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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 82071, Email to: neuron@uwyo.edu, Fax (307) 766 5526, Tel (307) 766 5602

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 will be 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?

Keywords

GABA; inhibition; cortex; microcircuits; synaptic plasticity; development

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Sensory experience drives the refinement of sensory maps in developing and adult sensory cortices (Wiesel, 1982; Crair et al., 1998; Merzenich et al., 1984; Stryker et al., 1978; Feldman and Brecht, 2005). Sensory deprivation causes the cortical area representing the deprived sensory input to shrink, and neighboring spared representations to enlarg, in somatosensory (Feldman and Brecht, 2005a; Merzenich et al., 1984), auditory (Merzenich and Sameshima, 1993), visual (Crair et al., 1998; Hubel et al., 1977; Wiesel, 1982) and language cortex (Neville and Bavelier, 2002). 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 (Sur and Leamey, 2001). Recently, cortical **inhibition** has been shown to play a vital role in the formation of critical periods for sensory plasticity (Hensch et al., 1998). However, both the process of experience-dependent postnatal maturation of neocortical inhibitory networks and the underlying mechanisms remain elusive (Alonso and Swadlow, 2005; Feldman, 2000; Micheva and Beaulieu, 1996). This review focuses on the mechanisms underlying activity-dependent

regulation of neocortical inhibitory circuits and the roles of inhibition in postnatal sensory map plasticity. Focus will be placed 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 circuit 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., 1999). During postnatal brain development, the reversal potential for $GABA_A$ mediated responses highly dependent upon intracellular Cl^- concentrations and is shifted from −46 mV (postnatal day 0) to −82 mV (>postnatal day 12; Owens et al., 1999). The increased expression of a K^+-Cl^- coupled co-transporter (KCC_2) is primarily responsible for the developmental switch of the GABA mediated response (Rivera et al., 1999).

Apart from the trophic actions of depolarizing GABA in early development, inhibitory networks are also recognized for playing crucial a role in experience-dependent refinement of neural networks. Distinct genes encode two isoforms of the GABA-synthesizing enzyme glutamic acid decarboxylase (GAD65 & GAD67). GAD67 is the larger protein, and provides a constitutive concentration of GABA throughout the 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 (Kash et al., 1999). However, the GAD65 knockout prevents ocular dominance plasticity (Hensch et al., 1998). In contrast, pharmacologically enhancing activity-dependent GABA transmission can prematurely enhance ocular dominance plasticity (Fagiolini et al., 1994; Iwai et al., 2003). 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 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 (Knott et al., 2002). Recent evidence also suggests that regulation of NMDA receptor subtype composition has no effect on barrel critical period formation (Lu et al., 2001). In the barrel cortex, GAD65 expression appears late in the critical period for barrel formation (Kiser et al., 1998), indicating GABA's role in the refinement of barrel structure. Additional 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 plasticity of excitatory connections, which follows a “use it or loose it” rule, i.e. connections with stimulated (or correlated) inputs grows stronger and connections with inactive (or uncorrelated) inputs grows weaker. This process was also known as the Hebbian rule (Hebb, 1955). A very compelling hypothesis about the role of inhibition in the formation of critical periods was that lateral cortical inhibition modulated the Hebbian-type plasticity by enhancing correlative activities of adjacent cortical neurons and producing anti-correlative activities in distal cells (Ferster, 2004). To serve this role, i.e. modulating the spike-timing and lateral spread of excitation, strength of inhibitory synapses must be developmentally regulated as well. Prior to the formation of neocortical critical periods, the strength of thalamocortical and intracortical glutamatergic synapses undergo drastic morphological, molecular and functional changes (Feldman et al., 1998; Feldman and Knudsen, 1998). Disturbances in the balance of excitation and inhibition in the neocortex induce cortical epileptic seizure. Therefore, a key requirement for 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 cortical local 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 (Shoykhet et al., 2005). 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 (Alonso and Swadlow, 2005). In an early study, sensory loss by selected whisker removal produces immediate disinhibition in the somatosensory cortex of behaving rats (Kelly et al., 1999). 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 (Knott et al., 2002; Micheva and Beaulieu, 1996). Recent studies of visual and auditory systems provide further evidence that the reorganization of inhibitory connections occurs at the circuitry level (Hensch et al., 1998c; Kim and Kandler, 2003). In the barrel cortex, active whisking enhances the emergence of mature inhibition (Kiser et al., 1998). In contrast, whisker trimming during the second through fourth postnatal week induced very robust down-regulation of perisomatic inhibitory synapses from fast-spiking basket cells. This down-regulation is accompanied by changes in presynaptic calcium dynamics and GAD expression in the nerve terminals as well (Jiao et al., 2006). Visual cortical GABAergic synapses of basket cells also show clearly defined dependence on sensory experience (Jiang et al., 2005). 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 (Morales et al., 2002, 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 (Majdan and Shatz, 2006; Tropea et al., 2006). Among these genes, genes for $GABA_A$ receptor subunits α2 & 3, β1 & 3 genes were found to be up-regulated

