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Review article

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The plasticitome of cortical interneurons

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Abstract

Hebb postulated that, to store information in the brain, assemblies of excitatory neurons coding for a percept are bound together via associative long-term synaptic plasticity. In this view, it is unclear what role, if any, is carried out by inhibitory interneurons. Indeed, some have argued that inhibitory interneurons are not plastic. Yet numerous recent studies have demonstrated that, similar to excitatory neurons, inhibitory interneurons also undergo long-term plasticity. Here, we discuss the many diverse forms of long-term plasticity that are found at inputs to and outputs from several types of cortical inhibitory interneuron, including their plasticity of intrinsic excitability and their homeostatic plasticity. We explain key plasticity terminology, highlight key interneuron plasticity mechanisms, extract overarching principles and point out implications for healthy brain functionality as well as for neuropathology. We introduce the concept of the plasticitome — the synaptic plasticity counterpart to the genome or the connectome — as well as nomenclature and definitions for dealing with this rich diversity of plasticity. We argue that the great diversity of interneuron plasticity rules is best understood at the circuit level, for example as a way of elucidating how the credit-assignment problem is solved in deep biological neural networks.

Sections

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Introduction

Long-term synaptic plasticity is widely understood to underlie learning and memory[1–3] as well as developmental circuit refinement[4–6]. Although he did not claim precedence[7], Donald Hebb[8] is generally attributed with the idea that learning in the brain is achieved by strengthening connections between simultaneously active excitatory neurons, often summarized as 'cells that fire together wire together'[9,10]. During Hebbian learning, this process leads to the formation of excitatory cell assemblies that code for percepts[11]. When presented with a partial percept, an assembly reactivates through recurrent excitation across excitatory neurons, thereby completing and recalling the percept[12]. As Hebb's postulate relies solely on excitatory to excitatory (E → E) synaptic plasticity, it is unclear how inhibitory interneurons (INs) might contribute. Consequently, some have speculated that INs lack conventional long-term plasticity[13]. As oscillatory inhibition provides a reference timekeeper for excitatory firing, it was also argued that INs should not be plastic[13]. In apparent agreement, synapses to and from INs typically lack dendritic spines, in which key processes for synaptic plasticity occur[14,15].

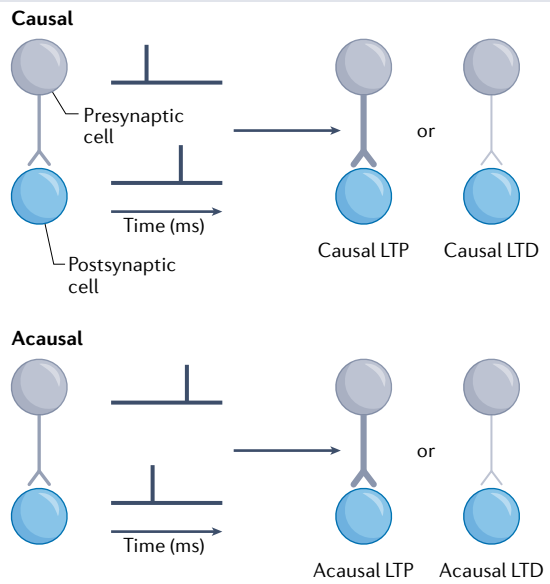
However, additional evidence indicates that INs are in fact plastic and play important functional roles, for instance in visual cortex critical period plasticity[16], somato-dendritic integration[17] and the stabilization of neuronal networks[18]. Interestingly, pioneering studies reported that many INs do not necessarily obey Hebb's postulate[19]. For example, connections from excitatory neurons to inhibitory INs (E → I) — in this case, basket cells (BCs) — in the hippocampus undergo anti-Hebbian long-term potentiation (LTP)[20], so in this case 'cells that do not fire together wire together'.

The diversity of different IN types[21–23] results in an even greater variety of E → I, I → E and I → I synapse type-specific plasticity learning rules[24]. Furthermore, these plasticity learning rules incorporate the induction of plasticity — the processes that elicit plasticity — as well as the expression of plasticity — the mechanisms that alter the strength of a synaptic connection. To provide an overview of cortical IN plasticity, we review synaptic plasticity at inputs to and outputs from INs, homeostatic plasticity of INs and intrinsic plasticity of INs. Throughout, we define key nomenclature. In this Review, we argue that to understand the complexity of circuit plasticity, a comprehensive database of all these diverse forms of brain plasticity is needed: the plasticitome[25], which is the synaptic plasticity equivalent to the connectome[26] or the genome[27]. To illustrate our point, we propose that the plasticitome will help to elucidate how the credit-assignment problem is solved in deep biological neural networks.

Box 1

Causal versus acausal activity

Causality is a key concept in spike timing-dependent plasticity (STDP)[42,43,231,232]. Although there are many types of causality[233], causal refers in STDP to a scenario in which presynaptic spiking occurs a few milliseconds before postsynaptic activity, so that presynaptic spiking is causally related to postsynaptic activation, as the former affects the latter (see the figure, top). The opposite temporal ordering is consequently termed acausal, which is when the presynaptic spiking fails to influence postsynaptic activity because the input arrives too late (see the figure, bottom). With this notation, causal spike pairings that result in potentiation can describe Hebbian plasticity. However, both causal and acausal forms of STDP can induce long-term potentiation (LTP) or long-term depression (LTD) (see the figure).



The ins and outs of IN plasticity

Cortical INs can be classified into types on the basis of the expression of molecular markers such as parvalbumin (PV), somatostatin (SST) or vasoactive intestinal peptide (VIP)[28–30]. PV^+, SST^+ and VIP^+ INs play different functional roles. To a first approximation, PV^+ BCs typically provide fast perisomatic feedforward inhibition of cortical pyramidal cells (PCs), whereas SST^+ Martinotti cells (MCs) mediate late-onset dendritic feedback inhibition of PCs[17,28–32]. However, VIP^+ INs chiefly target other INs, thereby typically disinhibiting local circuits[31]. We defer to specialized reviews for additional information on IN types[21–23,28–30] and IN plasticity[33–39]. In this section, we explore IN plasticity at the circuit level in cortical development, in re-routing information flow and in disinhibition to gate learning. In addition, we discuss the E/I balance, one, two and three-factor plasticity, and specific IN plasticity mechanisms.

IN plasticity in development

Cortical circuits are shaped by sensory experience during a developmental critical period[4] that is gated by inhibition[5,40]. For example, BCs determine visual cortex critical period plasticity[5,41]. However, here we focus less on gating by inhibition and more on IN plasticity, first in auditory and then in visual cortex development.

