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Review

Regulation of circuit organization and function through inhibitory synaptic plasticity

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Diverse inhibitory neurons in the mammalian brain shape circuit connectivity and dynamics through mechanisms of synaptic plasticity. Inhibitory plasticity can establish excitation/inhibition (E/I) balance, control neuronal firing, and affect local calcium concentration, hence regulating neuronal activity at the network, single neuron, and dendritic level. Computational models can synthesize multiple experimental results and provide insight into how inhibitory plasticity controls circuit dynamics and sculpts connectivity by identifying phenomenological learning rules amenable to mathematical analysis. We highlight recent studies on the role of inhibitory plasticity in modulating excitatory plasticity, forming structured networks underlying memory formation and recall, and implementing adaptive phenomena and novelty detection. We conclude with experimental and modeling progress on the role of interneuron-specific plasticity in circuit computation and context-dependent learning.

Highlights

Inhibitory synapses are continuously modified by experience through synaptic plasticity. Different learning rules have been proposed to describe the dependence of plasticity on firing rates, spike timing, calcium levels, and membrane potential.

Inhibitory plasticity affects dendritic, cellular, and network dynamics and influences excitatory plasticity at all levels.

Inhibitory plasticity shapes the formation of feedforward receptive fields and structured connectivity in recurrent circuits, supporting the formation and recall of memories and the generation of adaptive and novelty responses. of memories and the generation of adaptive and novelty responses.

Multiple inhibitory neuron subtypes and interneuron-specific plasticity support various computations, including context-dependent processing and pathway-specific selection, and play unique roles in supporting the stability and competition of neural assemblies.

Inhibition throughout development and adulthood

Long-term synaptic plasticity is widely considered to underlie circuit assembly and connectivity refinement during early postnatal development, as well as learning and memory in adulthood [1]. Over the past few decades, extensive studies have characterized the plasticity of synapses between excitatory neurons [2–5]. Consistent with Hebbian principles, coincident pre- and postsynaptic activity potentiates synaptic strength, which enhances the correlation between pre- and postsynaptic activity and further potentiates synaptic strength, potentially leading to runaway synaptic growth and abnormal seizure-like activity [6]. To prevent excessive excitation and maintain stable activity levels, neural circuits employ various mechanisms to dynamically coordinate changes in excitation and inhibition [7,8]. The modulation of inhibitory synapses onto excitatory neurons, called **inhibitory plasticity** (see Glossary), is one such mechanism encountered in different regions of the mammalian brain [9–14] (Box 1). Yet, understanding inhibitory plasticity and its functional implications in shaping network connectivity and dynamics remains challenging because of the different roles inhibitory plasticity might play, depending on the varying demands across an animal's lifetime, as well as the considerable anatomical, electrophysiological, and functional diversity of interneurons, which can undergo different forms of plasticity [15–17].

During early development, it has long been thought that the main inhibitory neurotransmitter in the adult, **gamma-aminobutyric acid (GABA)**, is depolarizing [18,19]. The early excitatory action of GABA has been implicated in the activity-dependent growth and differentiation of neurons and the establishment of neural circuits [20,21]. However, while GABA depolarizes immature cortical neurons *in vivo*, its action at the network level (at least in the neocortex) appears to be inhibitory [22–24]. The maturation of GABAergic synaptic transmission triggers the onset of a critical period in which sensory circuits are highly plastic and sensitive to perturbations [25]. During development and early life, the plasticity of inhibitory GABAergic synapses interacts with **excitatory plasticity** [10]. Multiple computational studies have demonstrated that this interaction shapes

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Box 1. Inhibitory plasticity in experiments and models

Inhibitory plasticity has been observed in different regions of the mammalian brain [9–12,35]. Experimentally, inhibitory plasticity can be induced by concurrent presynaptic hyperpolarization and postsynaptic depolarization [16,36–39], for instance, via high-frequency stimulation of input pathways [40,41] or pairing of pre- and postsynaptic spikes [16,36,42–44] (see [13] for an extensive summary of experimental studies on inhibitory plasticity).

In computational models, inhibitory plasticity is implemented by phenomenological learning rules, which simplify the underlying complex molecular and biochemical processes [13,14]. In these models, inhibitory synaptic change can depend on firing rates, precise spike times, or membrane potential based on the induction protocol used experimentally [45–49]. A commonly used inhibitory learning rule, which depends on spikes [also called **inhibitory spike-timing-dependent plasticity** (iSTDP)], is the **symmetric Hebbian learning rule** (see Figure I in Box 1). It has a symmetric window as a function of the time difference between pre- and postsynaptic spikes. Spikes near each other in time, independent of their order, lead to inhibitory **long-term potentiation (LTP)** , whereas pre- and postsynaptic spikes far from each other lead to inhibitory **long-term depression (LTD)** [45]. A similar symmetric iSTDP window has been found experimentally in the auditory cortex [44], in the orbitofrontal cortex [50], and in the hippocampus [16]. To account for the diversity of experimentally observed iSTDP windows, computational models have also investigated other learning window shapes, including **asymmetric Hebbian**, where pre-post spike pairs lead to LTP and post-pre spike pairs lead to LTD [51,52], as observed in entorhinal cortex [43]; **asymmetric anti-Hebbian**, where pre-post spike pairs lead to LTD and post-pre spike pairs lead to LTP [52]; and **symmetric anti-Hebbian** window, where spikes near each other in time lead to LTD, while spikes far from each other lead to LTP [53], as observed in hippocampus [36] (see Figure I in Box 1).