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 (Tropea et al., 2006). Thus activity-dependent regulation of gene expression appears to be a major means of remodeling inhibitory networks through experiences.

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 (Mower and Guo, 2001). In another study, both changes in $GABA_A$ receptor expression and synaptic functioning were initiated well before eye opening. Moreover, dark rearing could not prevent the robust up-regulation of alpha1 or the change in 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 (Heinen et al., 2004). 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 (Land et al., 1995). 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 property of presynaptic inhibitory boutons) are sensitive to regulation by sensory activities. On the other hand, postsynaptic properties of 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. In this study, it was reported that over-expression of BDNF promotes the maturation of GABA transmission in the absence of activity (via dark rearing) in the visual cortex (Gianfranceschi et al., 2003; Kiser et al., 1998). 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 (Marder and Goaillard, 2006; Turrigiano and Nelson, 2004). 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 (Wierenga et al., 2005). 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 (Marder and Goaillard, 2006;Turrigiano and Nelson, 2004). However, example of synaptic scaling of inhibitory synapses is 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 (Maffei et al., 2006; Wierenga et al., 2005). The mechanisms of synaptic scaling are poorly understood. It may involve presynaptic or postsynaptic changes and the release of neural active substance from glial cells (Stellwagen and Malenka, 2006). 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 vs. excitatory networks

Sensory experience drives the plasticity of the body map in developing adult sensory cortices (Sur and Leamey, 2001; Feldman and Brecht, 2005). 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 (Wiesel, 1982). Donald 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 (Hebb, 1955). Later, Gunther 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 is active (Stent, 1973). Long-term potentiation (LTP) and depression (LTD) of excitatory synaptic transmission has been demonstrated in almost all excitatory neurons (reviewed by Malenka and Bear, 2004). It is clear that cortical activity, mediated through glutamate receptors, contributes to the experience-dependent refinement of the sensory map (Crair et al., 1998). 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 (Bear et al., 1992), where the LTP and LTD appears 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 through the expansion of existing spines or through an 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 (Engert and Bonhoeffer, 1999; Maletic-Savatic et al., 1999). This increase requires the activation of 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 (Zhou et al., 2004).

There is little evidence available that would indicate a similar process occurs at specific cortical excitatory synapses onto neocortical interneurons (Alonso and Swadlow, 2005). In the hippocampus, where LTP of glutamatergic synapses onto pyramidal neurons is very robust; LTP of glutamatergic transmission has been reported in interneurons (Ouardouz and Lacaille, 1995; Laezza et al., 1999). However, a number of studies have documented the lack of long-term modifications in these synapses (McBain and Maccaferri, 1997; McBain et al., 1999). In the sensory cortices, input discrimination depends upon a delicate balance between inhibition and excitation (Alonso and Swadlow, 2005). 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 (Alonso and Swadlow, 2005; Turrigiano et al., 1998).