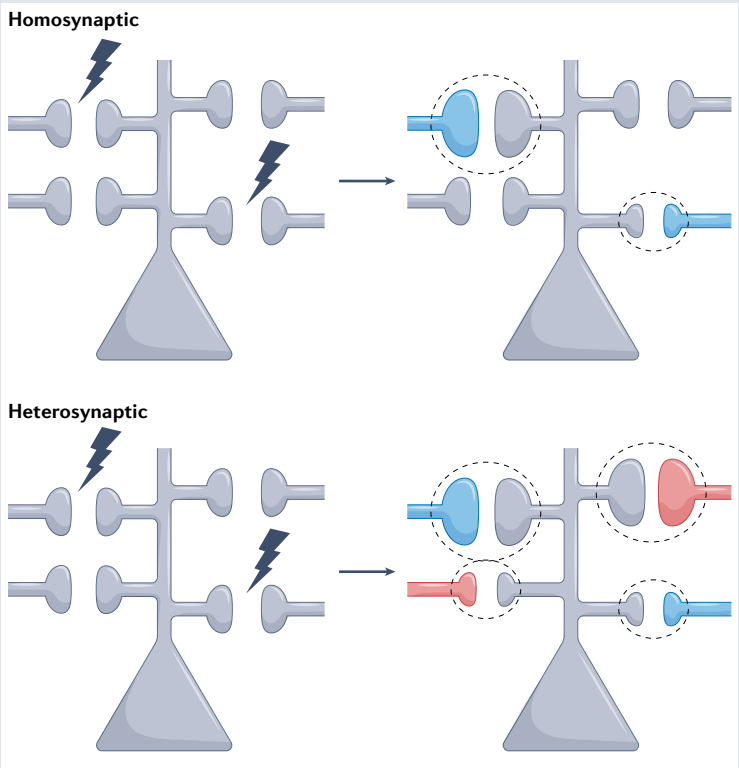
Spike timing-dependent plasticity (STDP)[42,43] at BC synapses onto layer 4 (L4) PCs has been studied in developing mouse auditory cortex[44]. At these synapses in young postnatal day 18–23 mice, causal firing induced I → E long-term depression (LTD), whereas acausal firing induced I → E LTP (Box 1). I → E disinhibition might thereby turn on plasticity to remodel immature circuits. However, critical period sensory experience switched causal I → E STDP from LTD to LTP, so that the mature plasticity learning rule in the adult brain elicited LTP irrespective of spiking order[44] (Box 1). Thus, sensory experience can remodel plasticity learning rules. Another study showed that this

Box 2

Input specificity versus heterosynaptic and homosynaptic plasticity

Homosynaptic plasticity refers to the outcome at a synapse that was active during the induction of plasticity (see the figure, top; homosynaptic in blue, synapse size changes illustrate plasticity, lightning bolts denote activity), whereas heterosynaptic refers to plasticity at synapses that were inactive during the induction of plasticity (see the figure, bottom; heterosynaptic in red)[234]. This nomenclature applies regardless of the plasticity induction protocol, for instance classical rate-dependent long-term potentiation (LTP) versus spike timing-dependent plasticity (STDP)[3].

Classical hippocampal LTP is thought to be input or synapse-specific[1,235] — not to be confused with synapse type-specific plasticity[24,54]. Without input specificity, the information storage capacity of a neuron is less than optimal[236] (but this does not mean that classical LTP with input specificity necessarily achieves optimality[237]). Mechanistically, this synapse specificity is thought to be guaranteed by its NMDA receptor (NMDAR) dependence in combination with biochemical compartmentalization mediated by dendritic spines[14,15]. In practice, synapse specificity breaks down at short distances even when synapses are made onto postsynaptic spines, leading to heterosynaptic LTP locally[238–240]. Furthermore, heterosynaptic plasticity is not limited to LTP, as heterosynaptic long-term depression (LTD)[241] was, in fact, discovered before homosynaptic LTD[242–244], perhaps because it was predicted by Gunther Stent[182]. In addition, heterosynaptic LTP and LTD can also be expressed at distal locations[127], not only at neighbouring synapses.



As many interneurons (INs) are aspiny[14,15], one might infer that plasticity of excitatory inputs onto INs is not input-specific. However, owing to high levels of endogenous calcium buffering[245], postsynaptic calcium signals may be quite localized even in aspiny INs[246]. The relevance and prevalence of such localization in IN plasticity remains to be explored in more detail.

temporally symmetric I → E STDP stably embeds auditory memories as non-conflicting Hebbian assemblies (see below)[18]. In summary, early I → E plasticity promoted critical period information storage in L4 PCs, whereas its mature equivalent favoured memory stability[18,44].

The findings described above at BC → L4 PC synapses[44] contrast with those obtained in the developing mouse auditory cortex at IN outputs onto L5 PCs[45]. Temporally symmetric STDP at IN → L5 PC synapses produced I → E LTP irrespective of spike ordering. Thus, during development, I → E plasticity learning rules may favour stability in L5 (ref. 45) but plasticity in L4 (ref. 44), highlighting how plasticity is specific to synapse type[24].

After STDP induction at the IN outputs onto L5 PCs in the developing mouse auditory cortex, heterosynaptic plasticity was also observed (Box 2) at excitatory and inhibitory inputs onto L5 PCs (Fig. 1) and helped to maintain spiking activity within reasonable bounds[45]. Both I → E and E → E heterosynaptic connections were depressed by causal spiking but were potentiated after acausal spiking. Interestingly, this heterosynaptic plasticity was found only in juvenile cortex, suggesting that it might be important for developmental circuit plasticity.

In developing primary visual cortex L4, LTP occurred at BC → PC connections when presynaptic spiking was causally paired with postsynaptic low-frequency firing or subthreshold depolarization[41,46]. Unlike observations from other studies in developing cortex[44,47,48], this I → E LTP did not require postsynaptic calcium[46]. Interestingly, visual deprivation during the critical period altered plasticity so that the BC → PC pairing elicited I → E LTD instead of I → E LTP[41]. Moreover, a second plasticity induction with the same pairing protocol depressed BC → PC connections such that synapses previously exhibiting I → E LTP returned to control response levels and synapses previously exhibiting I → E LTD underwent further LTD[41]. Thus, prior plasticity induction reshapes subsequent plasticity at BC outputs.

However, BC inputs might have plasticity learning rules that differ from those of BC outputs. In mouse visual cortex, the role of BCs in ocular dominance plasticity has been explored[16]. In classic experiments[49], monocular deprivation caused cortical excitatory neurons to lose responsiveness to the occluded eye. By contrast, BCs showed an unexpected initial shift in responsiveness towards the occluded eye (although see Kuhlman et al.[50], who found an initial reduction in PV^+ IN

