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The ins and outs of inhibitory synaptic plasticity: neuron types, molecular mechanisms and functional roles

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Abstract

GABAergic interneurons are highly diverse and their synaptic outputs express various forms of plasticity. Compelling evidence indicates that activity-dependent changes of inhibitory synaptic transmission play a significant role in regulating neural circuits critically involved in learning and memory and circuit refinement. Here, we provide an updated overview of inhibitory synaptic plasticity with a focus on the hippocampus and neocortex. To illustrate the diversity of inhibitory interneurons, we discuss the case of two highly divergent interneuron types, parvalbumin-expressing basket cells and neurogliaform cells, which support unique roles on circuit dynamics. We also present recent progress on the molecular mechanisms underlying long-term, activity-dependent plasticity of fast inhibitory transmission. Lastly, we discuss the role of inhibitory synaptic plasticity in neuronal circuits' function. The emerging picture is that inhibitory synaptic transmission in the CNS is extremely diverse, undergoes various mechanistically distinct forms of plasticity, and contributes to a much more refined computational role than initially thought. Both the remarkable diversity of inhibitory interneurons and the various forms of plasticity expressed by GABAergic synapses provide an amazingly rich inhibitory repertoire that is central to a variety of complex neural circuit functions, including memory.

Keywords

synaptic inhibition; synaptic plasticity; neural circuits; hippocampus; neocortex; memory

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Introduction

Synaptic plasticity is a fundamental phenomenon that refers to the ability of synapses to change their efficacy as a result of transient neuronal activity. It is believed to represent a major cellular event sculpting circuit dynamics and underlying learning and memory (Takeuchi *et al.*, 2014). Studies in animal models (e.g., rodents) established molecular mechanisms and neuronal circuits involved in this phenomenon (Luscher *et al.*, 2000; Herring & Nicoll, 2016). Most of the information on synaptic plasticity was initially obtained from excitatory synapses, but many experimental and computational studies more recently established that inhibitory synaptic plasticity (ISP) is also a major player in neuronal circuit mechanisms underlying memory processes (Hennequin *et al.*, 2017) as well as maintenance of circuit excitability (Nelson & Turrigiano, 2008). Identifying cellular and molecular mechanisms underlying ISP is important for several reasons: (i) ISP is expected to critically control the computation of cortical pyramidal neurons (Kullmann *et al.*, 2012; Hennequin *et al.*, 2017), (ii) it may promote stability of network activity following the formation of excitatory engrams (Barron *et al.*, 2017), which are defined as ensembles of neurons involved in storing and recalling memory, (iii) it is likely to be involved in brain disease, e.g., synaptic remodeling after stroke – (Berger *et al.*, 2019), or may be exploited for therapeutic intervention (Di Lazzaro *et al.*, 2018).

This review article focuses on GABAergic inhibitory synapses and ISP as a central contributor to fundamental circuit functions. We first provide a brief account of GABAergic neuron diversity in the cerebral cortex and hippocampus, and discuss how molecular properties at specific GABAergic synapses may confer distinct capacity for plasticity. Next, we review key molecular mechanisms underlying different forms of ISP, and speculate on how this diversity in mechanisms for ISP may support the wide palette of sophisticated contribution of inhibitory synapses to circuit computations. Finally, we discuss emerging hypotheses about the role of ISP. Thus, we bring together recent experimental and theoretical studies, and discuss how GABAergic neuron diversity and ISP heterogeneity contribute to neural circuit computations and complex brain functions such as learning and memory.

GABAergic neuron diversity

Cortical GABAergic neurons are diverse in their developmental origin, gene expression, morphology, function and connectivity (Gupta *et al.*, 2000; Klausberger & Somogyi, 2008; Tremblay *et al.*, 2016; Pelkey *et al.*, 2017; Fishell & Kepecs, 2019; Huang & Paul, 2019). This diversity is probably even more pronounced in the human cerebral cortex, where GABAergic cell types without apparent homology with rodent cortical cell types have been found (Boldog *et al.*, 2018). Combined information of dendritic and axonal patterns, molecular markers and functional activities of neurons is useful to determine cell types. Consistent with this, multiparametric methods have been endorsed to classify GABAergic neurons (Petilla Interneuron Nomenclature *et al.*, 2008; DeFelipe *et al.*, 2013). GABAergic cells are eminently target specific, selectively innervating subcellular domains of postsynaptic cells. For example, axo-axonic interneurons make synapses exclusively on the axon initial segment of cortical pyramidal cells (Somogyi *et al.*, 1983); basket cells

(BCs) target preferentially the somata and proximal dendrites of postsynaptic neurons (Thomson *et al.*, 1996; Tamas *et al.*, 1997), Martinotti and neurogliaform cells (NGFCs) target the dendrites of postsynaptic cells (Tamas *et al.*, 2003; Wang *et al.*, 2004), some neocortical interneurons preferentially target other interneurons (Pfeffer *et al.*, 2013). Functional specialization of inhibitory neurons provides subtle regulation of cortical networks. For example, cortical NGFCs provide feed-forward inhibition of distal dendrites of postsynaptic pyramidal neurons (Tamas *et al.*, 2003) and also elicit presynaptic inhibition of transmitter release (Olah *et al.*, 2009). A division of labor amongst interneuron types in governing network activity is well known in the hippocampus and cortex (Kawaguchi & Kubota, 1997; Klausberger & Somogyi, 2008; Tremblay *et al.*, 2016). Recent advances in high-throughput single-cell transcriptomics (scRNAseq) provided a new quantitative genetic framework to elucidate GABAergic neuron diversity (Poulin *et al.*, 2016; Shekhar *et al.*, 2016; Paul *et al.*, 2017; Que *et al.*, 2019). Given this diversity, it is possible that different GABAergic neuron types display different forms of ISPs, an idea that for now is supported by a limited amount of experimental data and will need further work (Horn & Nicoll, 2018; Schulz *et al.*, 2018).

Interneurons synapse specialization: molecular diversity of synapses from BC and NGFC

Here we will compare two GABAergic neuron types that are placed at the extremes of the GABAergic neuron diversity spectrum, namely, parvalbumin expressing (PV+) BCs and NGFCs of neorcortex and hippocampus. We will summarize molecular differences at the inhibitory synapses established by NGFCs and PV+ BCs, and discuss hypotheses about how these properties may endow synapses from these neuron types with distinct capacity for plasticity.

PV+ BCs mediate fast, phasic inhibition (Hefft & Jonas, 2005), in contrast NGFCs evokes volume transmission leading to slow inhibition (Capogna and Pearce, 2011). Information regarding synaptic-associated molecules expressed by PV BC+ and NGFCs is relatively abundant. By discussing their similarities and differences we can provide testable hypotheses about how molecular specificity may inform on interneuron-type specific signaling pathways underlying ISP. PV+ interneurons are estimated to be numerous (e.g, about 14% of CA1 hippocampal interneurons - (Bezaire & Soltesz, 2013) and elicit robust inhibitory responses in targeted principal neurons (Hu & Jonas, 2014), thus, they are likely to represent a significant group of interneuron mediating ISP in experimental conditions in which the presynaptic neuron is not identified (Vogels *et al.*, 2013). However, certain experimental settings allow for the specific identification of the inhibitory connection. For example, long-term potentiation (LTP) of cortical PV+ BC-mediated synaptic inhibition is elicited by visual deprivation (Maffei *et al.*, 2006). Spike timing dependent plasticity (STDP) has also been observed at this type of connection: short delay between spiking of a cortical PV+ BC and a principal neuron elicits long-term depression (LTD), whereas longer delays evoke LTP (Holmgren & Zilberter, 2001). More recently, cortical PV+ interneuron-mediated inhibition shows STDP that contributes to auditory map remodeling (Vickers *et al.*, 2018). In contrast to PV+ interneurons, much less is known on ISP mediated by NGFCs. In the

hippocampus, this interneuron type displays marked synaptic depression evoked by a train of presynaptic stimuli at theta frequency which has a recovery time constant of about 10 minutes (Karayannis *et al.*, 2010). Furthermore, the injection into a postsynaptic NGFC *in vitro* of a firing pattern recorded in a NGFC *in vivo* displays shorter-term retrograde synaptic depression lasting about 1 minute (Li *et al.*, 2014a). As for long-term ISP, the molecular properties we discuss below suggest that synapses established by NGFCs have the machinery for changing their synaptic efficacy. In support of this possibility, recent findings have implicated this interneuron subtype in memory processes in the cortex (Abs *et al.*, 2018).