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; Nayak et al., 1996; Leamey et al.,

2003). Large increases in intracellular Ca^{2+} levels activate CaMKII and induce LTP (Lledo et al., 1995), whereas smaller increases activate CN preferentially and can result in LTD (Nayak et al., 1996; Cummings et al., 1994). 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 (Beaumont et al., 2001; Isaac et al., 1997; Cooke and Bliss, 2003; Yang et al., 2005). However, both enzymes are lacking in most hippocampal interneurons (McBain et al., 1999; Yang et al., 2005). In developing sensory cortices, CaMKII is largely lacking in most neocortical interneurons (McDonald et al., 2002). Although heavily labeled calcineurin neurons appeared in layer IV of the barrel cortex between 3 and 5 weeks of age (Goto et al., 1993), 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, have shown that fast-spiking basket interneurons 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 (Goldberg and Yuste, 2005). Because local spikes and spatially control the expression of specific conductance underlies Hebbian plasticity, the differences in calcium dynamics indicate different mechanisms underlying activity-dependent plasticity in interneurons vs. 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 (Castro-Alamancos and Connors, 1996; Castro-Alamancos, 2004;Sur and Rubenstein, 2005), 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 (Greenberg et al., 1986). This type of regulation has been shown to be crucial for many different types of long-term neural plasticity (Nestler, 2001; Spitzer et al., 2000; West et al., 2002). A vast body of literature reveals the importance of NMDARs and 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 (BDNF) and maturation of specific GABAergic inhibitory networks

Brain-derived neurotrophic factor (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 (Lu, 2003), 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 was described in visual cortex, where maturation is influenced by visual experience during an 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 (Huang et al., 1999). Using organotypic cortical slice cultures from neonatal mice and biolistically transfected with green fluorescent protein (GFP) driven by the GAD67 promoter, Jin et. al., further showed that BDNF, released by neocortical pyramidal neurons in response to depolarization, enhances dendritic growth and branching in nearby inhibitory interneurons (Jin et al., 2003). 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 (Ohba et al., 2005). In addition, the activity-dependent scaling of inhibitory synaptic strength can be modulated by BDNF/TrkB-mediated signaling (Swanwick et al., 2006). In purified fast-spiking 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 up-regulation 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 (Berghuis et al., 2004).

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

N-methyl-D-aspartate receptors (NMDARs)—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 (Fiszman et al., 2005). 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 (Fiszman et al., 2005). In the developing *Xenopus* retinotectal system, repetitive light stimuli or theta burst stimulation of the optic nerve induces 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 (Lien et al., 2006).

Metabotropic glutamate receptors (mGluRs)—In a recent study (Liu et al., 1998), $mGluR_{1a}$, $mGluR_5$, and $mGluR_{2/3}$ were found to be concentrated in layer IV of 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 (Rema and Ebner, 1996). This finding suggests the involvement of mGluRs in the developmental plasticity of TC synapses during the establishment of the somatotopic whisker representational maps in SI (DeFelipe, 1997). In addition, an interaction between mGluRs and NMDARs has been demonstrated (Liu et al., 1998; Kotecha et al., 2003). A key component of this interaction may 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 (Spires et al., 2005). Furthermore, $mGluR_{1\&5}$ receptors were found in dendrites of neocortical and hippocampal interneurons (Muly et al., 2003), indicating a potential role in regulating excitation-inhibition matching.