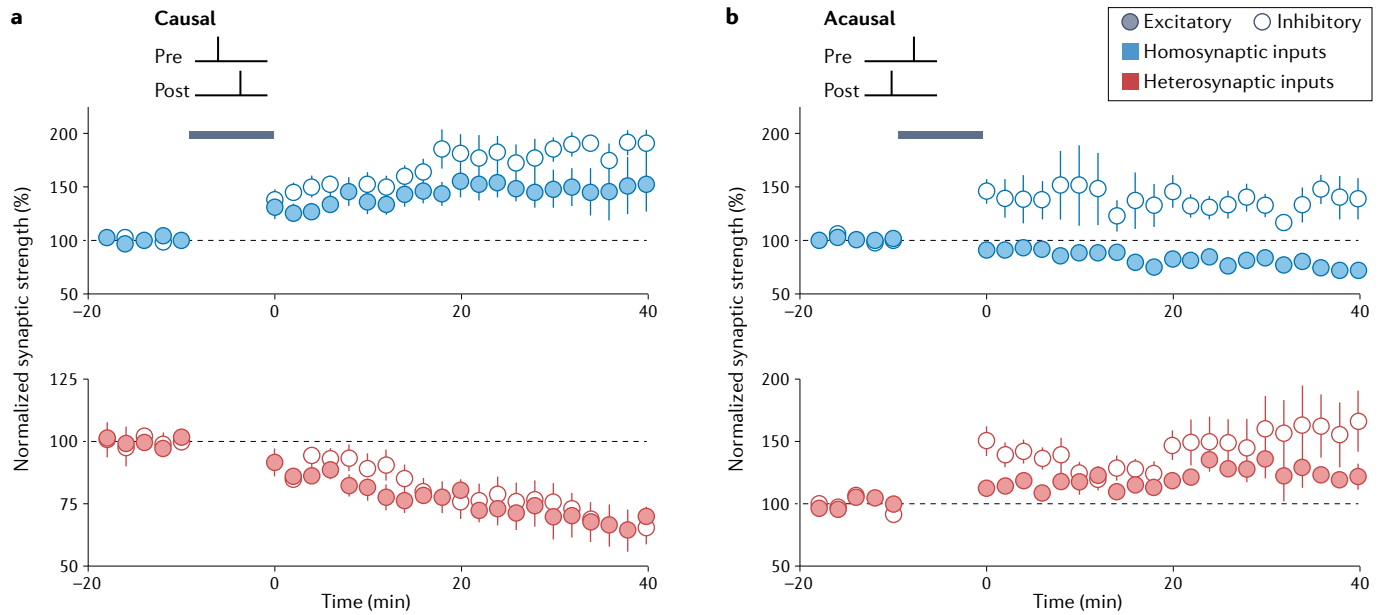


Fig. 1 | Cellular learning while normalizing synaptic weights by combining homosynaptic and heterosynaptic plasticity. Spike timing-dependent plasticity (STDP) was explored at excitatory and inhibitory inputs onto layer 5 (L5) pyramidal cells (PCs) in mouse auditory cortex[45]. **a**, Causal activity (Box 1) evoked excitatory to excitatory (E → E) long-term potentiation (LTP) at excitatory homosynaptic inputs and inhibitory to excitatory (I → E) LTP at inhibitory homosynaptic inputs (Box 2). By contrast, causal spiking elicited E → E long-term depression (LTD) at excitatory heterosynaptic inputs and I → E LTD at inhibitory heterosynaptic inputs. **b**, Acausal activity induced LTP for all input combinations (E → E and I → E) except for excitatory homosynaptic inputs, which yielded E → E LTD. Together, these forms of STDP help normalize synaptic strengths onto a neuron — similar to what other studies previously proposed[18,127] — while at the same time allowing co-activated excitatory and inhibitory synapses to strengthen or weaken together on a finer scale to store information in local circuits. Symbols show mean ± s.e.m. Post, postsynaptic; Pre, presynaptic. Panels **a** and **b** adapted with permission from ref. 45, Elsevier.

firing), only later preferring the open eye like excitatory neurons. Computer modelling showed how this unexpected responsiveness emerged from temporally symmetric E → I LTD[16] previously reported in BCs[51].

Critical period visual deprivation can also alter the E/I balance (see section below). For example, monocular deprivation nearly doubled open-eye responses in visual cortex L2/3 PCs, resulting from E → I plasticity reducing PV^+ IN firing[50].

Thus, IN plasticity has two seemingly conflicting roles as it promotes stability as well as gating critical period plasticity. These studies also illustrate the sheer diversity of plasticity learning rules at IN inputs and outputs, with striking differences across cortical layers and synapse types.

E/I balance and plasticity

Maintaining the E/I balance in the brain is critical for the stability and proper functioning of circuits. For example, L2/3 PCs in mouse developing primary visual cortex (postnatal day 14–23) receive inhibition proportional to excitation[52], but how is such balance achieved? A model where I → E synapses follow temporally symmetric I → E STDP gives rise to negative feedback to dynamically balance E/I in neural circuits[18,53] (Fig. 1). In this model, I → E synapses potentiated as a result of synchronous presynaptic and postsynaptic spiking, so when a cell's activity increased owing to potentiation of excitatory inputs, inhibition was also potentiated[18]. This way, I → E plasticity could balance activity levels without compromising E → E plasticity used for information storage. Thus, memory storage with I → E as well as E → E plasticity stably maintains the E/I balance without a need for fine tuning[53].

How does inhibition respond when circuit plasticity alters the E/I balance? In auditory cortex, E/I integration determines L5 PC spike probability in a timing-dependent manner[47]. Causal spike pairings elicited I → E and E → E LTP, which increased PC spike probability. However, acausal activity led to I → E LTP but E → E LTD, which decreased PC spike probability by altering the E/I balance. The magnitude of the I → E LTP was also greater when excitation was stronger, which helped balance the E/I ratio[47] in keeping with the above modelling study[18].

However, certain circumstances can shift the E/I balance. For example, in vitro visual cortex L4 BC → PC connections potentiated when presynaptic firing was paired with subthreshold postsynaptic depolarization, which can happen when sensory input is lost[41]. Furthermore, visual deprivation in vivo did not alter E → E connections in L4 of the visual cortex, but dramatically potentiated E → I and I → E signalling. I → E LTP mediated the increased inhibition, as visual deprivation prevented induction of I → E LTP in vitro[41]. Thus, after visual deprivation, I → E LTP might have a key role in vision degradation.

In conclusion, IN plasticity often serves to maintain the E/I balance and proper brain functioning. Thus, IN plasticity can consequently also rewire circuits to yield poor performance, resulting in pathological brain states.

One, two and three-factor plasticity

Classical cellular plasticity learning rules in the spirit of Hebb and STDP that require pairing of presynaptic and postsynaptic activity are known as two-factor plasticity (Box 3). However, plasticity does not always require correlated activity in connected neurons. For example, in barrel

cortex, stimulating L5 PCs alone induced non-associative I → E LTP at PV^+ IN inputs – a one-factor learning rule (Box 3) – that improved L5 PC spiking precision[48]. In addition, calcium influx in L5 PCs via postsynaptic L-type voltage-gated calcium channels triggered retrograde nitric oxide signalling and increased GABA release from PV^+ IN synapses. In other words, even though I → E LTP depended on postsynaptic and not presynaptic activity, it was oddly enough expressed presynaptically. This finding is intriguing because presynaptic plasticity impacts synaptic dynamics and synaptic information transfer, whereas postsynaptic plasticity does not[54,55]. Future research could clarify why this roundabout mechanism to achieve presynaptic expression of postsynaptically induced I → E LTP exists and whether non-associative I → E LTP of PV^+ BC-mediated inhibition is generally observed.

Another study found that excitatory inputs onto MCs that were not stimulated during E → I LTP induction still underwent plasticity[56]. Thus, this could be a form of heterosynaptic plasticity (Box 2) associated with STDP induction at other inputs onto the neocortical MCs. However, further investigation revealed that postsynaptic high-frequency MC spiking alone also induced E → I LTP or LTD[56], suggesting a one-factor plasticity learning rule, rather than two-factor heterosynaptic plasticity (Fig. 2a and Box 3). As something would still have to drive postsynaptic MC spiking, it could be argued that this is still two-factor plasticity[57].

