natl. Acad. Sci. USA* **99,** 7717–7721.

Miller, K. D. (1996). Synaptic economics: Competition and cooperation in synaptic plasticity. *Neuron* **17,** 371–374.

Miller, K. D., Keller, J. B., and Stryker, M. P. (1989). Ocular dominance column development: Analysis and simulation. *Science* **245,** 605–615.

Möhler, H., Fritschy, J. M., Crestani, F., Hensch, T., and Rudolph, U. (2004). Specific GABA (A) circuits in brain development and therapy. *Biochem. Pharmacol.* **68,** 1685–1690.

Morales, B., Choi, S. Y., and Kirkwood, A. (2002). Dark rearing alters the development of GABAergic transmission in visual cortex. *J. Neurosci.* **22,** 8084–8090.

Mower, A. F., Liao, D. S., Nestler, E. J., Neve, R. L., and Ramoa, A. S. (2002). cAMP/Ca2+ response element-binding protein function is essential for ocular dominance plasticity. *J. Neurosci.* **22,** 2237–2245.

Mower, G. D. (1991). The effect of dark rearing on the time course of the critical period in cat visual cortex. *Dev. Brain Res.* **58,** 151–158.

Murase, S., Mosser, E., and Schuman, E. M. (2002). Depolarization drives β-catenin into neuronal spines promoting changes in synaptic structure and function. *Neuron* **35,** 91–105.

Murphy, K. M., Beston, B. R., Boley, P. M., and Jones, D. G. (2005). Development of human visual cortex: A balance between excitatory and inhibitory plasticity mechanisms. *Dev. Psychobiol.* **46,** 209–221.

Müller, C. M., and Griesinger, C. B. (1998). Tissue plasminogen activator mediates reverse occlusion plasticity in visual cortex. *Nat. Neurosci.* **1,** 47–53.

Nase, G., Weishaupt, J., Stern, P., Singer, W., and Monyer, H. (1999). Genetic and epigenetic regulation of NMDA receptor expression in the rat visual cortex. *Eur. J. Neurosci.* **11,** 4320–4326.

Oray, S., Majewska, A., and Sur, M. (2004). Dendritic spine dynamics are regulated by monocular deprivation and extracellular matrix degradation. *Neuron* **44,** 1021–1030.

Ossipow, V., Pellissier, F., Schaad, O., and Ballivet, M. (2004). Gene expression analysis of the critical period in the visual cortex. *Mol. Cell Neurosci.* **27,** 70–83.

Pang, P., Teng, H. K., Zaitsev, E., Woo, N. T., Sakata, K., Zhen, S., Teng, K. K., Yung, W. H., Hempstead, B. L., and Lu, B. (2004). Cleavage of ProBDNF by tPA/plasmin is essential for long-term hippocampal plasticity. *Science* **306,** 487–491.

Parmer, R. J., Mahata, M., Mahata, S., Sebald, M. T., O'Conner, D. T., and Miles, L. A. (1997). Tissue plasminogen activator (tPA) is targeted to the regulated secretory pathway. *J. Biol. Chem.* **272,** 1976–1982.

Pham, T. A., Impey, S., Storm, D. R., and Stryker, M. P. (1999). CRE-mediated gene transcription in neocortical neuronal plasticity during the developmental critical period. *Neuron* **22,** 63–72.

Pham, T. A., Graham, S. J., Suzuki, S., Barco, A., Kandel, E. R., Gordon, B., and Lickey, M. E. (2004). A semi-persistent adult ocular dominance plasticity in visual cortex is stabilized by activated CRE. B. *Learn Mem.* **11,** 738–747.

Philpot, B. D., Sekhar, A. K., Shouval, H. Z., and Bear, M. F. (2001). Visual experience and deprivation bidirectionally modify the composition and function of NMDA receptors in visual cortex. *Neuron* **29,** 157–169.

Pizzorusso, T., Medini, P., Berardi, N., Chierzi, S., Faucett, J. W., and Maffei, L. (2002). Reactivation of ocular dominance plasticity in the adult visual cortex. *Science* **298,** 1248–1251.

Pouille, F., and Scanziani, M. (2001). Enforcement of temporal fidelity in pyramidal cells by somatic feed-forward inhibition. *Science* **293,** 1159–1163.

Prasad, S. S., *et al.* (2002). Gene expression patterns during enhanced periods of visual cortex plasticity. *Neuroscience* **111,** 35–45.

Prusky, G. T., and Douglas, R. M. (2003). Developmental plasticity of mouse visual acuity. *Eur. J. Neurosci.* **17,** 167–173.