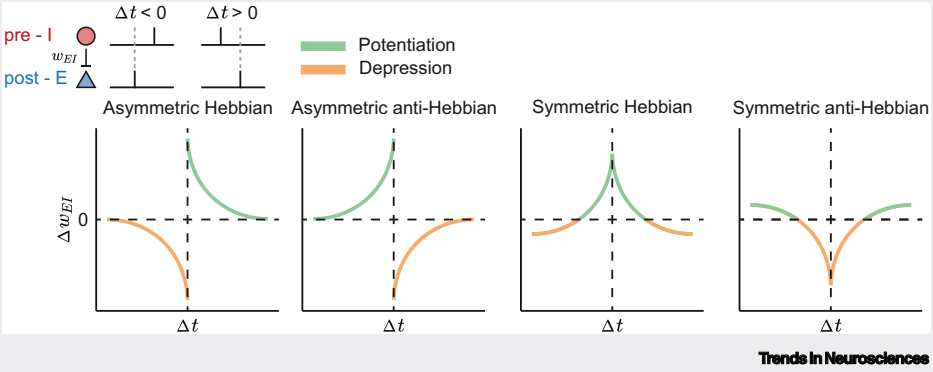

Figure I. Different learning windows of inhibitory spike-timing-dependent plasticity. Inhibitory plasticity can be parameterized into different idealized learning windows as a function of the timing difference between pre- and postsynaptic spikes Δt, leading to either inhibitory long-term potentiation ($\Delta w_{EI} > 0$, green) or inhibitory long-term depression ($\Delta w_{EI} < 0$, orange): asymmetric Hebbian [51,52], asymmetric anti-Hebbian [52], symmetric Hebbian [45], and symmetric anti-Hebbian [53].

network structures and establishes the appropriate network connectivity driven by developmental patterns of spontaneous activity and sensory experience [26–28]. Following sensory deprivation, especially during the critical period, inhibitory plasticity can regulate the balance of excitation and inhibition (E/I balance) and contribute to firing rate homeostasis [29,30]. To adapt to more complex environments, inhibitory plasticity continues to shape learning and network dynamics throughout adulthood. For example, different interneuron subtypes and interneuron-specific plasticity support diverse computations from context-dependent information processing to predictive coding [16,31–34]. Therefore, through plasticity, inhibition can adjust to the needs of the organism at various stages from development to adulthood.

Here, we present recent experimental and theoretical advances on inhibitory plasticity and the control it exerts on circuit connectivity and dynamics. We outline how inhibitory plasticity controls network firing rates and correlations, as well as the plasticity of excitatory connections. We discuss how the interaction of excitatory and inhibitory plasticity can influence the formation of

Glossary

Anti-Hebbian learning rule: a learning rule in which long-term depression is induced by presynaptic followed by postsynaptic spikes, the opposite of Hebb's principle.
Asymmetric Hebbian learning rule: a learning rule that is an asymmetric function of the difference in spike times of pre- and postsynaptic neurons. For asymmetric learning rules, pre-post spike pairs have the opposite impact on the weight change to that of post-pre spike pairs.
Disinhibition: loss or reduction of inhibition. Disinhibition can be induced in multiple ways, for example, via neuromodulators that reduce GABA release from inhibitory neurons onto excitatory neurons, or via increasing inhibition onto inhibitory neurons that target excitatory neurons.
Excitatory plasticity: the plasticity of synapses from an excitatory to another excitatory neuron.
Gamma-aminobutyric acid (GABA): a major inhibitory neurotransmitter in the adult brain.
Hebbian learning rule: a learning rule in which long-term potentiation is induced by presynaptic followed by postsynaptic spikes, in agreement with Hebb's principle.
Inhibition-stabilized network (ISN): a network consisting of excitatory and inhibitory neurons with strong recurrent excitation, which is stabilized by strong feedback inhibition generated in the circuit.
Inhibitory plasticity: the plasticity of synapses from an inhibitory to an excitatory neuron.
Inhibitory spike-timing-dependent plasticity (iSTDP): a process that adjusts the (inhibitory) synaptic strength based on the timing of presynaptic and postsynaptic spikes.
Long-term depression (LTD): a process involving the weakening of synapses between neurons.
Long-term potentiation (LTP): a process involving the strengthening of synapses between neurons.
Symmetric Hebbian learning rule: a learning rule that is a symmetric function of the difference in spike times of pre- and postsynaptic neurons. For symmetric learning rules, pre-post spike pairs have the same impact on the weight change to that of post-pre spike pairs.

different network connectivity structures, including, but not limited to, receptive fields and assemblies, modulate these structures during learning and memory formation, and generate adapted and novelty responses. Based on experimental evidence of different interneuron subtypes and their connectivity profiles, we also present modeling studies that explore differences in the plasticity at these synapses. Throughout, a picture emerges that highlights inhibition and inhibitory plasticity as key factors that control circuit dynamics, ensure appropriate circuit function, and provide a substrate for flexible and complex computations driving behavior throughout the entire life of an organism.

Inhibitory plasticity controls excitation at different spatiotemporal scales

To maintain stable activity levels, inhibitory plasticity can dynamically adjust the amount of inhibition at different spatial and temporal scales during both normal circuit operation and perturbation (Figure 1). At the network level, inhibition is thought to maintain healthy firing rates to prevent runaway dynamics leading to epileptic activity or decreases leading to complete silence (Figure 1A). However, in heavily interconnected neural circuits, the relationship between inhibition and network dynamics is more complicated. In such recurrently dominated networks, strong feedback inhibition generated by the circuit is needed to balance strong recurrent excitation. Both theoretical and experimental studies have put forward such inhibition stabilization as an essential property of cortical networks [54,55]. **Inhibition-stabilized networks (ISNs)** can perform various computations, including input amplification, response normalization, and network multistability [56–58]. A signature of inhibition stabilization is widely considered to be the paradoxical effect, whereby injecting excitatory currents into inhibitory neurons (e.g., via optogenetic stimulation of inhibitory neurons) decreases inhibitory firing [59]. Several circuit aspects, including recurrent excitatory-to-excitatory connection strengths and network activity, can dynamically shape inhibition stabilization [57,60]. For example, in networks where neuronal dynamics are nonlinear, changing the connection from inhibitory to excitatory neurons affects network activity and puts the network in different inhibition-stabilized regimes, as evaluated by the presence of the paradoxical effect (Figure 1B, [57,58,60]). Yet, detecting ISNs via the paradoxical effect is experimentally challenging due to the sensitivity of optogenetic stimulation strength [61] and the complexity introduced by multiple interneuron subtypes [62]. While inhibition stabilization is necessary for various computations, it is still unclear how it can be maintained in the presence of synaptic plasticity, for example, during learning, though recent work addresses this question in the context of balanced excitatory and inhibitory receptive field formation [63].