Salient features of hippocampal PV+ BCs and NGFCs are illustrated in Figure 1. Morphological properties of PV+ BCs and NGFCs are notably different. PV+ BCs have multiple dendrites that often cross layers (Gulyas *et al.*, 1999; Tukker *et al.*, 2013), suggesting heterogeneous inputs. In contrast, the dendrites of NGFCs are compact and arranged in a stellate fashion around the soma (Vida *et al.*, 1998), pointing to inputs from a more restricted set of afferent pathways. The axon of PV+ BC shows extensive arborization, and generates a divergent inhibitory output restricted to the perisomatic domain of postsynaptic targets (Sik *et al.*, 1995). The axon of NGFC is also extensive but it branches profusely and usually targets exclusively the dendritic domain of postsynaptic neurons in the hippocampus (Vida et al., 1998; Price et al., 2005), as in the neocortex (Tamas *et al.*, 2003). Molecular features of PV+ BCs and NGFCs are also quite different. A subpopulation of BCs expresses PV with an average concentration of 10 μM at the soma in hippocampal dentate granule cell layer. Because PV is a slow calcium buffer, it affects the time course of intracellular calcium transients in terminals after an action potential, and hence regulate short-term synaptic plasticity favoring synaptic depression (Eggermann & Jonas, 2011). In contrast, both neocortical and hippocampal NGFCs express an array of marker proteins, including α-actinin2, neuropeptide Y, neuronal nitric oxide synthase (nNOS), the transcription factor COUP-TFII and the extracellular matrix protein reelin (Price *et al.*, 2005; Fuentealba *et al.*, 2008; Olah *et al.*, 2009; Fuentealba *et al.*, 2010; Szabadics *et al.*, 2010). The presence of nNOS supports the idea that NGFCs synapses are plastic and this plasticity may have physiological significance (Makara *et al.*, 2007). When hippocampal NGFCs generate a theta rhythm-associated activity their synapses display inhibitory short-term synaptic plasticity onto pyramidal neurons. This phenomenon, called “firing-induced suppression of inhibition” (FSI) requires backpropagation of action potentials, postsynaptic calcium influx through L-type calcium channels, nNOS activity and NO retrograde release, and activation of NO-sensitive guanylyl cyclase receptors at presynaptic terminals (Li *et al.*, 2014a). FSI indirectly increases the amplitude of excitatory postsynaptic potentials (EPSPs), and may enhance spatial and temporal summation of excitatory inputs to NGFCs, thereby regulating their inhibition of pyramidal cells (Li *et al.*, 2014a). Neocortical PV+ BCs also show NO-dependent short-term plasticity, but its time scale is markedly different from the one exhibited by hippocampal NGFCs. Somatic depolarization of pyramidal cells in layer 5 triggers Ca^{2+}-dependent retrograde release of NO which diffuses to PV+ BC axon terminals and elicits a persistent increase of GABA release (Lourenco *et al.*, 2014).

Distinct synaptic organization for PV+ BC and NGFC

The synaptic organization of PV BCs and NGFCs is markedly different. A single neocortical NGFC axon has a release site density comparable to that of five or six BC axons (Olah *et al.*, 2009), suggesting that GABA released from NGFC axons can reach synaptic but also non-synaptic receptors. Moreover, axon boutons of NGFCs are often (Olah *et al.*, 2009), but not always (Tamas *et al.*, 2003; Price *et al.*, 2008; Fuentealba *et al.*, 2010), found 1–5 μm away from target dendrites, a surprisingly long distance compared to the 10–20 nm typically detected at conventional PV+ BC synapses (Tukker *et al.*, 2013). The release of GABA from neocortical NGFCs can also inhibit the release of glutamate or GABA from axon terminals located remotely from NGFC release sites (Olah *et al.*, 2009). Therefore, it has been suggested that NGFCs can mediate volume transmission (Olah *et al.*, 2009) wherein a widespread, prolonged, low-level GABA transient is produced by a dense array of NGFC release sites (Capogna & Pearce, 2011). Furthermore, at the postsynaptic level, data obtained with high resolution replica immunogold labeling indicate that all CA1 pyramidal cell somatic inhibitory synapses contain the α1, α2, β1, β2, β3 and γ2 subunits along with the adhesion molecule neuroligin-2 (NL-2) (Kerti-Szigeti & Nusser, 2016), whereas neocortical NGFCs synapses show also high level of $GABA_A$ receptors $GABA_A$Rs) containing δ subunits (Olah *et al.*, 2009). The presence of the δ subunits in $GABA_A$ receptors at synapses is unique to NGFCs, as receptors containing this subunit are typically located extrasynaptically (Farrant & Nusser, 2005; Belelli *et al.*, 2009). More recently, hippocampal NO-synthase expressing NGFCs have been found to activate postsynaptic α5-$GABA_A$ receptors which strongly contribute (50–80%) to the inhibitory synaptic conductance (Schulz *et al.*, 2018). Importantly, the inhibition of dendritic NMDA spikes via α5-$GABA_A$ receptors-containing synapses provides a mechanistic basis for the powerful control of NMDA receptor-dependent burst firing and synaptic plasticity in CA1 pyramidal cells by dendrite-targeting interneurons (Schulz *et al.*, 2018). Conversely, α5-$GABA_A$ receptors supply a negligible contribution to perisomatic inhibition elicited by fast-spiking PV interneurons (Schulz *et al.*, 2018). Whether synaptic junctions formed by PV+ BCs or NGFCs also differ in the organization of postsynaptic molecular components, such as scaffolding proteins (e.g., gephyrin, collybistin), adhesion proteins (e.g., NL-2), kinases (e.g., PKC, ERK1/ERK2) and proteases (e.g., calpain) for $GABA_A$R phosphorylation/dephosphorylation, is currently not known. These molecular components are pivotal for localization, stability and regulation of baseline as well as plastic GABAergic signaling (Chiu *et al.*, 2019).

A distinctive functional feature is that action potentials of PV+ BC have fast kinetics that evoke $GABA_A$R-mediated inhibitory postsynaptic responses with a time constant of 5–10 ms (Cobb *et al.*, 1995), whereas NGFCs have broader spikes that evoke slow postsynaptic inhibitory potentials (time constant can be > 30 ms) (Tamas *et al.*, 2003). Upon repetitive stimulation, inhibitory responses evoked by both PV+ BCs and NGFCs show marked depression (Hefft & Jonas, 2005; Karayannis *et al.*, 2010).

Overall, PV+ BCs synapses onto their target neurons have been convincingly shown to express pre- and postsynaptic molecular motifs apt to confer fast neurotransmission proper of this GABAergic neuron type. These motifs include the tight “nanodomain”

coupling between Ca^{2+} channels and release sensors for exocytosis, promoting efficacy and temporal precision of neurotransmitter release, as well as shortening the synaptic delay (Bucurenciu *et al.*, 2008). Furthermore, a subpopulation of PV+ interneurons in the neocortex and hippocampus uses the synaptotagmin 2 isoform as a release sensor protein for neurotransmitter release (Kerr *et al.*, 2008), in contrast to the most common synaptotagmin 1 expressed in principal cells (Geppert *et al.*, 1994). The synaptotagmin 2 isoform has the fastest Ca^{2+} binding kinetics among synaptotagmin family proteins, a feature that is likely to contribute to fast neurotransmission. Conversely, direct measurements of presynaptic Ca^{2+} transients in hippocampal NGFCs reveal slow decaying Ca^{2+} transients at axonal boutons (Price *et al.*, 2008), consistent with the slow kinetics of neurotransmission elicited by this neuron type.

