



# GABAergic synapses: their plasticity and role in sensory cortex

Trevor C. Griffen<sup>1,2,3\*</sup> and Arianna Maffei<sup>1,4\*</sup>

<sup>1</sup> SUNY Eye Research Consortium, Buffalo, NY, USA

<sup>2</sup> Program in Neuroscience, SUNY – Stony Brook, Stony Brook, NY, USA

<sup>3</sup> Medical Scientist Training Program, SUNY – Stony Brook, Stony Brook, NY, USA

<sup>4</sup> Department of Neurobiology and Behavior, SUNY – Stony Brook, Stony Brook, NY, USA

## Edited by:

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## \*Correspondence:

Trevor C. Griffen and Arianna Maffei, Department of Neurobiology and Behavior, Life Science Building Rm. 548, SUNY-Stony Brook, Stony Brook, NY 11794, USA  
e-mail: trevor.griffen@stonybrook.edu;  
arianna.maffei@stonybrook.edu

The mammalian neocortex is composed of a variety of cell types organized in a highly interconnected circuit. GABAergic neurons account for only about 20% of cortical neurons. However, they show widespread connectivity and a high degree of diversity in morphology, location, electrophysiological properties and gene expression. In addition, distinct populations of inhibitory neurons have different sensory response properties, capacities for plasticity and sensitivities to changes in sensory experience. In this review we summarize experimental evidence regarding the properties of GABAergic neurons in primary sensory cortex. We will discuss how distinct GABAergic neurons and different forms of GABAergic inhibitory plasticity may contribute to shaping sensory cortical circuit activity and function.

**Keywords:** synaptic plasticity, GABA, inhibitory neurons, sensory cortex, inhibition

## INTRODUCTION

The many varieties of synaptic plasticity provide a high degree of flexibility to neural circuits, allowing organisms to adapt to changing environments and learn from their experiences. In primary sensory cortex different forms of synaptic plasticity can be induced by manipulations of sensory drive, some of which are limited to specific developmental windows (Hubel and Wiesel, 1970; Carmignoto and Vicini, 1992; Finnerty et al., 1999; Morales et al., 2002; Hensch, 2004; Maffei and Turrigiano, 2008a; Espinosa and Stryker, 2012; Levelt and Hübener, 2012). While most studies of sensory cortical plasticity have focused on the role of glutamatergic synapses, it is now clear that GABAergic inputs and their plasticity play a fundamental role in cortical circuit refinement throughout life.

GABAergic neurons comprise a variety of cell types with distinct physiological characteristics, anatomical locations and capacities for plasticity (Markram et al., 2004; Ascoli et al., 2008; Caspary et al., 2008; Maffei, 2011; Méndez and Bacci, 2011; Rudy et al., 2011; Vitalis and Rossier, 2011; Taniguchi, 2014). This diversity may be one of the most important features of cortical circuits, as it confers a wide range of possibilities for stabilizing, refining the activity of and setting the state of other neurons and neural circuits (Földy et al., 2004; Santhakumar and Soltesz, 2004). Tools to facilitate the direct investigation of these diverse neurons have only recently become available; therefore, our understanding of the role of GABAergic neurons in cortical circuit function is just beginning.

In this review we will discuss recent findings on the role of GABAergic synaptic transmission and plasticity in sensory cortex. We will focus on the role of local inhibitory circuits; however,

it should be noted that long range projecting inhibitory neurons have been identified in neocortex (Germroth et al., 1989). These neurons have only recently begun to be functionally characterized (Melzer et al., 2012), suggesting that much work still needs to be done to fully understand the diversity of connectivity and action of GABAergic neurons in the brain. GABAergic interneurons are involved in sharpening sensory responses and regulating circuit excitability, and they are a *sine qua non* of experience-dependent circuit refinement (Ben-Ari et al., 2004; Heimel et al., 2011; Isaacson and Scanziani, 2011; Maffei, 2011; Levelt and Hübener, 2012; Le Magueresse and Monyer, 2013). We will provide evidence for these functions and discuss possible mechanisms involved, as well as common and unique features of GABAergic synaptic plasticity in different sensory cortices. We will conclude with an attempt to reconcile seemingly discrepant experimental results and suggest issues that in our opinion need to be addressed to push this field forward.

## GABAergic INHIBITION AND COMPUTATION IN SENSORY CORTEX

The contribution of inhibition to neural network computation goes beyond that of only a regulator of circuit excitability. Inhibitory neurons form highly interconnected networks of electrically and synaptically coupled neurons, and they have a wide range of anatomical and physiological properties ideally suited for driving broad network synchronization (Kawaguchi and Kubota, 1997; Tamás et al., 1998; Galarreta and Hestrin, 1999; Gibson et al., 1999; Amitai, 2001; Galarreta and Hestrin, 2002; Pfeiffer et al., 2013; Taniguchi, 2014). Many individual GABAergic neurons connect broadly to local excitatory neurons and specifically

to local inhibitory neurons, allowing them to exert their influence over large portions of neural circuits (Hestrin and Galarreta, 2005; Oswald et al., 2009; Packer and Yuste, 2011; Fino et al., 2013; Pfeiffer et al., 2013). GABAergic inhibitory neurons are, therefore, ideally situated to contribute to the generation of activity associated with wakefulness and cognitive processing (Tamás et al., 2000; Whittington et al., 2000; Oswald et al., 2009).

Inhibitory and excitatory inputs interact dynamically to maintain neural networks in a balanced state that favors neural computations (McCormick, 2002; Haider and McCormick, 2009). They are dynamically coordinated and co-activated during both spontaneous and sensory evoked activity both in acute slice preparations (Adesnik and Scanziani, 2010; Graupner and Reyes, 2013) and *in vivo* (Okun and Lampl, 2008; Adesnik and Scanziani, 2010). The coordination of excitatory and inhibitory inputs is believed to underlie dynamic modifications of functional cortical connectivity, and these rapid changes in functional connectivity may be necessary for sculpting sensory responses (Haider et al., 2007; Haider and McCormick, 2009). According to computational models, coordinated and balanced excitation and inhibition can promote decorrelated network activity, which would favor efficient information processing (Renart et al., 2010).

## DIVERSITY OF INHIBITORY NEURONS AND THEIR CONNECTIVITY

Computational models and theories of cortical function often treat inhibitory neurons as a single functional class. However, cortical circuits contain groups of GABAergic neurons that can be distinguished according to their functional properties (Markram et al., 2004; Rudy et al., 2011; Taniguchi, 2014). The heterogeneity of GABAergic neuron subtypes has long hindered our understanding of inhibitory circuits and their specific roles in different aspects of circuit function; therefore, principles for identifying and naming the distinct populations of inhibitory neurons across species are being discussed to facilitate comparisons of results obtained from different species and experimental approaches (Ascoli et al., 2008; DeFelipe et al., 2013). One of the most important features of interneurons is their axonal morphology, which can be used to determine the primary subcellular compartment (axons, dendrites, or soma) that they target for inhibition (Somogyi et al., 1998).

In addition, differential gene expression has become a useful tool for identifying populations of interneurons. Nearly all sensory cortical GABAergic neurons are thought to detectably express one, and only one, of three proteins: the calcium binding protein parvalbumin (PV), the peptide hormone somatostatin (SOM), or the ionotropic serotonin receptor 5HT<sub>3a</sub>R (Kawaguchi and Kubota, 1997; Lee et al., 2010, 2013; Rudy et al., 2011). Expression of the peptide hormone vasoactive intestinal peptide (VIP) delineates a specific subpopulation of 5HT<sub>3a</sub>R positive interneurons (Lee et al., 2010; Rudy et al., 2011). Because these markers identify distinct populations and account for nearly all GABAergic neurons, they have provided a useful starting point for the functional investigation of groups of inhibitory neurons in sensory cortex (Rudy et al., 2011); however, there is some overlap in the expression of PV and SOM mRNA, and many more markers have been identified both immunohistochemically and

through genetic screens that may help identify important functional subclasses (Cauli et al., 1997, 2000; Markram et al., 2004; Freund and Katona, 2007; Lee et al., 2010; DeFelipe et al., 2013; Taniguchi, 2014).

Interneurons have long been classified by their distinct morphological phenotypes and biophysical properties, and these correspond reasonably well with genetic markers. However, the evidence upon which these classifications are drawn relies on observations made across several species, brain regions and ages. These classifications represent the most common features of interneurons marked by these genes that have been observed, but the heterogeneity within these groups has not been systematically studied, especially across development, cortical layers and cortical regions. Most PV expressing neurons show fast spiking (FS) patterns when depolarized and can be classified morphologically as either basket cells or chandelier cells (Kawaguchi and Kubota, 1993; Wang et al., 2002; Markram et al., 2004; Xu and Callaway, 2009; Rudy et al., 2011). Basket cells have axons that synapse predominantly onto the soma and the perisomatic regions of cortical pyramidal neurons, wrapping around the soma like a basket (Kawaguchi and Kubota, 1997; Tamás et al., 2000). Chandelier cells, with axonal boutons resembling candlesticks or “cartridges” (Szentágothai and Arbib, 1974), are a population of interneurons whose axons predominately contact axon initial segments (Somogyi, 1977). Chandelier cells were originally thought to comprise a homogeneous subpopulation of FS PV positive neurons; however, recent evidence that many chandelier cells do not express PV suggests that two types of functionally distinct chandelier cells could exist (Taniguchi et al., 2013; Taniguchi, 2014). While most PV neurons are FS, depending upon the recording and classification method considered, not all PV neurons are FS and not all FS neurons are PV positive (Gray and McCormick, 1996; Cauli et al., 1997; Markram et al., 2004; Ma et al., 2006; Moore and Wehr, 2013; Taniguchi et al., 2013; but see Rudy et al., 2011).

The largest subgroup of SOM expressing neurons is Martinotti cells, which have regular spiking (RS) action potential widths when depolarized, and vertical axons that preferentially target superficial dendritic tufts (Kawaguchi and Kubota, 1997; Thomson et al., 2002; Wang et al., 2004; Ali and Thomson, 2008). However, SOM expressing synapses have also been observed on soma (Gonchar et al., 2002). In addition, a subgroup of SOM positive neurons has spike widths characteristic of FS cells and extensive axonal arborization within layer 4 (Ma et al., 2006; Miyoshi et al., 2007; Xu et al., 2013). The morphology and subcellular targeting of these neurons has not been fully characterized.