More broadly, inhibitory plasticity can operate as a homeostatic process and control network activity following perturbation [64,65]. A classical paradigm to explore this process experimentally is elevating or suppressing the activity of cultured neurons, which triggers the potentiation or depression of spontaneous inhibitory synaptic currents into the perturbed neurons [66,67]. In the living animal, a perturbation may involve sensory deprivation, for example, the removal of whiskers in the somatosensory system or the closure of an eye in the visual system [68,69]. Here, inhibitory plasticity could be involved both during the initial circuit response leading to the decrease in network firing rates, as well as later on during their recovery. Initially, the strong potentiation of recurrent inhibition onto excitatory neurons could contribute to the early decrease of network firing rates [30,70,71]. The subsequent gradual upregulation of firing rates could be triggered by the loss of inhibitory synapses onto excitatory neurons [72,73], or the decreased spontaneous inhibitory current frequency [74,75] and amplitude [64,68]. In sum, inhibitory plasticity could act as a common driver behind the homeostatic regulation of network activity immediately after or during a prolonged period following sensory perturbation across sensory cortices.

How could inhibitory plasticity achieve this homeostatic regulation of excitatory firing rates? One answer lies in the concept of E/I balance, which inhibitory plasticity can establish and maintain at

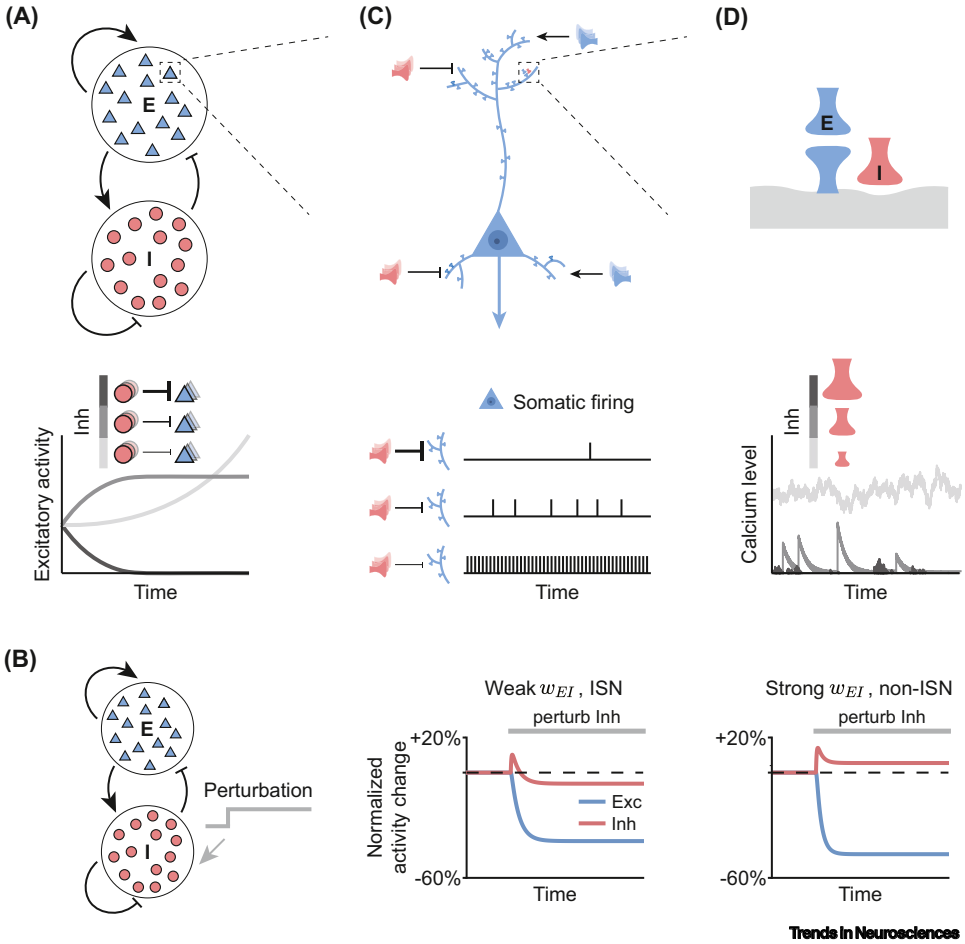

Figure 1. Inhibitory control of excitation at different scales. (A) At the network level (top), inhibition (Inh) affects excitatory population activity (bottom). Excessive inhibition can silence excitatory activity, insufficient inhibition can lead to the explosion of excitatory activity, while the appropriate amount of inhibition stabilizes network dynamics and maintains excitatory activity at a modest level. **(B)** Left: Assessing inhibition stabilization via the paradoxical effect by perturbing the inhibitory population. Middle: For weak inhibitory weights (w_{EI}), network activity is high and the network is in the inhibition-stabilized network (ISN) regime. Injecting additional excitatory currents into inhibitory neurons ('perturb Inh') leads to a paradoxical decrease of the inhibitory population response. Right: For strong w_{EI}, network activity is low and the network is in the non-ISN regime. Injecting additional excitatory currents into inhibitory neurons ('perturb Inh') does not generate a paradoxical response. (C)At the single neuron level (top), inhibition affects somatic firing (bottom). Excessive inhibition generates very little spiking, insufficient inhibition leads to high levels of spiking, while appropriate amount of inhibition leads to appropriate spiking levels. (D) At the dendritic level (top), inhibition influences the local calcium level (bottom). Excessive inhibition leads to extremely low calcium level locally on the dendrite, insufficient inhibition leads to extraordinarily high local calcium level, while the appropriate amount of inhibition leads to an appropriate local calcium level.

the network, cellular, and subcellular level, with different computational implications for circuit processing (Box 2) [29,74–78]. E/I balance is typically quantified by the E/I ratio, defined as the ratio of excitatory to inhibitory input currents. The E/I ratio can in return also affect the amount of inhibitory plasticity, with high initial E/I ratios resulting in stronger inhibitory potentiation, as shown in the mouse auditory cortex [44,79].