4.3.) Gamma-aminobutyric acid (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 (Watt et al., 2000). 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 (Woodin et al., 2003; Fiumelli et al., 2005). 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 feed-forward inhibition, generate reliable and robust sensory-mediated action potentials and robust feed-forward inhibitory synaptic potentials that regulate firing of spiny neurons (Sun et al., 2006). Evidence linking spike timing of interneuron ***a*** to interneuron ***b*** is rare during sensory processing (except when ***a*** & ***b*** are connected via gap junctions, Fig. 1). In addition, early sensory deprivation and persistent sensory deprivation appears to have opposite effects on the strength of GABAergic transmission (Morales et al., 2002; Sun et al., 2006; Turrigiano and Nelson, 2004). 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 bidirectional 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 (Wang et al., 2006). 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 (Woodin et al., 2003; Fiumelli et al., 2005; Wang et al., 2006). GABA also plays an essential role for 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 (Ge et al., 2006). In adult neocortex, neurogenesis occurs in GABAergic interneurons as well (Dayer et al., 2005), 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 (Majdan and Shatz, 2006;Tropea et al., 2006). In one recent study, Majdan and Shatz showed that there are two pool of genes, a common sets of genes (~10 genes) and an age-related gene pools (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 sets. Thus, critical period formation and experience-dependent plasticity appear to be regulated by common genes as well as age-related genes (Majdan and Shatz, 2006). 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), 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 (Tropea et al., 2006) $GABA_A$ receptor subunits α2 & 3, β1 & 3 genes were found to be up-regulated by monocular derivation or dark rearing. Other genes, such as GAD67 and parvalbumin, which have been implicated in experience-dependent plasticity, and all have been found to be affected by visual experiences (Tropea et al., 2006). Further experiments examining the physiological consequences of altered gene expression will certainly help to clarify mechanisms underlying the experience-dependent plasticity.

5. What are the functional consequences to a neural network?

There are different types of interneuerons whose laminar location, synaptic targets, firing properties and functions are extremely diverse (Kawaguchi and Kondo, 2002; Somogyi et al., 1998; Staiger et al., 2000;Thomson et al., 2002; Staiger et al. 1996). Neocortical local circuits can also be further divided into interlaminar and intralaminar connections (Thomson et al., 2002). Next the focus will center on inhibitory networks involved in mediating feed-forward inhibition in the sensory cortex.

5.1.) Feed-forward inhibition and receptive field

Sensory-mediated intracortical inhibition plays a role in the shaping of sensory cortical receptive fields (Nelson, 1991; Vidyasagar et al., 1996; Swadlow, 2002 & 2003). A powerful feed-forward inhibitory mechanism could serve to constrain the size of supra-threshold receptive fields and to modify the temporal response property of targeted cortical neurons (e.g. Fig 1). In the somatosensory cortex, putative inhibitory interneurons with sensitive and broadly tuned feed-forward inhibitory properties have been described in the rabbit and rat (Swadlow, 2002 & 2003; Simons, 1978).

Rodent whisker sensory input is represented somatopically in the barrel field of layer IV of S1 neocortex (Woolsey and Van der, 1970). A cohort of morphologically distinct excitatory neurons and inhibitory interneurons has been described in layer IV barrels (Keller and White, 1987; Woolsey and Van der, 1970). 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 (Egger et al., 1999; Feldmeyer et al., 1999; Feldmeyer et al., 2002; Petersen and Sakmann, 2000). By contrast, interneurons only represent about 10 % to 30% of the total number of neurons within the barrel cortex (Simons, 1978; Keller and White, 1987; Micheva and Beaulieu, 1995). 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 (e.g. Chagnac-Amitai and Connors, 1989). 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 (Sun et al., 2006, Fig. 3). The average conductance of uIPSCs from individual FS interneurons is about 10 fold greater than that of uEPSCs in spiny neurons. This difference, together with rapid feed-forward inhibition, serves to counteract the convergent cortical excitation from spiny neurons (Sun et al., 2006, Fig. 2 & 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 feed-forward inhibition, since networks of electrically coupled FS cells produce highly synchronized activities (Amitai et al., 2002;

