Reviews in the Neurosciences, 18, 295-310 (2007)

The Missing Piece in the 'Use It or Lose It' Puzzle: Is Inhibition Regulated by Activity or Does it Act on its Own Accord?

Qian-Quan Sun

Laboratory of Neural Development and Learning, Department of Zoology and Physiology and Neuroscience Program, University of Wyoming, Laramie, WY, USA

SYNOPSIS

We have gained enormous insight into the mechanisms underlying both activity-dependent and (to a lesser degree) -independent plasticity of excitatory synapses. Recently, cortical inhibition has been shown to play a vital role in the formation of critical periods for sensory plasticity. As such, sculpting of neuronal circuits by inhibition may be a common mechanism by which activity organizes or reorganizes brain circuits. Disturbances in the balance of excitation and inhibition in the neocortex provoke abnormal activities, such as epileptic seizures and abnormal cortical development. However, both the process of experience-dependent postnatal maturation of neocortical inhibitory networks and its underlying mechanisms remain elusive. Mechanisms that match excitation and inhibition are central to achieving balanced function at the level of individual circuits. The goal of this review is to reinforce our understanding of the mechanisms by which developing inhibitory networks are able to adapt to sensory inputs, and to maintain their balance with developing excitatory networks. Discussion is centered on the following questions related to experience-dependent plasticity of neocortical inhibitory networks: 1) What are the roles of GABAergic inhibition in the postnatal maturation of neocortical circuits? 2) Does the maturation of neocortical inhibitory circuits proceed in an activity-dependent manner or do they develop independently of sensory inputs? 3) Does activity regulate inhibitory networks in the same way it regulates excitatory networks? 4) What are the molecular and cellular mechanisms that underlie the activity-dependent maturation of inhibitory networks? 5) What are the functional advantages of experience-dependent plasticity of inhibitory networks to network processing in sensory cortices?

KEY WORDS

GABA, inhibition, cortex, microcircuits, synaptic plasticity, development

INTRODUCTION

Sensory experience drives the refinement of sensory maps in developing and adult sensory cortices /13,22,75,103,122/. Sensory deprivation causes the cortical area representing the deprived sensory input to shrink, and neighboring spared representations to enlarge, in somatosensory /22, 75/, auditory /76/, visual /13,45,122/ and language /86/ cortex. Contributions from both genes and neural activity instruct the development of sensory maps. Tremendous progress has been made toward understanding both the process of maturation of excitatory networks, and the mechanisms underlying the activity-dependent modification of glutamatergic synapses in principal neurons /105/. Recently, cortical **inhibition** has been shown to

Accepted: 12 January, 2007

Reprint address:
Qian-Quan Sun
Laboratory of Neural Development and Learning
Department of Zoology and Physiology and Neuroscience Program
University of Wyoming
Dept. 3166, 1000 E. University Ave
Laramie, WY 82071, USA
e-mail: neuron@uwyo.edu

play a vital role in the formation of critical periods for sensory plasticity /41/. However, both the process of experience-dependent postnatal maturation of neocortical inhibitory networks and the underlying mechanisms remain elusive /1,21,78/. The present review focuses on the mechanisms underlying activity-dependent regulation of neocortical inhibitory circuits and the roles of inhibition in postnatal sensory map plasticity. Focus is placed on the following questions related to experience-dependent plasticity of neocortical inhibitory networks: 1) What are the roles of gamma-aminobutyric acid (GABA)ergic inhibition in the postnatal maturation of neocortical circuits? 2) Does the maturation of neocortical inhibitory circuits proceed in an activity-dependent manner or do they develop independently of sensory inputs? 3) Does activity regulate inhibitory networks in the same way it regulates excitatory networks? 4) What are the molecular and cellular mechanisms that underlie the activity-dependent maturation of inhibitory networks? 5) What are the functional advantages of experience-dependent plasticity of inhibitory networks to network processing in sensory cortices?

1. ROLE OF GABAERGIC SYNAPTIC INHIBITION IN POSTNATAL CORTICAL DEVELOPMENT

In the immature hippocampus and neocortex, GABAergic interneurons form functional synapses earlier than glutamatergic neurons. These pioneering interneurons form functional 'inhibitory networks' that generate excitatory depolarizing potentials thought to be very important for the early development of the neural networks. Several important functions of GABA have been elucidated, particularly its role as a trophic factor that influences cell proliferation, migration, and circuit maturation (reviewed by Owens *et al.* /89/). During postnatal brain development, the reversal potential for $GABA_A$ mediated responses is highly dependent upon intracellular Cl^- concentrations and is shifted from -46 mV (postnatal day 0) to -82 mV (>postnatal day 12) /89/. The increased expression of a K^+/Cl^- coupled co-transporter (KCC_2) is primarily responsible for the developmental switch of the GABA mediated response /93/.

Apart from the trophic actions of depolarizing GABA in early development, inhibitory networks are also recognized for playing a crucial role in experience-dependent refinement of neural networks. Distinct genes encode two isoforms of the GABA-synthesizing enzyme glutamic acid decarboxylase, GAD65 and GAD67. GAD67 is the larger protein, and provides a constitutive concentration of GABA throughout the central nervous system (CNS). Mice lacking GAD67 show a significant reduction in brain GABA concentrations, and die at birth. GAD65 is found primarily in the synaptic terminals, and serves the rapid changes in synaptic demand following intense neuronal activity. Mice lacking GAD65 survive and develop normal gross cortical morphology, and normal adult GABA concentrations /51/. However, the GAD65 knockout prevents ocular dominance plasticity /41/. In contrast, pharmacologically enhancing activity-dependent GABA transmission can prematurely enhance ocular dominance plasticity /20,47/. In normal wild-type animals, enhancing local existing GABA transmission did not perturb visual responsiveness but did widen ocular dominance column spacing. This suggests that local cortical inhibitory synapses might modulate incoming thalamocortical (TC) inputs (Fig. 1). Despite these clear demonstrations of the importance of intracortical inhibition in visual cortical plasticity, the underlying mechanisms involved are not clear. These experiments suggest the important roles of GABA in experience-dependent early cortical development. In the somatosensory cortex, the role of cortical inhibition in shaping barrel plasticity is even less clear. It is unknown whether genetic deletion of fast GABAergic transmission will affect cortical barrel formation. However, indirect evidence suggests that inhibition may be at least partially responsible for the activity-dependent barrel plasticity. For example, enhancing whisker activity increases the number of GABA synapses formed on dendritic spines /57/. Recent evidence also suggests that regulation of NMDA receptor subtype composition has no effect on barrel critical period formation /66/. In the barrel cortex, GAD65 expression appears late in the critical period for barrel formation /56/, indicating GABA's role in the refinement of barrel structure. Additional

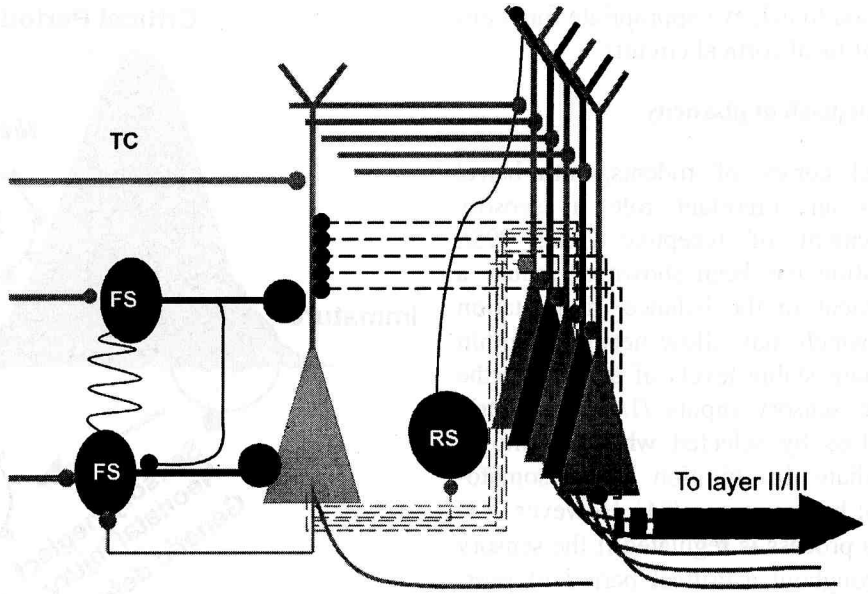

Fig. 1: Role of basket cells in sensory-mediated feed-forward inhibition and modulation of receptive field properties. Thalamocortical (TC) excitatory synapses form synaptic connections onto spiny stellate cells as well as fast-spiking basket cells, which form connections via gap junctions. Spiny stellate cells out-number basket cells and form elaborate recurrent connections with other spiny stellate cells. However, the strength of the fast-spiking (FS) cell-mediated perisomatic inhibition is on average 10 times larger than the intracortical excitatory synaptic excitation. Therefore sensory feedforward inhibition plays a very important role in modulating receptive field properties by limiting the lateral propagation of intracortically mediated recurrent excitations and spike-timing of sensory mediated spikes in spiny stellate cells. Black cells: interneurons and inhibitory synapses; gray cells: spiny stellate cells and glutamatergic synapses.

experiments that thoroughly examine the roles of GABA in barrel plasticity are necessary for understanding the roles of inhibition in somatosensory cortical development.