Box 3

One, two and three factors in plasticity

One-factor plasticity

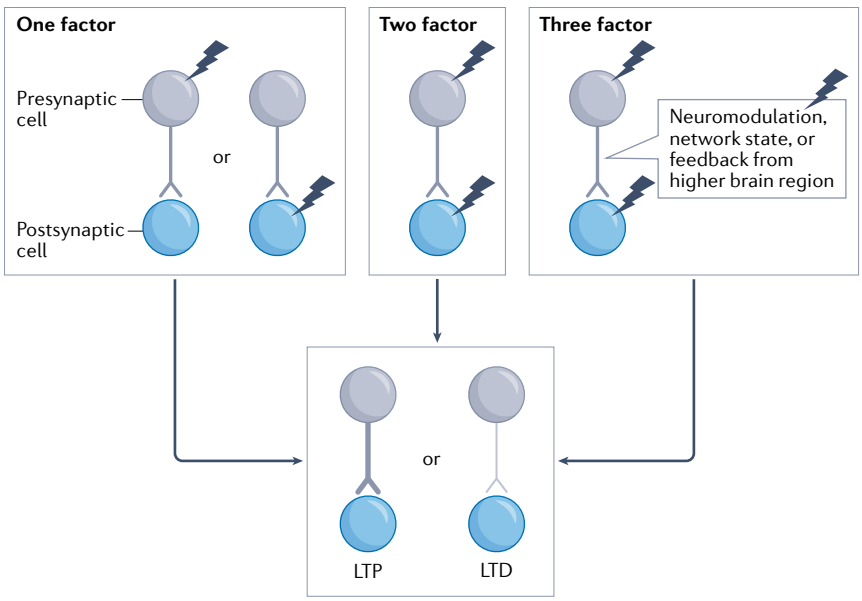
Some forms of synaptic plasticity are determined by presynaptic or postsynaptic activity alone and are therefore known as one-factor plasticity learning rules (see the figure, left; lightning bolt denotes activity). A classic example of a one-factor rule is long-term potentiation (LTP) at mossy fibre inputs onto hippocampal CA3 pyramidal cells (PCs), which chiefly depends on presynaptic activity[247].

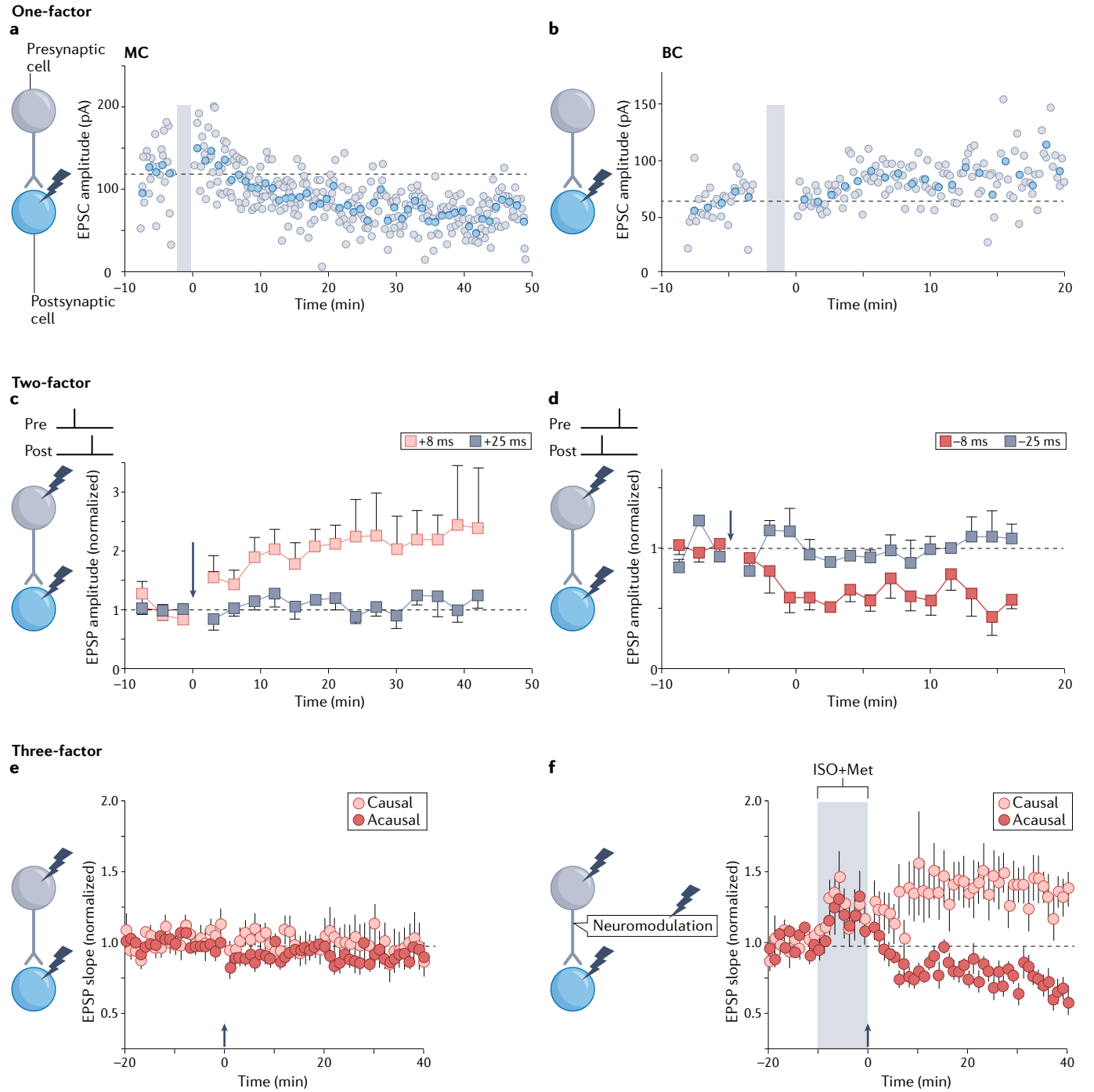
Two-factor plasticity

Hebbian plasticity is a local plasticity learning rule determined by activity in both the presynaptic and postsynaptic neurons (see the figure, middle). Neuroscience theoreticians therefore like to refer to Hebbian learning as a two-factor learning rule, as plasticity is determined by two parameters[248]. Another example of two-factor plasticity is dependence on the precise temporal order of presynaptic and postsynaptic spiking in spike timing-dependent plasticity (STDP)[3]. Postsynaptic activity can be in the form of local dendritic spikes[14] or subthreshold depolarization[249], meaning that the postsynaptic neuron need not produce axonal spiking output to satisfy a two-factor learning rule[196,250].

Three-factor plasticity

Controlling what is learned, and when, should require a third factor that can gate Hebbian learning on and off, or modulate information storage (see the figure, right). Such forms of plasticity are called neo-Hebbian[251] three-factor plasticity learning rules[248,252,253], where the third factor could be a more global effector such as neuromodulation[179], network state[254] or feedback from a higher brain region to enable attention to guide learning, for example in deep networks[196]. It is furthermore possible for more than three factors to be involved[196]. LTD, long-term depression.





Either way, even though presynaptic activation was not required, inputs with low initial release probability were more prone to E → I LTP, whereas those with high release probability were susceptible to E → I LTD[56], showing that the state of the presynaptic terminals mattered for the plasticity outcome. Similarly, high-frequency BC spiking elicited one-factor E → I LTP or LTD (Fig. 2b) that correlated with initial release probability[56]. These results nicely illustrate the intricacies of interpreting plasticity experiments.

In the visual cortex, excitatory inputs onto neocortical L2/3 SST$^+$ INs potentiated following theta burst stimulation (TBS)[58]. Postsynaptic voltage clamp at −90 mV during TBS still yielded E → I LTP, suggesting a one-factor plasticity learning rule, as postsynaptic activity was not needed. In addition, this E → I LTP did not need postsynaptic calcium signalling and was presynaptically expressed[58]. Similar to a classic example of presynaptically expressed one-factor plasticity, hippocampal mossy fibre E → I LTP[59], protein kinase A was necessary for this E → I LTP[58].