Various inhibitory plasticity rules have been proposed to regulate E/I balance in computational models [45,51,52,80–82]. The best-studied model of inhibitory plasticity, which has a symmetric Hebbian learning window (see Figure I in Box 1), can establish a precise E/I balance at the single-

Box 2. Different types of E/I balance

Neural circuits are known to maintain E/I balance [7,10]. E/I balance generally refers to the coregulation of excitation and inhibition and is typically measured by the ratio of excitatory and inhibitory inputs [10]. When excitation and inhibition are balanced at the population level but not necessarily at the single neuron level, the E/I balance is known as global balance [95,102]. Global balance can be achieved via input-dependent inhibitory plasticity rules [84]. If excitatory and inhibitory input currents onto a single neuron are balanced, or co-tuned, across the stimulus space, this is referred to as detailed balance [76–78,103]. Detailed balance can be established via inhibitory plasticity rules, which maintain a target firing rate at the single neuron level [45]. Additionally, when excitatory and inhibitory inputs are balanced also on a millisecond timescale, as observed experimentally [104,105], the E/I balance is known as tight balance, and loose balance otherwise [106]. The coexistence of tight and detailed balance is referred to as precise E/I balance and has been observed in several circuits, such as the zebrafish homolog of olfactory cortex [107] and mammalian hippocampus [108], where it is involved in efficient memory storage, millisecond-range input gating, and subthreshold gain control.

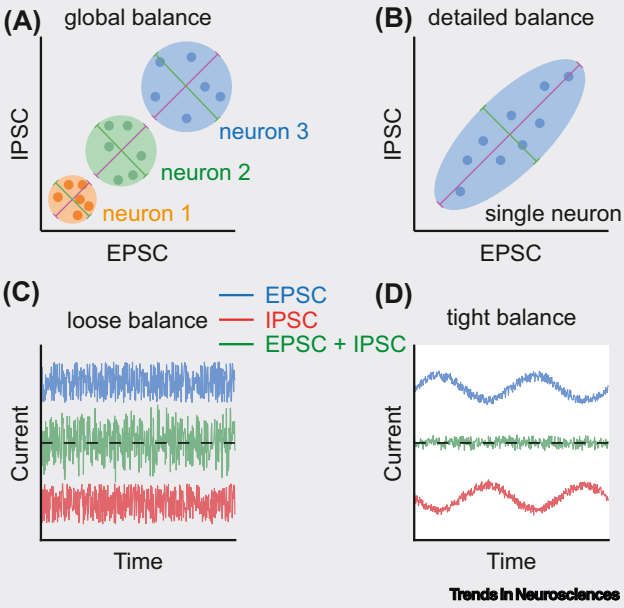

Figure I. Different types of excitation/inhibition (E/I) balance. (A) Global balance is characterized by a high degree of correlation between excitatory postsynaptic currents (EPSCs) and inhibitory postsynaptic currents (IPSCs) at the population level but a low degree of correlation for individual neurons across stimuli. Each dot represents a neuron–stimulus pair. Data for different neurons are marked in different colors. (B) Detailed balance is characterized by a high degree of correlation between EPSCs and IPSCs at the individual neuron level across stimuli. (C) Loose balance is characterized by a low degree of correlation between EPSCs and IPSCs over time. (D) Tight balance is characterized by tightly correlated EPSCs and IPSCs on a millisecond timescale. Panels (A) and (B) are adapted from [107].

neuron level on a millisecond timescale [45,83]. The learning rule achieves the balance by a negative feedback mechanism, which increases inhibitory synaptic strength for high postsynaptic firing rates and decreases inhibitory strength for low firing rates to counteract deviations from a target firing rate (Figure 1C), therefore maintaining a firing rate set-point for each individual neuron. How such a negative feedback mechanism might be implemented biologically remains an open question (see [14] for a discussion of the molecular mechanisms underlying inhibitory plasticity). Due to the resulting robust homeostatic properties, this rule is commonly used in recurrent network models [28,45]. Computational work has proposed several alternatives, including an input-dependent inhibitory plasticity rule [84], or a voltage-dependent plasticity rule [49], both of which can achieve firing rate heterogeneity as observed experimentally [69,85]. One caveat of all these inhibitory plasticity rules is the mismatch between timescales assumed in models and timescales measured in experiments. Most computational models rely on fast inhibitory plasticity

to guarantee homeostasis and establish an E/I balance [48,65]; however, it takes several tens of minutes to reach a stable baseline of inhibitory synaptic strength following plasticity induction in the mouse auditory cortex [44,76,78].

Recent experimental evidence suggests that E/I balance can even extend to local dendritic segments of single neurons [86] (Figure 1D). Inhibitory synapses form and change in strength to complement the dendritic organization of excitatory synaptic inputs, which often form local clusters based on coactivation [87,88], to regulate excitatory synaptic dynamics and plasticity [86,89,90]. For example, in the hippocampus, stimulating clustered excitatory synapses has been shown to trigger the *de novo* formation of inhibitory synapses [91], and a push–pull plasticity mechanism has been found to maintain the balance of local dendritic excitatory and inhibitory strength [92]. Also, inhibitory synapses in the neocortex remain stable if located in the proximity of excitatory synapses during normal visual experience [72]. Thus, while the presence of E/I balance on local stretches of dendrites is supported by experimental data, how it emerges during early postnatal development and how it is maintained during learning and perturbations remains an open question.

Besides regulating E/I balance and firing rates, inhibitory plasticity plays a more nuanced role in controlling the firing patterns of single neurons. By regulating the precise arrival of inhibitory inputs relative to excitatory inputs, experiments in the hippocampus have showed that inhibition can close or open the time window in which a spike is triggered [93]. Inhibitory plasticity can therefore dramatically affect the spike generation properties and spiking statistics of excitatory neurons, including neuronal input–output functions [94], pairwise spike correlations and spiking regularity [95,96], and criticality [97,98]. Both experimental and modeling work have showed that potentiating inhibition can decorrelate network activity [24,99,100] and switch network firing regimes [95] from oscillatory states supporting memory consolidation [101] to asynchronous irregular states supporting high memory capacity, despite the presence of noise [81]. Such switching could occur at different behavioral state transitions (e.g., from sleep to wake). Yet, direct evidence of inhibitory plasticity contributing to a dynamical switching between network firing regimes remains to be examined experimentally.

Inhibitory control of excitatory plasticity

Experimental evidence has revealed that excitatory plasticity is jointly determined by factors like pre- and postsynaptic firing rates [2,4], spike timing [3,4], and dendritic calcium levels [5]. Since inhibition can influence all of these factors, it naturally also affects excitatory plasticity [12,109–111].