2. DOES THE MATURATION OF NEOCORTICAL INHIBITORY NETWORKS PROCEED IN AN ACTIVITY-DEPENDENT MANNER OR DO THEY DEVELOP INDEPENDENTLY OF SENSORY INPUTS, OR BOTH?

Cortical inhibition plays a vital role in the formation of critical periods for visual plasticity. How does inhibition contribute to the formation of neocortical critical periods? The current dogma regarding sensory map plasticity is centered on the plasticity of excitatory connections, which follows a 'use it or loose it' rule, i.e. connections with stimulated (or correlated) inputs grow stronger and connections with inactive (or uncorrelated) inputs grow weaker. This process is also known as the Hebbian rule /39/. A very compelling hypothesis about the role of inhibition in the formation of critical periods was that lateral cortical inhibition modulated Hebbian-type plasticity by enhancing the correlative activities of adjacent cortical neurons and producing anti-correlative activities in distal cells /28/. To serve this role, i.e. modulating the spike-timing and lateral spread of excitation, the strength of inhibitory synapses must also be developmentally regulated. Prior to the formation of neocortical critical periods, the strength of thalamocortical and intracortical glutamatergic synapses undergoes drastic morphological, molecular and functional changes /23,25/. Disturbances in the balance of excitation and inhibition in the neocortex induce cortical epileptic seizure. Therefore, a key requirement for the maturation of sensory cortices, based on a 'use it or loose it' rule, was that excitation and inhibition must be

delicately balanced to achieve appropriate functioning at the level of local cortical circuits.

2.1. Experience-dependent plasticity

In the barrel cortex of rodents, intra-barrel inhibition plays an important role in sensory mediated refinement of receptive fields /95/. Sensory deprivation has been shown to induce a dynamic adjustment in the balance of excitation and inhibition, which may allow networks within layer 4 to maintain stable levels of activity in the face of variable sensory inputs /1/. In an early study, sensory loss by selected whisker removal produces immediate disinhibition in the somatosensory cortex of behaving rats /54/. However, it is unclear how this process is regulated if the sensory loss persists throughout a critical period of postnatal development. There is considerable evidence suggesting that the amount of inhibitory neurotransmitter (GABA), its receptors, and the number of synapses, are correlated with levels of neuronal activity /57,78/. Recent studies of visual and auditory systems provide further evidence that the reorganization of inhibitory connections occurs at the circuitry level /41,55/. In the barrel cortex, active whisking enhances the emergence of mature inhibition /56/. In contrast, whisker trimming during the second through fourth postnatal week induced very robust downregulation of perisomatic inhibitory synapses from fast-spiking basket cells. This downregulation is accompanied by changes in presynaptic calcium dynamics and also GAD expression in the nerve terminals /49/. Visual cortical GABAergic synapses of basket cells also show clearly defined dependence on sensory experience /48/. Between the time at which the eyes first open and the end of the critical period for experience-dependent plasticity, the total GABAergic input converging onto layer II/III pyramidal cells of the visual cortex increases threefold. This increase reflects changes in the number of quanta released by presynaptic axons and is prevented by dark rearing (sensory deprivation). Thus, sensory experience appears to play a permissive role in the maturation of intracortical GABAergic circuits /79/ (Fig. 2). Recently, using microarray analysis combined with other molecular and immunohistochemical methods, a set of signaling genes, whose expression is regulated by visual deprivation, were identified /68,111/. Among these genes, genes for $GABA_A$ receptor subunits $\alpha 2$, $\alpha 3$, $\beta 1$ and $\beta 3$ were found to be upregulated by monocular derivation or dark rearing. Other genes, such as those encoding for GAD67 and parvalbumin, have been implicated in experience-dependent plasticity, and were all found to be affected by visual experiences /111/. Thus activity-dependent regulation of gene expression appears to be a major means of remodeling inhibitory networks through experiences.

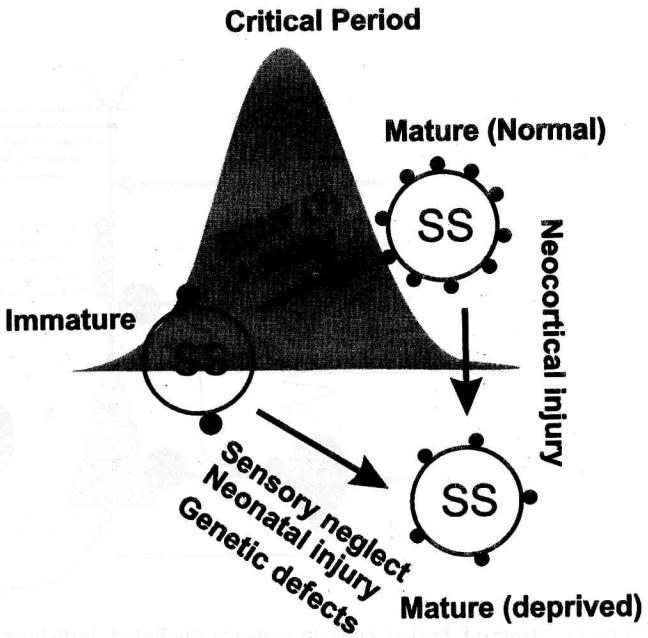

Fig. 2: Postnatal maturation and plasticity of perisomatic inhibitory synaptic boutons in sensory cortices. Perisomatic inhibitory synapses undergo a process of activity-dependent maturation during the first few postnatal weeks. This process is presumably regulated via activity-dependent processes and is delayed or diminished by sensory neglect or neonatal injury. As implicated, the maturation of the inhibitory network plays a role in activity-dependent formation of sensory critical periods. Mature inhibitory circuits can be changed into an 'immature' network if the cortices are injured. SS = spiny stellate cell.

2.2. Activity-independent plasticity

In addition to these clearly defined activity-dependent processes that underlie GABAergic maturation, activity-independent plasticity has been reported in the sensory cortices. It has been reported that both GAD67, which produces the basal pool of GABA, and GAD65, which is specialized to respond to short-term increases in demand in synaptic terminals, develop normal levels of expression and normal intracellular and laminar distributions in the absence of visual input /80/. In another study, changes in both $GABA_A$ receptor expression and synaptic functioning were initiated well before eye opening. Moreover, dark rearing could not prevent the robust upregulation of $\alpha 1$ or the change in spontaneous inhibitory postsynaptic current (sIPSC) kinetics, indicating that these parameters are not dependent upon sensory (visual) input. Dark rearing experiments have shown that a lack of extrinsic input to the visual cortex does not affect the overall developmental regulation of synaptic functioning of $GABA_A$ receptors /40/. In the barrel cortex, the density of $GABA_A$ receptors is reduced in lamina IV following complete loss of peripheral afferent input. However, less severe tactile deprivation, which is known to affect cortical neuron responsiveness, produces little or no change in $GABA_A$ receptor distribution /60/. Taken together these results imply that certain components of the GABAergic network, particularly the presynaptic features of the GABAergic system (such as total number of synaptic boutons, functional active synapses, and properties of presynaptic inhibitory boutons), are sensitive to regulation by sensory activities. On the other hand, the postsynaptic properties of the GABAergic system (such as postsynaptic $GABA_A$ receptor subunits) may be regulated by activity-independent processes. The results of the following studies will help to further our understanding of the dilemma between the activity-dependent and -independent components of GABAergic maturation. It was reported that overexpression of brain-derived neurotrophic factor (BDNF) promotes the maturation of GABA transmission in the absence of activity (via dark rearing) in the visual cortex /34,56/. Therefore, trophic factors, such as BNDF, appear to regulate the maturation of the GABAergic system; however, the release of BDNF is activity-dependent and developmentally regulated. A further understanding of these different components of GABAergic maturation and how they are regulated is of great importance to future studies.