Beierlein et al., 2003). This could have profound influences on the generation of thalamocortical mediated feed-forward inhibition. Essentially, the electrical coupling allows the firing FS neurons to be “phase locked” to their electrically coupled partners (Beierlein et al., 2000; Gibson et al., 1999), and thus contribute to the synchronization of FS spikes. In addition, the electrical coupling might increase the probability of firing in FS networks because a supra-threshold EPSP in one FS interneuron might increase the firing probability of its electrically coupled partners which have TC inputs slightly below the threshold. Feed-forward 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 (Swadlow, 2002 & 2003; Sun et al., 2006, Fig. 3). Furthermore, FS neurons and spiny neurons could have different receptive field properties (Swadlow, 2002 & 2003). 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 (Sun et al., 2006). 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 feed-forward inhibition that occurs immediately following pyramidal neuron APs (Wehr and Zador, 2003). 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 feed-forward inhibition controls both the temporal precision and, likely, the receptive field (Bruno and Simons, 2002). In the visual cortex, a sensitive and broadly tuned feed-forward inhibition could account for the contrast-invariant orientation tuning seen in feline visual cortex. However, the existence of such interneurons in cat visual cortex is uncertain (Hirsch and Martinez, 2006).

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 (Egger et al., 1999; Froemke and Dan, 2002; Feldman et al., 1999; Nelson et al., 2002). Experience-dependent synaptic plasticity in the sensory cortex requires precision in spike- timing of the postsynaptic 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. Zhang and Knudsen have found that the pattern of feed-forward inhibition is less dynamic than the pattern of feed-forward excitation at the site of map plasticity (Zheng and Knudsen, 1999; Zheng and Knudsen, 2001). In a second sets of experiments, the intracortical inhibitory influences upon developing visual afferents are 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 (Hensch et al., 1998; Hensch and Stryker, 2004). Similar roles of inhibition in the somatosensory cortex have also been implicated (Foeller et al., 2005). These results suggest that intracortical inhibition, presumably via modulating spike patterns of spiny neurons, regulate the experience-dependent plasticity and columnar organization (cf. Fig. 1). Interestingly, in a rat model of neocortical dysplasia, LTP is impaired, presumably due to diminished GABAergic inhibitory connections in affected areas (Peters et al., 2004). In animal models of epilepsy and patients with developmental epilepsy (van Rijckevorsel, 2006), 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 (von der et al., 2006). Mental retardation, and learning difficulties is also common problems in several neurological disorders (such as autism and fragile-X syndrome),

and were accompanied by a perturbation of inhibition and excitation (Dong and Greenough, 2004).

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 (Marder and Goaillard, 2006; Turrigiano and Nelson, 2004). In sensory deprived cortices, lateral excitation is enhanced whereas feed-forward and feed-back 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 (Rutherford et al., 1997). 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 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; ***6)*** 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.

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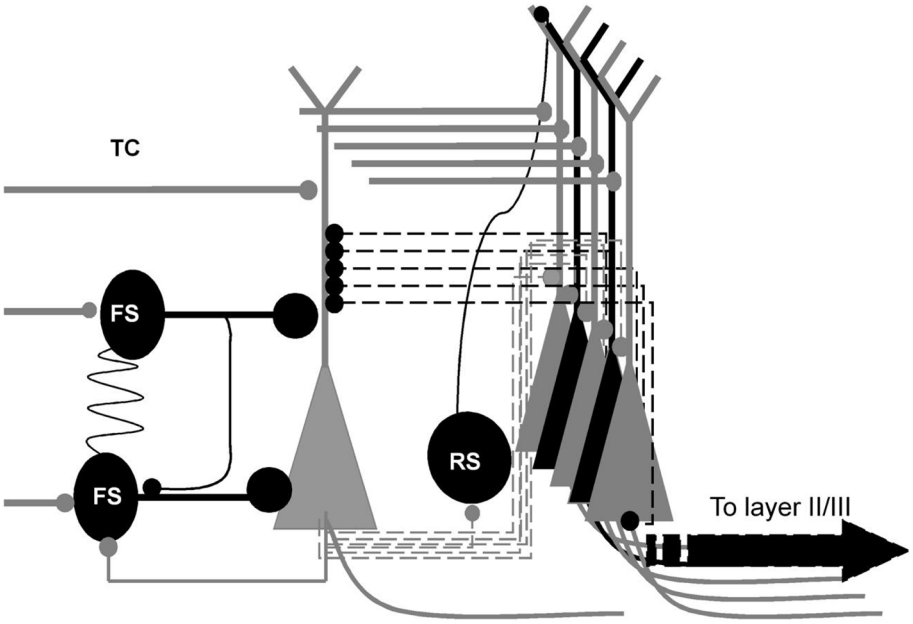

Figure 1. Role of basket cells in sensory-mediated feed-forward inhibition and modulation of receptive field properties

Thalamocortical excitatory synapses 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 FS-mediated perisomatic inhibition is on average 10 times larger than the intracortical excitatory synaptic excitation. Therefore the sensory feed-forward inhibition plays a very important role in modulating the 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.