VIP is expressed in cells with morphologies consistent with both dendrite and soma targeting interneurons (Lorén et al., 1979; Morrison et al., 1984; Kawaguchi and Kubota, 1996, 1997; Lee et al., 2010; Miyoshi et al., 2010). 5HT<sub>3a</sub>R/VIP- neurons comprise the majority of layer 1 neurons and neurogliaform cells (Lee et al., 2010). Neurogliaform cells form gap junction connections with many other classes of cortical interneurons (Simon et al., 2005). They have been proposed to use primarily volume rather than synaptic transmission of GABA (Oláh et al., 2009); however, they have the capacity to regulate specific portions of neural circuits (Chittajallu et al., 2013).

Beyond preference for targeting specific subcellular compartments, patterns of connectivity within and between interneuron subtypes and pyramidal neurons are beginning to emerge. For example, while PV and SOM positive neurons frequently contact pyramidal neurons, VIP positive neurons rarely inhibit pyramidal neurons (Pfeffer et al., 2013). Instead, VIP neurons predominantly inhibit SOM neurons (Lee et al., 2013; Pfeffer et al., 2013; Pi et al., 2013), which in turn target VIP and PV neurons (Pfeffer et al., 2013). This connectivity scheme places VIP neurons in an ideal position to mediate disinhibition of excitatory neurons (Lee et al., 2013; Pi et al., 2013). In the primary input layer of sensory cortex, layer 4, basket cells receive direct thalamic input (Beierlein et al., 2003; Cruikshank et al., 2007) and can therefore shape cortical circuit activation through feedforward control over excitatory neuron activity (Gabernet et al., 2005). In addition to inhibiting excitatory neurons, many PV positive neurons target other PV positive neurons (Galarreta and Hestrin, 1999, 2002; Pfeffer et al., 2013).

The ability to perform experiments *ex vivo* in rodent models has allowed for high resolution analysis of biophysical properties and local connectivity of different populations of inhibitory neurons. For example, it was recently shown that even within the PV positive population of inhibitory neurons in primary visual cortex (V1), distinct biophysical properties (Helm et al., 2013) correlate with the level of expression of the SAP97 scaffold protein (Akgul and Wollmuth, 2013). Since inhibitory neuron populations with distinct biophysical properties, molecular markers, birth dates and birth regions have been identified, it has become possible to label specific subpopulations using genetic approaches to facilitate identification and recording from these groups of inhibitory neurons both *ex vivo* and *in vivo* (Taniguchi et al., 2011; Taniguchi, 2014).

While genetic approaches to marking neurons in intact animals are extremely powerful and promising, some of the strategies to genetically label interneuron populations may interfere with GABAergic transmission (Tamamaki et al., 2003; Wang et al., 2009; see discussion of the GAD67-GFP ( $\Delta$ neo) mouse line below) or mislabel neurons, potentially leading to confounds in the interpretation of the data, or producing contrasting findings (Hu et al., 2013). For example, neurons expressing Cre-dependent genes via the somatostatin promoter (Taniguchi et al., 2011) include a population (up to 5–10% of labeled neurons) of FS PV neurons (Hu et al., 2013; Pfeffer et al., 2013), while this degree of overlap has not been observed using immunohistochemical staining (Lee et al., 2010). In addition, the level of expression of neuronal markers used to identify inhibitory neurons can change during development (Wahle, 1993; Felmy and Schneggenburger, 2004) and/or in an activity-dependent fashion (Gomes da Silva et al., 2010; Martin del Campo et al., 2012; Hou and Yu, 2013), possibly affecting the classification of inhibitory neurons. Similarly, the subcellular compartments targeted by inhibitory synapses are under genetic control and can be modified in an activity dependent manner (Bloodgood et al., 2013). Finally, some functionally distinct population of inhibitory neurons may be distinguishable only by graded levels of gene expression, making them difficult to manipulate with genetically encoded tools alone. Comparing the properties, connectivity and function of

inhibitory neurons in different circuits, species and developmental stages will be necessary to distinguish general properties of inhibitory neuron function from specific properties that depend on interneuron subtype, species, region or experimental manipulation. However, the heterogeneity within marked populations and potential plasticity of markers and subcellular targets must be taken into account.

## MANIPULATING AND MEASURING THE ACTIVITY OF GABAergic NEURONS *IN VIVO*

Several approaches have been employed to study the activity of GABAergic neurons *in vivo* (Table 1). The characteristic narrow spike waveform of FS inhibitory neurons allows them to be identified and separated from RS neurons, which are mostly pyramidal cells, in extracellular and juxtacellular recordings. Because identification of waveforms extracellularly is prone to error (Henze et al., 2000; González-Burgos et al., 2005; Gold et al., 2006), channelrhodopsins (ChR) can be expressed in subsets of interneurons and photoactivated to rapidly induce spikes and more precisely identify units recorded extracellularly (Cardin, 2012; Moore and Wehr, 2013). Multielectrode recording arrays are useful for recording extracellularly from several neurons simultaneously, but many are limited in their ability to record from superficial layers. Whole cell recording with *post-hoc* morphological reconstruction allows for more precise laminar identification than is possible with extracellular recordings, and depolarization induced firing patterns and membrane potential fluctuations can be measured. However, due to the size of interneurons relative to pyramidal neurons and their relative scarcity, this technique has low yield. To improve yield and specificity, recordings can be performed in transgenic animals expressing fluorescent markers in populations of GABAergic neurons. Using two-photon microscopy, patch pipettes can be targeted to neurons either expressing or lacking a specific marker (Liu et al., 2009; Gentet et al., 2010). Fluorescent labeling of GABAergic neurons can also be combined with calcium imaging, which greatly increases the number of neurons that can be simultaneously recorded from at the expense of resolving precise numbers of action potentials (Sohya et al., 2007; Kerlin et al., 2010). Unfortunately, techniques relying on transgenic animals and two photon microscopy are largely limited to studying the superficial layers of mouse cortex at present.

Whole cell recordings can also be used to measure inhibitory drive postsynaptically. Somatic inhibitory and excitatory currents/conductances can be measured to investigate how inhibition contributes to shaping sensory responses (Anderson et al., 2000). The dynamic reversal potential of a sensory response can also be calculated, allowing inferences to be made about the contribution of excitatory and inhibitory receptors to the response (Crochet et al., 2011; Sachidhanandam et al., 2013). These techniques are limited, however, in that they may fail to fully resolve inputs to distal dendrites. Distal inhibitory inputs may effectively shunt excitatory inputs that would have led to regenerative activity (Gidon and Segev, 2012) without themselves being fully resolved. Functional GABA mediated inhibition has been observed that requires regenerative dendritic activity to be measurable (Palmer et al., 2012). Measuring inhibitory

**Table 1 | Approaches for recording the activity of inhibitory neurons and inhibitory postsynaptic responses *in vivo*.**

Technique	Cell type identification	Acquirable data	Limitations	Selected references
Extracellular recordings	Spike width (FS vs. RS)	Spikes	Prone to misidentification, some arrays limited to deep layers	Simons, 1978; Swadlow and Weyand, 1987; Henze et al., 2000; González-Burgos et al., 2005; Gold et al., 2006
	Optogenetics	Spikes	Some arrays limited to deep layers	Cardin, 2012; Moore and Wehr, 2013
Juxtacellular recordings	Spike width (FS vs. RS)	Spikes	Low yield, cannot identify RS interneurons	Wu et al., 2008; Liu et al., 2009
	Two-photon guided targeting	Spikes	Superficial layers	Liu et al., 2009; Ma et al., 2010; Runyan et al., 2010
	Reconstruction	Spikes	Low yield	Wu et al., 2008; Ma et al., 2010; Runyan et al., 2010
Whole cell patch of interneurons	Reconstruction, depolarization induced firing patterns	Membrane potential, spikes	Very low yield	Azouz et al., 1997; Zhu and Connors, 1999; Hirsch et al., 2003; Monier et al., 2003
	Two-photon guided targeting	Membrane potential, spikes	Superficial layers, low yield	Gentet et al., 2010, 2012
Calcium dye imaging	Genetic labeling	Changes in calcium concentration	Superficial layers, cannot resolve individual spikes	Sohya et al., 2007; Kerlin et al., 2010
Whole cell patch of pyramidal neurons	Reconstruction, depolarization induced firing patterns	Somatic inhibitory/excitatory conductances, response reversal potentials	May not resolve dendritic inhibition	Anderson et al., 2000; Martinez et al., 2002; Crochet et al., 2011

FS, fast spiking width. RS, regular spiking width.

currents/conductances requires minimizing the contribution of voltage gated channels and would obscure their inhibition. Further, the analysis of inhibitory responses with this approach does not allow experimenters to selectively identify the contribution of distinct inhibitory neuron subgroups to inhibitory synaptic potentials (or currents) evoked by sensory stimuli.

Pharmacology, genetics, optogenetics and alterations in sensory experience have all been used to manipulate GABAergic neurotransmission *in vivo* (Table 2). Application of the potent GABA<sub>A</sub> receptor agonist muscimol has been used to increase inhibition (Reiter and Stryker, 1988); however, the ubiquity of GABA<sub>A</sub> receptors makes it difficult to interpret the results of these experiments as being due specifically to increased synaptic and extrasynaptic inhibition versus the secondary effect of dampening all cortical activity. Benzodiazepines allosterically enhance GABAergic neurotransmission at specific GABA<sub>A</sub> receptors with benzodiazepine binding sites (Benke and Möhler, 2006; Gielen et al., 2012) and are therefore a more selective tool for probing inhibitory circuit function. Conversely, GABAergic transmission can be disrupted either by administering GABA receptor antagonists or by impairing GABA synthetic pathways. For example, chronic administration of the GAD antagonist 3-mercaptopropionic acid (3-MPA) lowers cortical GABA (Harauzov et al., 2010). Transgenic mice that have altered expression of proteins related to GABAergic neuron function

can be used to study the effects of either developmental or induced changes in GABAergic function (Hanover et al., 1999; Huang et al., 1999; Tamamaki et al., 2003; Fagiolini et al., 2004; Wang et al., 2009; Palmer et al., 2012; Nahmani and Turrigiano, 2014). To study the roles of interneuron groups in sensory processes, the light gated ion channel/pumps ChR and halorhodopsin/archaeorhodopsin (HaR/ArchR) can be specifically expressed to excite or inhibit a class of neurons upon photoactivation (Cardin, 2012). While results using photoactivation are certainly interesting, it is unclear how artificially evoked (Cardin, 2012), broad patterns of interneuron activation relate to their physiological activation by sensory stimuli. A bold approach to increasing the specificity of photoactivation is to use single cell electroporation to limit expression to a small number of cells (Cottam et al., 2013).