2.3. Homeostatic synaptic plasticity

Homeostatic synaptic plasticity is a form of plasticity that is triggered by changes in the overall level of activity of a neural circuit and has a crucial role in stabilizing the activity of neurons and networks /71,113/. Without this stabilizing mechanism, activity-dependent forms of plasticity could drive neural activity towards runaway excitation or quiescence. Homeostatic plasticity is mediated by mechanisms that include global changes in synaptic strength, changes in neuronal excitability, and the regulation of synapse number. Synaptic scaling is a major form of homeostatic plasticity that scales synaptic strength up or down to compensate for prolonged changes in activity /121/. Because homeostatic plasticity occurs in the absence of sensory activity, this type of regulation can be considered a form of **activity-independent plasticity**. Glutamatergic synapses and glutamatergic cells are known to exhibit very well characterized synaptic scaling and other forms of homeostatic plasticities in the visual cortex and other sensory regions /71,113/. However, examples of synaptic scaling of inhibitory synapses are very sparse. In the visual cortex, homeostatic potentiation of inhibitory feedback between interneurons and excitatory neurons may underlie the loss of visual responsiveness to the deprived eye /67,121/. The mechanisms of synaptic scaling are poorly understood. It may involve presynaptic or postsynaptic changes and the release of neural active substance(s) from glial cells /101/. It is important to test how GABAergic neurons undergo homeostatic changes and other activity-independent changes under various sensory deprivation paradigms and to examine the potential mechanisms underlying such homeostatic changes.

3. COMPARISON OF ACTIVITY-DEPENDENT REGULATION OF INHIBITORY VERSUS EXCITATORY NETWORKS

Sensory experience drives the plasticity of the body map in developing adult sensory cortices /22,105/. Early studies of visual receptive field plasticity during early postnatal life have established the role of activity in fine-tuning the receptive field properties of a visual cortical neuron, where inputs from the two eyes can either 'associate' or 'compete', depending on how well they are correlated /122/. Hebb postulated that associative memories are formed in the brain by a process of synaptic modification that strengthens connections when presynaptic activity correlates with postsynaptic firings /39/. Later, Stent modified this proposal by including mechanisms of synaptic weakening, i.e. connections weaken when they are inactive at the same time that postsynaptic neurons are active /102/. Long-term potentiation (LTP) and depression (LTD) of excitatory synaptic transmission has been demonstrated in almost all excitatory neurons (reviewed by Malenka and Bear /69/). It is clear that cortical activity, mediated via glutamate receptors, contributes to the experience-dependent refinement of the sensory map /13/. Although the cellular mechanisms underlying changes in cortical maps are not entirely clear, considerable evidence now confirms that LTP and LTD, or similar processes, are induced at specific cortical excitatory synapses onto principal neurons during map plasticity /3/, where LTP and LTD appear to induce either synaptic strengthening or elimination, respectively. The increase in synaptic strength that occurs during LTP is likely to involve structural changes in dendritic spines, either by the expansion of existing spines or by increased connectivity mediated via the addition of new spines. LTP causes a rapid local increase in the extension of filopodia and the formation of new spines at the site of stimulation /19,70/. This increase requires the activation of *N*-methyl-D-aspartate (NMDA) receptors and can be induced by a focal application of Ca^{2+}. Induction of LTD is accompanied by a marked shrinkage of spines. The spine shrinkage requires activation of NMDA receptors and calcineurin, similar to that for LTD. This activity-induced spine shrinkage may contribute to the activity-dependent elimination of synaptic connections /128/.

There is little evidence available that would indicate a similar process occurs at specific cortical excitatory synapses onto neocortical interneurons /1/. In the hippocampus, where LTP of glutamatergic synapses onto pyramidal neurons is very robust, LTP of glutamatergic transmission has been reported in interneurons /59,88/. However, a number of studies have documented the lack of long-term modifications in these synapses /72,73/. In the sensory cortices, input discrimination depends upon a delicate balance between inhibition and excitation /1/. Selective LTP of excitatory transmission to spiny neurons, without a corresponding potentiation of inhibitory transmission, would lead to a compromise of spatial and temporal precision and a degradation in the fidelity of signal processing /1,112/.

In excitatory neurons, postsynaptic forms of LTP and LTD of glutamatergic synapses are dependent on Ca^{2+}-signaling cascades, mostly on two key enzymes, calcineurin (CN) and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) /61,82/. Large increases in intracellular Ca^{2+} levels activate CaMKII and induce LTP /64/, whereas smaller increases preferentially activate CN and can result in LTD /14,82/. These two enzymes provide a switch-like mechanism for regulating glutamate receptor-dependent Ca^{2+} signaling processes, such as AMPA receptor trafficking and neurite outgrowth in cortical pyramidal neurons /4,12,46,125/. However, both enzymes are lacking in most hippocampal interneurons /72,125/. In developing sensory cortices, CaMKII is largely lacking in most neocortical interneurons /74/. Although heavily labeled calcineurin neurons appear in layer IV of the barrel cortex between 3 and 5 weeks of age /37/, it is unclear which neuronal subtypes express CN. Interneurons and excitatory neurons also differ in intracellular calcium dynamics induced by excitatory synaptic inputs. In excitatory neurons, Ca^{2+} influx is compartmentalized in dendritic spines, which cortical interneurons lack. Different subtypes of cortical interneurons also vary in the Ca^{2+} signals they generate. Using two photon confocal imaging techniques, Goldberg and Yuste /36/ have shown that fast-spiking basket inter-

neurons are coincidence detectors: AMPA receptors generate fast Ca^{2+} microdomains in speed-optimized circuits, whereas dendrite-targeting interneurons may serve as burst detectors: active dendrites amplify local synaptic inputs and generate global Ca^{2+} signals. Because local spikes spatially controlling the expression of specific conductance underlies Hebbian plasticity, the differences in calcium dynamics indicate different mechanisms underlying activity-dependent plasticity in interneurons versus pyramidal neurons.

4. WHAT ARE THE MOLECULAR AND CELLULAR MECHANISMS THAT REGULATE THE MATURATION OF INHIBITORY NETWORKS?

Patterned sensory inputs provide pathway-specific and glutamate receptor-dependent increases in intracellular calcium /9,10,106/, which in turn activate downstream signaling cascades that are important for the formation and stabilization of synapses. Neuronal activity induces gene transcription by modulating transcriptional activators and repressors /38/. This type of regulation has been shown to be crucial for many different types of long-term neural plasticity /85,99,120/. A vast body of literature reveals the importance of NMDA receptors (NMDARs) and metabotropic glutamate receptors (mGluRs) in the development of ***excitatory*** neural networks and their plasticity. Information regarding involvement of both NMDARs and mGluRs in experience-dependent plasticity of intracortical glutamatergic synapses on ***inhibitory*** interneurons is sparse. In most examples mentioned below, activity induces calcium influx, which in turn regulates gene transcription in GABAergic neurons. This type of regulation occurs during synaptogenesis throughout synaptic plasticity.

4.1. Brain-derived neurotrophic factor and maturation of specific GABAergic inhibitory networks

BDNF is essential for the differentiation of multiple interneuron subtypes and the formation of their synaptic contacts. The expression and release of BDNF correlates with the amount of excitatory neuronal activity /65/, suggesting that it might act in a feedback dependent manner to maintain a balance between excitation and inhibition during development. A role of BNDF in modulating the maturation of the neocortical inhibitory network has been described in the visual cortex, where maturation is influenced by visual experience during the early postnatal period. In transgenic mice in which the postnatal rise of BDNF was accelerated, the maturation of GABAergic innervation and inhibition was also accelerated. These transgenic mice also showed a precocious development of visual acuity and an earlier termination of the critical period for ocular dominance plasticity. This study indicates that BDNF promotes the maturation of cortical inhibition during early postnatal life, thereby regulating the critical period for visual cortical plasticity /44/. Using organotypic cortical slice cultures from neonatal mice biolistically transfected with green fluorescent protein (GFP) driven by the GAD67 promoter, Jin *et al.* /50/ further showed that BDNF, released by neocortical pyramidal neurons in response to depolarization, enhances dendritic growth and branching in nearby inhibitory interneurons. In another study, it was found that postsynaptic BDNF-TrkB signaling contributes to the target-selective potentiation of inhibitory presynaptic machinery. Since BDNF is expressed in an activity-dependent manner *in vivo*, this selectivity may be one of the key mechanisms by which the independence of functional neuronal circuits is maintained /87/. In addition, the activity-dependent scaling of inhibitory synaptic strength can be modulated by BDNF/TrkB-mediated signaling /109/. In purified fast-spiking (FS) interneuronal culture preparations, BDNF promoted FS cell differentiation by increasing the somatic diameter, dendritic branching, and the frequency of action potential firing. In addition, BDNF treatment led to a significant upregulation of synaptophysin and vesicular GABA transporter expression, components of the synaptic machinery critical for GABA release, which was paralleled by an increase in synaptic strength /7/.