Qian, Z., Gilbert, M. E., Colicos, M. A., Kandel, E. R., and Kuhl, D. (1993). Tissue-plasminogen activator is induced as an immediate-early gene during seizure, kindling and long-term potentiation. *Nature* **361,** 453–457.

Quinlan, E. M., Philpot, B. D., Huganir, R. L., and Bear, M. F. (1999). Rapid, experience-dependent expression of synaptic NMDA receptors in visual cortex *in vivo*. *Nat. Neurosci.* **2,** 352–357.

Ramoa, A. S., Paradiso, M. A., and Freeman, R. D. (1988). Blockade of intracortical inhibition in kitten striate cortex: Effects on receptive field properties and associated loss of ocular dominance plasticity. *Exp. Brain Res.* **73,** 285–296.

Reiter, H. O., and Stryker, M. P. (1988). Neural plasticity without postsynaptic action potentials: Less-active inputs become dominant when kitten visual cortical cells are pharmacologically inhibited. *Proc. Natl. Acad. Sci. USA* **85,** 3623–3627.

Reiter, H. O., Waitzman, D. M., and Stryker, M. P. (1986). Cortical activity blockade prevents ocular dominance plasticity in the kitten visual cortex. *Exp. Brain Res.* **65,** 182–188.

Renger, J. J., Hartman, K. N., Tsuchimoto, Y., Yokoi, M., Nakanishi, S., and Hensch, T. K. (2002). Experience-dependent plasticity without long-term depression by type 2 metabotropic glutamate receptors in developing visual cortex. *Proc. Natl. Acad. Sci. USA* **99,** 1041–1046.

Rubenstein, J. L., and Merzenich, M. M. (2003). Model of autism: Increased ratio of excitation/inhibition in key neural systems. *Genes Brain Behav.* **2,** 255–267.

Rudolph, U., Crestani, F., and Möhler, H. (2001). GABA(A) receptor subtypes: Dissecting their pharmacological functions. *Trends Pharmacol. Sci.* **22,** 188–194.

Rudy, B., and McBain, C. J. (2001). K_v3 channels: Voltage-gated K+ channels designed for high-frequency repetitive firing. *Trends Neurosci.* **24,** 517–526.

Saghatelyan, A. K., Dityater, A., Schmidt, S., Schuster, T., Bartsch, U., and Schachn, M. (2001). Reduced perisomatic inhibition, increased excitatory transmission, and impaired long-term potentiation in mice deficient for the extra-cellular matrix glycoprotein tenascin-R. *Mol. Cell Neurosci.* **17,** 226–240.

Sanes, J. R., and Lichtman, J. W. (1999). Can molecules explain long-term potentiation? *Nat. Neurosci.* **2,** 597–604.

Sawtell, N. B., Frenkel, M. Y., Philpot, B. D., Nakazawa, K., Tonegawa, S., and Bear, M. F. (2003). NMDA receptor-dependent ocular dominance plasticity in adult visual cortex. *Neuron* **38,** 977–985. Erratum *Neuron* **39**, 727.

Schoop, V. M., Gardziella, S., and Muller, C. M. (1997). Critical period-dependent reduction of the permissiveness of cat visual cortex tissue for neuronal adhesion and neurite growth. *Eur. J. Neurosci.* **9,** 1911–1922.

Shatz, C. J., and Stryker, M. P. (1978). Ocular dominance in layer IV of the cat's visual cortex and the effects of monocular deprivation. *J. Physiol. (Lond.)* **281,** 267–283.

Shaw, C., and Cynader, M. (1984). Disruption of cortical activity prevents ocular dominance changes in monocularly deprived kittens. *Nature* **308,** 731–734.

Shimegi, S., Fischer, Q. S., Yang, Y., Sato, H., and Daw, N. W. (2003). Blockade of cyclic AMP-dependent protein kinase does not prevent the reverse ocular dominance shift in kitten visual cortex. *J. Neurophysiol.* **90,** 4027–4032.

Shiosaka, S., and Yoshida, S. (2000). Synaptic microenvironments-structural plasticity, adhesion molecules, proteases and their inhibitors. *Neurosci. Res.* **37,** 85–89.

Sieghart, W. (1995). Structure and pharmacology of γ-aminobutyric $acid_A$ receptor subtypes. *Pharmacol. Rev.* **47,** 181–234.