Alterations in sensory experience that induce changes in GABAergic circuitry can be studied *in vivo* to allow inferences to be made about the effects of the circuit change on sensory responses. These inferences are, of course, limited by the plethora of changes that may be induced in cortical and subcortical circuits: excitatory, inhibitory and neuromodulatory. In this review, we will consider changes in sensory experience in three categories. Sensory deprivation will refer to manipulations that lead to an overall reduction of sensory drive (e.g., binaural hearing loss, dark rearing, or trimming all whiskers on a vibrissal pad).

**Table 2 | Tools for manipulating inhibition *in vivo*.**

Class	Tools	Examples	Advantages	Limitations	Selected references
Pharmacology	GABA <sub>A</sub> receptor agonists	Muscimol		Broadly acting, silences neurons	Reiter and Stryker, 1988
	GABA <sub>A</sub> receptor allosteric enhancers	Benzodiazepines and zolpidem	Enhances GABAergic transmission directly	Broadly acting	Fagiolini and Hensch, 2000; Hensch and Stryker, 2004
	GABA <sub>A</sub> receptor antagonists	Picrotoxin and bicuculline	Blocks GABAergic transmission directly	Broadly acting	Sillito, 1975; Kyriazi et al., 1996
	GABA synthesis inhibitors	3-MPA		Broadly acting	Harauzov et al., 2010
	Growth factors	IGF-1	Probe signaling cascades	Broadly acting, actions beyond inhibition	Maya-Vetencourt et al., 2012
Genetics	Overexpression	BDNF	Ubiquitous or targeted overexpression	Depend on expression system	Hanover et al., 1999; Huang et al., 1999
	Knockout	GAD65	Full, ubiquitous knockout	Present through development	Fagiolini and Hensch, 2000
	Conditional knockout/knockdown		Targeted	Depends on knockout/knockdown system	
Optogenetics	Photoactivation	ChR	Targets genetic cell classes, good temporal response	Non-physiological stimulation parameters, non-physiological neurotransmission	Atallah et al., 2012; Cardin, 2012; Lee et al., 2012; Wilson et al., 2012
	Photo-inhibition	HaR/ArchR	Targets genetic cell classes	Incomplete inhibition, slow kinetics	Atallah et al., 2012; Gentet et al., 2012; Lee et al., 2013
Sensory experience	Sensory deprivation	Dark rearing, hearing loss, whisker removal	Delays circuit development	Non-specific effects	Benevento et al., 1992; Chittajallu and Isaac, 2010
	Environmental enrichment	Exercise, sensory enrichment	Re-opens critical periods	Non-specific effects	Sale et al., 2007
	Sensory alterations	Monocular Lid suture, selective whisker removal, high frequency hearing loss	Critical period plasticity useful for modeling human disease	Induces complex changes at excitatory and inhibitory synapses	Hubel and Wiesel, 1970; Drew and Feldman, 2009; Yang et al., 2011

3-MPA, 3-mercaptopyropionic acid. ChR, channelrhodopsin. HaR, halorhodopsin. ArchR, archaerhodopsin.

This type of manipulation is typically initiated shortly after birth. Deprivation of one sensory modality can alter cortical circuit activity and responsiveness to sensory stimuli even in sensory areas that are not directly driven by the sensory organ that has been manipulated (Zheng et al., 2014). Environmental enrichment will refer adding objects to an animal's cage that provide multisensory stimulation (Sale et al., 2009). Sensory alteration will refer to manipulations that reduce, or fundamentally alter, a specific sensory input, usually asymmetrically, without eliminating it entirely (e.g., monocular lid suture, surgical strabismus, selective hearing ablation and selective whisker removal). When these manipulations are induced during sensitive periods in post-natal development, they often lead to diminished sensory function if later reversed (Hubel and Wiesel, 1970; Carmignoto and Vicini, 1992; Finnerty et al., 1999; Morales et al., 2002; Hensch, 2004; Maffei and Turrigiano, 2008a; Espinosa and Stryker, 2012; Levelt and Hübener, 2012).

## GABAergic NEURON SENSORY RESPONSE PROPERTIES

The diversity of genetic, morphological and electrophysiological properties, as well as patterns of connectivity of GABAergic neurons, suggests that different cell types may have distinct functional properties. Studies of GABAergic neurons' receptive field properties have confirmed this hypothesis, yet sometimes with contrasting results. This is not too surprising, given that important functional differences exist between cortical layers and neuronal subtypes, and different recording techniques selectively favor certain layers and interneuron subtypes over others (Table 1). Additionally, the laminar distribution and cortical organization of neurons with different response properties differs strikingly between species. Cats have ocular dominance and orientation columns, while rodents and rabbits do not (Hubel and Wiesel, 1963; Tiao and Blakemore, 1976; Murphy and Berman, 1979; Grinvald et al., 1986; Métin et al., 1988; Girman et al., 1999; Schuett et al., 2002; Van Hooser et al., 2005). **Cats, rats, and**

mice all have different laminar distributions of neurons with simple and complex visual receptive fields (Hubel and Wiesel, 1962; Kelly and Van Essen, 1974; Gilbert, 1977; Gilbert and Wiesel, 1979; Lin et al., 1979; Parnavelas et al., 1983; Niell and Stryker, 2008). These interspecies differences in the gross organization of neuronal response properties raise the possibility that some features of inhibitory neuron response properties may also be species specific.

In cat V1 there is evidence in favor of FS inhibitory neurons being both broadly and narrowly tuned to sensory stimuli (Azouz et al., 1997; Hirsch et al., 2003; Cardin et al., 2007; Nowak et al., 2008). Tuning appears to vary by cortical layer, as FS neurons in the primary thalamorecipient layer, layer 4, are either broadly tuned or untuned (Hirsch et al., 2003; Cardin et al., 2007; Nowak et al., 2008). FS neurons outside layer 4 show tuning similar to RS neurons (Cardin et al., 2007), but are more binocularly driven (Aton et al., 2013). This suggests that inhibition may modulate sensory response properties in a lamina-specific fashion. In awake rabbits, putative layer 4 FS neurons have broader orientation, direction and frequency tuning, are more binocular and are more sensitive to contrast than putative RS neurons (Swadlow and Weyand, 1987; Swadlow, 1988; Zhuang et al., 2013).

In the anesthetized mouse, populations of interneurons identified as either PV positive or FS are more broadly tuned for orientation than both excitatory neurons (Niell and Stryker, 2008; Kuhlman et al., 2011; Zariwala et al., 2011; Atallah et al., 2012; Li et al., 2012b; Cottam et al., 2013; Runyan and Sur, 2013; but see Runyan et al., 2010) and SOM interneurons (Ma et al., 2010; Cottam et al., 2013). FS neurons are also more binocularly responsive than RS neurons (Yazaki-Sugiyama et al., 2009; Kameyama et al., 2010). Within the PV population, however, there is great tuning diversity, with some PV neurons being well tuned (Runyan et al., 2010; Zariwala et al., 2011; Runyan and Sur, 2013). Interestingly, PV neurons with longer dendrites have broader orientation selectivity than those with shorter dendrites (Runyan and Sur, 2013). Some of the heterogeneous aspects of PV neuron tuning may be due to the diversity of morphological groups of neurons expressing PV: basket cells (small and large) and a subgroup of chandelier cells. While both basket and chandelier cells exert powerful control over pyramidal neuron excitability and firing, they receive distinct sets of inputs, at least in somatosensory cortex (Xu and Callaway, 2009). SOM neurons exhibit weaker responses to visual stimuli than either excitatory or PV neurons (Ma et al., 2010) and exhibit sharper population orientation tuning than PV neurons (Ma et al., 2010; Cottam et al., 2013). Using optogenetic photoactivation of a small number of SOM neurons, it was shown that during visual stimulation, SOM neurons are able to more strongly inhibit responses of PV neurons than excitatory neurons. Interestingly, SOM neuron photoactivation sharpened PV neuron tuning (Cottam et al., 2013).

In layer 2/3 of GAD67-GFP ( $\Delta$ neo) mice, GABAergic neurons are only weakly orientation selective (Sohya et al., 2007; Bonin et al., 2011), and have similar binocularity to glutamatergic neurons (Gandhi et al., 2008). In these mice no difference in selectivity exists between FS and RS GABAergic neurons (Liu et al., 2009) or between SOM, PV, or VIP positive neurons (Kerlin et al.,

2010). However, GAD67-GFP ( $\Delta$ neo) mice have reduced orientation selectivity of both GABAergic (Runyan et al., 2010) and glutamatergic neurons compared with control strains (Hagihara and Ohki, 2013; but see Liu et al., 2009). GAD67-GFP ( $\Delta$ neo) mice have decreased expression of GAD67 (Wang et al., 2009). Furthermore, their levels of GABA are reduced neonatally and in the adult (Tamamaki et al., 2003). These caveats should be carefully considered when interpreting data obtained using this strain.

In primary auditory cortex (A1) of anesthetized cats, putative FS inhibitory neurons have short response latencies and broad spectral tuning (Atencio and Schreiner, 2008). Similarly, rat layer 4 FS neurons have faster response latencies and broader tuning than layer 4 pyramidal neurons (Wu et al., 2008). In mice, units identified extracellularly as FS have faster response latencies and broader tuning than RS units (Moore and Wehr, 2013). Once subdivided into PV positive and PV negative units, however, PV positive units did not differ in frequency tuning or response latency from PV negative units, but did have higher spontaneous and evoked firing rates. They also had shallower response gain and were less well tuned for stimulus intensity than PV negative units. Very narrowly tuned PV positive neurons were found, but very rarely. These findings were interpreted as evidence for a role of PV neurons in modulating gain and intensity tuning (Moore and Wehr, 2013). Differently, in superficial layers PV neurons were found to be more broadly tuned than either excitatory or SOM positive neurons, while SOM neurons showed delayed responses compared to PV and excitatory neurons (Li et al., 2014b). VIP neurons are also tone responsive; however, their tuning properties have not been characterized (Pi et al., 2013).