4.2. Ionotropic and metabotropic glutamate receptors and experience-dependent plasticity of interneuronal networks

a) N-Methyl-D-aspartate receptors

Local GABA circuits contribute to sensory experience-dependent refinement of neuronal connections in the developing nervous system. A few recent studies showed that GABAergic synapses themselves can be rapidly modified by sensory stimuli. Like experience-dependent plasticity in excitatory networks, NMDARs appear to play an important role in the plasticity of GABAergic synapses. However, the cellular mechanisms by which NMDARs regulate GABAergic synapses appear to differ from those observed in excitatory synapses, in that their actions take place in presynaptic terminals /29/. In developing cerebellar cultures, NMDARs alter GABAergic synapses by increasing the size of the terminal and the spontaneous GABA release. These findings support recent results which show parallel changes in inhibitory synaptic efficacy *in vivo* in the molecular layer of the cerebellum /29/. In the developing *Xenopus* retinotectal system, repetitive light stimuli or theta burst stimulation of the optic nerve induce LTP of glutamatergic inputs, but LTD of GABAergic inputs to the same tectal neuron. The LTD is due to a reduction in presynaptic GABA release and requires activation of presynaptic NMDARs and coincident, high-level GABAergic activity. Thus, the presynaptic NMDAR may function as a coincidence detector for adjacent glutamatergic and GABAergic activities, leading to coordinated synaptic modification by sensory experience /62/.

b) Metabotropic glutamate receptors

In a recent study /63/, $mGluR_{1a}$, $mGluR_5$, and $mGluR_{2/3}$ were found to be concentrated in layer IV of the somatosensory cortex from its early differentiation, and were densely expressed in the barrel hollows, peaking between P4 and P9, a time when intense $NMDAR_1$ immunoreactivity was present in layer IV /92/. These findings suggest the involvement of mGluRs in the developmental plasticity of thalamocortical (TC) synapses during the establishment of somatotopic whisker representational maps in SI /16/. In addition, an interaction between mGluRs and NMDARs has been demonstrated /58,63/. A key component of this interaction may be due to synergistic changes of intracellular calcium signaling. For example, mGluRs, via the phospholipase C-b1 (PLC-b1) signaling pathway, regulate intracellular calcium signaling pathways. Indeed, in both PLC-b1 and $mGluR_5$ knockout mice, barrel formation in somatosensory cortex was disrupted /98/. Furthermore, $mGluR_{1\&5}$ receptors were found in dendrites of neocortical and hippocampal interneurons /81/, indicating a potential role in regulating excitation-inhibition matching.

4.3. GABA-mediated self-regulation

Spontaneous Ca^{2+} transients expressed prior to synaptogenesis regulate the developmental appearance of GABA. In cultured *Xenopus* spinal neurons, GAD, the enzyme responsible for GABA synthesis, is regulated by a Ca^{2+}-dependent process and parallels the appearance of GABA. GAD67 transcripts first appear in the embryonic spinal cord during the period in which these Ca^{2+} spikes are generated, in a pattern that is temporally and spatially appropriate to account for differentiation of GABAergic interneurons /118/. In mature circuits, a role for GABA in mediating activity-dependent plasticity has also been implicated. In hippocampal cultures and acute hippocampal slices, coincident pre- and postsynaptic activation of the GABAergic interneurons led to a persistent change in inhibitory synaptic strength /30,123/. Is it possible that these mechanisms regulate excitation and inhibition matching in the sensory cortex *in vivo*? During sensory processing, FS interneurons, which are involved in sensory feedforward inhibition, generate reliable and robust sensory-mediated action potentials and robust feedforward inhibitory synaptic potentials that regulate firing of spiny neurons /104/. Evidence linking spike timing of interneuron *a* to interneuron *b* is rare during sensory processing (except when *a* and *b* are connected via gap junctions [see Fig. 1]). In addition, early sensory deprivation and persistent sensory deprivation appear to have opposite effects on the strength of GABAergic transmission /79, 104,113/. Very interestingly, in a recent study, it was shown that GABAergic synaptic strength can

be regulated bi-directionally. In the subthalamic nucleus (STN), rebound burst firing of STN neurons induces long-lasting bi-directional modifications of GABAergic synaptic transmission in STN neurons. The potentiation or depression of IPSPs was associated with a negative or positive shift in the reversal potential of IPSPs /117/. In all these above-mentioned examples, the modification required Ca^{2+} influx through postsynaptic L-type Ca^{2+} channels and was due to a local decrease in K^+/Cl^- co-transport activities /30,117,123/. GABA also plays an essential role in synaptic integration of newly generated excitatory neurons in the adult brain, and for activity-dependent regulation of adult neurogenesis. In hippocampal dentate gyrus, newborn granule cells of the adult hippocampus are tonically activated by ambient GABA before being sequentially innervated by GABA- and glutamate-mediated synaptic inputs. This effect appears to be related to the excitatory action of GABA /33/. In adult neocortex, neurogenesis occurs in GABAergic interneurons as well /15/; however, it is unclear whether GABA plays a similar role.

4.4. Effects of sensory experience on activity-dependent gene regulation: gene profiling studies

Recently, using microarray analysis combined with other molecular and immunohistochemical methods, a pool of signaling genes, whose expression is regulated by visual deprivation (produced by monocular enucleation [ME]) in visual cortex, were identified /68,111/. In one recent study, Majdan and Shatz /68/ showed that there are two pools of genes, a common sets of genes (~10 genes) and an age-related gene pool (about 50 genes), that are regulated differently by sensory deprivation (dark rearing). The common gene set defines a MAP kinase signaling pathway, and are regulated by vision at all ages studied. Dark rearing does not perturb the regulation of this common gene set, but instead profoundly changes the regulation of the age-specific gene set. Thus, critical period formation and experience-dependent plasticity appear to be regulated by common genes as well as age-related genes. Among the common sets of target genes, MAP kinase signaling pathways have been implicated in experience-dependent, -independent and homeostatic plasticity of inhibitory networks. The roles of other genes that are regulated only at specific ages in regulating inhibitory networks are largely unknown. Among these genes, connexin 43, annexin XI, regulator of G-protein signaling gene 4 (RGS4), and Rho-associated, coiled-coil forming protein kinase p160 (Rock-2) are known to be involved in regulating gap junction coupling, dendritic morphology, and the synaptic properties of inhibitory interneurons. In another related study /111/, $GABA_A$ receptor subunits $\alpha 2$ and $\alpha 3$, $\beta 1$ and $\beta 3$ genes were found to be upregulated by monocular derivation or dark rearing. Other genes, such as GAD67 and parvalbumin, which have been implicated in experience-dependent plasticity, have all been found to be affected by visual experiences /111/. Further experiments examining the physiological consequences of altered gene expression will certainly help to clarify the mechanisms underlying experience-dependent plasticity.

5. WHAT ARE THE FUNCTIONAL CONSEQUENCES OF A NEURAL NETWORK?

There are different types of interneuerons whose laminar location, synaptic targets, firing properties and functions are extremely diverse /52,97,100, 110/. Neocortical local circuits can also be further divided into interlaminar and intralaminar connections /110/. Next the focus will center on inhibitory networks involved in mediating feedforward inhibition in the sensory cortex.

5.1. Feedforward inhibition and receptive field

Sensory-mediated intracortical inhibition plays a role in the shaping of sensory cortical receptive fields /83,107,108,115/. A powerful feedforward inhibitory mechanism could serve to constrain the size of suprathreshold receptive fields and to modify the temporal response property of targeted cortical neurons (see Fig. 1). In the somatosensory cortex, putative inhibitory interneurons with sensitive and broadly tuned feedforward inhibitory properties have been described in the rabbit and rat /96,107,108/.

Rodent whisker sensory input is represented somatopically in the barrel field of layer IV of S1 neocortex /124/. A cohort of morphologically distinct excitatory neurons and inhibitory interneurons has been described in layer IV barrels /53,124/. The vast majority (70-90%) of neurons within layer IV of a barrel forms a reciprocally connected excitatory network, and are the major targets for TC inputs /18,26,27,91/. By contrast, interneurons only represent about 10-30% of the total number of neurons within the barrel cortex /53,77,96/. In order for precise registration of sensory information to take place without runaway recurrent excitation in the population, excitation and inhibition must be delicately balanced /11/. How does the inhibition supplied by a limited number of interneurons provide the necessary inhibitory control of activities within an excitatory network? The ratio of excitatory and inhibitory synapses and their distribution are at least as important as the numbers of involved cells, e.g., single chandelier cells likely control the firing of many pyramidal neurons. This dilemma can only be resolved through the quantitative analysis of the properties of unitary inhibitory and excitatory synaptic events in layer 4. In a recent study, we have shown that there is a striking contrast between the strength of unitary GABAergic inhibitory and glutamatergic excitatory synaptic events /104/ (Fig. 3). The average conductance of unitary IPSCs (uIPSCs) from individual FS interneurons is about 10-fold greater than that of uEPSCs in spiny neurons. This difference, together with rapid feedforward inhibition, serves to counteract the convergent cortical excitation from spiny neurons /104/ (Figs. 2 and 3). Cross-correlation analysis of TC-evoked polysynaptic responses from pairs of unconnected spiny neurons located in the same barrel suggests that these cells receive inhibition from a common group of interneurons. FS interneurons are likely to be the major source of local feedforward inhibition, since networks of electrically coupled FS cells produce highly synchronized activities /2,6/. This could have profound influences on the generation of TC-mediated feedforward inhibition. Essentially, the electrical coupling allows the firing FS neurons to be 'phase locked' to their electrically coupled partners /6,35/, and thus contribute to the synchronization of FS