Fig. 2 | One, two or more factors can determine IN plasticity. One-factor[56], two-factor[51] and three-factor[62] plasticity learning rules have all been described at excitatory connections onto neocortical interneurons (INs). **a**, At excitatory inputs onto neocortical Martinotti cells (MCs), postsynaptic high-frequency spiking alone elicited excitatory to inhibitory (E → I) long-term potentiation (LTP) or long-term depression (LTD) depending on initial release probability, in this example E → I LTD. **b**, Similarly, postsynaptic high-frequency basket cell (BC) spiking evoked E → I LTP or LTD, in this sample E → I LTP. Thus, the two results in panels **a** and **b** exemplify one-factor long-term plasticity. Grey circles are individual responses; blue circles are averages over 1 min. **c**, Causal spiking (Box 1) at an 8 ms temporal difference but not at a 25 ms difference induced E → I LTP at excitatory inputs onto neocortical MCs. **d**, Acausal activation at an 8 ms time difference but not at a 25 ms difference triggered E → I LTD. Thus, the two results in panels **c** and **d** combined reveal that the plasticity outcome is determined by two factors: presynaptic spiking and postsynaptic spiking. **e**, Irrespective of timing, presynaptic and postsynaptic spiking did not induce plasticity at excitatory inputs onto neocortical BCs. **f**, However, when presynaptic and postsynaptic activation was combined with a third factor — β-adrenergic and α1-adrenergic-receptor stimulation (ISO + Met) — causal E → I LTP and acausal E → I LTD were observed. Thus, the two results in panels **e** and **f** combined reveal that the plasticity outcome is determined by three factors: presynaptic spiking, postsynaptic spiking and adrenergic neuromodulation. Symbols show mean ± s.e.m. EPSC, excitatory postsynaptic currents; EPSP, excitatory postsynaptic potential; Post, postsynaptic; Pre, presynaptic. Panels **a** and **b** adapted from ref. 56, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/). Panels **c** and **d** Adapted with permission from ref. 51, copyright (2007) Society for Neuroscience. Panels **e** and **f** adapted from ref. 62, CC BY 3.0 (https://creativecommons.org/licenses/by/3.0/).

However, in apparent disagreement with one-factor plasticity, excitatory inputs onto visual cortex L2/3 MCs have a two-factor plasticity learning rule, with causal activity inducing E → I LTP and acausal E → I LTD[51] (Fig. 2c,d and Box 3). The reason for this apparent discrepancy is unclear.

Plasticity can also depend on factors other than presynaptic and postsynaptic activity, such as neuromodulation[60] and network state[61], and this can be referred to as three-factor plasticity (Box 3). For example, neuromodulation controls the polarity of E → I STDP at excitatory synapses onto mouse visual cortex INs[62] (Fig. 2e,f). It was observed that neither causal nor acausal spiking led to plasticity at excitatory inputs onto BCs or MCs (Box 1) in untreated acute slices. However, application of an α1-adrenergic receptor agonist resulted in E → I LTD at both synapse types irrespective of spike order. Conversely, application of a β-adrenergic-receptor agonist resulted in E → I LTP at both synapse types irrespective of spike order. When α1-adrenergic and β-adrenergic receptors were simultaneously activated, causal stimulation elicited E → I LTP whereas acausal elicited E → I LTD. Thus, neuromodulators can greatly influence the plasticity outcome.

The need for neuromodulation as a third factor is a likely explanation for why plasticity experiments are notoriously variable. For example, although the above acute slice study found bidirectional STDP at excitatory inputs onto BCs[62], other researchers found only E → I LTD[51] or only E → I LTP[63]. These conflicting acute slice studies could be reconciled by the need for neuromodulation, because experimental conditions can affect endogenous neuromodulation[62]. The acute slice preparation itself might also impact basal levels of AMPA receptor (AMPAR) phosphorylation[64], which could alter the neuromodulation of E → I STDP[65].

In summary, whereas one and two-factor plasticity learning rules typically depend only on local activity, three-factor learning rules generally include more global, circuit-wide information. Thus, three-factor plasticity could enable gating of information storage such as that based on attention or circuit output error.

Re-routing information flow

IN plasticity can reshape PC somato-dendritic integration. For example, SST^+ INs inhibit cortical PC dendrites, whereas PV^+ BCs inhibit cortical PCs perisomatically[14,15]. Moreover, timing-dependent I → E LTP at SST^+ IN inputs and timing-dependent I → E LTD at PV^+ IN inputs affect the responsiveness of hippocampal CA1 PCs to different excitatory pathways[17]. In addition, I → E LTP of dendritic SST^+ IN inhibition decreased CA1 PC spike probability driven by dendrite-targeting entorhinal cortex inputs, whereas I → E LTD of PV^+ IN somatic inhibition increased CA1 PC spike probability driven by proximal CA3 excitatory inputs. Thus, the combined SST/PV inhibitory plasticity in CA1 PCs shifted the E/I balance to prioritize CA3 over entorhinal cortex inputs. Interestingly, computer modelling showed that SST^+ IN I → E LTP also stabilizes newly formed hippocampal place cells and prevents interference of place cell activity in novel real-world environments, whereas PV^+ IN I → E LTD maintains place cell spike output[17]. Thus, IN plasticity not only altered the E/I balance and the PC spiking output but also enabled PC input source switching between projections from CA3 and entorhinal cortex.

IN plasticity can also change information flow across cortical layers. A study further investigating the one-factor I → E LTP of PV^+ IN inputs to L5 PCs[48] (see above) found that potentiated inhibition of L5 PCs effectively prevented information transfer from L2/3 to L5 (ref. 66). In addition, this I → E LTP affected γ-oscillation phase locking of PCs. As excitatory synaptic inputs in different layers carry different information[14,15], these studies highlight how IN plasticity affects cognitive function by influencing cortical information flow.

Disinhibition and plasticity

Many IN types themselves receive inhibition[67,68]. Thus, increased inhibition onto inhibitory cells — known as disinhibition — can increase network excitation via an I → I → E connectivity motif. However, an important distinction from direct E → E excitation is that I → I → E disinhibition requires that the intermediate INs are active, as otherwise the initial disinhibitory cell cannot affect the recipient excitatory cell. Therefore, plasticity of disinhibition is expected to serve an important role in regulating activity in the brain, with implications for pathology such as epilepsy[69]. In agreement, inhibition of disinhibitory VIP^+ INs can reduce seizure duration[70].

Disinhibition occurs in healthy brains as well. For example, auditory receptive field plasticity is enhanced by long-lasting auditory cortex disinhibition triggered by nucleus basalis cholinergic neuromodulation[71]. Associative fear learning in the auditory cortex also relies on long-lasting disinhibition[72]. Foot shock-triggered cholinergic activation of L1 INs inhibits L2/3 PV^+ INs[73], which by its similar impact probably emulates quiet wakefulness in associative fear learning in the auditory cortex of the healthy brain[72].

Locomotion has likewise been shown to enhance spiking activity and plasticity in adult mouse visual cortex[74,75]. Mechanistically, VIP^+ IN → SST^+ IN cortical disinhibition mediated this I → I → E enhancement of visual cortex activity and plasticity[76]. It was later demonstrated that optogenetic activation of VIP^+ INs or silencing of SST^+ INs in stationary

mice enhanced adult plasticity, suggesting that locomotion itself did not necessarily underlie the enhancement[77]. Similarly, inhibition of motor cortex SST$^+$ INs by VIP$^+$ INs was necessary for L2/3 PC sequential activation and correlated with improved motor learning[78].