In the barrel portion of primary somatosensory cortex (S1) in rats (paralyzed, anesthetized or sedated) and awake rabbits, putative FS inhibitory neurons show broader sensitivity to the direction of whisker deflection and/or to the number of whiskers stimulated than RS units (Simons, 1978; Simons and Carvell, 1989; Swadlow, 1989; Bruno and Simons, 2002; Gabernet et al., 2005; but see Zhu and Connors, 1999). In addition, they show faster and more reliable responses to stimulation than putative excitatory neurons, especially in layer 4 (Simons, 1978; Swadlow, 1989; Armstrong-James et al., 1993; Bruno and Simons, 2002; Swadlow and Gusev, 2002), where both excitatory and inhibitory neurons are driven monosynaptically from the thalamus (Beierlein et al., 2003; Cruikshank et al., 2007). Within rat layer 2/3, chandelier cells have broader receptive fields than other FS interneurons (Zhu et al., 2004). Within layer 1, deep-projecting GABAergic neurons are well tuned and respond to stimuli rapidly, whereas local interneurons respond slowly and are poorly tuned (Zhu and Zhu, 2004). In the hindpaw region of S1, a sizable portion of inhibitory neurons respond to ipsilateral stimulation (Palmer et al., 2012). Differently from rats and rabbits, putative FS inhibitory neurons in layer 4 of mouse barrel cortex show similar angular tuning to RS units (Kwegyir-Afful et al., 2013). In contrast to other cell types in mouse layer 2/3, SOM neurons are active during quite wakefulness and inhibited during sensation (Gentet et al., 2012). The inhibition of SOM neurons in S1 during whisking is dependent upon VIP neurons, which

are driven to increase their activity during whisking by primary motor cortex (Lee et al., 2013).

Few studies have examined the tuning of GABAergic inhibitory interneurons in primary chemosensory cortices. In the primary gustatory cortex (GC) of anesthetized rats, putative FS inhibitory neurons are primarily tuned to one or two (of four) tastants, almost always including NaCl; while RS units are more broadly tuned and may respond several tastants (Yokota et al., 2011). In the primary olfactory cortex (Pir) of anesthetized rats, layer 1 GABAergic neurons are broadly tuned to odors compared to layer 2/3 pyramidal neurons (Poo and Isaacson, 2009).

Finally, recent studies have identified putative inhibitory interneuron involvement in multisensory integration and learning. Inhibitory neurons in layer 2/3 of a mouse visuotactile area between visual and somatosensory cortices exhibit less multisensory enhancement of evoked responses than pyramidal neurons, and their activation suppresses multisensory enhancement of activity in pyramidal neurons (Olcese et al., 2013). In mouse V1, a local inhibitory circuit can be driven by an auditory stimulus (Iurilli et al., 2012), and in GC of awake rats, a few putative FS inhibitory neurons were found that respond to auditory cues that triggered expectation of taste delivery (Samuelson et al., 2012). Mouse A1 layer 2/3 VIP neurons and layer 1 interneurons inhibit other GABAergic neurons during auditory fear conditioning (Letzkus et al., 2011) and discrimination tasks (Pi et al., 2013), respectively.

While it is clear that there are lamina and species specific interneuron response properties, some common features exist within cell types (Table 3). FS and PV neurons, which predominantly provide somatic, perisomatic and axonal inhibition, tend to be broadly and bilaterally tuned, especially within layer 4. Differently, SOM neurons, which predominantly provide dendritic inhibition, tend to be less strongly responsive to, or inhibited by, stimuli, and those that are responsive to stimuli are tuned intermediately compared to PV and pyramidal neurons. It is unclear how FS SOM neurons and RS PV neurons fit into this scheme. Little is known about the tuning properties of 5HT3aR neurons, whether VIP positive or negative; however, the VIP positive subgroup has been implicated in mediating disinhibition during associative learning and active sensation (Lee et al., 2013; Pi et al., 2013). When comparisons have been made between subgroups of these populations, differences in response properties tied to morphology have been observed. Full understanding of the roles of GABAergic neurons, therefore, will require more detailed investigations of these subclasses, as well as further investigation into the function of genetically identified interneuron classes in subgranular layers.

### GABAergic INHIBITION AND SENSORY RESPONSES IN EXCITATORY CELLS

The varied response properties of GABAergic neurons make them ideal candidates to modulate the activity of excitatory neurons during sensory processing. *In vivo* pharmacological manipulation of GABAergic transmission alters receptive fields properties in a number of different species and cortical regions, suggesting a role for cortical inhibition in controlling the stimulus preference and receptive field structure of excitatory neurons (Sillito,

1975, 1979; Sillito et al., 1980; Kyriazi et al., 1996; Tremere et al., 2001; Li et al., 2002; Foeller et al., 2005; Jeong et al., 2009; Razak and Fuzessery, 2009; Isaacson and Scanziani, 2011; Katzner et al., 2011). However, the results of grossly disrupting or augmenting inhibition in cortex do not provide evidence that GABAergic neurons dynamically shape receptive fields, and their contribution to shaping the receptive fields of glutamatergic neurons is hotly debated (Isaacson and Scanziani, 2011; Liu et al., 2011; Wu et al., 2011; Priebe and Ferster, 2012). Depending on the location and specificity of inhibitory inputs onto a pyramidal cell, GABAergic neurons with a range of tuning properties could contribute inhibition tuned similar to, more tightly than or more broadly than excitatory inputs to that neuron, or tonic, stimulus invariant inhibition.

There is general agreement that an inhibitory mechanism contributes to pyramidal neurons having narrower spiking receptive fields than subthreshold receptive fields (Priebe and Ferster, 2008; Isaacson and Scanziani, 2011; Tan et al., 2011; Wu et al., 2011). This sharpening effect of inhibition occurs, at least in part, through an “iceberg” effect, where inhibition contributes to the spike threshold, below which changes in membrane potential do not alter firing. This effect can occur independently of the relative tuning widths of inhibitory and excitatory inputs (see Isaacson and Scanziani, 2011). Static changes in the level of inhibition, independent of tuning, could alter the sharpness of the membrane potential dynamics in response to spiking input/output transformation, effecting a change in gain. Inhibitory inputs with different tuning than excitatory inputs, if they exist, would provide additional sharpening (Wu et al., 2008; Liu et al., 2011).

In V1, lateral inhibition could account for many receptive field properties, including orientation tuning, spatial segregation of light and dark receptive subfields, direction selectivity, contrast invariance and suppression. However, it has also been proposed that most of these response properties can be accounted for by a model based on the properties of feedforward, excitatory thalamic inputs that have been observed *in vivo*, coupled with a spike threshold determined in part by inhibitory inputs (Priebe and Ferster, 2012). However, the ability to account for most receptive field properties without lateral inhibition does not rule out a role for lateral inhibition. We will focus our discussion on the evidence for and against lateral inhibition being observed and playing a role in shaping receptive fields.

Inhibitory and excitatory light and dark receptive subfields are largely spatially segregated in the visual cortex of cats (Ferster, 1988; Hirsch et al., 1998; Priebe and Ferster, 2005). The spatial opposition of inhibition and excitation was proposed to allow for linear summation of inputs: at a given location within a receptive field, dark and light stimuli evoke opposite responses (Priebe and Ferster, 2005). Conversely, voltage clamp recordings from simple cells in mice have revealed spatial overlapping of receptive subfields, with inhibitory light and dark subfields similarly centered and lying between slightly segregated excitatory light and dark subfields. This suggests a role for inhibition in the segregation of light and dark receptive fields in mice (Liu et al., 2010).

Orientation tuning of excitatory and inhibitory inputs to pyramidal neurons has been observed to be either similarly tuned (Anderson et al., 2000; Tan et al., 2011) or to have a variety

**Table 3 | Tuning width of inhibitory neurons by cell type.**

Interneuron class	Sensory cortex	Layers	Tuning	Species	References
FS	V1	4	Broadly tuned	Cat, Rabbit, Mouse	Swadlow and Weyand, 1987; Swadlow, 1988; Cardin et al., 2007; Li et al., 2012b; Zhuang et al., 2013
		4	Mixed	Cat	Hirsch et al., 2003
		2/3, 5/6	Well-tuned	Cat	Cardin et al., 2007
	A1	Mixed	Broadly tuned	Cat, Mouse	Niell and Stryker, 2008; Nowak et al., 2008
		Mixed	Mixed	Cat	Azouz et al., 1997
		4, Mixed	Broadly tuned	Cat, Rat, Mouse	Atencio and Schreiner, 2008; Wu et al., 2008; Moore and Wehr, 2013
	S1	4, Mixed	Broadly tuned	Rat, Rabbit	Simons, 1978; Simons and Carvell, 1989; Swadlow, 1989; Bruno and Simons, 2002; Gabernet et al., 2005
4, Mixed		Well-tuned	Rat, Mouse	Zhu and Connors, 1999; Kwegyir-Afful et al., 2013	
GC	Mixed	Well-tuned	Rat	Yokota et al., 2011	
PV	V1	2/3, 4	Broadly tuned	Mouse	Ma et al., 2010; Kuhlman et al., 2011; Zariwala et al., 2011; Atallah et al., 2012; Cottam et al., 2013; Runyan and Sur, 2013
		2/3	Mixed	Mouse	Runyan et al., 2010; Zariwala et al., 2011; Runyan and Sur, 2013
	A1	2/3	Broadly tuned	Mouse	Li et al., 2014b
		Mixed	Well-tuned	Mouse	Moore and Wehr, 2013
Chandelier	S1	2/3	Broadly tuned	Rat	Zhu et al., 2004
SOM	V1	2/3, 4	Well-tuned	Mouse	Ma et al., 2010; Cottam et al., 2013
	A1	2/3	Well-tuned	Mouse	Li et al., 2014b
VIP	A1		Tone responsive, tuning unknown	Mouse	Pi et al., 2013
Layer 1	S1	1: deep projecting	Well-tuned	Rat	Zhu and Zhu, 2004
	S1	1: local	Broadly tuned	Rat	Zhu and Zhu, 2004
	Pir	1	Broadly tuned	Rat	Poo and Isaacson, 2009

FS, fast spiking width; V1, primary visual cortex; A1, primary auditory cortex; S1, primary somatosensory cortex; GC, primary gustatory cortex; Pir, primary olfactory cortex; PV, parvalbumin positive neurons; SOM, somatostatin positive neurons; VIP, vasoactive intestinal peptide positive neurons.

of tuning schemes (Martinez et al., 2002; Monier et al., 2003) in cat V1. Orientation tunings of inhibition and excitation were found to be similar in layers 2–4 but different in layer 5 (Martinez et al., 2002). In mice, similar tuning (Tan et al., 2011) and tuning of inhibition just broader than excitation (Liu et al., 2011; Li et al., 2012b) have both been reported. To address whether specific subclasses of inhibitory neurons have the capacity to alter orientation tuning, optogenetic stimulation has been used to control the activation of GABAergic neurons during visual stimulation while recording responses in superficial excitatory neurons. Photoactivation of PV neurons preferentially inhibited responses to optimal orientation without changing orientation selectivity (Atallah et al., 2012; Wilson et al., 2012), while photoactivation of SOM neurons inhibited responses at all orientations equally, sharpening orientation selectivity (Wilson et al., 2012). However, in a contrasting study PV neuron photoactivation sharpened orientation selectivity with minimal effects at optimal orientations,

while SOM and VIP positive neurons' photoactivation suppressed firing but did not alter orientation tuning (Lee et al., 2012). Further, performance in an orientation discrimination task was improved by selective photoactivation of PV positive neurons (Lee et al., 2012). The differences in results may be due to the stimulation parameters used (Lee et al., 2012). As discussed above, it is unclear how these results relate to physiological roles of inhibitory neurons.