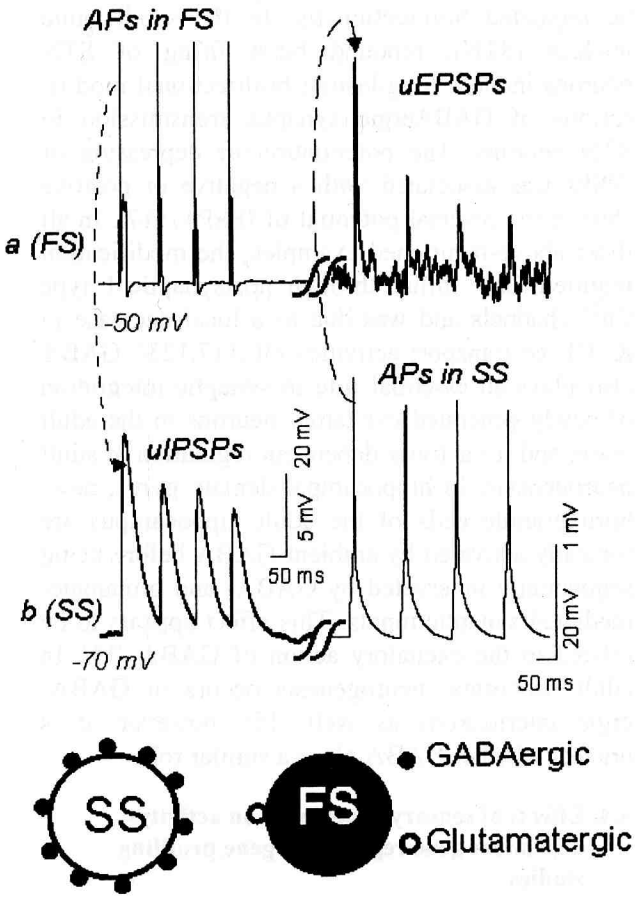

Fig. 3: **Reciprocal synaptic connection between spiny stellate cells and basket cells. Top:** Paired recordings from a reciprocally connected fast-spiking (FS) cell (**a**) and spiny stellate (SS) cell (**b**) show unitary synaptic potentials elicited by trains (b, left) or single action potentials (b, right) in the presynaptic cell. **B1:** Trains of action potentials (APs) elicited by depolarizing currents (250 pA, 100 ms) in FS cell a (top left) evoked unitary (u) IPSPs in cell b (bottom left, dotted line and arrow), while action potentials in SS cell b (bottom right, dashed line and arrow) elicited uEPSPs in cell a (top, left). Note that the amplitude of uIPSPs is >10 times larger than the uEPSPs. uIPSPs were recorded as outward currents due to high intracellular pipette Cl^- content. **Bottom:** Note that inhibitory synaptic boutons (from a single basket cell) in a spiny neuron outnumber glutamatergic boutons from single spiny neurons in the basket cell. Adapted from Sun *et al.* /104/.

spikes. In addition, the electrical coupling might increase the probability of firing in FS networks because a suprathreshold excitatory postsynaptic potential (EPSP) in one FS interneuron might increase the firing probability of its electrically coupled partners which have TC inputs slightly below the threshold. Feedforward inhibition, provided by the FS interneurons, limits the TC-mediated excitation of spiny neurons and reduces the likelihood that disynaptic reciprocal excitation will occur, particularly when TC input is weak /104,107,108/ (Fig. 3). Furthermore, FS neurons and spiny neurons could have different receptive field properties /107,108/. Our results show that FS cell activation can result in selective inhibition of spiking in spiny neurons located in the same barrel and in adjacent barrels /104/. This conclusion supports the idea that FS neurons are involved in modifying receptive field properties in barrel cortices. In the auditory cortex, one of the roles of cortical inhibition in sound processing is to increase the temporal precision. This is achieved via feedforward inhibition that occurs immediately following pyramidal neuron action potentials (APs) /119/. However, there are no differences in receptive fields between excitatory neurons and inhibitory neurons in auditory cortex. This finding is different from somatosensory cortex, where feedforward inhibition controls both the temporal precision and, likely, the receptive field /8/. In the visual cortex, sensitive and broadly tuned feedforward inhibition could account for the contrast-invariant orientation tuning seen in the feline visual cortex. However, the existence of such interneurons in cat visual cortex is uncertain /43/.

5.2. Importance of inhibitory networks in experience-dependent refinement of sensory maps

Inhibition may play an important role in activity-dependent plasticity which underlies some of the most fundamental aspects of circuit maturation, such as sensory mediated refinement of receptive fields /18,24,32,84/. Experience-dependent synaptic plasticity in the sensory cortex requires precision in spike-timing of the post-synaptic excitatory cortical neurons. The role of inhibition in experience-dependent plasticity becomes clearer with two recent studies carried out in the auditory cortex and visual cortex. In the first series of studies, the influence of GABA-mediated inhibition on adaptive adjustment of the owl's auditory space map during the initial phase of plasticity was studied. Zheng and Knudsen found that the pattern of feedforward inhibition is less dynamic than the pattern of feedforward excitation at the site of map plasticity /126,127/. In a second set of experiments, the intracortical inhibitory influences upon developing visual afferents were further examined by altering intrinsic GABA-mediated inhibition with benzodiazepines in the visual cortex. Local enhancement by agonist (diazepam) infusion did not perturb visual responsiveness, but did widen column spacing. An inverse agonist (DMCM) produced the opposite effect. Thus, intracortical inhibitory circuits shape the geometry of incoming thalamic arbors, suggesting that cortical columnar architecture depends on neuronal activity /41,42/. Similar roles of inhibition in the somatosensory cortex have also been implicated /31/. These results suggest that intracortical inhibition, presumably via modulating spike patterns of spiny neurons, regulate the experience-dependent plasticity and columnar organization (Fig. 1). Interestingly, in a rat model of neocortical dysplasia, LTP is impaired, presumably due to diminished GABAergic inhibitory connections in affected areas /90/. In animal models of epilepsy and in patients with developmental epilepsy /114/, where the balance of inhibition and excitation was disturbed, the capacity for forming Hebbian forms of plasticity (in animals) and learning (in humans) is severally undermined /116/. Mental retardation and learning difficulties are also common problems in several neurological disorders (such as autism and fragile-X syndrome), and are accompanied by perturbation of inhibition and excitation /17/.

Homeostatic synaptic plasticity also regulates excitation and inhibition separately within recurrent cortical networks to preserve balanced function during constant activity-dependent changes in synaptic drive /71,113/. In sensory deprived cortices, lateral excitation is enhanced whereas feedforward and feedback inhibition are reduced, leading to enhanced Hebbian plasticity and a

strengthening of synaptic connections between deprived and spared cortex. In cultured cortical and hippocampal networks, activity blockade reversibly decreases perisomatic inhibition and increases the quantal distribution of EPSCs in pyramidal neurons /94/. Thus, it appears that inhibition and excitation onto pyramidal neurons are regulated in opposite directions by activity blockade.

6. CONCLUDING REMARKS

Experience and the resulting changes in neuronal activity shape the nervous system and its function. Activity-dependent changes in neuronal function are essential for the survival of the animal and normal brain function. The impact of restricting neuronal activity through sensory neglect is evident in the human population. Each year in the United States alone, over 500,000 children suffer from 'neglect', and these children have a much higher probability of emotional, behavioral, cognitive, and physical delays than normal children. As such, research aimed at identifying mechanisms underlying activity-induced plasticity of brain circuits and brain function has immediate health relevance. It is becoming clearer that the GABAergic inhibitory circuit plays a very important role in sensory-dependent refinement of functional neocortical circuits. Future experiments aimed at unraveling the mechanisms underlying activity-dependent plasticity of inhibitory circuits will help to further develop the concept that early experiences shape the structure of neocortical excitatory networks, and they also fine-tune the inhibitory networks to maintain a balance between excitation and inhibition. These types of experiments will also help to determine the correlation between patterns of synaptic maturation and the occurrence of critical periods for forming functional sensory inhibitory structure. In this vein, several priorities of future experiments should be addressed: 1) the mechanisms involved in the activity-dependent maturation of brain inhibitory circuits *in vivo*; 2) roles and mechanisms of GABAergic activity in regulating the presynaptic and postsynaptic properties of GABAergic synaptic connections; 3) roles of sensory experiences in regulating GABA-mediated self-regulation; 4) roles and mechanisms of glutamatergic synaptic transmission in regulating the presynaptic and postsynaptic properties of GABAergic synaptic connections and their modulation by sensory activity; 5) experience-dependent regulation of dendritic-targeting interneurons and interlaminar or intercolumar inhibitory connections; and 6) the homeostatic synaptic plasticity of GABAergic synapses and its regulation by sensory experiences in different sensory structures. Thoroughly understanding inhibition-excitation matching will bridge the gap between the experience-dependent plasticity of synapses and the maturation of functionally relevant neocortical circuits. It will also help us to gain further insights into the mechanisms underlying several developmentally related neurological disorders, such as cortical dysplasia, schizophrenia, epilepsy and dyslexia, in which early unfavorable endogenous and exogenous conditions create a long-lasting impact on the mature cortex.