The spiking patterns of PV+ BCs and NGFCs detected *in vitro* and *in vivo* are also quite characteristic. PV+ BCs show remarkable high action potential frequency (> 10 Hz) (Sik *et al.*, 1995), whereas hippocampal NGFCs fire maximally up to 10 Hz during theta network oscillations *in vivo* (Fuentealba *et al.*, 2010) under basal conditions without applying any stimulation. Neocortical and hippocampal NGFCs also display a so-called barrage firing (Sheffield *et al.*, 2011; Suzuki *et al.*, 2014; Chittajallu *et al.*, 2020), a persistent spiking activity occurring up to several minutes after cells' stimulation, which can reach frequencies up to 130 Hz. Because of prominent frequency-dependent synaptic depression, it is still unclear how much inhibition is provided to postsynaptic targets during NGFC barrage firing.

At the circuit level, a major difference between PV+ BCs and NGFCs is that PV+ BCs mediate both feedforward (FF) and feedback (FB) inhibition (Hu *et al.*, 2010), whereas NGFCs only mediate FF inhibition (Capogna & Pearce, 2011). This has been well characterized in hippocampus. CA1 afferent glutamatergic axons (e.g. from entorhinal cortex or Schaffer collaterals) elicit FF inhibition via parallel activation of CA1 pyramidal cells, PV+ BCs and NGFCs. CA1 pyramidal cells driven by the same glutamatergic axons in turn activate PV+ BCs, but not NGFCs, recruiting circuit-specific FB inhibition. The speed of both FF and FB inhibition elicited by PV+ BCs is high; the latency of disynaptic inhibition under physiological conditions is less than 2 ms (Miles, 1990). Hippocampal NGFCs evoke much slower FF inhibition onto CA1 pyramidal neurons and influence the temporal integration of incoming excitatory signals on a longer time scale (Price *et al.*, 2008). Hippocampal PV+ BCs powerfully inhibit spiking of postsynaptic neurons due to the perisomatic location of its GABAergic synapses, but also elicit rebound spiking after postsynaptic hyperpolarization that promote network synchronization activity *in vitro* (Cobb *et al.*, 1995). Rebound spiking has also been observed *in vivo* (Adhikari *et al.*, 2012). Neocortical NGFCs inhibit the dendrites of postsynaptic neurons and reduce dendritic Ca^{2+} signals *in vitro* (Perez-Garci et al., 2006) and *in vivo* (Abs *et al.*, 2018). This neuron type presynaptically inhibits the release of glutamate from nearby excitatory terminal via a $GABA_B$ receptor mediated mechanism (Olah *et al.*, 2009). In addition, PV+ BCs have specific functions in microcircuits. FF inhibition by CA1 hippocampal PV+ BCs sharpens the window for temporal summation of EPSPs and action potential initiation in principal neurons (Pouille & Scanziani, 2001), and broadens the dynamic range of activity in principal neuron ensembles (Pouille *et al.*, 2009). Conversely, lateral FB inhibition promotes a "winner-takes-all" mechanism, enforcing spiking in principal cells with the

strongest input, and inhibiting activity in the weaker principal cells (de Almeida *et al.*, 2009). PV+ BCs could also contribute to other circuit functions such as sparsification of activity (Pernia-Andrade & Jonas, 2014), pattern separation (Leutgeb *et al.*, 2007), and grid-to-place code conversion (de Almeida *et al.*, 2009). For a review on the role of PV+ BC in these events see also Hu et al, Science 2010 (Hu *et al.*, 2010). Hippocampal PV+ BCs usually enhance their spiking activity during network oscillations (Klausberger & Somogyi, 2008). Experimental manipulation of PV+ interneuron activity showed that these neurons modulate several phenomena such as the shape of place fields and the phase precession in CA1 pyramidal neurons (Royer *et al.*, 2012), the gain of sensory responses (Lee *et al.*, 2012), the regulation of learning (Donato *et al.*, 2013). Much less is known on the functional role of NGFCs. Hippocampal NGFCs preferentially spike phased-locked to theta network oscillations (Fuentealba *et al.*, 2010). In addition, activity of NGFCs is increased during fear memory retrieval in an auditory associative fear learning test. This effect is specific to NGFC, as the activity of another group of dendrite-targeting interneurons, those expressing SST, remains unaltered (Abs *et al.*, 2018). Based on the distinct molecular and structural features, it is conceivable that synapses established by PV+ BCs and NGFCs onto principal neurons engage distinct mechanisms of ISP, which can mediate long-term redistribution of synaptic inhibition impinging on different compartments of pyramidal neurons. Recent experimental evidence appears to support this prediction (Horn & Nicoll, 2018).

Molecular mechanisms of Inhibitory Synaptic Plasticity

In addition to the molecular heterogeneity of inhibitory neurons and their synapses, there is also remarkable diversity in the mechanisms underlying ISP (for more extensive reviews, see (Gaiarsa *et al.*, 2002; Castillo *et al.*, 2011; Luscher *et al.*, 2011; Kullmann *et al.*, 2012; Maffei *et al.*, 2017; Chiu *et al.*, 2019). Although such diversity imposes an additional challenge to the study of ISP, some mechanistic principles have been identified. As for excitatory synaptic plasticity, ISP can be expressed presynaptically as changes in GABA release, or postsynaptically as changes in GABA receptor number or function (Figure 2). In this section, we summarize recent advances and emerging mechanisms on long-term, activity-dependent strengthening and weakening of fast inhibitory transmission mediated by $GABA_A$Rs –i.e. I-LTP and I-LTD, respectively. While we will focus on data from synapses of the rodent neocortex and hippocampus, other brain areas sharing similar mechanisms of ISP will be cited in order to highlight generalizability.

Presynaptic forms of ISP

Presynaptic I-LTP and I-LTD are widely expressed throughout the brain (Castillo *et al.*, 2011; Castillo, 2012). Here, GABAergic terminals integrate diverse signals to induce long-lasting changes in GABA release by a (poorly understood) mechanism that may involve changes in the release machinery, presynaptic Ca^{2+} influx, as well as presynaptic structural changes (Castillo, 2012; Yang & Calakos, 2013; Atwood *et al.*, 2014; Monday *et al.*, 2018). Induction is commonly mediated by retrograde signals mobilized following transient, repetitive activation of nearby excitatory synapses – in a form of heterosynaptic plasticity – or repetitive firing of the postsynaptic neuron. Presynaptic Ca^{2+} elevations, via voltage-gated calcium channels (VGCCs) or presynaptic NMDA receptors (pre-NMDARs),

activate metabolic cascades that may play a permissive, modulatory or instructive role in the induction of presynaptic ISP (Castillo, 2012; Monday *et al.*, 2018). Diverse chemical messengers act as retrograde signals (Regehr *et al.*, 2009), and a number of these messengers mediate ISP. Chief among them are endocannabinoids (eCBs), brain-derived neurotrophic factor (BDNF) and nitric oxide (NO). In some cases, ISP can be induced by presynaptic signals alone –i.e. in the absence of retrograde signals (Castillo *et al.*, 2011).

The best-characterized form of presynaptic ISP is probably the eCB-mediated I-LTD. In many brain regions, repetitive activation of glutamatergic inputs triggers eCB mobilization from the postsynaptic cell to the presynaptic terminal, where they bind to $G_{i/o}$-coupled type 1 cannabinoid receptors (CB_1) to suppress GABA release in a long-term manner (Castillo *et al.*, 2012). Typically, eCB-mediated I-LTD is triggered by postsynaptic activation of group I metabotropic glutamate receptors (mGluR-I), leading to the production of diacylglyercol (DAG) by phospholipase C (PLC). Diacylglycerol lipase (DGL) converts DAG to the major eCB 2-AG, which is released from the postsynaptic cell and travels back across the synapse to activate presynaptic CB_1 receptors (Heifets & Castillo, 2009; Kano *et al.*, 2009). eCB-mediated I-LTD has been reported in several areas of the rodent brain, including the hippocampus (Chevaleyre & Castillo, 2003), amygdala (Marsicano *et al.*, 2002; Azad *et al.*, 2004), dorsal striatum (Adermark *et al.*, 2009), hypothalamus (Crosby *et al.*, 2011), and visual cortex (Jiang *et al.*, 2010; Sun *et al.*, 2015). In the hippocampus and basolateral amygdala (Freund *et al.*, 2003; Vereczki *et al.*, 2016), CCK+ (regular-spiking), but not in PV+ (fast-spiking) interneurons, selectively express CB_1 receptors (Freund *et al.*, 2003). However, this dichotomy is less clear in other brain areas (Younts & Castillo, 2014). Theta-burst firing of CA1 pyramidal neurons for a few minutes, by raising intracellular calcium and mobilizing eCBs, is sufficient to induce hippocampal I-LTD at both somatic and dendritic inhibitory synapses (Younts *et al.*, 2013).