Silver, M. A., and Stryker, M. P. (1999). Synaptic density in geniculocortical afferents remains constant after monocular deprivation in the cat. *J. Neurosci.* **19,** 10829–10842.

Soghomonian, J. J., and Martin, D. L. (1998). Two isoforms of glutamate decarboxylase: Why? *Trends Pharmacol.* **19,** 500–505.

Somogyi, P., Tamas, G., Lujan, R., and Buhl, E. H. (1998). Salient features of synaptic organisation in the cerebral cortex. *Brain Res. Rev.* **26,** 113–135.

Song, S., Miller, K. D., and Abbott, L. F. (2000). Competitive Hebbian learning through spike-timing-dependent synaptic plasticity. *Nat. Neurosci.* **3,** 919–926.

Tagawa, Y., Kanold, P. O., Majdan, M., and Shatz, C. J. (2005). Multiple periods of functional ocular dominance plasticity in mouse visual cortex. *Nat. Neurosci.* **8,** 380–388.

Taha, S., and Stryker, M. P. (2002). Rapid ocular dominance plasticity requires cortical but not geniculate protein synthesis. *Neuron* **34,** 425–436.

Takahashi, T., Svoboda, K., and Malinow, R. (2003). Experience strengthening transmission by driving AMPA receptors into synapses. *Science* **299,** 1585–1588.

Tanaka, H., Shan, W., Phillips, G. R., Arndt, K., Bozdagi, O., Shapiro, L., Huntley, G. W., Benson, D. L., and Colman, D. R. (2000). Molecular modification of N-cadherin in response to synaptic activity. *Neuron* **25,** 93–107.

Tang, Y. P., Shimizu, E., Dube, G. R., Rampon, C., Kerchner, G. A., Zhuo, M., Liu, G., and Tsien, J. Z. (1999). Genetic enhancement of learning and memory in mice. *Nature* **401,** 63–69.

Trachtenberg, J. T., and Stryker, M. P. (2001). Rapid anatomical plasticity of horizontal connections in the developing visual cortex. *J. Neurosci.* **21,** 3476–3482.

Trachtenberg, J. T., Trepel, C., and Stryker, M. P. (2000). Rapid extragranular plasticity in the absence of thalamocortical plasticity in the developing primary visual cortex. *Science* **287,** 2029–2032.

Turrigiano, G. G., and Nelson, S. B. (2004). Homeostatic plasticity in the developing nervous system. *Nat. Rev. Neurosci.* **5,** 97–107.

Wan, H., Warburton, E. C., Zhu, X. O., Koder, T. J., Park, Y., Aggelton, J. P., Cho, K., Bashir, Z. I., and Brown, M. W. (2004). Benzodiazepine impairment of perirhinal cortical plasticity and recognition memory. *Eur. J. Neurosci.* **20,** 2214–2224.

Wang, X., Merzenich, M. M., Sameshima, K., and Jenkins, W. M. (1995). Remodelling of hand representation in adult cortex determined by timing of tactile stimulation. *Nature* **378,** 71–75.

Wannier-Morino, P., Rager, G., Sonderegger, P., and Grabs, D. (2003). Expression of neuroserpin in the visual cortex of the mouse during the developmental critical period. *Eur., J. Neurosci.* **17,** 1853–1860.

Welker, E., Soriano, E., and Van der Loos, H. (1989). Plasticity in the barrel cortex of the adult mouse: Effects of peripheral deprivation on GAD-immunoreactivity. *Exp. Brain Res.* **74,** 441–452.

Wiesel, T. N., and Hubel, D. H. (1963). Single-cell responses in striate cortex of kittens deprived of vision in one eye. *J. Neurophysiol.* **26,** 1003–1017.

Willshaw, D. J., and von der Malsburg, C. (1976). How patterned neural connections can be set up by self-organization. *Proc., R. Soc. Lond. B Biol. Sci.* **194,** 431–445.

Yokoi, M., Mori, K., and Nakanishi, S. (1995). Refinement of odor molecule tuning by dendrodendritic synaptic inhibition in the olfactory bulb. *Proc. Natl. Acad. Sci. USA* **92,** 3371–3375.

Yuste, R., and Bonhoeffer, T. (2001). Morphological changes in dendritic spines associated with long-term synaptic plasticity. *Annu. Rev. Neurosci.* **24,** 1071–1089.

Further Reading

Tyler, W. J., and Pozzo-Miller, L. (2004). Miniature synaptic transmission and BDNF modulates dendritic spine growth and form in rat CA1 neurons. *J. Physiol. (Lond.)* **553.2,** 497–509.