In experiments, the frequency of presynaptic stimulation can determine the sign of excitatory synaptic plasticity, with low-frequency stimulation favoring excitatory LTDand high-frequency stimulation inducing excitatory LTP [2]. Decreasing inhibition decreases the excitatory LTD/LTP threshold, making LTP induction easier, while increasing inhibition increases the LTD/LTP threshold and makes LTP induction more difficult [112] (Figure 2A). Based on these results, computational studies have demonstrated that a change of the inhibitory input (e.g., via inhibitory plasticity) can shift the threshold between LTP and LTD [47,48]. By keeping the firing rates exactly at the LTD/LTP threshold, inhibitory plasticity has been suggested as a mechanism to effectively switch excitatory plasticity off [48] (Figure 2A). Any deviation of the firing rates (e.g., via **disinhibition**) can then turn on excitatory plasticity. Such gating of excitatory plasticity has also been modeled at the level of individual inhibitory inputs on dendritic trees by affecting the amplitude of backpropagating action potentials and calcium spikes [113,114] (Figure 2B). Therefore, changes in inhibition can switch excitatory plasticity on or off, regulate how much plasticity is induced, or even dictate the sign of excitatory plasticity [38,115].

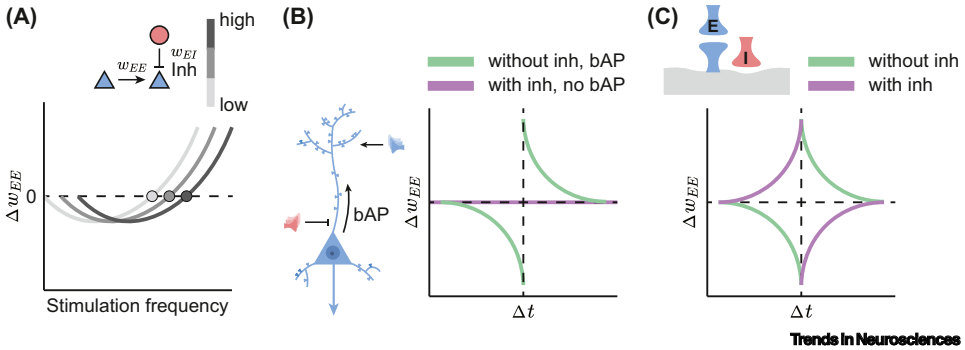

Figure 2. Inhibitory control of excitatory plasticity. (A) The level of inhibition (Inh), modulated by inhibitory weights (w_{EI}) or inhibitory firing rates, controls excitatory plasticity (Δw_{EE}). Higher (lower) level of inhibition leads to higher (lower) long-term depression (LTD)/long-term potentiation (LTP) threshold of excitatory plasticity as a function of the presynaptic stimulation frequency. Different dots represent corresponding LTD/LTP thresholds that separate the depression ($\Delta w_{EE} < 0$) and potentiation ($\Delta w_{EE} > 0$) of excitatory synapses onto excitatory neurons. Different grays represent different levels of inhibition. Panel (A) is adapted from [48,112]. (B) Strong inhibitory input can switch excitatory plasticity on or off via gating of a backpropagating action potential (bAP). In the absence of inhibition, the bAP propagates into the dendrite and spike-timing-dependent plasticity at the excitatory synapse is induced (green). By contrast, in the presence of inhibition, the bAP is suppressed and no synaptic plasticity is induced (purple). Panel (B) is adapted from [113]. **C.** (C) Local inhibitory input can affect calcium concentration in the dendritic spine and flip the excitatory spike-timing-dependent plasticity. Panel (C) is adapted from [115,125].

Multiple experimental studies have suggested disinhibition as a mechanism for the gating of excitatory plasticity [116]. Disinhibition can be induced by neuromodulators, including but not limited to acetylcholine, noradrenalin, and oxytocin [10,76], or by disinhibitory pathways involving multiple interneuron subtypes [117,118] (Box 3). For instance, elevated activity in vasoactive intestinal peptide (VIP)-expressing inhibitory neurons receiving top-down inputs can suppress activity in somatostatin (SST)-expressing inhibitory neurons and, as a result, disinhibit excitatory neurons and control excitatory plasticity [111,117–120].

At the dendritic level, inhibitory input onto the dendrite can affect postsynaptic calcium concentration at nearby excitatory spines [111,121] and, therefore, influence local excitatory plasticity [122,123]. Computational models have proposed that the dynamic local balancing of excitation by inhibition can change the shape of the learning rule for excitatory synapses [124–126]. For example, blocking inhibitory inputs can flip the spike-timing-dependency of excitatory plasticity [125], consistent with previous experimental findings [115] (Figure 2C). Furthermore, local changes in excitatory and inhibitory synapses are coordinated with each other via crosstalk, giving rise to the codependence of excitatory and inhibitory plasticity [7,8]. While these works clearly show that inhibitory synapses can control excitatory plasticity at multiple spatial scales, how this control is used during learning and its impact on behavior remains to be explored.

Inhibitory plasticity in the formation of structured networks and resulting computation

Non-random structure is a hallmark of biological networks. Multiple computational studies have demonstrated that various network structures can form from the coordinated interaction between excitatory and inhibitory plasticity. This includes the emergence of receptive fields [45,47,48], place fields [27], and grid fields [27] through the refinement of feedforward excitatory and inhibitory connectivity, typically in settings with a single postsynaptic neuron based on input statistics [51–53]. In recurrent circuits, inhibitory plasticity also shapes neuronal assemblies [26,48] and chain-like structure [127,128], as well as ensuing tuning diversity and efficient sensory representation [100].

Box 3. Interneuron diversity

Interneurons exhibit high anatomical, electrophysiological, and functional diversity [157,158]. In the mouse neocortex, three major classes of interneurons expressing parvalbumin (PV), somatostatin (SST), and vasoactive intestinal peptide (VIP) constitute more than 80% of GABAergic interneurons [15]. Distinct interneuron subtypes target different domains of pyramidal cells. More specifically, PV neurons preferentially target perisomatic regions of pyramidal neurons, whereas SST neurons target distal dendritic regions of pyramidal neurons that also receive inhibition from neuron-derived neurotrophic factor (NDNF)-expressing interneurons in layer 1 [15,159].