BDNF/TrkB-mediated I-LTP is induced by activity-dependent release of BDNF from either axon terminals or dendrites (Edelmann *et al.*, 2014), and is typically observed in immature circuits (Castillo *et al.*, 2011). There is good evidence that dendritically released BDNF mediates I-LTP by activating presynaptic TrkB receptors in the hippocampus (Gubellini *et al.*, 2005; Sivakumaran *et al.*, 2009) and visual cortex (Inagaki *et al.*, 2008). This ISP is initiated by intracellular Ca^{2+} rise via NMDARs or VGCCs, or calcium release from intracellular stores. As in eCB-mediated I-LTD (Heifets *et al.*, 2008), input-specificity of BDNF-mediated I-LTP may derive from a requirement for coincident presynaptic interneuron activity to enhance TrkB signaling (Liu *et al.*, 2007; Edelmann *et al.*, 2014). The effects of BDNF/TrkB signaling on GABAergic transmission and plasticity are particularly complex (Lu *et al.*, 2014), given that BDNF can increase the number of GABAergic terminals (Marty *et al.*, 2000; Hong *et al.*, 2008; Jiao *et al.*, 2011), but can also modulate the expression of the chloride transporter KCC2 (see below), and the surface expression, localization and function of $GABA_A$Rs.

NO-mediated I-LTP of GABA release has been reported in neocortex and other brain areas. In layer 5 pyramidal neurons of the somatosensory cortex, postsynaptic Ca^{2+} rise following repetitive firing activates nitric oxide synthase (NOS) and mobilizes NO to induce presynaptic I-LTP (Lourenco *et al.*, 2014). NO readily permeates through the membrane

and presumably stimulates presynaptic guanylate cyclase (GC), thereby augmenting cGMP levels to enhance GABA release via an unknown mechanism. The NO-dependent increase in GABA release is selective for perisomatic inhibition from PV+ but not SST+ interneurons (Lourenco *et al.*, 2014) indicating cell-type specificity for this form of ISP. In several other brain areas (Castillo *et al.*, 2011), NO-mediated I-LTP is also induced by repetitive activation of glutamatergic inputs and NMDAR-mediated postsynaptic Ca^{2+} rise, which activates NOS. However, evidence for this heterosynaptic mechanism of ISP at hippocampal and neocortical synapses is lacking.

Retrograde signaling is a highly regulated process (Iremonger *et al.*, 2013), allowing for multiple points of modulation and cross-talk with several signaling systems. For example, theta-burst stimulation in layer 2/3 neurons of somatosensory cortex induces I-LTD that requires BDNF-TrkB signaling, but not mGluR-I activation (Zhao *et al.*, 2015). Activation of presynaptic, $G_{i/o}$-coupled type 2 dopamine receptors (D_2R) act synergistically with CB_1 downstream signaling to induce I-LTD in the prefrontal cortex (Chiu *et al.*, 2010), suggesting additional layers of modulatory complexity in presynaptic terminals. Lastly, in CA1 pyramidal neurons, STDP-induced I-LTD requires coactivation of (presumably presynaptic) $G_{i/o}$-coupled M_2-type muscarinic acetylcholine receptors and eCB signaling (Ahumada *et al.*, 2013).

ISP can be induced homosynaptically in the absence of retrograde signaling (Castillo, 2012). This is the case of fast-spiking interneurons in layer 2/3 of the mouse visual cortex where repetitive activity of these neurons can induce presynaptic I-LTP that likely relies on presynaptic calcium influx via P/Q type calcium channels (Sarihi *et al.*, 2012). Adding to the diversity of presynaptic mechanisms for ISP, there is evidence that neuromodulatory systems can also induce ISP. A good example can be found at PV+ to CA2 pyramidal cell synapses, where activation of presynaptic $G_{i/o}$-coupled delta-opioid receptors, likely acting on the release machinery, induces a form of presynaptic I-LTD reminiscent of eCB-dependent I-LTD (Piskorowski & Chevaleyre, 2013). Other presynaptic metabotropic receptors (Atwood *et al.*, 2014) may also contribute to the induction of ISP.

Postsynaptic forms of ISP

In many cases activity-dependent ISP relies on postsynaptic modifications such as changes in the properties or number of $GABA_A$Rs expressed at the synapse (Luscher *et al.*, 2011; Vithlani *et al.*, 2011). Here, we briefly summarize the induction and expression mechanisms underlying this form of plasticity. Postsynaptic ISP can be induced by repetitive firing of the postsynaptic neuron, coordinated activity of the GABAergic interneuron and the postsynaptic neuron, or heterosynaptically by repetitive activation of nearby glutamatergic synapses (Gaiarsa *et al.*, 2002; Castillo *et al.*, 2011; Lourenco *et al.*, 2014; Chiu *et al.*, 2019). A common theme is that Ca^{2+} rise either via VGCCs or NMDARs sets in motion a metabolic cascade of events that leads to changes in $GABA_A$R function or number. In layer 5 pyramidal neurons of rat visual cortex, repetitive firing from a depolarized membrane potential, induces I-LTD at somatic inhibitory synapses, whereas cell firing during slow membrane voltage oscillations induces I-LTP. Interestingly, while I-LTD is mediated by L-type calcium channels, I-LTP is mediated by R-type calcium channels, suggesting that the

relative amount of calcium entry through these channels determines the polarity of this ISP (Kurotani *et al.*, 2008). As mentioned above, timing of pre and postsynaptic activity is also important for the polarity of ISP (Holmgren & Zilberter, 2001), although the relationship between timing and sign of plasticity differs from that reported for excitatory synapses (Bi & Poo, 2001). Pairing of presynaptic burst activity and subthreshold postsynaptic depolarization also induces I-LTP at PV+ and layer 4 pyramidal neuron synapses in the developing visual cortex (Maffei *et al.*, 2006; Wang & Maffei, 2014). This plasticity is occluded by visual deprivation, a manipulation that potentiates inhibitory transmission, suggesting that I-LTP can occur *in vivo*.

Glutamatergic activity can induce heterosynaptic, postsynaptic ISP by activating ionotropic (typically NMDARs) or mGluRs. (Ouardouz & Sastry, 2000). This form of postsynaptic I-LTP has recently been reported at dendritic synapses between SST+ interneurons and layer 2/3 pyramidal neurons of the mouse medial prefrontal cortex (Chiu *et al.*, 2018). I-LTD induction in the CA1 area of the hippocampus relies on a similar mechanism (Lu *et al.*, 2000). Earlier studies (Aizenman *et al.*, 1998) documented a form of NMDAR-dependent I-LTP requiring postsynaptic calcium rise in DCN neurons induced by high frequency stimulation of glutamatergic inputs.