ACKNOWLEDGEMENTS

Research conducted in the author's laboratory is supported by National Institutes of Health grant P20 RR15640 from NCRR and 5R01NS057415-02 from NINDS. I thank Mr. Andrew Young for editing the manuscript.

REFERENCES

1. Alonso JM, Swadlow HA. Thalamocortical specificity and the synthesis of sensory cortical receptive fields. J Neurophysiol 2005; 94: 26-32.
2. Amitai Y, Gibson JR, Beierlein M, Patrick SL, Ho AM, Connors BW, Golomb D. The spatial dimensions of electrically coupled networks of interneurons in the neocortex. J Neurosci 2002; 22: 4142-4152.
3. Bear MF, Press WA, Connors BW. Long-term potentiation in slices of kitten visual cortex and the effects of NMDA receptor blockade. J Neurophysiol 1992; 67: 841-851.
4. Beaumont V, Zhong N, Fletcher R, Froemke RC, Zucker RS. Phosphorylation and local presynaptic protein synthesis in calcium- and calcineurin-dependent induction of crayfish long-term facilitation. Neuron 2001; 32: 489-501.
5. Beierlein M, Gibson JR, Connors BW. A network of electrically coupled interneurons drives synchronized inhibition in neocortex. Nat Neurosci 2000; 3: 904-910.

6. Beierlein M, Gibson JR, Connors BW. Two dynamically distinct inhibitory networks in layer 4 of the neocortex. J Neurophysiol 2003; 90: 2987-3000.
7. Berghuis P, Dobszay MB, Sousa KM, Schulte G, Mager PP, Hartig W, Gorcs TJ, Zilberter Y, Ernfors P, Harkany T. Brain-derived neurotrophic factor controls functional differentiation and microcircuit formation of selectively isolated fast-spiking GABAergic interneurons. Eur J Neurosci 2004; 20: 1290-1306.
8. Bruno RM, Simons DJ. Feedforward mechanisms of excitatory and inhibitory cortical receptive fields. J Neurosci 2002; 22: 10966-10975.
9. Castro-Alamancos MA. Dynamics of sensory thalamocortical synaptic networks during information processing states. Prog Neurobiol 2004; 74: 213-247.
10. Castro-Alamancos MA, Connors BW. Short-term synaptic enhancement and long-term potentiation in neocortex. Proc Natl Acad Sci USA 1996; 93: 1335-1339.
11. Chagnac-Amitai Y, Connors BW. Synchronized excitation and inhibition driven by intrinsically bursting neurons in neocortex. J Neurophysiol 1989; 62: 1149-1162.
12. Cooke SF, Bliss TV. The genetic enhancement of memory. Cell Mol Life Sci 2003; 60: 1-5.
13. Crair MC, Gillespie DC, Stryker MP. The role of visual experience in the development of columns in cat visual cortex. Science 1998; 279: 566-570.
14. Cummings JA, Nicola SM, Malenka RC. Induction in the rat hippocampus of long-term potentiation (LTP) and long-term depression (LTD) in the presence of a nitric oxide synthase inhibitor. Neurosci Lett 1994; 176: 110-114.
15. Dayer AG, Cleaver KM, Abouantoun T, Cameron HA. New GABAergic interneurons in the adult neocortex and striatum are generated from different precursors. J Cell Biol 2005; 168: 415-427.
16. DeFelipe J. Types of neurons, synaptic connections and chemical characteristics of cells immunoreactive for calbindin-D28K, parvalbumin and calretinin in the neocortex. J Chem Neuroanat 1997; 14: 1-19.
17. Dong WK, Greenough WT. Plasticity of nonneuronal brain tissue: roles in developmental disorders. Ment Retard Dev Disabil Res Rev 2004; 10: 85-90.
18. Egger V, Feldmeyer D, Sakmann B. Coincidence detection and changes of synaptic efficacy in spiny stellate neurons in rat barrel cortex. Nat Neurosci 1999; 2: 1098-1105.
19. Engert F, Bonhoeffer T. Dendritic spine changes associated with hippocampal long-term synaptic plasticity. Nature 1999; 399: 66-70.
20. Fagiolini M, Pizzorusso T, Berardi N, Domenici L, Maffei L. Functional postnatal development of the rat primary visual cortex and the role of visual experience: dark rearing and monocular deprivation. Vision Res 1994; 34: 709-720.
21. Feldman DE. Inhibition and plasticity. Nat Neurosci 2000; 3: 303-304.
22. Feldman DE, Brecht M. Map plasticity in somatosensory cortex. Science 2005; 310: 810-815.
23. Feldman DE, Knudsen EI. Experience-dependent plasticity and the maturation of glutamatergic synapses. Neuron 1998; 20: 1067-1071.
24. Feldman DE, Nicoll RA, Malenka RC. Synaptic plasticity at thalamocortical synapses in developing rat somatosensory cortex: LTP, LTD, and silent synapses. J Neurobiol 1999; 41: 92-101.
25. Feldman DE, Nicoll RA, Malenka RC, Isaac JT. Long-term depression at thalamocortical synapses in developing rat somatosensory cortex. Neuron 1998; 21: 347-357.
26. Feldmeyer D, Egger V, Lubke J, Sakmann B. Reliable synaptic connections between pairs of excitatory layer 4 neurones within a single 'barrel' of developing rat somatosensory cortex. J Physiol 1999; 521: 169-190.
27. Feldmeyer D, Lubke J, Silver RA, Sakmann B. Synaptic connections between layer 4 spiny neurone-layer 2/3 pyramidal cell pairs in juvenile rat barrel cortex: physiology and anatomy of interlaminar signalling within a cortical column. J Physiol 2002; 538: 803-822.
28. Ferster D. Neuroscience. Blocking plasticity in the visual cortex. Science 2004; 303: 1619-1621.
29. Fiszman ML, Barberis A, Lu C, Fu Z, Erdelyi F, Szabo G, Vicini S. NMDA receptors increase the size of GABAergic terminals and enhance GABA release. J Neurosci 2005; 25: 2024-2031.
30. Fiumelli H, Cancedda L, Poo MM. Modulation of GABAergic transmission by activity via postsynaptic Ca^{2+}-dependent regulation of KCC2 function. Neuron 2005; 48: 773-786.
31. Foeller E, Celikel T, Feldman DE. Inhibitory sharpening of receptive fields contributes to whisker map plasticity in rat somatosensory cortex. J Neurophysiol 2005; 94: 4387-4400.
32. Froemke RC, Dan Y. Spike-timing-dependent synaptic modification induced by natural spike trains. Nature 2002; 416: 433-438.
33. Ge S, Goh EL, Sailor KA, Kitabatake Y, Ming GL, Song H. GABA regulates synaptic integration of newly generated neurons in the adult brain. Nature 2006; 439: 589-593.
34. Gianfranceschi L, Siciliano R, Walls J, Morales B, Kirkwood A, Huang ZJ, Tonegawa S, Maffei L. Visual cortex is rescued from the effects of dark rearing by overexpression of BDNF. Proc Natl Acad Sci USA 2003; 100: 12486-12491.
35. Gibson JR, Beierlein M, Connors BW. Two networks of electrically coupled inhibitory neurons in neocortex. Nature 1999; 402: 75-79.
36. Goldberg JH, Yuste R. Space matters: local and global dendritic Ca^{2+} compartmentalization in cortical interneurons. Trends Neurosci 2005; 28: 158-167.
37. Goto S, Nagahiro S, Korematsu K, Ushio Y, Fukunaga K, Miyamoto E, Hofer W. Cellular colocalization of calcium/calmodulin-dependent protein kinase II and