Experiments examining the role of inhibition in sharpening tuning width in sensory areas other than V1 have yielded similarly contrasting results. In rodent A1, frequency tuning of inhibitory inputs has been found to be approximately similar to (Wehr and Zador, 2003; Zhang et al., 2003; Tan et al., 2004; Froemke et al., 2007; Tan and Wehr, 2009; Dornn et al., 2010; Li et al., 2014a) or slightly broader than (Wu et al., 2008; Sun et al., 2010) excitatory inputs. In addition, intensity tuning of excitatory and inhibitory inputs to non-monotonically tuned



neurons has been observed to be similarly (Wehr and Zador, 2003) and differentially tuned (Wu et al., 2006; Tan et al., 2007). In rat Pir, inhibitory inputs to layer 2/3 pyramidal neurons are broadly tuned to odors (Poo and Isaacson, 2009).

Experimental evidence in favor of a role for lateral inhibition in sharpening the selectivity of tuning curves has been found, but it has not been observed consistently either within species or cortical regions (Table 4; Priebe and Ferster, 2012). Possible reasons for these inconsistencies include anesthetic choices, stimulus parameters, age of animals, recording layers and experimental approaches. Recent data from layer 2/3 of mouse V1 demonstrated that in awake mice the ratio of inhibition to excitation observed in response to visual stimuli is much greater than under anesthesia (Haider et al., 2013). Further, strong inhibition could be evoked by stimulation in the receptive field surround only during wakefulness (Haider et al., 2013). Thus, the state of a neuron or network can profoundly affect receptive field properties and alter the function of inhibition within a circuit. In layer 4 of mouse V1, increasing the contrast of a grating stimulus broadens inhibitory tuning, leading to contrast-dependent sharpening of orientation selectivity (Li et al., 2012a). Age-dependent sharpening (Dorn et al., 2010) and widening (Sun et al., 2010) of inhibitory tunings have been reported in rat A1. Developmental

broadening of inhibition, both in the tuning of PV neurons and in inhibitory inputs to pyramidal cells has been observed in mouse V1 (Kuhlman et al., 2011; Li et al., 2012b). Therefore, there may be specific conditions and developmental windows in which lateral inhibition contributes substantially to sharpening neuronal receptive fields. A neural network computational model has been developed that can operate in both co-tuned and lateral inhibition modes, depending upon the input received (Levy and Reyes, 2011), and another set of theoretical models suggests that the diversity of receptive fields seen *in vivo* may be accounted for by the existence of multiple network architectures existing simultaneously (de la Rocha et al., 2008; Piëch et al., 2013). These results, coupled with the limitations of recording inhibition somatically, make definitive conclusions against a role for lateral inhibition in sharpening response selectivity tenuous.

The relative timing of excitatory and inhibitory inputs to a neuron can influence its ability to integrate inputs. Inhibition that follows excitation with a brief delay can create a narrow temporal window within which spiking can occur (Wehr and Zador, 2003; Wilentz and Contreras, 2004; Higley and Contreras, 2006). If the delay before the onset of inhibition varies with the stimulus, this delay could participate in coding. In rat S1, excitatory and inhibitory inputs to layer 3 and 4 neurons are poorly tuned

**Table 4 | Relative tuning of excitatory and inhibitory somatic conductances/currents in excitatory neurons.**

Sensory cortex: stimulus parameter	Layers	Anesthesia	Age	Species	Inhibitory and excitatory tuning widths	References
V1: Orientation	Mixed, 2/3, 4	Thiopental, ketamine/thiopental, diprivan/sufentanil citrate, pentobarbital/chlorprothixene	Adult	Cat, Mouse	Co-tuned	Anderson et al., 2000; Martinez et al., 2002; Tan et al., 2011
	4	Urethane/chlorprothixene	Pre-critical period	Mouse	Co-tuned	Li et al., 2012b
	Mixed	Alfaxalone/alfadolone,	Mixed	Cat	Mixed	Monier et al., 2003
	5	Ketamine/thiopental, diprivan/sufentanil citrate	Adult	Cat	Different excitatory and inhibitory tuning	Martinez et al., 2002
	2/3, 4	Urethane/chlorprothixene	Adult, critical period	Mouse	Inhibition broader than excitation	Liu et al., 2011; Li et al., 2012b
A1: Frequency	Mixed, 3–5	Ketamine/medetomidine, pentobarbital	Pre-critical period, critical period, adult	Rat, Mouse	Co-tuned/Similar	Wehr and Zador, 2003; Zhang et al., 2003; Tan et al., 2004; Froemke et al., 2007
	Mixed	Ketamine/xylazine	Pre-critical period	Rat	Different excitatory and inhibitory tuning	Dorn et al., 2010
	Mixed	Ketamine/xylazine	Adult	Rat	Co-tuned	Dorn et al., 2010
	4	Ketamine/xylazine	Pre-critical period	Rat	Co-tuned	Sun et al., 2010
	4	Ketamine/xylazine	Adult	Rat	Inhibition broader than excitation	Wu et al., 2008; Sun et al., 2010
A1: Intensity	Mixed	Ketamine/medetomidine	Pre-critical period/critical period	Rat	Co-tuned/Similar	Wehr and Zador, 2003
	Mixed, 4	Ketamine/xylazine, pentobarbital	Adult	Rat	Umbalanced	Wu et al., 2006; Tan et al., 2007
Pir: Odor	2/3	Urethane, ketamine	Pre-critical period, critical period	Rat	Inhibition broader than excitation	Poo and Isaacson, 2009

for the direction of a whisker deflection; however, the temporal gap before the onset of inhibition is greatest for the preferred direction (Wilent and Contreras, 2005). In layer 6 of rat A1, a majority of pyramidal neurons receive strong tone-evoked synaptic inhibition prior to excitation and are thus inhibited by tonal stimulation (Zhou et al., 2010). Interestingly, the time course of excitatory and inhibitory responses to oriented gratings in V1 differs between species: inhibition and excitation wax and wane in opposition in cats (Hirsch et al., 1998; Anderson et al., 2000; Monier et al., 2003; Priebe and Ferster, 2005; Tan et al., 2011), while they are modulated synchronously in the mouse (Tan et al., 2011). Species-specific differences in light and dark receptive subfields have been proposed to underlie this discrepancy (Tan et al., 2011).

In addition to possibly mediating spike timing and tuning curves, inhibition may play a role in response suppression and in maintaining sparseness of spiking responses. Response suppression occurs when a stimulus that would not by itself alter firing of a neuron inhibits the response of that neuron to another stimulus. While GABAergic neurons mediate some forms of response suppression, they likely do not mediate all response suppression. For example, when two tones of the same frequency are played in rapid succession, the cortical response to the second tone is suppressed. As both the onset and offset of stimuli can evoke neuronal responses with transient inhibitory and excitatory components, one hypothesis explaining this effect involves the first tone's offset evoking inhibition that suppresses the response to the second tone (Borg-Graham et al., 1998; Wehr and Zador, 2005; Scholl et al., 2010). However, Scholl et al. found that in rat A1 there is different frequency tuning of inputs for tone onset and offset (Scholl et al., 2010). This differential tuning allows the onset and offset of a given tone to evoke different excitatory and inhibitory current ratios, albeit transiently. Therefore, "forward" suppression of a second tone of the same frequency can only be mediated through feedforward inhibition generated by the first tone's onset if the second tone follows within the brief time window of the first tone's onset inhibitory current (Scholl et al., 2010).

In V1, a stimulus placed adjacent to a neuron's spiking receptive field can alter its responses to stimuli within the spiking receptive field, a phenomenon referred to as surround suppression. Surround suppression has been shown to be mediated, at least in part, through intracortical inhibition (Ozeki et al., 2009; Haider et al., 2010; Adesnik et al., 2012). However, there may be multiple mechanisms through which surround suppression occurs, depending on the nature of the stimuli. For example, in cats, surround suppression by optimally oriented gratings decreases the total excitatory and inhibitory inputs onto a cell: a transient increase in inhibition can be evoked by surround stimuli, which ultimately leads to suppression of both cortical excitatory and inhibitory inputs (Ozeki et al., 2009). For "naturalistic" stimuli, movies of wildlife, adding stimuli to the receptive field surround increases spiking reliability and firing sparseness (Haider et al., 2010). This effect is mediated through an increase in evoked inhibitory potentials throughout the stimulus duration and corresponds with an increase in FS interneuron firing (Haider et al., 2010). Perhaps the discrepancies between these

studies could be accounted for by the ever changing nature of the "naturalistic" stimuli, with the many moving edges evoking successive bouts of inhibition that blend together (Haider et al., 2010). In layer 2/3 of awake mice, inhibition through SOM positive interneurons accounts for approximately 30% of surround suppression by optimally oriented gratings (Adesnik et al., 2012).

In layer 5 of S1, stimulation of the ipsilateral paw just prior to stimulating the contralateral paw suppresses the neuronal response to the contralateral paw. This suppression is mediated by layer 1 interneurons driven by colossal projections that provide dendritic inhibition via GABA<sub>B</sub> receptor activation (Pérez-Garci et al., 2006; Palmer et al., 2012). These findings suggest that multiple intracortical mechanisms exist to generate suppression, with different mechanisms likely contributing to the suppression of different types of stimuli.