The multiplicity of interneuron subtypes is implicated in diverse computations and cognitive functions, such as locomotion-induced gain modulation [160], selective attention [127], context-dependent modulation [31,33], predictive processing [32,161], and gating of synaptic plasticity [117,120]. For instance, long-range cortico-cortical projections activating upstream VIP neurons in the primary visual cortex exert spatially specific top-down modulation of visual processing, resembling selective attention [127]. In predictive processing framework, mismatches between sensory inputs and internally generated predictive signals evoke the activity of prediction-error neurons [32]. In the layer 2/3 of the primary visual cortex, prediction-error neurons balance inhibitory visual input mediated by SST against excitatory motor-related predictive input targeting VIP [161].

Strongly interconnected groups of excitatory neurons form assemblies, which have been proposed to be the basis of associative memory [129,130]. Inhibition can influence excitatory assemblies in two distinct ways. First, inhibitory neurons may be nonspecific and nonpreferentially target different excitatory assemblies, known as 'blanket of inhibition' [131] (Figure 3A). Second, inhibition may be stimulus-specific if distinct inhibitory neurons receive stimulus-specific feedforward drive, or if excitatory and inhibitory neurons with a similar stimulus tuning connect more strongly and form E/I assemblies, known as stimulus-specific feedback inhibition [132] (Figure 3B).

While many mechanisms are involved in the formation of excitatory assemblies [133], computational models have proposed an important role of inhibitory plasticity in preventing runaway excitation that results from the assemblies' repeated coactivation and preventing winner-take-all dynamics whereby a single assembly is always active [26,28,48]. Specific to forming E/I assemblies, both inhibitory synapses onto excitatory neurons and excitatory synapses onto inhibitory neurons need to be plastic in the recurrent circuit [63,134]. The resulting co-tuned feedback inhibition in networks with E/I assemblies can support network stability [60,132], changes in neuronal variability [135], and decision making in the presence of noise [136].

Irrespective of whether inhibition is unspecific or specific, modeling studies suggest that the plasticity of lateral inhibitory connections across assemblies can ensure that different memories encoded by different assemblies are easily discriminated [50,137]. Concurrently, multiple experimental studies have found evidence for the role of inhibition in memory recall. For instance, inactive memories can be unmasked by suppressing inhibitory neurons [138]. Using E/I assemblies as a model for associative memories, the inactive memories seem to remain in the quiescent state until being recalled by disinhibition [138,139]. Recent work in the human neocortex has further suggested that specific inhibition can avoid inappropriate interference of overlapping memories and permit continual learning [140,141].

The activation of E/I assemblies shaped by inhibitory plasticity has also been hypothesized to underlie the adaptation of behavioral responses to repeated stimulation (i.e., 'habituation') [139,142]. The ability to adapt to repeated stimuli, detect unexpected stimuli in the environment, and identify their relevance to execute appropriate behavioral reactions is important for survival. Inhibitory plasticity has been suggested to be important in shaping adaptation to repeated responses also at the cellular level in the mouse auditory cortex [143]. A recent computational study has provided a mechanistic insight on how inhibitory plasticity can shape the responses to repeated and novel stimuli [144]. While the repeated presentation of a stimulus evokes initially high activity of the excitatory assembly representing the stimulus, the subsequent increase of

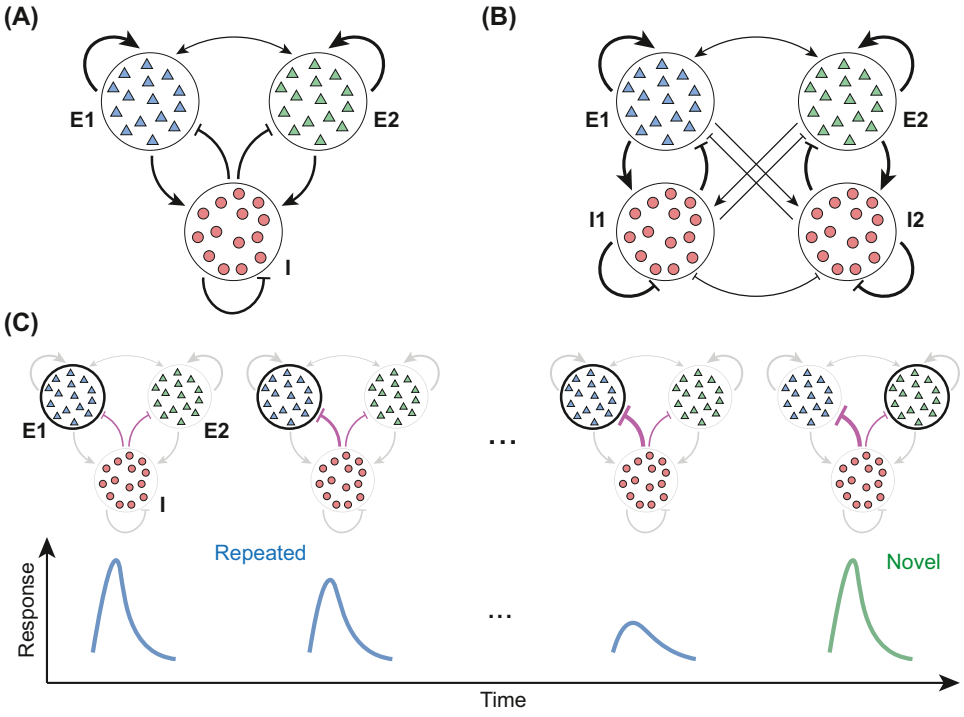

Figure 3. Unspecific versus specific inhibitory connectivity and the generation of adaptive and novelty responses. (A) Network with unspecific inhibition, in which different excitatory assemblies are inhibited by a single inhibitory population. (B) Network with stimulus-specific feedback inhibition, in which distinct excitatory assemblies are inhibited by non-overlapping inhibitory subpopulations. (C)The repeated and novel stimuli activate distinct excitatory assemblies, E1 and E2, respectively (activation marked with bold circles). Repeated presentation of the same stimulus leads to an increase of specific inhibitory synaptic strength onto the E1 assembly and a reduction of the evoked response (blue), while presenting the novel stimulus triggers a high response due to the weak inhibitory synaptic strength onto the E2 assembly (green).

inhibitory synaptic strengths suppresses the ensuing responses upon stimulus repetition. By contrast, a novel stimulus evokes a high response of its corresponding excitatory assembly since the inhibitory synapses onto the assembly do not potentiate (Figure 3C). While both blanket and stimulus-specific inhibition can capture adapted and elevated responses to repeated and novel stimuli, stimulus-specific inhibition is necessary for other adaptive phenomena [144]. This includes stimulus-specific adaptation, whereby excitatory neurons that are equally driven by two stimuli exhibit a higher response to the rarely presented stimulus, but a lower response to the frequently presented stimulus [145].