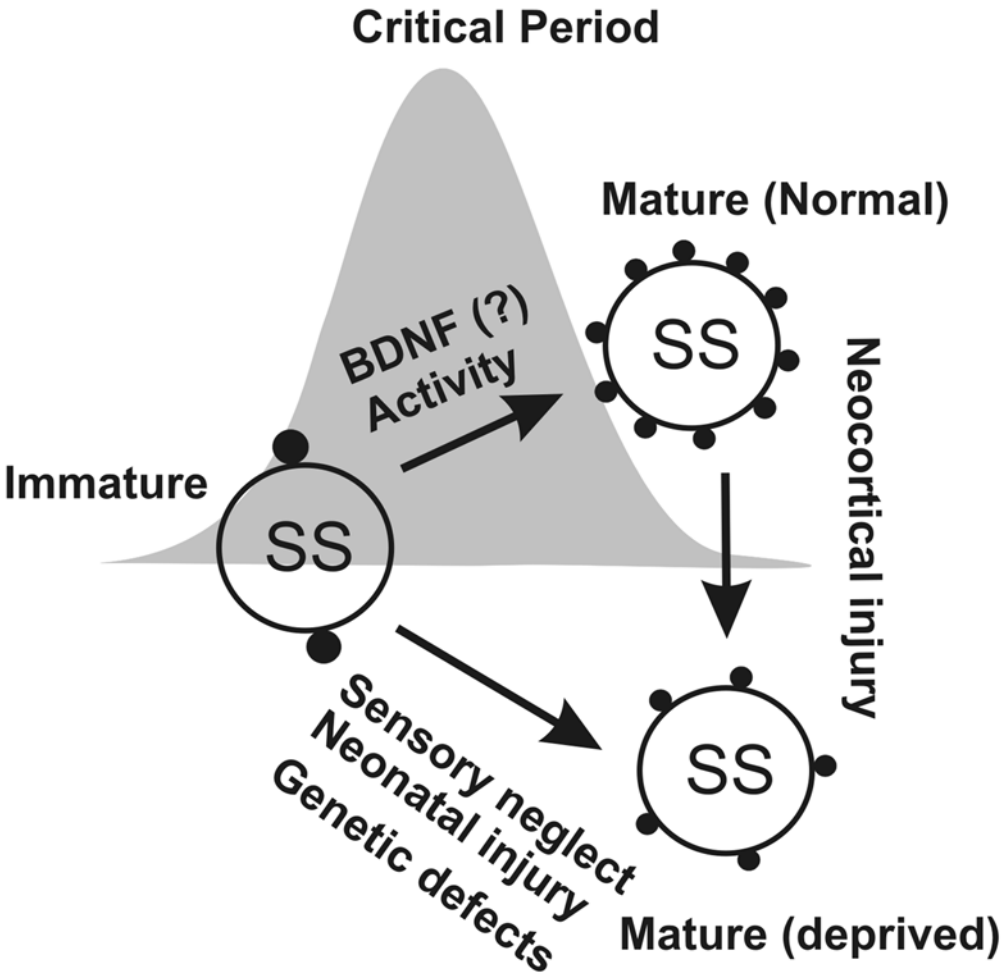

Figure 2. Postnatal maturation and plasticity of perisomatic inhibitory synaptic boutons in sensory cortices

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 the sensory neglect or neonatal injury. As implicated, the maturation of inhibitory network plays a role in activity-dependent formation of sensory critical periods. Mature inhibitory circuits can be changed into ‘immature network’, if the cortices are injured.