Inhibition is ideally suited to contribute to the maintenance of response sparseness. Interestingly, while S1/barrel cortex layer 2/3 pyramidal neurons uniformly show membrane potential responses to whisker stimulation, only ~10% spike during active touch (Crochet et al., 2011). This has been attributed to whisker responses having reversal potentials below spike threshold (Crochet et al., 2011; Sachidhanandam et al., 2013). These responses have reversal potentials well below those of excitatory receptors, suggesting that GABA receptor mediated currents may contribute to preventing these neurons from reaching spike threshold (Sachidhanandam et al., 2013). In favor of this interpretation, there is experimental evidence that whisker stimulation activates inhibitory neurons (Simons, 1978; Simons and Carvell, 1989; Swadlow, 1989; Armstrong-James et al., 1993; Zhu and Connors, 1999; Bruno and Simons, 2002; Swadlow and Gusev, 2002; Beierlein et al., 2003; Zhu et al., 2004; Zhu and Zhu, 2004; Gabernet et al., 2005; Cruikshank et al., 2007; Kwegyir-Afful et al., 2013; Lee et al., 2013; Sachidhanandam et al., 2013) and increases inhibitory drive onto excitatory neurons (Wilent and Contreras, 2005). Optogenetic photoactivation of PV neurons during a detection task both masked subthreshold responses and prevented behavioral responses (Sachidhanandam et al., 2013). These results suggest that inhibition can be precisely tuned to allow sparse firing in layer 2/3, keeping most neurons just below spike threshold after stimulation.

Additional circuit precision can be gained through subcellular compartment specific inhibition. While S1 layer 5 pyramidal neurons are rarely connected to each other directly, they are more commonly coupled disynaptically through layer 5 Martinotti cells (Silberberg and Markram, 2007). When activated, these Martinotti cells can prevent the generation of calcium spikes in the dendritic tufts of layer 5 pyramidal neurons (Murayama et al., 2009). Modeling of this circuit suggests that Martinotti cells are responsible for maintaining the dynamic range of dendritic calcium responses to paw shock that are observed *in vivo* (Murayama et al., 2009).

GABAergic neurons do not only contact excitatory neurons, but form networks of electrically and synaptically coupled interneurons, often comprised of the same cell type, that can be activated synchronously (Hestrin and Galarreta, 2005; Oswald et al., 2009; Pfeffer et al., 2013). This connectivity is especially well suited to allow for synchronization of local circuits and is

thought to contribute to the generation of oscillatory network behaviors (Tamás et al., 2000; Whittington et al., 2000; Oswald et al., 2009). The synchronicity of membrane potential oscillations between neurons can vary depending on stimuli. Neurons with similar receptive fields increase their membrane potential cross-correlation in response to optimal stimuli and decrease it in response to non-optimal stimuli (Lampl et al., 1999). Regardless of relative tuning, coherence in the gamma band between neurons increases for a wide variety of visual stimulus conditions (Yu and Ferster, 2010). Fast rhythmic bursting cells can fire bursts of action potentials in the gamma range (20–80 Hz) in response to visual stimuli, possibly contributing to visually evoked gamma oscillations (Cardin et al., 2005). This evoked gamma activity is dependent upon synaptic drive and is not generated only by the membrane properties of the chattering cells (Cardin et al., 2005). Gamma frequency oscillations measured in local field potentials can be evoked *in vivo* by optogenetic stimulation of PV positive neurons, suggesting that FS neurons may drive stimulus-evoked activity in the gamma band (Cardin et al., 2009). Photoactivation of these neurons to drive gamma oscillations during whisker deflection increases the precision of excitatory neuron responses and alters the amplitude and timing of responses in an oscillation phase dependent manner (Cardin et al., 2009).

Future work will be necessary to unravel how specific interneuron subtypes contribute to modulating sensory responses, fully understand the roles they play in higher order processing, and address whether there are specific conditions under which lateral inhibition sharpens receptive fields. One recent study in auditory cortex has begun to examine the cell type specific contributions of inhibition to modulating pyramidal cell activity during learning: VIP neurons were found to respond preferentially to reinforcement (Pi et al., 2013). SOM neurons were rapidly inhibited by VIP neurons, which caused an increase in firing of a subset of pyramidal neurons. This finding was interpreted to mean that activation of VIP neurons by reinforcement cues alters the gain of pyramidal neurons via disinhibition of SOM neurons (Pi et al., 2013). Together, the results presented in this section raise the intriguing possibility that the diversity in morphology and biophysical properties of GABAergic neurons is matched by their many functions.

## DEVELOPMENT OF GABAergic NEURONS AND SYNAPSES IN SENSORY CORTEX

GABAergic neurons and synapses undergo a process of postnatal maturation which extends for quite some time after birth and co-occurs with the development of many functional properties of excitatory neurons (Espinosa and Stryker, 2012). Here, we will focus on the developmental changes that occur after inhibitory neurons have reached their target location within the cortical mantle and after GABAergic synaptic transmission has transitioned from excitatory to inhibitory. Exhaustive readings of earlier developmental processes can be found elsewhere (see Cherubini et al., 1991; Xu et al., 2003; Li and Xu, 2008; Gelman and Marín, 2010; Rudy et al., 2011; Ben-Ari et al., 2012; Ciceri et al., 2013; Taniguchi, 2014).

The intrinsic properties of inhibitory neurons change during postnatal development. In rodent V1, PV FS neurons show

a progressive decrease in membrane time constant, cell capacitance and action potential width and an increase in intrinsic excitability during the first 2 weeks after eye opening (Goldberg et al., 2011; Lazarus and Huang, 2011). Conversely, SOM positive neurons show a progressive increase in membrane time constant, input resistance and spike frequency adaptation (Lazarus and Huang, 2011). The properties of inhibitory synapses also change during this developmental time window (Morales et al., 2002; Heinen et al., 2004; Maffei and Turrigiano, 2008a; Pinto et al., 2010). During the postnatal weeks following eye opening there is a progressive increase in  $\alpha 1$  containing GABA<sub>A</sub> receptors and a progressive decrease in  $\alpha 3$  and  $\alpha 5$  containing GABA<sub>A</sub> receptors. Significant changes also occur in the expression of  $\gamma$ ,  $\delta$  and  $\epsilon$  subunits (Heinen et al., 2004). Changes in receptor subunit composition underlie changes in conductance, clustering and susceptibility to allosteric modulators: all factors that play fundamental roles in determining the amplitude and time course of postsynaptic events (Bosman et al., 2002; Heinen et al., 2004; Möhler, 2006; Eyre et al., 2012). In mature brains GABA<sub>A</sub> receptors containing specific  $\alpha$  subunits are primarily located in specific subcellular compartments:  $\alpha 1$  and  $\alpha 3$  containing receptors are enriched at synapses on the soma and perisomatic regions of pyramidal neurons (Klausberger et al., 2002),  $\alpha 2$  containing receptors are preferentially located at axo-axonal synapses (Nusser et al., 1996),  $\alpha 5$  containing receptors are preferentially located at dendritic synapses (Ali and Thomson, 2008), and  $\alpha 4$  and  $\alpha 6$  containing receptors predominantly mediate extrasynaptic inhibition (Wisden et al., 2002; Chandra et al., 2006; Wu et al., 2012). Whether GABA<sub>A</sub> receptor subunits are similarly localized during development is not known; however, the observed changes in levels of expression suggest that changes in the subcellular targeting of GABAergic synapses may occur.

Comparable processes of protracted maturation of inhibitory synapses have been reported in A1 and S1. In both regions there is a progressive increase in spontaneous IPSC amplitude (Kobayashi et al., 2008; Zhang et al., 2011; Takesian et al., 2012), and in A1 there are many developmentally regulated changes in inhibitory neuron intrinsic properties and in evoked synaptic strength (Takesian et al., 2010, 2012, 2013; Oswald and Reyes, 2011; Kinnischtzke et al., 2012).

Developmental changes in inhibitory circuit function go beyond subunit composition, strength and kinetic properties. Inhibitory drive tends to increase during postnatal development (Blue and Parnavelas, 1983; Morales et al., 2002; Chattopadhyaya et al., 2004; Maffei and Turrigiano, 2008a; Kuhlman et al., 2011; Li et al., 2012b). Changes in the strength of inhibitory inputs have been shown to decrease the ability of excitatory neurons to fire action potentials (Saraga et al., 2008; Pouille et al., 2013). Thus, developmental regulation of inhibitory synaptic strength may have significant effects on the activity of excitatory neurons. Precise patterns of neural activity are required for the induction of different forms of plasticity; therefore, changes in circuit activity may alter how stimuli drive changes at synapses. Patterns of activity or sensory experiences that facilitate the induction of long term potentiation (LTPi) or depression (LTDi) at inhibitory synapses could gate the induction of specific forms of plasticity at glutamatergic synapses in cortical

circuits (Levelt and Hübener, 2012). Gating of excitatory plasticity could occur by altering activity patterns of glutamatergic neurons (Aton et al., 2013), by activating neuromodulatory signals (Huang et al., 2013) and/or through the activation of intracellular signaling cascades (Hayama et al., 2013; Wang and Maffei, 2014).

The capacity for plasticity at inhibitory synapses in V1 changes sharply during postnatal development at a time point corresponding to the transition between the pre-critical and the critical periods for visual cortical plasticity (Lefort et al., 2013). In response to the same pattern of activity, monosynaptic connections from FS neurons onto layer 4 pyramidal neurons show LTD<sub>i</sub> in the pre-critical period and LTP<sub>i</sub> in the critical period (Lefort et al., 2013). This shift in capacity for plasticity parallels that reported for layer 4 recurrent excitatory connections (Wang et al., 2012). Surprisingly, the switch in sign of plasticity at excitatory synapses can be reversed by inducing inhibitory plasticity in a connection specific fashion, indicating that inhibitory inputs may contribute to selective rewiring of local circuits despite their widespread connectivity (Wang and Maffei, 2014). This interaction between inhibitory and excitatory plasticity is mediated by G-protein signaling; therefore, it may affect the pyramidal neuron long after its induction (Wang and Maffei, 2014). Such a signaling crosstalk between mechanisms for excitatory and inhibitory plasticity could provide a memory trace that promotes experience-dependent rewiring of local microcircuits with a high degree of specificity and contributes to developmental circuit refinement.