calcineurin in the rat cerebral cortex and hippocampus. Neurosci Lett 1993; 149: 189-192.
38. Greenberg ME, Ziff EB, Greene LA. Stimulation of neuronal acetylcholine receptors induces rapid gene transcription. Science 1986; 234: 80-83.
39. Hebb DO. The mammal and his environment. Am J Psychiatry 1955; 111: 826-831.
40. Heinen K, Bosman LW, Spijker S, van Pelt J, Smit AB, Voorn P, Baker RE, Brussaard AB. $GABA_A$ receptor maturation in relation to eye opening in the rat visual cortex. Neuroscience 2004; 124: 161-171.
41. Hensch TK, Fagiolini M, Mataga N, Stryker MP, Baekkeskov S, Kash SF. Local GABA circuit control of experience-dependent plasticity in developing visual cortex. Science 1998; 282: 1504-1508.
42. Hensch TK, Stryker MP. Columnar architecture sculpted by GABA circuits in developing cat visual cortex. Science 2004; 303: 1678-1681.
43. Hirsch JA, Martinez LM. Circuits that build visual cortical receptive fields. Trends Neurosci 2006; 29: 30-39.
44. Huang ZJ, Kirkwood A, Pizzorusso T, Porciatti V, Morales B, Bear MF, Maffei L, Tonegawa S. BDNF regulates the maturation of inhibition and the critical period of plasticity in mouse visual cortex. Cell 1999; 98: 739-755.
45. Hubel DH, Wiesel TN, LeVay S. Plasticity of ocular dominance columns in monkey striate cortex. Philos Trans R Soc Lond B Biol Sci 1977; 278: 377-409.
46. Isaac JT, Crair MC, Nicoll RA, Malenka RC. Silent synapses during development of thalamocortical inputs. Neuron 1997; 18: 269-280.
47. Iwai Y, Fagiolini M, Obata K, Hensch TK. Rapid critical period induction by tonic inhibition in visual cortex. J Neurosci 2003; 23: 6695-6702.
48. Jiang B, Huang ZJ, Morales B, Kirkwood A. Maturation of GABAergic transmission and the timing of plasticity in visual cortex. Brain Res Brain Res Rev 2005; 50: 126-133.
49. Jiao Y, Zhang C, Yanagawa Y, Sun QQ. Major effects of sensory experiences on the neocortical inhibitory circuits. J Neurosci 2006; 26: 8691-8701.
50. Jin X, Hu H, Mathers PH, Agmon A. Brain-derived neurotrophic factor mediates activity-dependent dendritic growth in nonpyramidal neocortical interneurons in developing organotypic cultures. J Neurosci 2003; 23: 5662-5673.
51. Kash SF, Tecott LH, Hodge C, Baekkeskov S. Increased anxiety and altered responses to anxiolytics in mice deficient in the 65-kDa isoform of glutamic acid decarboxylase. Proc Natl Acad Sci USA 1999; 96: 1698-1703.
52. Kawaguchi Y, Kondo S. Parvalbumin, somatostatin and cholecystokinin as chemical markers for specific GABAergic interneuron types in the rat frontal cortex. J Neurocytol 2002; 31: 277-287.
53. Keller A, White EL. Synaptic organization of GABAergic neurons in the mouse SmI cortex. J Comp Neurol 1987; 262: 1-12.
54. Kelly MK, Carvell GE, Kodger JM, Simons DJ. Sensory loss by selected whisker removal produces immediate disinhibition in the somatosensory cortex of behaving rats. J Neurosci 1999; 19: 9117-9125.
55. Kim G, Kandler K. Elimination and strengthening of glycinergic/GABAergic connections during tonotopic map formation. Nat Neurosci 2003; 6: 282-290.
56. Kiser PJ, Cooper NG, Mower GD Expression of two forms of glutamic acid decarboxylase (GAD67 and GAD65) during postnatal development of rat somatosensory barrel cortex. J Comp Neurol 1998; 402: 62-74.
57. Knott GW, Quairiaux C, Genoud C, Welker E. Formation of dendritic spines with GABAergic synapses induced by whisker stimulation in adult mice. Neuron 2002; 34: 265-273.
58. Kotecha SA, Jackson MF, Al Mahrouki A, Roder JC, Orser BA, MacDonald JF. Co-stimulation of mGluR5 and N-methyl-D-aspartate receptors is required for potentiation of excitatory synaptic transmission in hippocampal neurons. J Biol Chem 2003; 278: 27742-27749.
59. Laezza F, Doherty JJ, Dingledine R. Long-term depression in hippocampal interneurons: joint requirement for pre- and postsynaptic events. Science 1999; 285: 1411-1414.
60. Land PW, De Blas AL, Reddy N. Immunocytochemical localization of $GABA_A$ receptors in rat somatosensory cortex and effects of tactile deprivation. Somatosens Mot Res 1995; 12: 127-141.
61. Leamey CA, Ho-Pao CL, Sur M. Role of calcineurin in activity-dependent pattern formation in the dorsal lateral geniculate nucleus of the ferret. J Neurobiol 2003; 56: 153-162.
62. Lien CC, Mu Y, Vargas-Caballero M, Poo MM. Visual stimuli-induced LTD of GABAergic synapses mediated by presynaptic NMDA receptors. Nat Neurosci 2006; 9: 372-380.
63. Liu XB, Munoz A, Jones EG. Changes in subcellular localization of metabotropic glutamate receptor subtypes during postnatal development of mouse thalamus. J Comp Neurol 1998; 395: 450-465.
64. Lledo PM, Hjelmstad GO, Mukherji S, Soderling TR, Malenka RC, Nicoll RA. Calcium/calmodulin-dependent kinase II and long-term potentiation enhance synaptic transmission by the same mechanism. Proc Natl Acad Sci USA 1995; 92: 11175-11179.
65. Lu B. BDNF and activity-dependent synaptic modulation. Learn Mem 2003; 10: 86-98.
66. Lu HC, Gonzalez E, Crair MC. Barrel cortex critical period plasticity is independent of changes in NMDA receptor subunit composition. Neuron 2001; 32: 619-634.
67. Maffei A, Nataraj K, Nelson SB, Turrigiano GG. Potentiation of cortical inhibition by visual deprivation. Nature 2006; 443: 81-84.
68. Majdan M, Shatz CJ. Effects of visual experience on activity-dependent gene regulation in cortex. Nat