Together, these studies show how behavioural activation and concomitant disinhibition can boost plasticity and learning. Although many forms of disinhibition exist, VIP$^+$ INs consistently feature in I → I → E disinhibition[67,68,79]. Yet not all VIP$^+$ INs are disinhibitory[67] and not all disinhibitory neurons express VIP[67,68]. Moreover, although these studies boosting plasticity and learning did not report disinhibitory plasticity as such, studies similar to those discussed earlier of auditory receptive field plasticity[50] and ocular dominance plasticity[71] reported long-lasting disinhibitory changes, perhaps of the I → I → E format. However, in a clearcut report of disinhibitory plasticity, hippocampal VIP$^+$ INs release enkephalin to long-term disinhibit CA2 PCs by heterosynaptic I → E LTD of PV$^+$ IN outputs in social memory formation[80].

Although it remains unclear how enkephalin depressed PV$^+$ IN outputs[80], other researchers have shown that, in hippocampal IN STDP, reduced chloride co-transporter activity alters the chloride gradient at the synapse to locally depolarize the GABAergic reversal potential, which reduces I → E driving force[81]. Surprisingly, this long-lasting I → E disinhibition in addition mediates synapse-specific potentiation of excitation[82,83] (Box 2). Through this mechanism, E → E neurotransmission from CA3 to CA1 can counterintuitively be boosted in the long term without LTP of excitatory synapses[82,83].

In sum, few studies have directly explored long-lasting disinhibitory plasticity, so more research is needed to clarify how long-lasting disinhibitory plasticity contributes to learning[67,68,79]. Even so, a principle emerging from these studies is that disinhibition is generally associated with wakefulness and attention as well as with plasticity and learning.

IN plasticity mechanisms

GABA receptors. Similar to AMPARs in excitatory plasticity[84,85], postsynaptic $GABA_A$ receptor ($GABA_AR$) trafficking unsurprisingly plays a role in the expression of inhibitory LTP and LTD[33,86]. However, $GABA_ARs$ have also been implicated in the induction of inhibitory plasticity. For example, postsynaptic metabotropic $GABA_B$ receptors ($GABA_BRs$) were required for the induction of I → E LTP at visual cortex L4 inhibitory inputs onto L5 PCs[87] and for the induction of causal I → E LTD at auditory cortex BC → PC connections[44]. Similarly, visual cortex I → E LTP required $GABA_BR$-mediated potentiation of $GABA_ARs$, meaning that induction of and expression of inhibitory plasticity were mediated by different GABA receptor types[41,46].

NMDA receptors. The dual need for postsynaptic depolarization and presynaptically released glutamate provides postsynaptic NMDA receptors (NMDARs) with a well-known capacity for coincidence detection in Hebbian plasticity and in STDP[14,15,88]. Thus, it is expected that NMDARs can trigger plasticity at glutamatergic inputs to INs. However, surprisingly, NMDARs can also elicit plasticity at GABAergic synapses.

NMDAR activation can translocate activated CaMKII to inhibitory synapses[89] to enhance GABAergic currents in the long term[90]. For example, NMDA application induced I → E LTP at inhibitory inputs to PCs in dissociated hippocampal culture and the NMDAR-dependent I → E LTP was postsynaptically expressed and required CaMKII signalling[91]. Furthermore, synaptic recruitment of extrasynaptic gephyrin – a postsynaptic inhibitory scaffold protein – combined with CaMKII phosphorylation of $GABA_ARs$ immobilized pre-existing surface $GABA_ARs$ at the synapse, thereby potentiating inhibition. The physiological relevance of these in vitro findings was verified in mice following monocular deprivation during the visual cortex critical period as L4 PCs accumulated $GABA_ARs$ and upregulated gephyrin, in agreement with potentiation of inhibition[91]. These findings, in addition to those implicating I → E LTP in visual deprivation[41] (see above), suggest that accumulation of $GABA_ARs$ in L4 PCs following monocular deprivation results from I → E LTP at inhibitory connections from SST$^+$ and/or PV$^+$ INs.

In an interesting twist compared with the finding that L5 PC firing induces I → E LTP at PV$^+$ IN inputs[48] (see above), increased prefrontal cortex L2/3 PC activity selectively potentiated inhibition from SST$^+$ INs, but not from PV$^+$ or VIP$^+$ INs[92]. This synapse type-specific I → E LTP required postsynaptic NMDAR activation as well as CaMKIIα signalling and relied on the postsynaptic insertion of β2-subunit-containing $GABA_ARs$. Unlike SST$^+$ INs that were potentiated with increased PC activity, PV$^+$ IN-mediated inhibition was potentiated only when NMDAR signalling was disrupted[92].

By contrast, another study showed that PV$^+$ IN-mediated GABA release in L3 of the prefrontal cortex was potentiated by presynaptic NMDARs[93]. These unconventional presynaptic NMDARs were once considered controversial, but the emerging consensus is that they exist at many synapse types[94–96]. However, some synapse types do not have presynaptic NMDARs (for instance, visual cortex L5 PC → BC connections[97]).

Calcium-permeable AMPA receptors. Because they require presynaptic and postsynaptic activity, postsynaptic NMDARs implement the equivalent of a logical 'AND' gate[98]. In a similar vein, owing to their polyamine-mediated inward rectification[20,99], postsynaptic calcium-permeable AMPA receptors (CP-AMPARs) achieve a logical 'AND-NOT' gate[98] because they are maximally opened when bound by presynaptically released glutamate but not depolarized by postsynaptic activity. As CP-AMPARs are ideal detectors of presynaptic spiking combined with no postsynaptic spiking (AND-NOT gating), they seem perfectly suited for triggering anti-Hebbian calcium-dependent plasticity[20,99]. Consistent with this, a series of studies found that TBS combined with postsynaptic hyperpolarization induced CP-AMPAR-dependent E → I LTP at excitatory inputs to distinct CA1 hippocampal IN types – including oriens-lacunosum moleculare cells, bistratified cells, BCs and ivy cells – whereas TBS combined with postsynaptic spiking did not[20,99–101].

Similarly, low-intensity TBS of excitatory inputs onto hippocampal BCs and bistratified cells elicited CP-AMPAR-dependent E → I LTP, whereas high-intensity TBS resulted in E → I LTD[102]. Surprisingly, CP-AMPARs were better recruited by high-intensity rather than low-intensity TBS[102]. The increased CP-AMPAR-mediated calcium influx triggered release from internal calcium stores, resulting in local dendritic calcium supralinearities and E → I LTD instead of E → I LTP[102].