Interneuron-specific plasticity and its functional implications

Inhibitory neurons can be divided into multiple distinct subtypes based on their electrophysiological, morphological, and transcriptomic properties (Box 3). Accumulating evidence also suggests that synapses from and to different interneuron subtypes undergo distinct forms of synaptic plasticity [16,17,37,146,147]. Computational models have capitalized on these experimental results of interneuron-specific plasticity and explored its role in different settings. In feedforward networks, modeling work has showed that the receptive field of a neuron may not be solely determined by the feedforward excitatory weight profiles, but is heavily modulated by inhibition from different pathways [53]. By exploring several candidate plasticity rules for the different inhibitory pathways, the authors found that the neuron's receptive field strongly depends on the

modulatory state of inhibition as an example of context-dependence [53].

Recent studies in the rodent hippocampus have identified learning rules describing the LTD of parvalbumin (PV) synapses and the LTP of SST synapses onto excitatory pyramidal neurons in CA1 during physiological activity patterns [16]. As PV and SST mainly target perisomatic regions receiving inputs from CA3 and distal dendritic regions receiving inputs from pyramidal neurons in entorhinal cortex, respectively, both experiments and modeling suggest that interneuron-specific plasticity might prioritize inputs from one pathway over another [16] (Figure 4A). As stronger inhibition resulting from the potentiation of SST synapses onto excitatory neurons can limit excitatory plasticity [120], modeling has suggested that interneuron-specific plasticity can promote the stability of place cells [16]. Recent experiments in CA1 suggest that even synapses from different interneurons targeting the same perisomatic regions of excitatory neurons can undergo opposite changes when animals explore novel environments [17] (Figure 4B). Since these two types of interneurons preferentially receiving different inputs fire at different phases of network theta rhythms associated with memory encoding and retrieval [148], the opposite regulation of interneuron-specific plasticity may impact memory formation and maintenance. Future computational models could help uncover how the opposing plasticity mechanisms support long-term memories.

In addition to hippocampus, interneuron-specific plasticity rules based on spike timing have been reported in layer 2/3 of mouse orbitofrontal cortex and implicated in assembly formation in recurrent network models [50]. More specifically, PV synapses onto excitatory neurons follow a symmetric Hebbian learning rule and appear to be important for network stability; by contrast, SST synapses onto excitatory neurons follow an asymmetric Hebbian learning rule and appear to enhance competition between assemblies [50] (Box 1). Although a learning rule has not yet been characterized for neuron-derived neurotrophic factor (NDNF)-expressing interneurons, experimental studies have revealed that inhibition mediated by NDNF interneurons in layer 1 of the auditory cortex changes after associative auditory fear conditioning , and have suggested that NDNF interneurons and their plasticity are involved in the formation of associative memories [149].

While significantly less studied, recent work has begun to explore synapses between inhibitory neurons, including their impact on E/I balance in recent connectomic studies [150], on generating long neuronal timescales that support working memory, and on memory storage in computational models [151,152]. Yet, little is known about the plasticity of these inhibitory-to-inhibitory connections experimentally. Computational models here play an important role in revealing the functional consequences of this type of plasticity. For instance, a two-stage model showed that an initial stage of SST to PV plasticity guides the subsequent plasticity of excitatory-to-excitatory connections in a recurrent network underlying visual stimulus selectivity [153]. Recent modeling work has also begun investigating recurrent network models where multiple synapse types are simultaneously plastic and found that experimentally observed dynamics and computations can emerge from the complex interplay of many plasticity mechanisms. Given the high-dimensional space of learning rule parameters, when such models succeed in finding stable regimes, they can provide predictions for the learning mechanisms in real biological circuits. Deriving learning rules via optimizing a desired function has provided a new promising approach to study plasticity [154,155]. In an elegant example, recent studies derived plasticity rules from the perspective of optimizing a loss function to achieve firing rate set-points; the emergent networks could then generate self-sustained, inhibition-stabilized dynamics [156] and stimulus-specific feedback inhibition [134]. Even without deriving novel learning rules, combining classical Hebbian plasticity with synapse-type-specific competition for synaptic resources can yield novel dynamics such as the development of stimulus selectivity, E/I balance, decorrelated neural activity, assembly structures, and response normalization [63].