Neurosci 2006; 9: 650-659.
69. Malenka RC, Bear MF. LTP and LTD: an embarrassment of riches. Neuron 2004; 44: 5-21.
70. Maletic-Savatic M, Malinow R, Svoboda K. Rapid dendritic morphogenesis in CA1 hippocampal dendrites induced by synaptic activity. Science 1999; 283: 1923-1927.
71. Marder E, Goaillard JM. Variability, compensation and homeostasis in neuron and network function. Nat Rev Neurosci 2006; 7: 563-574.
72. McBain CJ, Freund TF, Mody I. Glutamatergic synapses onto hippocampal interneurons: precision timing without lasting plasticity. Trends Neurosci 1999; 22: 228-235.
73. McBain CJ, Maccaferri G. Synaptic plasticity in hippocampal interneurons? A commentary. Can J Physiol Pharmacol 1997; 75: 488-494.
74. McDonald AJ, Muller JF, Mascagni F. GABAergic innervation of alpha type II calcium/calmodulin-dependent protein kinase immunoreactive pyramidal neurons in the rat basolateral amygdala. J Comp Neurol 2002; 446: 199-218.
75. Merzenich MM, Nelson RJ, Stryker MP, Cynader MS, Schoppmann A, Zook JM. Somatosensory cortical map changes following digit amputation in adult monkeys. J Comp Neurol 1984; 224: 591-605.
76. Merzenich MM, Sameshima K. Cortical plasticity and memory. Curr Opin Neurobiol 1993; 3: 187-196.
77. Micheva KD, Beaulieu C. Postnatal development of GABA neurons in the rat somatosensory barrel cortex: a quantitative study. Eur J Neurosci 1995; 7: 419-430.
78. Micheva KD, Beaulieu C. Quantitative aspects of synaptogenesis in the rat barrel field cortex with special reference to GABA circuitry. J Comp Neurol 1996; 373: 340-354.
79. Morales B, Choi SY, Kirkwood A. Dark rearing alters the development of GABAergic transmission in visual cortex. J Neurosci 2002; 22: 8084-8090.
80. Mower GD, Guo Y. Comparison of the expression of two forms of glutamic acid decarboxylase (GAD67 and GAD65) in the visual cortex of normal and dark-reared cats. Brain Res Dev Brain Res 2001; 126: 65-74.
81. Muly EC, Maddox M, Smith Y. Distribution of mGluR1α and mGluR5 immunolabeling in primate prefrontal cortex. J Comp Neurol 2003; 467: 521-535.
82. Nayak AS, Moore CI, Browning MD. Ca^{2+}/calmodulin-dependent protein kinase II phosphorylation of the presynaptic protein synapsin I is persistently increased during long-term potentiation. Proc Natl Acad Sci USA 1996; 93: 15451-15456.
83. Nelson SB. Temporal interactions in the cat visual-system. 3. Pharmacological studies of cortical suppression suggest a presynaptic mechanism. J Neurosci 1991; 11: 369-380.
84. Nelson SB, Sjostrom PJ, Turrigiano GG. Rate and timing in cortical synaptic plasticity. Philos Trans R Soc Lond B Biol Sci 2002; 357: 1851-1857.
85. Nestler EJ. Molecular basis of long-term plasticity underlying addiction. Nat Rev Neurosci 2001; 2: 119-128.
86. Neville H, Bavelier D. Human brain plasticity: evidence from sensory deprivation and altered language experience. Prog Brain Res 2002; 138: 177-188.
87. Ohba S, Ikeda T, Ikegaya Y, Nishiyama N, Matsuki N, Yamada MK. BDNF locally potentiates GABAergic presynaptic machineries: target-selective circuit inhibition. Cereb Cortex 2005; 15: 291-298.
88. Ouardouz M, Lacaille JC. Mechanisms of selective long-term potentiation of excitatory synapses in stratum oriens/alveus interneurons of rat hippocampal slices. J Neurophysiol 1995; 73: 810-819.
89. Owens DF, Liu XL, Kriegstein AR. Changing properties of $GABA_A$ receptor-mediated signaling during early neocortical development. J Neurophysiol 1999; 82: 570-583.
90. Peters O, Redecker C, Hagemann G, Bruehl C, Luhmann HJ, Witte OW. Impaired synaptic plasticity in the surround of perinatally acquired dysplasia in rat cerebral cortex. Cereb Cortex 2004; 14: 1081-1087.
91. Petersen CCH, Sakmann B. The excitatory neuronal network of rat layer 4 barrel cortex. J Neurosci 2000; 20: 7579-7586.
92. Rema V, Ebner FF. Postnatal changes in NMDAR1 subunit expression in the rat trigeminal pathway to barrel field cortex. J Comp Neurol 1996; 368: 165-184.
93. Rivera C, Voipio J, Payne JA, Ruusuvuori E, Lahtinen H, Lamsa K, Pirvola U, Saarma M, Kaila K. The K^+/Cl^- co-transporter KCC2 renders GABA hyperpolarizing during neuronal maturation. Nature 1999; 397: 251-255.
94. Rutherford LC, DeWan A, Lauer HM, Turrigiano GG. Brain-derived neurotrophic factor mediates the activity-dependent regulation of inhibition in neocortical cultures. J Neurosci 1997; 17: 4527-4535.
95. Shoykhet M, Land PW, Simons DJ. Whisker trimming begun at birth or on postnatal day 12 affects excitatory and inhibitory receptive fields of layer IV barrel neurons. J Neurophysiol 2005; 94: 3987-3995.
96. Simons DJ. Response properties of vibrissa units in rat SI somatosensory neocortex. J Neurophysiol 1978; 41: 798-820.
97. Somogyi P, Tamas G, Lujan R, Buhl EH. Salient features of synaptic organisation in the cerebral cortex. Brain Res Brain Res Rev 1998; 26: 113-135.
98. Spires TL, Molnar Z, Kind PC, Cordery PM, Upton AL, Blakemore C, Hannan AJ. Activity-dependent regulation of synapse and dendritic spine morphology in developing barrel cortex requires phospholipase C-β1 signalling. Cereb Cortex 2005; 15: 385-393.
99. Spitzer NC, Lautermilch NJ, Smith RD, Gomez TM. Coding of neuronal differentiation by calcium transients. Bioessays 2000; 22: 811-817.
100. Staiger JF, Kotter R, Zilles K, Luhmann HJ. Laminar characteristics of functional connectivity in rat barrel

cortex revealed by stimulation with caged-glutamate. Neurosci Res 2000; 37: 49-58.
101. Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF-alpha. Nature 2006; 440: 1054-1059.
102. Stent GS. A physiological mechanism for Hebb's postulate of learning. Proc Natl Acad Sci USA 1973; 70: 997-1001.
103. Stryker MP, Sherk H, Leventhal AG, Hirsch HV. Physiological consequences for the cat's visual cortex of effectively restricting early visual experience with oriented contours. J Neurophysiol 1978; 41: 896-909.
104. Sun QQ, Huguenard JR, Prince DA. Barrel cortex microcircuits: thalamocortical feedforward inhibition in spiny stellate cells is mediated by a small number of fast-spiking interneurons. J Neurosci 2006; 26: 1219-1230.
105. Sur M, Leamey CA. Development and plasticity of cortical areas and networks. Nat Rev Neurosci 2001; 2: 251-262.
106. Sur M, Rubenstein JL. Patterning and plasticity of the cerebral cortex. Science 2005; 310: 805-810.
107. Swadlow HA. Thalamocortical control of feed-forward inhibition in awake somatosensory 'barrel' cortex. Philos Trans R Soc Lond B Biol Sci 2002; 357: 1717-1727.
108. Swadlow HA. Fast-spike interneurons and feedforward inhibition in awake sensory neocortex. Cereb Cortex 2003; 13: 25-32.
109. Swanwick CC, Murthy NR, Kapur J. Activity-dependent scaling of GABAergic synapse strength is regulated by brain-derived neurotrophic factor. Mol Cell Neurosci 2006; 31: 481-492.
110. Thomson AM, West DC, Wang Y, Bannister AP. Synaptic connections and small circuits involving excitatory and inhibitory neurons in layers 2-5 of adult rat and cat neocortex: triple intracellular recordings and biocytin labelling in vitro. Cereb Cortex 2002; 12: 936-953.
111. Tropea D, Kreiman G, Lyckman A, Mukherjee S, Yu H, Horng S, Sur M. Gene expression changes and molecular pathways mediating activity-dependent plasticity in visual cortex. Nat Neurosci 2006; 9: 660-668.
112. Turrigiano GG, Leslie KR, Desai NS, Rutherford LC, Nelson SB. Activity-dependent scaling of quantal amplitude in neocortical neurons. Nature 1998; 391: 892-896.
113. Turrigiano GG, Nelson SB. Homeostatic plasticity in the developing nervous system. Nat Rev Neurosci 2004; 5: 97-107.
114. van Rijckevorsel K. Cognitive problems related to epilepsy syndromes, especially malignant epilepsies. Seizure 2006; 15: 227-234.
115. Vidyasagar TR, Pei X, Volgushev M. Multiple mechanisms underlying the orientation selectivity of visual cortical neurones. Trends Neurosci 1996; 19: 272-277.
116. von der Brelie C, Waltereit R, Zhang L, Beck H, Kirschstein T. Impaired synaptic plasticity in a rat model of tuberous sclerosis. Eur J Neurosci 2006; 23: 686-692.
117. Wang L, Kitai ST, Xiang Z. Activity-dependent bidirectional modification of inhibitory synaptic transmission in rat subthalamic neurons. J Neurosci 2006; 26: 7321-7327.
118. Watt SD, Gu X, Smith RD, Spitzer NC. Specific frequencies of spontaneous Ca^{2+} transients upregulate GAD 67 transcripts in embryonic spinal neurons. Mol Cell Neurosci 2000; 16: 376-387.
119. Wehr M, Zador AM. Balanced inhibition underlies tuning and sharpens spike timing in auditory cortex. Nature 2003; 426: 442-446.
120. West AE, Griffith EC, Greenberg ME. Regulation of transcription factors by neuronal activity. Nat Rev Neurosci 2002; 3: 921-931.
121. Wierenga CJ, Ibata K, Turrigiano GG. Postsynaptic expression of homeostatic plasticity at neocortical synapses. J Neurosci 2005; 25: 2895-2905.
122. Wiesel TN. Postnatal development of the visual cortex and the influence of environment. Nature 1982; 299: 583-591.
123. Woodin MA, Ganguly K, Poo MM. Coincident pre- and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl^- transporter activity. Neuron 2003; 39: 807-820.
124. Woolsey TA, Van der Loos H. The structural organization of layer IV in the somatosensory region (SI) of mouse cerebral cortex. The description of a cortical field composed of discrete cytoarchitectonic units. Brain Res 1970; 17: 205-242.
125. Yang Y, Fischer QS, Zhang Y, Baumgartel K, Mansuy IM, Daw NW. Reversible blockade of experience-dependent plasticity by calcineurin in mouse visual cortex. Nat Neurosci 2005; 8: 791-796.
126. Zheng W, Knudsen EI. Functional selection of adaptive auditory space map by $GABA_A$-mediated inhibition. Science 1999; 284: 962-965.
127. Zheng W, Knudsen EI. GABAergic inhibition antagonizes adaptive adjustment of the owl's auditory space map during the initial phase of plasticity. J Neurosci 2001; 21: 4356-4365.
128. Zhou Q, Homma KJ, Poo MM. Shrinkage of dendritic spines associated with long-term depression of hippocampal synapses. Neuron 2004; 44: 749-757.