Importantly, E → I LTP was not elicited at Schaffer collateral inputs to cholecystokinin INs, which lack CP-AMPARs[99]. This finding reaffirms the view that CP-AMPARs are key determinants of IN plasticity. Furthermore, this exemplifies synapse type-specific plasticity in the hippocampus[24,54,103,104], as synapses formed by the same axon had distinct long-term plasticity depending on the target cell type. In addition, these findings in the hippocampus are likely to generalize to neocortex, where CP-AMPARs are also synapse type-specifically expressed[105,106].

mGlu receptors. The mGlu receptors (mGluRs) have consistently been implicated in IN plasticity. For example, E → I LTP at excitatory inputs onto CA1 SST^+ INs has a well-established need for mGluR1 signalling[107–109]. However, mGluR5 but not mGluR1 signalling was required for TBS-induced E → I LTP at L2/3 visual cortex PC → BC synapses[63]. As it has been shown previously that mGluR1 and mGluR5 are localized to different dendritic microdomains[110], it is possible that the distinct E → I synapse types in the hippocampus and neocortex have differential requirements for mGluR-mediated E → I LTP. Interestingly, mGluRs have also been implicated in E → I LTD at excitatory connections to fast-spiking INs in L2/3 somatosensory cortex and in CA1 (refs. 51,102). Unlike E → E LTD, mGluR1-mediated E → I plasticity might not require endocannabinoid signalling (see below), but does require phospholipase C activation and inositol-1,4,5-triphosphate-mediated Ca^{2+} elevation instead[51].

Cholinergic receptors. It is has been long known that acetylcholine plays a crucial role in learning and memory[111,112]. Indeed, studies have implicated cholinergic activation in disinhibitory plasticity and learning[71,72], perhaps as a third factor (Box 3). Muscarinic acetylcholine receptor (mAChR) activation also abolished disinhibition-mediated I → E LTP[113]. However, contextual fear learning strengthened hippocampal inhibition through nicotinic acetylcholine receptor (nAChR) but not mAChR activation[114]. Other studies have reported apparently conflicting results between the role of nAChRs and mAChRs in IN plasticity[115,116], highlighting a need for further research.

Endocannabinoid signalling. Retrograde signalling plays an important role in IN plasticity. Endocannabinoids, a group of lipophilic molecules that bind the CB1 and CB2 cannabinoid receptors, are among the best studied retrograde signalling molecules[117]. Endocannabinoid signalling underlies plasticity in many brain regions[117–120], in particular I → E LTD[36,117]. For example, heterosynaptic I → E plasticity (Box 2) in CA1 relied on retrograde endocannabinoid signalling elicited by postsynaptic mGluR5 activation[121]. Activated presynaptic CB1 receptors then downregulated GABA release, leading to I → E LTD. Similarly, other studies found endocannabinoid-mediated I → E LTD in visual cortex[122,123].

INs and homeostatic plasticity

Activity needs to propagate through neuronal networks of the brain without dying out or growing uncontrollably, which requires finely tuned E/I balance[124,125]. Neuronal activity should also remain within reasonable bounds, that is within a target firing zone in which a neuron can respond dynamically to its inputs[125]. Thus, neurons and circuits require a stabilizing principle, which is known as homeostatic plasticity. This form of plasticity provides negative feedback on a timescale of 12–48 h, thereby acting similarly to a thermostat for neuronal activity.

There are many mechanisms that work in concert to stabilize neuronal circuits[14,15], such as short-term plasticity[126], heterosynaptic E → E LTD[127] and intrinsic plasticity[128] (see below), but synaptic scaling was the first form of homeostatic plasticity described in mammals. In an in vitro preparation, mouse visual cortex PCs recovered from firing rate perturbations on a timescale of many hours by scaling the strength of all their glutamatergic inputs up or down[129]. Importantly, these changes in synaptic strength occurred in a multiplicative manner across all excitatory inputs of a neuron, therefore keeping stored information intact by preserving the relative differences in synaptic strength among inputs[129]. Thus, neurons can maintain reasonable activity levels without losing the information stored in their differentially weighted synaptic inputs.

Excitatory and inhibitory synapses should contribute to homeostasis in different ways. For example, to maintain homeostasis, decreased activity should presumably be met with increased excitation and decreased inhibition. In the study that first described synaptic scaling, suppressing network activity with tetrodotoxin (TTX) increased the miniature excitatory postsynaptic current amplitude in excitatory neurons by way of synaptic scaling, whereas the miniature excitatory postsynaptic current amplitude in inhibitory INs was unaffected[129]. In another study using the same paradigm, the miniature inhibitory postsynaptic current amplitude and frequency in PCs were reduced, mediated by decreases in postsynaptic $GABA_AR$ numbers as well as decreased presynaptic GABA release[130]. Furthermore, ~50% of synapses no longer expressed detectable levels of $GABA_ARs$, thus reducing the number of functional GABAergic synapses and contributing to the decreased miniature inhibitory postsynaptic current frequency observed. In addition, inhibitory synaptic scaling occurred proportionally across all inhibitory synapses of the recorded neurons, just as with synaptic scaling of excitatory connections[130].

Interestingly, in contrast to the in vitro findings[130], TTX blockade led to increases in miniature inhibitory postsynaptic current amplitude and frequency in CA1 in vivo[131]. This discrepancy highlights that additional complexities of synaptic scaling might be found in the intact brain.

With this caveat in mind, brain-derived neurotrophic factor (BDNF) — which is released by PCs in an activity-dependent manner[132] — mediates synaptic scaling in cultured INs by increasing the quantal amplitude of excitatory inputs[133]. This suggests a model of BDNF-mediated homeostatic regulation whereby increased activity in PCs leads to increased BDNF release from PCs, which in turn scales up excitation in INs. Interestingly, BDNF also reduces quantal amplitude in PCs, but this occurs at a lower BDNF concentration than that required to increase quantal amplitude in INs[133]. This points to the unique role of INs in stabilizing network excitation without compromising PC → PC synaptic transmission during periods of high activity.

Critical period visual deprivation has been a key tool to study homeostatic plasticity in vivo. Eyelid suture causes an initial decrease in inhibitory activity that rebounds to pre-deprivation levels the next day, which precedes a similar biphasic modulation in excitatory neuron activity[134]. Rapid structural changes such as spine loss and IN dendritic branch retraction[135–138] also contribute to activity regulation. GABAergic bouton loss further decreases inhibition[135,136]. This structural loss of inhibition could, via LTP, help reorganize excitatory circuits following visual deprivation[136]. Thus, IN plasticity does more than maintain homeostasis during visual deprivation, it also helps restructure local networks.

In summary, homeostatic plasticity in the intact brain is more complex than homeostatic plasticity in vitro. Although INs clearly have a role in vivo, their contribution extends beyond maintaining homeostasis to other functions such as re-routing circuits.

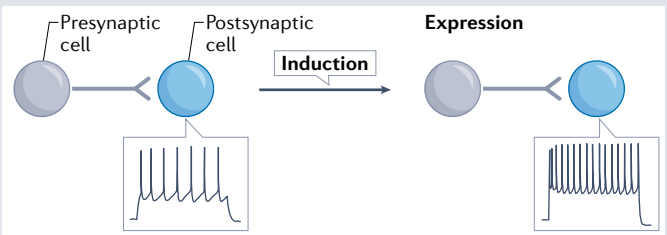
Intrinsic plasticity of INs

There is accumulating evidence that, in addition to synaptic plasticity, information storage in neural circuits also involves the modulation of neuronal intrinsic excitability[139]. Plasticity of intrinsic excitability (Box 4) — also known as intrinsic plasticity — typically involves the sustained modification of a neuron's intrinsic electrical properties by either neuronal or synaptic activity[140–142]. Intrinsic plasticity is typically mediated by changes in voltage-gated ion channels in the membrane, which can affect both passive and active membrane properties[139,141,142].