The expression mechanisms of postsynaptic ISP are diverse. Increases or decreases in channel function can occur as a result of $GABA_AR$ phosphorylation by multiple kinases, including, CaMKII, PKC, PKA and Src (Vithlani *et al.*, 2011). $GABA_ARs$ are further controlled by constitutive cycling, regulating insertion and removal, as well as lateral diffusion at the synaptic membrane surface (Luscher *et al.*, 2011; Vithlani *et al.*, 2011; Maynard & Triller, 2019; Pizzarelli *et al.*, 2019; Tomita, 2019). The number of $GABA_ARs$ at the cell surface is regulated by endocytosis and exocytosis. Evidence that postsynaptic I-LTP is due to $GABA_AR$ insertion in the plasma membrane comes from the observation that intracellular loading of botulinum toxin or tetanus toxin, which blocks vesicular exocytosis and insertion of new receptors into the plasma membrane, reduces this potentiation in layer 5 pyramidal neurons in the rat visual cortex (Kurotani *et al.*, 2008). The activation of NMDARs by either exogenous agonists or endogenous glutamate potentiates GABAergic synapses from SST+, but not PV+, interneurons in pyramidal neurons of layer 2/3 of prefrontal cortex (Chiu *et al.*, 2018). Furthermore, intracellular cellular loading of a peptide that interferes with endocytosis, not only blocks I-LTD but uncovers I-LTP in layer 5 pyramidal neurons (Kurotani *et al.*, 2008).

The molecular mechanisms involved in postsynaptic $GABA_AR$ plasticity have been largely investigated in heterologous systems and cultured neurons where the circuit architecture is not preserved and where “plasticity” is commonly induced using various chemical methods (Vithlani *et al.*, 2011; Petrini *et al.*, 2014; Maynard & Triller, 2019; Pizzarelli *et al.*, 2019; Tomita, 2019). While informative, these studies may not capture the nuances of synaptic inhibition and activity-dependent ISP (i.e. I-LTP, I-LTD) *in vivo*, including the remarkably diverse interneuron subtypes, and the unique postsynaptic sub-cellular compartments (e.g. soma, axon, proximal and remote dendrites) (Chiu *et al.*, 2019). While new molecular players continue to be discovered (Uezu *et al.*, 2016; Martenson *et al.*, 2017) and the nanoscale molecular structure of the GABAergic postsynaptic density is better understood

(Pennacchietti *et al.*, 2017; Crosby *et al.*, 2019), more work is required to elucidate the molecular basis underlying $GABA_AR$ regulation in postsynaptic ISP, especially in preparations where the circuit architecture is preserved. This includes the precise role of scaffolding and auxiliary proteins in receptor trafficking, and the postsynaptic molecular determinants of ISP heterogeneity.

Postsynaptic GABAergic plasticity can occur independently of direct receptor regulation. In hippocampal neurons, coincident pre- and postsynaptic activity alters the activity of the K^+/Cl^- co- transporter KCC2, resulting in long-lasting changes in the reversal potential of GABAergic synaptic currents (Woodin *et al.*, 2003). In this case, plasticity is induced by the activation of postsynaptic VGCCs. This mechanism should affect all inhibitory synapses, in a neuron type-independent manner. This plastic change in GABAergic synaptic strength, which is dependent on coincident pre- and postsynaptic spiking, should set the level of inhibition in accordance to the temporal pattern of postsynaptic excitation (Woodin et al., 2003). ISP induced by regulation of the reversal potential of GABA currents has powerful effects on the ability of pyramidal neurons to generate action potentials (Saraga *et al.*, 2008), providing powerful control over activity propagation in neural circuits.

Inhibitory plasticity and circuit function

A growing body of evidence highlighted the contribution of inhibitory neurons to a variety of neural circuit functions (Maffei, 2017). Different populations of GABAergic neurons are activated during behaviors (Kepecs & Fishell, 2014). However, very little is currently known about the function of GABAergic ISP.

Several circuit computations are thought to depend on inhibitory circuits (Kepecs & Fishell, 2014). Experimental results and computational/theoretical approaches strongly suggest that GABAergic circuits are engaged in establishing the flow of signals in cortical circuits. A prominent example is lateral inhibition, a process by which the flow of signals is directed by dampening the activation of neighboring neurons (Kayser & Miller, 2002). GABAergic inhibition is also thought to contribute to adjusting the excitability of principal neurons through subtractive or divisive normalization (Pouille *et al.*, 2009; Silver, 2010; Mejias *et al.*, 2014; Seybold *et al.*, 2015; Bhatia *et al.*, 2019): the modulation of neurons input/output function that determines the sensitivity of neurons responsiveness to small changes in incoming input (gain). Differences in tuning of responses to stimuli between principal neurons, relatively narrowly tuned to incoming inputs, and GABAergic inhibitory neurons, mostly broadly tuned (but see (Moore & Wehr, 2013)), contribute to adjusting the magnitude of principal neurons responsiveness to incoming activity (Cardin *et al.*, 2007).

Experimental work showed that somatodendritic targeting inhibitory neurons are primarily involved in this process (Cardin *et al.*, 2008; Pouille *et al.*, 2013; Keller *et al.*, 2018), though a contribution of perisomatic targeting neurons to gain modulation has also been reported (Atallah *et al.*, 2012; Lourenco *et al.*, 2020). These apparently opposing findings raise the possibility that distinct inhibitory neuron groups could contribute to the same computational function through different mechanisms, and that the recruitment of specific neuron groups or

mechanisms may depend on local circuit connectivity or network state (Mejias & Longtin, 2014).

At the network level, inhibitory neurons are thought to contribute to network synchronization and to the generation of oscillatory patterns of activity (Vierling-Claassen *et al.*, 2010; Avoli, 2019). The connectivity of neural circuits and the distinct firing properties of different neuron groups (e.g. fast spiking GABAergic neurons versus regular spiking principal cells) can shape network oscillations by the alternation of neurons activation (Cardin *et al.*, 2009; Drexel *et al.*, 2017; Panthi & Leitch, 2019). As specific oscillatory rhythms are associated with distinct cognitive functions, alterations in the coupling between excitatory and inhibitory neurons can results in changes in networks states (Francavilla *et al.*, 2018; Pala & Petersen, 2018).

The theoretical framework established to better investigate these functions tends to consider inhibition as a uniform system that is broadly connected and primarily recurrent (van Vreeswijk & Sompolinsky, 1996; Vogels & Abbott, 2009; Kanashiro *et al.*, 2017; Huang *et al.*, 2019). This approach is supported by reports of widespread connectivity of different groups of inhibitory neurons (Fino & Yuste, 2011; Fino *et al.*, 2013) suggesting that GABAergic inhibition may act by modulating circuits broadly without specificity. It is also supported by studies showing GABAergic neurons broad tuning to incoming stimuli (Cardin *et al.*, 2007; Li *et al.*, 2015a; Li *et al.*, 2015b; Hayashi *et al.*, 2018; Li *et al.*, 2019), a property that renders them not particularly sensitive to the granular features of an input.

However, there is evidence that the tuning of inhibitory neurons to incoming stimuli is not always broader than that of principal cells (Moore & Wehr, 2013; Camillo *et al.*, 2018; Khan *et al.*, 2018), and can be modified by experience (Dorrn *et al.*, 2010; Cai *et al.*, 2018). While it is reliably found that inhibitory neurons connect broadly to principal neurons in cortical circuits, specificity can be achieved through selective targeting of neuronal compartments by distinct groups of neurons with distinct molecular identities (Somogyi *et al.*, 1983; Thomson *et al.*, 1996; Tamas *et al.*, 2003; Wang *et al.*, 2004; Chamberland & Topolnik, 2012; Paul *et al.*, 2017), or by activity-dependent changes in inhibitory synapses efficacy that depend on the level of activity of the postsynaptic neuron (Wang & Maffei, 2014; Chiu *et al.*, 2018; Lourenco *et al.*, 2020). Furthermore, inhibitory synapses can change their efficacy in response to shifts in circuit excitability (Maffei *et al.*, 2004; Maffei *et al.*, 2006), a diverse array of patterns of activity (Woodin *et al.*, 2003; Chevaleyre *et al.*, 2007; Younts *et al.*, 2013; Petrini *et al.*, 2014; D'Amour J & Froemke, 2015), can display distinct mechanisms depending on the identity of the presynaptic neuron (Chiu *et al.*, 2018) and the level of activity of the postsynaptic neuron (Vogels *et al.*, 2013; Wang & Maffei, 2014) supporting the interpretation that inhibition and ISP contribute to sculpting circuit activity and function in a more refined fashion than previously anticipated.