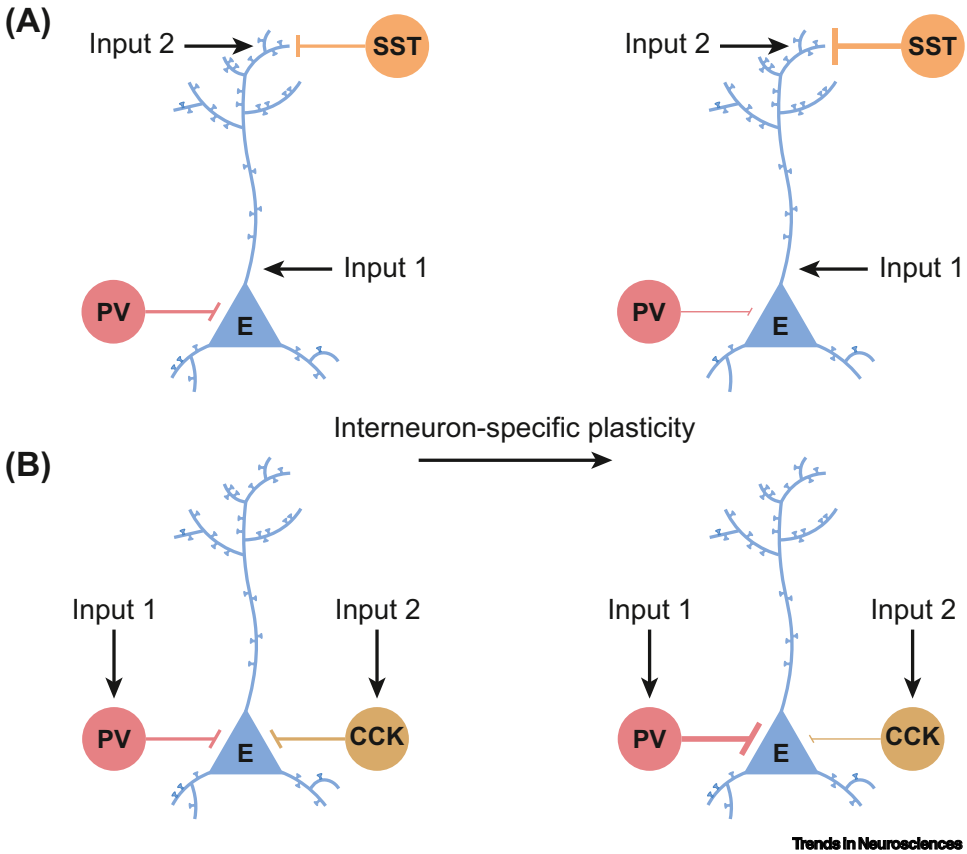

Figure 4. Interneuron-specific plasticity. (A) Inhibitory synapses from parvalbumin (PV)- (red) and somatostatin (SST)- (orange) expressing neurons onto hippocampal CA1 pyramidal neurons (blue) are weakened and enhanced, respectively, during physiological firing patterns [16]. This interneuron-specific plasticity can prioritize proximal input from CA3 over distal input from entorhinal cortex. (B) Perisomatic inhibitory synapses from PV- (red) and cholecystokinin (CCK)- expressing (brown) neurons onto recently activated hippocampal CA1 pyramidal neurons (blue) undergo long-term potentiation and long-term depression, respectively when animals are engaged in novel environments [17].

Concluding remarks and future perspectives

Over the past two decades, our understanding of the inhibitory control of circuit organization and dynamics, as well as the potential to modulate this control via plastic inhibition, has significantly grown. Inhibitory synapses in the brain are highly dynamic and regulated by various plasticity mechanisms, including short-term plasticity operating at the timescale of milliseconds to seconds [162] as well as long-term plasticity acting at the timescale of minutes to hours [44]. Here, we summarized studies on the long-term plasticity of inhibitory-to-excitatory synapses, referred to as inhibitory plasticity. As discussed in this review, abundant evidence suggests that inhibitory plasticity is important for establishing and maintaining E/I balance, achieving firing rate homeostasis, controlling excitatory plasticity, and shaping network connectivity throughout the entire life of an organism. Nonetheless, it remains unclear if the learning rules that characterize inhibitory plasticity in development are the same as those operating in adulthood (see Outstanding questions). Complementary to the growing number of experimental studies on inhibitory plasticity, theoretical and computational approaches have played an important role in synthesizing the available data to reveal how inhibition regulates various aspects of circuit function. This has generated mechanistic insights into the function of inhibitory plasticity at several spatial scales, from the local dendritic regulation of E/I balance, to the cellular control of spiking properties, and the maintenance of stable

Outstanding questions

Neuronal activity during development is typically generated spontaneously in the absence of sensory experience. This activity operates on much slower timescales (hundreds of milliseconds) compared with the sensory-driven activity patterns (few to tens of milliseconds) in adulthood. Do the activity-dependent learning rules that characterize inhibitory plasticity integrate activity at different timescales in development and adulthood?

The phenomenological learning rules that determine how inhibitory plasticity depends on rates and spike timing can be modulated by various external factors. How do different neuromodulators, behavioral states, and environmental perturbations affect inhibitory plasticity rules?

How are phenomenological descriptions of inhibitory plasticity implemented with the biological machinery of molecular interactions?

Distinct forms of E/I balance might be beneficial for different demands in development versus adulthood. How are different types of E/I balance dynamically regulated by inhibitory plasticity over multiple timescales to serve specific goals?

E/I balance also exists at different spatial scales. Are there shared principles underlying the establishment of E/I balance across these different scales? What are the functional implications of breaking E/I balance at some spatial scales but not others?

Interneurons come in diverse subtypes, receive inputs from different pathways, and target excitatory neurons in different locations (e.g., cell body versus dendrite). This diversity is also reflected in the types of plasticity rules experienced at the synapses. How can interneuron-specific plasticity rules be described as a function of firing rates, spike timing, and calcium level?

Inhibitory plasticity rules might also differ across brain regions. How do different brain regions coordinate the potentially different forms of inhibitory plasticity they express to maintain biologically reasonable activity levels and process information?

activity patterns and connectivity structures at the network level. At the same time, we have highlighted that inhibitory control also occurs at multiple temporal scales from the regulation of fast spiking to the slower calcium dynamics and even slower timescales at which measurable changes in synaptic strength can be observed.

Despite this progress, many open challenges remain due to the high diversity of inhibitory neurons and the interneuron-specific plasticity at different synapse types. Experimentally, the development of transgenic and recording techniques opens new possibilities to record activity from multiple interneuron subtypes simultaneously and probe the rules that govern synaptic plasticity. Concurrently, computational models and theories are becoming paramount. First, they are essential to understand the complex interactions of different plasticity mechanisms, especially in highly recurrent circuits with non-intuitive dynamics. Second, models can explore candidate plasticity mechanisms and study their functional implications. Last, theoretical work also enables the exploration of more abstract concepts, like inhibition-stabilization, as general frameworks for circuit processing, which can be established and modulated through inhibitory plasticity.

Different computations, such as selective attention, context-dependent modulation, and predictive processing, typically require diverse interneuron subtypes with specific synaptic connections. How do interneuron-specific plasticity mechanisms establish the network connectivity enabling diverse computations?

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Declaration of interests

The authors declare no conflicts of interest.

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