During the developmental window in which inhibitory synapses mature, there are also substantial changes in glutamatergic receptor subunit composition, subcellular localization and function (Carmignoto and Vicini, 1992; Nase et al., 1999; Hensch, 2004; Corlew et al., 2007; Yashiro and Philpot, 2008), voltage signal propagation through the cortical circuit (Barkat et al., 2011; Griffen et al., 2013) and receptive field properties (Fagiolini et al., 1994; Katz and Shatz, 1996; Huang et al., 1999; Zhang et al., 2001; Inan and Crair, 2007; Wang et al., 2010; Espinosa and Stryker, 2012; Chen et al., 2014; Li et al., 2014a). Whether and how GABAergic neurotransmission contributes to these developmental processes is not fully understood. Evidence is beginning to emerge that changes in the receptive fields of the inhibitory drive onto excitatory neurons may at least partially underlie developmental receptive field sharpening (Dornn et al., 2010; Sun et al., 2010; Li et al., 2012b). However, the underpinning synaptic and circuit mechanisms of this process remain elusive.

### SENSORY DEPRIVATION IMPAIRS THE DEVELOPMENT OF GABAergic INHIBITION

The maturation of inhibitory synapses is strongly influenced by sensory experience. Visual deprivation induced by raising animals in the dark from birth or shortly thereafter disrupts visual response properties (Benevento et al., 1992; Fagiolini et al., 1994; Gianfranceschi et al., 2003; but see Rochefort et al., 2011) and delays the formation of mature innervation onto excitatory neurons; whereas dark rearing started after eye opening does not affect inhibitory drive (Morales et al., 2002; Maffei et al., 2010). Dark rearing decreases the level of expression of GAD65 in layer

2/3 inhibitory neurons (Kreczko et al., 2009) and prevents postnatal increases in IPSC amplitude onto pyramidal neurons from occurring, consistent with a delay in GABAergic input maturation (Morales et al., 2002). Interestingly, dark rearing mice blocks the developmental broadening of the orientation tuning of PV neurons, but it does not fully prevent the developmental sharpening of the orientation tuning of pyramidal neurons in layers 2–4 (Kuhlman et al., 2011; Rochefort et al., 2011; Li et al., 2012b), or of the inhibitory inputs to layer 4 pyramidal neurons (Li et al., 2012b). Dark rearing also delays the maturational increase in the coincidence of binocular inputs to pyramidal neurons in layers 2–4 (Chen et al., 2014). Pharmacologically enhancing inhibition with benzodiazepines early in development disrupts binocular matching of orientation preference in complex cells (Wang et al., 2010, 2013a), widens the spacing of orientation columns and disrupts direction selectivity (Hensch and Stryker, 2004). Together with sensory deprivation experiments, these results suggest that the normal development of GABAergic inhibition is essential for the proper maturation of visual cortex.

Auditory experience also plays a major role in the development of inhibitory inputs in A1, as early hearing loss, either conductive or sensorineural, alters GABAergic neurotransmission (Kotak et al., 2005, 2008; Takesian et al., 2010, 2012). Early conductive hearing loss delays the developmental decrease in IPSC decay time constant (Takesian et al., 2012), and produces a significant, long lasting decrease in spontaneous IPSC amplitude, suggesting the induction of long term depression of inhibitory drive (Takesian et al., 2012). Auditory experience is not only necessary for the maturation of inhibition in A1, but also regulates the capacity for plasticity at inhibitory synapses (Xu et al., 2010) and the feedforward thalamocortical drive onto different classes of inhibitory neurons (Takesian et al., 2013).

While whisker plucking prevents the maturation of feedforward inhibition onto excitatory neurons in the barrel cortex (Chittajallu and Isaac, 2010), the mechanisms engaged in driving GABAergic synapse maturation in S1 are unknown. Across cortices, early sensory deprivation delays the maturation of inhibitory synapses, but how experience-dependent, developmentally regulated cellular and synaptic changes in inhibition directly influence sensory responses is unclear.

### GABAergic MATURATION AND CRITICAL PERIOD PLASTICITY

Experiments with early sensory deprivation have shown that sensory experience is necessary for the maturation of inhibitory neurons and their synapses. However, if sensory manipulations are started later in postnatal development, for example during identified sensitive periods whose onset has been shown to correlate with the time course of the maturation of inhibition, sensory cortex is highly sensitive to even brief alterations in sensory drive (Hubel and Wiesel, 1970; Carmignoto and Vicini, 1992; Finnerty et al., 1999; Morales et al., 2002; Hensch, 2004; Maffei and Turrigiano, 2008a; Espinosa and Stryker, 2012; Levelt and Hübener, 2012). For example, monocular lid suture decreases the ratio of V1 neuronal spiking responses to the stimulation of the closed eye compared with the open eye, a phenomenon known as ocular dominance plasticity (Wiesel and Hubel, 1963). Ocular

dominance plasticity is effectively induced by lid suture during a limited time window in postnatal development known as a critical period (Hubel and Wiesel, 1970; Fagiolini et al., 1994; Gordon and Stryker, 1996).

The maturation of inhibitory synapses has been proposed as a critical step for the modulation of the onset and duration of critical periods (Hensch et al., 1998). Manipulations of inhibition *in vivo* during early postnatal development shift the onset of the critical period for visual cortical plasticity in V1. In GAD65 knockout mice, which have low levels of GABA throughout life, the critical period never opens (Fagiolini and Hensch, 2000). Increasing intracortical inhibitory drive with benzodiazepines or zolpidem in early development, or at any time in GAD65 knockouts, leads to the onset of a window for ocular dominance plasticity (Fagiolini and Hensch, 2000; Fagiolini et al., 2004; Wang et al., 2013a; Chen et al., 2014). This effect is mediated by GABA<sub>A</sub> receptors containing  $\alpha 1$  subunits, which are preferentially located at FS to pyramidal neuron somatic synapses (Fagiolini and Hensch, 2000; Klausberger et al., 2002; Iwai et al., 2003; Fagiolini et al., 2004; Katagiri et al., 2007). Either overexpressing BDNF or removing polysialic acid accelerates the development of inhibitory synapses and causes a precocious critical period (Hanover et al., 1999; Huang et al., 1999; Di Cristo et al., 2007). Similarly, sensory deprivation by dark rearing prolongs the onset of sensitivity to ocular dominance plasticity until the animal is introduced to light (Cynader and Mitchell, 1980; Mower and Christen, 1985; Mower, 1991; Fagiolini et al., 1994).

Conversely, pharmacologically decreasing inhibition in adult animals can reopen a window for ocular dominance plasticity (Harauzov et al., 2010; Maya-Vetencourt et al., 2012). This can be accomplished by reducing cortical GABA with GAD inhibitors, with the peptide hormone IGF-1, or by blocking GABA<sub>A</sub> receptors (Harauzov et al., 2010; Maya-Vetencourt et al., 2012). Environmental enrichment, which also decreases intracortical inhibition, can restore the capacity for ocular dominance plasticity in adult rodents in an IGF-1 dependent manner (Sale et al., 2007; Baroncelli et al., 2010; Maya-Vetencourt et al., 2012). Direct evidence that the age of inhibitory neurons, rather than overall inhibitory tone, plays a major role in critical period regulation comes from experiments where implants of GABAergic neural progenitors from embryonic mice were made into V1 of older mice. These implants later opened a window for ocular dominance plasticity that matched the age of the implanted neurons (Southwell et al., 2010). Substantial evidence exists that the maturation of inhibition regulates the timing of critical periods. Uniformly, manipulations that prevent that maturation of inhibition prevent the onset of critical periods, while those that enhance inhibition early in development cause a precocious critical period. Once inhibition has matured, reducing inhibition acutely can restore the capacity for ocular dominance plasticity. Manipulations that delay or accelerate the onset of the critical period for visual cortical plasticity, dark rearing and benzodiazepine application, also disrupt receptive field properties (see previous section), suggesting that inhibitory neurons play a fundamental role in the development of sensory cortex under normal conditions.

## SENSORY ALTERATION INDUCED PLASTICITY AT INHIBITORY SYNAPSES

Alterations in sensory experience are not only dependent upon cortical inhibitory tone to induce plasticity; they also induce specific plastic changes at inhibitory synapses. Altering sensory drive engages inhibitory plasticity differently depending on the age of the animal, the nature of the change in sensory drive, and the specific synapses examined. For example, monocular lid suture induces rapid changes in inhibitory synaptic strength and drive, whether the lid is sutured before or after eye opening (Maffei et al., 2004, 2006, 2010; Wang et al., 2011; Kuhlman et al., 2013; Wang and Maffei, 2014). However, brief monocular lid suture before eye opening decreases drive from FS neurons onto pyramidal neurons in layer 4 of V1 (Maffei et al., 2004), whereas lid suture of the same duration started during the critical period potentiates FS to pyramidal neuron synapses in layer 4, both pre- and post-synaptically (Maffei et al., 2006; Nahmani and Turrigiano, 2014).

Removing a single row of whiskers during the first 2–3 postnatal weeks leads to an early potentiation of whisker responses in layer 2/3 of S1 after 3 days of deprivation followed by a loss of responses after 5–10 days (Drew and Feldman, 2009; Li et al., 2014a). Responses in layer 4 are not changed by this manipulation (Drew and Feldman, 2009; Li et al., 2014a). Different from lid suture, removing a single row of whiskers induces potentiation of FS to pyramidal neuron synapses in layer 2/3, where sensory plasticity is expressed (House et al., 2011).

In adult animals one of the main effects of sensory manipulation is the induction of structural changes in inhibitory neurons. A reduced number of dendritic spines has been reported in a subpopulation of inhibitory neurons following adult monocular retinal lesioning (Keck et al., 2011), suggesting that they may become less effectively activated by sensory stimuli. In addition, monocular lid suture in adult animals leads to a decrease in the number of inhibitory inputs onto layer 2/3 pyramidal neurons (van Versendaal et al., 2012), and the fraction of dynamic inhibitory synapses onto layer 2/3 pyramidal neuron spines and shafts increases (Chen et al., 2012). Thus, in adult V1 unilateral manipulation of visual drive induces a rapid restructuring of inhibitory inputs, possibly leading to an overall decreased inhibitory drive onto layer 2/3 pyramidal neurons.