These experimental findings, together with novel approaches to neural network models that incorporate feedforward inhibition (Troyer *et al.*, 1998; Miller, 2003; Miska *et al.*, 2018), differential effects of distinct population of inhibitory neurons (Vierling-Claassen *et al.*, 2010; Hertag & Sprekeler, 2019; Wilmes & Clopath, 2019) and plasticity rules for inhibitory

synapses (Vogels *et al.*, 2011; Wilmes & Clopath, 2019), provide new insights into the contributions of inhibition and ISP to circuit function.

Inhibition and ISP as mechanisms to stabilize circuit excitability

One of the better characterized roles of changes in efficacy of inhibitory synapses is that of stabilizer (or homeostatic regulator) of circuit excitability (Turrigiano *et al.*, 1998). Experimental work showed that the efficacy of GABAergic inhibitory synapses can change in response to network activity in a compensatory fashion: acting to preserve excitatory neurons excitability in the absence of circuit activity (Kilman *et al.*, 2002). A similar effect was observed in response to manipulation of sensory drive in rodents, whereby loss of visual drive induced two distinct forms of plasticity of GABAergic synapses at soma-targeting and dendrite-targeting inhibitory neurons (Maffei *et al.*, 2004). The idea that ISP can participate in the maintenance of circuit excitability was further confirmed in a variety of different cortical circuits and its implications have been further explored experimentally (House *et al.*, 2011; Campanac *et al.*, 2013; Graupner & Reyes, 2013; Xue *et al.*, 2014; Froemke, 2015) and with theoretical/computational approaches (van Vreeswijk & Sompolinsky, 1996; Vogels & Abbott, 2009; Lo *et al.*, 2015; Rubin *et al.*, 2017).

The hypothesis emerging from this work is that balanced excitation and inhibition is crucial for neural circuit function and that ISP plays an important role in this balancing process. The displacement from balance is thought to be needed for processing incoming inputs, and subsequent induction of ISP would bring the system back to a stable set point (Nelson & Turrigiano, 2008). Under these premises, changes in inhibitory synaptic efficacy are induced to adjust inhibitory tone and oppose shifts in network activity (Vogels *et al.*, 2011). Overall, this principle is conceptually quite similar to the proposed role for homeostatic plasticity (Turrigiano & Nelson, 2000). Nevertheless, several neural network models implement a stabilizing form of ISP by adapting Hebbian-like rules (Vogels *et al.*, 2013), and approach that has the advantage of modulating the induction of ISP depending on the level of circuit activity, as well as on the timing of pre- and postsynaptic activity (Vogels *et al.*, 2013; Wang & Maffei, 2014). Models including ISP provide a substantial advancement from models that do not include it, as they do not require as much parameter adjustment, and can recapitulate a variety of experimental results. However, even these models are not fully capable of reflecting the complex, self-generating dynamics of a neural network and are not yet capable to account for the diversity of forms of ISP of which spike timing-dependent forms are just a subset (Chevaleyre *et al.*, 2007; Kullmann *et al.*, 2012; Wang & Maffei, 2014).

GABAergic inhibitory synaptic plasticity, learning and memory

The initial reports that GABAergic synapses are plastic, suggested that ISP contributes to cortical circuit refinement (Komatsu & Iwakiri, 1993; Maffei *et al.*, 2004; Maffei *et al.*, 2006) and possibly learning (Kano, 1995; Buzsaki, 1997; Nugent *et al.*, 2007). Since these pioneering studies, experimental work demonstrated that changes in inhibitory synaptic efficacy are associated with adaptation of olfactory responses in drosophila (Das *et al.*, 2011), with changes in sensory experience (Maffei *et al.*, 2004; Maffei *et al.*, 2006; House *et al.*, 2011; D'Amour J & Froemke, 2015; Cai *et al.*, 2018), fear conditioning (Letzkus *et*

al., 2011; Xu *et al.*, 2014; Lucas *et al.*, 2016) and exposure to drugs of abuse (Nugent *et al.*, 2007; Dacher & Nugent, 2011). The specific mechanisms by which ISP contributes to learning and memory are only beginning to being unraveled. Experimental work is currently focused on determining the mechanisms of ISP (Maffei, 2011; Kullmann *et al.*, 2012; Younts & Castillo, 2014; Chiu *et al.*, 2019) and the role of ISP in information transfer (Lourenco *et al.*, 2020). Computational work has only recently begun to introduce ISP in network models (Vogels *et al.*, 2011; Mongillo *et al.*, 2018) and theoretical ideas are being developed regarding its functional role (Barron *et al.*, 2017; Hennequin *et al.*, 2017; Sprekeler, 2017; Mongillo *et al.*, 2018).

The efficacy of inhibitory synapses is sensitive to changes in sensory inputs (Maffei *et al.*, 2004; Maffei *et al.*, 2006; Dorrn *et al.*, 2010; Takesian *et al.*, 2012; Kotak *et al.*, 2013; Gainey *et al.*, 2016). This is especially prominent during windows of heightened sensitivity to changes in sensory drive (Hensch, 2005b; Sanes & Kotak, 2011; Li *et al.*, 2014b; Cai *et al.*, 2018). A model tested the possibility that gradient-like changes in inhibitory tone may contribute to the experience-dependent development of ocular dominance in rodent visual cortex (Toyoizumi *et al.*, 2013). This idea was based on results showing that the postnatal maturation of inhibitory synaptic drive is essential for regulating onset and duration of the critical period for visual cortical plasticity (Hensch, 2005a). While this effect is thought to depend on the maturation of PV+ inhibitory neurons (Katagiri *et al.*, 2007), inhibitory tone could also potentially be modulated by changes in synaptic transmission from different inhibitory neuron types, including NGFCs which signal through both synaptic and volume transmission (Olah *et al.*, 2009)

Recent theoretical work suggests that ISP also plays a central role in learning and memory (Vogels *et al.*, 2011; Wilmes & Clopath, 2019). A current working hypothesis is that ISP is induced to rebalance the network following plastic changes at excitatory synapses (Vogels *et al.*, 2011; Sprekeler, 2017). Potentiation of glutamatergic synapses is associated with memory formation and the emergence of memory engrams (Fig.3A) (Ryan *et al.*, 2015; Tonegawa *et al.*, 2015; Bocchio *et al.*, 2017). Nevertheless, the formation of multiple memory engrams that can partially overlap, may saturate the dynamics range of neural circuits, leading to saturation of storage capacity (Rashid *et al.*, 2016; Mongillo *et al.*, 2017). Recent experimental work proposed that ISP may act to protect stored memories by contributing to inhibitory engrams that rebalance circuit activity (Fig. 3B) (Koolschijn *et al.*, 2019). The definition of inhibitory engram is currently ambiguous: it is not specified whether it is a counter-engram that depends on ISP at inhibitory synapses onto the principal neurons participating in the memory engram, or a group of coactivated inhibitory neurons counterbalancing the excitability of the engram circuit, but not directly connected to the engram neurons. In network models, the inhibitory engram mediated by ISP would stabilize network excitability while preserving relative differences at excitatory connections (Abbott & Nelson, 2000; Renart *et al.*, 2003). This would preserve memories and maintain the dynamic range of circuit excitability so that it is permissive to the formation and storage of new memories. Conceptually, the role inhibitory engrams is an upgraded version of the well-established idea that the primary role of inhibition is to keep circuit excitability in check. In this case ISP would be induced to prevent overactivation of a subcircuit of excitatory

neurons (Barron *et al.*, 2017). Instead of providing widespread control on excitability, ISP would act in a more restricted fashion.