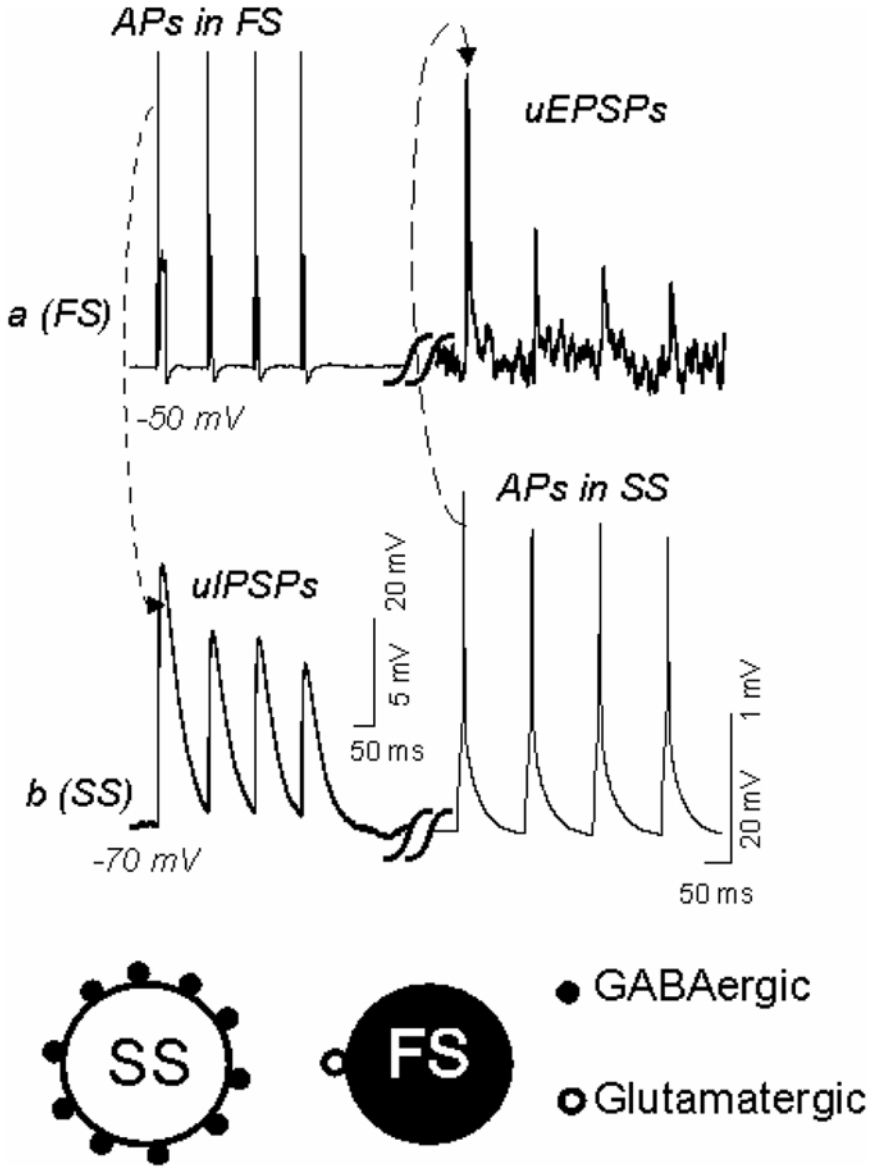

Figure 3. Reciprocal synaptic connection between spiny stellate cells and basket cells

Top: Paired recordings from a reciprocally connected fast-spiking cell (a) and spiny stellate cell (b) show unitary synaptic potentials elicited by trains (B1) or single action potentials (B2) in the presynaptic cell. B1, Trains of action potentials (APs) elicited by depolarizing currents (250 pA, 100 ms) in cell a (top left) evoked unitary (u) IPSPs in cell b (bottom left, dotted line and arrow), while action potentials in 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 out-numbers glutamatergic boutons from single spiny neurons in the basket cell. This figure was modified from Sun et al, 2006.