While pharmacologically manipulating inhibition can change the potential for experience-dependent plasticity, global changes in circuit excitability may not be the ideal mechanism for fine-scale refinement of cortical circuit connectivity. Fine scale circuit refinement may require local, possibly synapse specific, regulation of inhibition. The age, layer and cell type specific changes in inhibitory synapses observed following monocular lid suture could provide highly specific modulation of inhibition. The layer 4 FS to pyramidal neuron synapses that are potentiated rapidly following monocular lid suture are sensitive to benzodiazepines, suggesting that they could play a role in critical period regulation (Maffei et al., 2006; Katagiri et al., 2007; Wang and Maffei, 2014). Induction of LTPi at these synapses, either through lid suture or acutely, switches the sign of plasticity induced at pyramidal neuron recurrent synapses by slow wave stimulation from long term potentiation of excitation (LTPe) to long term depression of

excitation (LTDe) (Wang et al., 2012; Wang and Maffei, 2014). Acute depotentiation of the FS to pyramidal neuron synapses following lid suture restores the capacity for induction of LTPe, demonstrating that the control of inhibitory plasticity over the capacity for plasticity at excitatory synapses is modulated by experience (Wang and Maffei, 2014). While synapse specific, experience-dependent inhibitory control over excitatory plasticity has only been shown to exist in one microcircuit, this finding raises the intriguing possibility that plasticity at inhibitory synapses may control the expression of other forms of plasticity throughout cortex.

Experience-dependent reductions in inhibitory drive have been proposed to have a homeostatic role in contributing to the maintenance of neuronal activity in the face of altered sensory drive (Maffei et al., 2004; Maffei and Turrigiano, 2008b; Yang et al., 2011; Shao et al., 2013). Lid suture prior to the critical period decreases inhibitory synaptic strength onto excitatory neurons in layer 4 (Maffei et al., 2004). This homeostatic plasticity could be detected as a decrease in the spontaneous inhibitory drive and an increase in the spontaneous excitatory drive onto pyramidal neurons (Maffei et al., 2004). The induction of homeostatic inhibitory plasticity by monocular lid suture is developmentally regulated and shows layer specificity (Maffei et al., 2004; Maffei and Turrigiano, 2008b).

High decibel, high frequency sounds can lead to selective high frequency hearing loss, reorganization of the frequency map in A1 and tinnitus (Yang et al., 2011). Selective hearing loss leads to decreases in spontaneous inhibitory events and tonic inhibition thought to compensate for decreased sensory drive (Yang et al., 2011). Pharmacologically enhancing inhibition successfully eliminates tinnitus, while directly reducing excitation does not (Yang et al., 2011).

Whisker removal during a critical period for S1 plasticity reduces feedforward excitatory drive from layer 4 onto both layer 2/3 FS and pyramidal neurons, likely decreasing the activation of layer 2/3 by sensory input (House et al., 2011; Li et al., 2014a). This reduction in feedforward drive is compensated for by a robust decrease in the ability of layer 2/3 pyramidal neurons to recruit recurrent inhibition (Shao et al., 2013). These results coupled with the finding of FS to pyramidal neuron synaptic potentiation in layer 2/3 (House et al., 2011) suggest that a combination of homeostatic and Hebbian plasticity mechanisms contribute to rewiring the superficial layers of the barrel cortex.

Different forms of inhibitory synaptic plasticity can be engaged to refine or control local circuits. Despite widespread connectivity (Fino and Yuste, 2011; Packer and Yuste, 2011), the diversity of inhibitory neurons, and the selective sensitivity of distinct inhibitory synapses make them well suited to contribute to the maintenance of network excitability, large scale regulation of sensory cortical circuits and fine scale experience-dependent refinement of local microcircuits.

## INHIBITION AND CHANGES IN RESPONSES FOLLOWING SENSORY ALTERATIONS

Understanding how changes in GABAergic neurons and their synapses contribute to changing sensory responses and maintaining homeostasis of firing rates in the face of altered sensory drive

will be essential to pushing the field of experience-dependent plasticity forward. Recent work has shown that a brief unilateral reduction in visual drive strongly modulates the binocularity of FS inhibitory neurons. While FS inhibitory neurons are normally more binocular than pyramidal neurons (Swadlow, 1988; Yazaki-Sugiyama et al., 2009; Aton et al., 2013), soon after the onset of monocular lid suture or eye patching, layer 2/3 FS neurons are more strongly driven by the closed eye (Yazaki-Sugiyama et al., 2009; Aton et al., 2013; but see Kuhlman et al., 2013), although their spontaneous firing frequency is reduced (Yazaki-Sugiyama et al., 2009; Aton et al., 2013; Hengen et al., 2013). This increase in FS responsiveness to the deprived eye could contribute to reducing excitatory neuron responsiveness to that eye (Yazaki-Sugiyama et al., 2009). Interestingly, if the unilateral deprivation is maintained for several days both changes in ocular dominance of layer 2/3 FS neurons (Yazaki-Sugiyama et al., 2009; Aton et al., 2013; Kuhlman et al., 2013) and their spontaneous firing frequency are reversed (Aton et al., 2013; Hengen et al., 2013; but see Yazaki-Sugiyama et al., 2009). In layer 4 pyramidal neurons of mice, brief monocular lid suture similarly decreases both peak evoked excitatory and inhibitory conductances, and longer deprivation selectively reduces inhibition driven by the open eye (Ma et al., 2013). Differently, in rats longer monocular lid suture reduces excitation and inhibition driven by the deprived eye equally (Iurilli et al., 2013). Together, these results suggest that other mechanisms, such as changes in thalamocortical drive (Shatz and Stryker, 1978; LeVay et al., 1980; Khibnik et al., 2010; Wang et al., 2013b) may cooperate with altered intracortical inhibition to mediate the functional effects of sensory deprivation.

At first glance, studies showing that monocular lid suture does not affect the ratio of excitatory and inhibitory inputs to layer 4 pyramidal neurons (Iurilli et al., 2013; Ma et al., 2013) appear contradictory to the hypothesis that potentiation of inhibition directly suppresses visual responses (Maffei et al., 2006). However, many questions still exist. Visual stimuli used in these experiments were either moving bars or drifting gratings presented over seconds, or noise stimuli presented for several hundred milliseconds. Stimuli were presented only to one eye at a time. Additionally, only peak responses obtained during stimuli presented at peak orientation were examined (Iurilli et al., 2013; Ma et al., 2013). However, FS neurons in visual cortex have response properties that make them ideally suited to modulate extremely rapid visual responses to stimuli presented binocularly (Swadlow and Weyand, 1987; Swadlow, 1988; Yazaki-Sugiyama et al., 2009; Kameyama et al., 2010; Cardin, 2012; Aton et al., 2013; Zhuang et al., 2013). Additionally, their broad tuning raises the possibility that they could contribute to changes in orientation tuning or response suppression following lid suture. Alternatively, changes in patterns of FS neuron activity and synaptic strength could gate activity at other neurons' synapses (Levelt and Hübener, 2012; Wang and Maffei, 2014). Finally, recordings of somatic inhibitory conductances are unable to resolve differential contributions from interneuron subgroup: changes in input from one group may be offset by opposite changes in input from other groups. A recent study examining changes in excitatory and inhibitory conductances following whisker removal underscores the difficulty in

interpreting results using this technique (Li et al., 2014a). Short and long durations of whisker trimming reduce evoked excitatory and inhibitory drive, but both decrease inhibition more than excitation. Interestingly, brief whisker trimming increases evoked spiking responses, while longer removal decreases responses (Li et al., 2014a). Thus, additional circuit mechanisms beyond evoked somatic excitatory and inhibitory balance must contribute to this change in responsiveness.

Two particularly exciting studies have shed light on possible roles of inhibitory plasticity in modulating sensory responses. In addition to reducing inhibition in layer 2/3, whisker trimming significantly reduces gamma oscillations in the circuit driven by the deprived whisker (Shao et al., 2013), suggesting that sensory changes in inhibitory drive may modulate network state. Whether reducing evoked gamma oscillations *in vivo* favors the induction of plasticity is not known. Like lid suture, long term monocular strabismus disrupts ocular dominance (Hubel and Wiesel, 1965), and strabismus leads to binocular suppression, whereby monocular stimuli elicit stronger responses than binocular stimuli (Sengpiel and Blakemore, 1994; Sengpiel et al., 1994). Strabismus was shown to induce binocular suppression through a selective increase in inhibitory drive during binocular stimulation (Scholl et al., 2013). These results suggest that changes in cortical inhibition induced by sensory experience may alter sensory processing in more subtle and complex ways than simply repressing unilateral deprived organ (whisker or eye) responses to optimal stimuli.

Changes in inhibitory drive are certainly not the sole mechanism at play in the experience-dependent rewiring of sensory cortex, as trophic factors, excitatory synapses, neuron intrinsic properties and extracellular matrix interactions have all been shown to contribute to the altered visual response properties and ocular dominance (Berardi et al., 2003; Levelt and Hübener, 2012). Determining how inhibitory neurons and their plasticity contribute to cortical function will require a more comprehensive understanding of how specific subclasses of inhibitory neurons contribute to sensory responses. Techniques that isolate the specific contribution of interneuron groups will need to be combined with detailed analyses of circuit and cellular properties. Many different mechanisms of GABAergic plasticity have been identified (see Castillo et al., 2011; Maffei, 2011). To manipulate these specific forms of inhibitory plasticity, it will be necessary to first identify the parameter space for their induction and expression. Specific mechanisms can then be manipulated to assess their roles in modulating neurons' response properties.

## CONCLUSIONS

The maturation and plasticity of GABAergic neurons play fundamental roles in the development of sensory cortex. Inhibitory synaptic transmission and plasticity may affect critical period timing, specific receptive field properties, spike timing and other temporal aspects of coding, gain, neural synchrony, spontaneous and evoked firing rates, the capacity for plasticity at other synapses, and contribute to the homeostasis of circuit excitability. The role of all the distinct population of inhibitory neurons in the experience-dependent reorganization of cortical circuits has not been fully explored, but there is sufficient evidence to

show that different inhibitory neuron types may be engaged to modulate different aspects of neuron response properties. The challenge ahead lies in identifying the distinct roles of inhibitory neurons in cortical circuits and in determining how their plasticity contributes to modulating other neurons' response properties, connectivity, and capacity for plasticity. Development of new tools and experimental approaches to selectively manipulate specific mechanisms of inhibitory plasticity will be instrumental for determining their role in sensory cortex development and function.

## ACKNOWLEDGMENTS

Support: NIH/R01 EY019885 to Arianna Maffei. Trevor C Griffen was supported by NIHGM MSTP Training award T32-GM008444. We thank Melissa Haley for insightful comments on the manuscript.

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**Conflict of Interest Statement:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 20 January 2014; accepted: 12 March 2014; published online: 26 March 2014.  
Citation: Griffen TC and Maffei A (2014) GABAergic synapses: their plasticity and role in sensory cortex. *Front. Cell. Neurosci.* 8:91. doi: 10.3389/fncel.2014.00091  
This article was submitted to the journal *Frontiers in Cellular Neuroscience*.  
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