A caveat of the inhibitory engram idea stems from its reliance of a temporal sequence in which the induction of excitatory plasticity precedes changes in inhibitory synaptic efficacy (Hennequin *et al.*, 2017): plasticity at excitatory synapses is induced during learning, shifting the balance between excitation and inhibition, then ISP is induced to restore balance (Vogels *et al.*, 2011). Experimental evidence in favor of such a sequence of events has been reported in some cortical circuits (Kuhlman *et al.*, 2013). Nevertheless, changes in inhibition can be induced before or together with excitatory plasticity at recurrent synapses (Wang & Maffei, 2014; Gainey *et al.*, 2018). Firing rates of inhibitory neurons recover more rapidly than those of excitatory neurons following brief sensory deprivation (Hengen *et al.*, 2013), indicating that the temporal sequence suggested by the inhibitory engram hypothesis is not generally applicable. Furthermore, the baseline ratio of excitatory and inhibitory charge onto cortical pyramidal neurons is shifted toward inhibition (Tatti *et al.*, 2017), suggesting that disinhibition may be needed for excitatory plasticity to be induced. Finally, the ratio of excitation and inhibition is circuit and experience-dependent (Tatti *et al.*, 2017; Bridi *et al.*, 2019), adding complexity to how ISP may affect learning. These data are consistent with theoretical work suggesting that sparse cortical activity depends on inhibition being dominant, and with experimental results indicating that disinhibition of cortical circuits is permissive for learning (Froemke *et al.*, 2007; Letzkus *et al.*, 2011; Kuhlman *et al.*, 2013). This alternative framework suggests that depression of inhibitory synaptic transmission facilitates the induction of excitatory plasticity correlated with the formation of associations between conditioned and unconditioned stimuli. In support of this idea, a study demonstrated that excitatory and inhibitory plasticity cooperatively interact in an anticorrelated fashion, with potentiation of inhibition facilitating depression of convergent excitatory synapses, and depression of GABAergic synapses enabling potentiation of glutamatergic input onto the same postsynaptic target (Wang & Maffei, 2014). As this crosstalk is connection-specific and relies on postsynaptic activity (Maffei *et al.*, 2006; Wang & Maffei, 2014), it has sufficient resolution to modulate single cortical connections instead of acting as a broad balancing factor.

Finally, it is unclear whether long term ISP would be necessary if its role is to restore the balance between excitation and inhibition. Homeostatic synaptic plasticity can be a slow process effectively restoring stability over the course of several hours to a few days (Kilman *et al.*, 2002; Lambo & Turrigiano, 2013; Whitt *et al.*, 2014; Glazewski *et al.*, 2017). Such time course is compatible with the idea that changes in inhibitory synaptic transmission restore circuit excitability to a balanced state. However, ISP in the form of I-LTP or I-LTD is typically induced rapidly, is long-lasting (Woodin *et al.*, 2003; Chevaleyre *et al.*, 2007; Nugent *et al.*, 2007; Wang & Maffei, 2014), and recruits complex post translational mechanisms that can lead to structural and functional changes in inhibitory connectivity (Tyagarajan *et al.*, 2011; Petrini *et al.*, 2014; Ghosh *et al.*, 2015). These effects are comparable to what is typically reported for long term plasticity at excitatory synapses (Herring & Nicoll, 2016).

It has been proposed that ISP can act as a form of metaplasticity (Chevaleyre & Castillo, 2004; Xu *et al.*, 2014), a set of changes that alter the state of a principal neuron modulating its responsiveness to incoming activity (Abraham, 2008). This hypothesis is compatible with the experimental results discussed above, but does not fully explain the duration of the changes in synaptic strength, unless we consider ISP as a direct contributor to memory storage. Indeed, a long lasting state change in a neuron, whether excitatory or inhibitory, may serve as memory signature shaping how this neuron (or circuit) will be activated by future stimuli. Instead of contributing to rebalance, or protect, the memory engram activated by excitatory plasticity, long lasting changes in GABAergic synapses and their plasticity would expand the dynamic range of circuit plasticity, thus being a central component of the memory trace (Fig 3C).

Conclusions

Inhibitory synaptic transmission is extremely diverse and undergoes various mechanistically distinct forms of activity-dependent plasticity. Such diversity endows neural circuits with a broad repertoire for inhibitory control of neural circuits. By sampling inputs widely, as GABAergic neurons are often less narrowly tuned than their excitatory counterpart, and connecting broadly to many excitatory neurons, inhibitory circuits have the capacity of influencing cortical computations quite significantly. Their plasticity - which can result in changes in GABA release, or in synapse-specific or connection-specific changes in GABAergic responses - the diversity of neuron types, postsynaptic target regions and cellular mechanisms available to change synaptic efficacy, make them fundamental contributors to complex and sophisticated processes including learning, memory and other cognitive functions.

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Abbreviations:

2-AG	2-arachidonoylglycerol
BC	basket cell
BDNF	brain-derived neurotrophic factor
CB_1	type 1 cannabinoid receptors
CCK	cholecystokinin
DAG	diacylglyercol
DGL	diacylglycerol lipase
D_2R	type 2 dopamine receptors
eCB	endocannabinoid

EPSP	excitatory postsynaptic potential
ERK	extracellular signal-regulated kinase
FB	feedback
FF	feedforward
FSI	Firing Induced Suppression of Inhibition
GABA	gamma amino butyric acid
GC	guanylate cyclase
ISP	inhibitory synaptic plasticity
KCC2	potassium chloride co-transporter
LTD	long-term depression
LTP	long-term potentiation
mGluR-I	group I metabotropic glutamate receptors
NGFC	neurogliaform cell
NL-2	neuroligin-2
NMDA	N-methyl-D-aspartate
nNOS	neuronal nitric oxide synthas
NO	nitric oxide
PLC	phospholipase C
PV	parvalbumin
PKC	protein kinase C
scRNAseq	single cell RNA sequence
STDP	Spike timing dependent plasticity
TrkB	tropomysin related kinase B
VGCC	voltage-gated calcium channel

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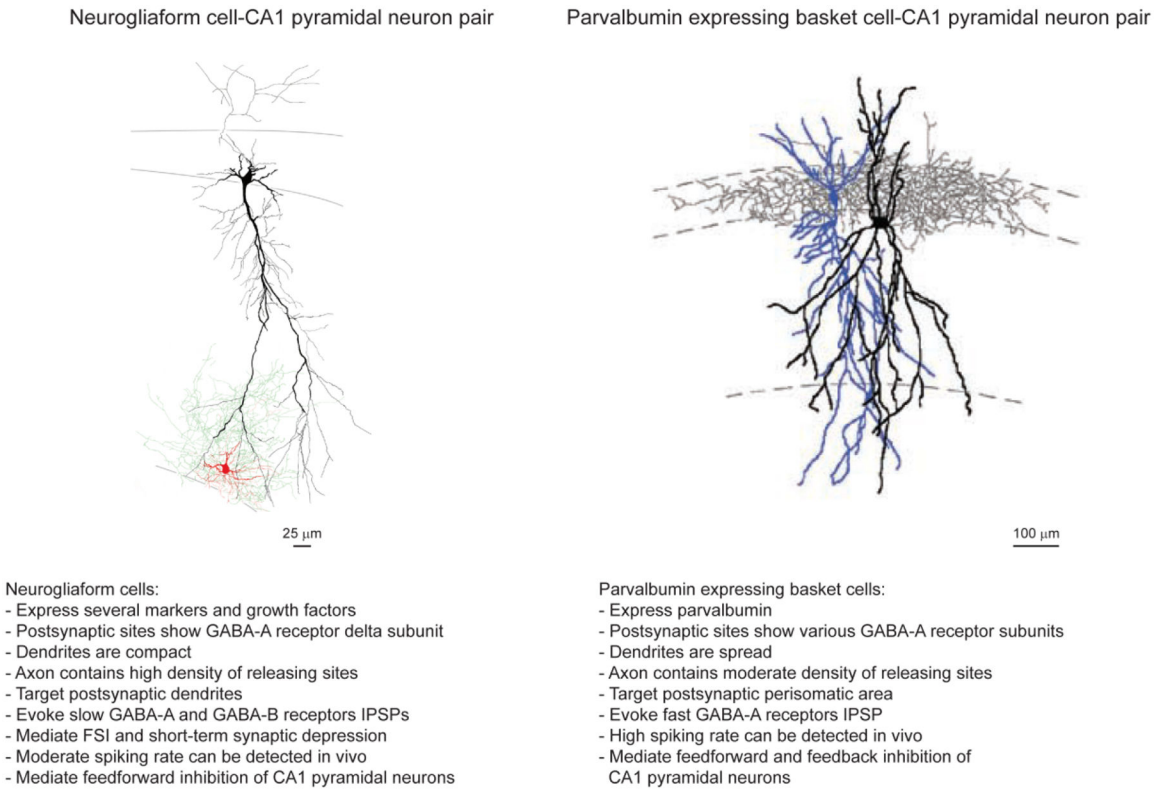

Figure 1. Interneuron diversity: neurogliaform and parvalbumin expressing basket cells.

Left. Reconstruction of a neurogliaform cell (NGFC, soma and dendrites, red; axon, green) and a CA1 pyramidal neuron (soma and dendrites, black) recorded from a rat in vitro. Salient features detected in NGFCs are listed below the image. The picture is taken from Price et al, J. Neurosci., 28(27):6974–6982, 2008(Price *et al.*, 2008). **Right**. Reconstruction of a parvalbumin expressing basket cell (BC, soma and dendrites, black; axon, gray) and a CA1 pyramidal neuron (soma and dendrites, blue) recorded from a rat in vitro. Key features observed in BCs are listed below the image. The picture is taken from Foldy et al, Nature Neurosci.,13(9):1047–1049, 2010 (Foldy *et al.*, 2010).

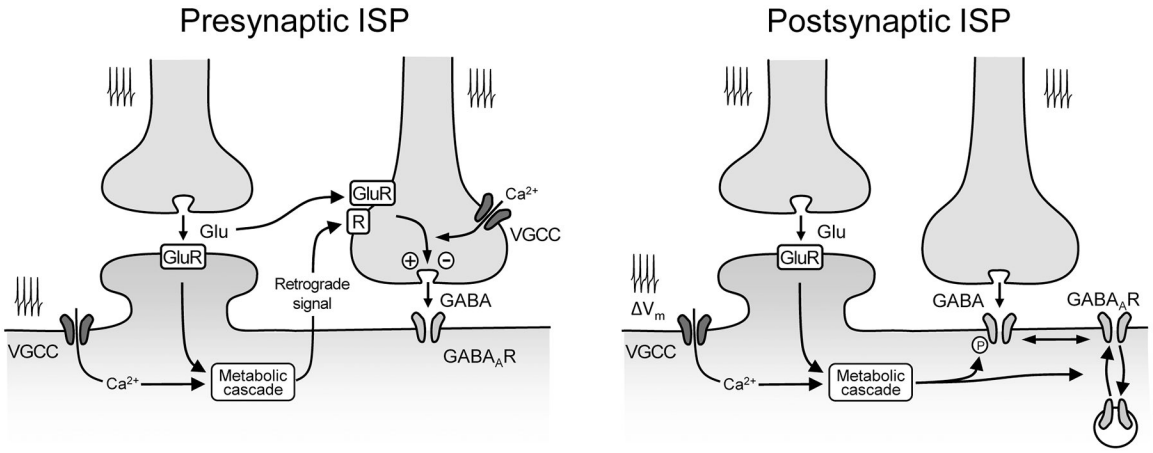

Figure 2. Molecular mechanisms underlying activity-dependent forms of ISP.

Left. Presynaptic ISP commonly involves activation of postsynaptic glutamate receptors (GluR), e.g. NMDAR and mGluR-I, and mobilization of retrograde signals that induce long-lasting changes in GABA release, by targeting a presynaptic receptor (R). Glutamate released from neighboring terminals, by activating glutamate receptors (e.g. NMDARs) on GABAergic terminals, can also induce presynaptic ISP. Coincident presynaptic and postsynaptic activity, via voltage-gated calcium channels (VGCC), can contribute to the mobilization of retrograde signals and/or modulation of downstream signaling in the GABAergic terminal. **Right.** Postsynaptic ISP can be induced by coordinated presynaptic and postsynaptic activity, including subthreshold changes in membrane potential (ΔVm), and GluR (NMDAR or mGluR-I) activation. Such activities set in motion a metabolic cascade of events that results in exo/endocytosis, lateral diffusion and phosphorylation/dephosphorylation of $GABA_A$Rs

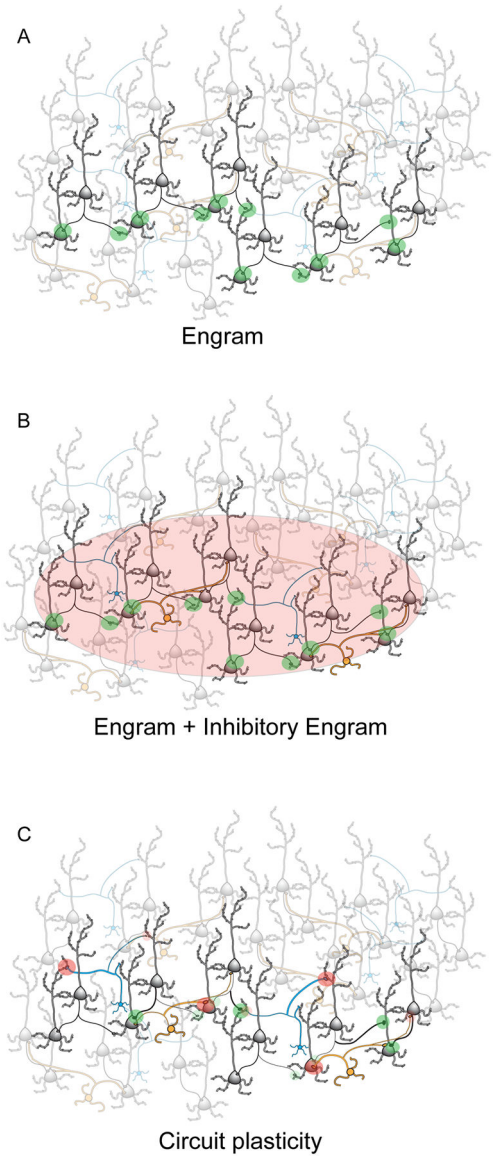

Figure 3. Inhibitory plasticity as a mechanism for circuit reconfiguration.

Simplified diagram of how inhibitory plasticity can increase the dynamic range of neural circuits. Black and grey: pyramidal neurons; yellow: soma targeting inhibitory neurons; blue: dendrite targeting inhibitory neurons. **A.** Plasticity at excitatory synapses is thought to facilitate the activation of memory storage units (engrams). Green shaded areas and thick lines indicate the site of LTP at excitatory connections. The darker neurons highlight an example engram, while the surrounding faded neurons are part of the circuit but do not participate in the excitatory engram. **B.** In this diagram, the excitatory engram shown in A is paired with an inhibitory engram triggered by ISP. As the inhibitory engram is not defined to be connection-specific (Hennequin *et al.*, 2017), the area of influence of the inhibitory engram is indicated by the red shaded area. Greed shaded areas and thick lines indicate LTP at excitatory synapses. Neurons not participating in either the excitatory or the inhibitory engrams are shown in lighter colors. **C.** The diagram shows how connection-specific LTP

and LTD at excitatory and inhibitory synapses can expand the dynamic range of the circuit, facilitating the accommodation of multiple engrams. Large green shaded areas and thick black lines indicate LTP at excitatory synapses; small green shaded areas and thin black lines indicate LTD at excitatory synapses. Large red shaded areas and thick yellow and blue lines indicate LTP at inhibitory synapses; small red shaded areas and think yellow and blue lines indicate LTD at inhibitory synapses. In this diagram both excitatory and inhibitory plasticity are connection-specific. Cooperative interactions between excitatory and inhibitory plasticity are taken into account to indicate the site of LTP and LTD at both populations of synaptic connections (see (Wang & Maffei, 2014; Hennequin *et al.*, 2017)).