Box 4

Plasticity of intrinsic excitability

In addition to altering synapses, plasticity can change a cell's intrinsic biophysical properties. As with synaptic plasticity, the outcome can be bidirectional, as the excitability of a cell may be upregulated (depicted in the figure) or downregulated. This plasticity of intrinsic excitability — or intrinsic plasticity for short — has been studied extensively in excitatory neurons[14,15,139,172]. In fact, the first long-lasting potentiation study also reported increased postsynaptic excitability in addition to synaptic strengthening, a concept known as excitatory postsynaptic potential (EPSP)-spike potentiation[172,174,175]. Indeed, intrinsic plasticity can often be elicited in parallel with synaptic plasticity[173–175,255], but intrinsic plasticity can also be triggered in its absence[256]. Furthermore, intrinsic plasticity can work together with Hebbian plasticity and provide positive feedback to promote cellular learning[173,175,256], but it can also support homeostasis via negative feedback[140]. In addition, intrinsic plasticity can operate in a cell-wide manner[255,256] or can be spatially limited to a subset of dendritic compartments[174,257]. As intrinsic plasticity affects all inputs (or at least a large group of them), it results in a loss of input specificity and information storage density (concepts described in Box 2). Mechanistically, intrinsic plasticity is typically implemented by changes in ion channel densities[14,15,139,172], but increased activity can physically move the spike initiation zone farther from the soma to downregulate neuronal excitability in at least some circumstances[258]. In summary, there is a considerable diversity of intrinsic plasticity rules, but intrinsic plasticity has been relatively poorly studied in interneurons (INs).



In vitro models

Intrinsic IN plasticity is readily elicited in vitro, which provides excellent experimental control. For example, in hippocampal slices, dentate gyrus INs were persistently depolarized by ~8 mV after perforant-path tetanization, which increased dentate gyrus IN excitability[143]. However, the membrane potential of granule cells was unaffected[143], thereby demonstrating target specificity in the synaptically induced intrinsic plasticity[24,103]. By contrast, hippocampal mossy fibre stimulation at 30 Hz decreased dentate gyrus PV^+ IN excitability[144]. This effect was similarly target specific as it was not observed in granule cells. A computational approach later demonstrated that this PV^+ IN intrinsic plasticity affects the coherence and frequency of network firing in silico[145].

In CA1, Schaffer collateral high-frequency stimulation enhanced feedforward inhibition by persistently increasing PV^+ IN intrinsic excitability[146]. As found for dentate gyrus INs[143,144], this synaptically induced intrinsic plasticity was target-specific as it could not be observed in stratum pyramidale INs[146]. However, this CA1 PV^+ IN intrinsic plasticity was not due to depolarized membrane potential but, rather, due to reduced action potential threshold[146]. Together, these in vitro studies show that IN intrinsic plasticity generally is specific to cell type, similar to how synaptic plasticity is specific to synapse type[24]. In vitro models also lend themselves nicely for mechanistic studies of intrinsic plasticity.

Compared with plasticity studies in animals, human plasticity has been relatively poorly explored[147]. For this reason, a study explored activity-dependent tuning of intrinsic excitability in hippocampal and neocortical L1 circuits in mice and humans[148]. It revealed that neurogliaform cells — a prominent type of GABAergic IN — underwent persistent barrage firing[149] mediated by Kv4 K^+ channels[148] in both mice and humans. Because this intrinsic excitability mechanism is paralleled in rodent and human cortex, this study demonstrated an evolutionarily conserved process that might be critical for proper brain functioning[148].

In addition to activity enhancement, suppressing activity also elicits intrinsic plasticity. For example, 2-day activity blockade with the fast sodium channel blocker TTX increased the intrinsic excitability of cortical PCs in vitro[140,150]. Subsequent exploration of whether these changes depended on neuronal identity revealed that the intrinsic excitability of cultured bipolar GABAergic INs also increased in response to activity blockade[151]. This IN intrinsic plasticity was achieved by modification of voltage-dependent conductance, as reflected by a reduction of the rheobase current required to reach action potential threshold. Interestingly, IN intrinsic plasticity was prevented if BDNF was added during TTX blockade[151]. Similar experience-dependent forms of IN intrinsic plasticity have since been found in somatosensory[123,152–156], motor[157], prefrontal[158] and auditory[159] cortices, suggesting that intrinsic plasticity is broadly used in cortical circuits to achieve activity homeostasis.

In somatosensory cortex organotypic slices, TTX blockade increased the excitability of L2/3 SST^+ INs[123] (Fig. 3a), similar to earlier findings in cell-cultured bipolar GABAergic INs[151]. Downregulation of the passive leak current as well as of the sag current, which increased input resistance while preserving resting membrane potential, mediated this intrinsic plasticity in the L2/3 SST^+ INs[123]. TTX blockade also increased intrinsic excitability of somatosensory cortex L2/3 PV^+ INs via a decreased action potential threshold[153]. Surprisingly, both excitatory and inhibitory cortical neurons might increase their excitability in response to activity deprivation, which is not really in keeping with a homeostatic role[160], as IN output is negative. Thus, increased IN excitability in response to activity blockade by TTX could be considered non-homeostatic and a form of positive feedback, as it translates to increased inhibition in response to decreased activity[123].

However, TTX blockade could be an unrealistic tool for activity manipulation as spiking is abolished rather than just reduced. In contrast to these earlier findings that relied on pharmacological blockade[123,150,153], studies of intrinsic plasticity in cortical inhibitory INs that did not abolish activity completely but, rather, decreased activity in a graded, naturalistic manner by sensory deprivation revealed that this reduced IN excitability[152,154,156,157,159]. Thus, this form of disinhibitory intrinsic plasticity could homeostatically stabilize sensory circuits during ongoing changes in sensory experience[156], as discussed next.

In vivo models

PV^+ INs have often been targeted in studies of experience-dependent intrinsic plasticity. For example, in juvenile mouse barrel cortex, 3-week sensory deprivation by whisker trimming reduces PV^+ IN excitability[152,154]. Interestingly, subsequent work found that just 24 h of whisker-map sensory deprivation reduced PV^+ IN excitability by increasing the

spike threshold (Fig. 3b), while leaving excitatory and inhibitory synaptic input unaffected[156]. Thus, natural variation in sensory experience could rapidly adjust feedforward inhibition via PV$^+$ IN intrinsic plasticity[156].

In a related study of motor cortex PV$^+$ IN firing properties, 48 h of activity deprivation in vivo reduced inhibitory output measured in vitro[157]. In activity-deprived motor cortex, PV$^+$ INs had lower maximum firing rates with a surprisingly atypical adapting firing pattern and broad action potentials[157]. Because the characteristic fast non-accommodating narrow spiking pattern of cortical BCs develops in the first four postnatal weeks[161–163], it is possible that in the absence of appropriate activity, these motor cortex PV$^+$ INs might have been left in an underdeveloped state[157]. The reduced PV$^+$ IN excitability could also be a homeostatic compensation to counteract the lack of activity in vivo, reduced L2/3 PV$^+$ IN excitability was found compared with sham controls[156]. Thus, sensory deprivation reduced PV$^+$ IN-mediated inhibition in an apparently homeostatic manner, because this helped to stabilize barrel cortex PCs via disinhibition. It is unclear why these two studies[123,156] show opposing forms of intrinsic plasticity, but candidate explanations include differences in SST$^+$ INs versus PV$^+$ INs, activity blockade versus activity reduction, in vitro versus in vivo or developmental stage. Symbols show mean ± s.e.m. PV, parvalbumin; SST, somatostatin. Panel **a** adapted with permission from ref. 123, APS. Panel **b** adapted from ref. 156, CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

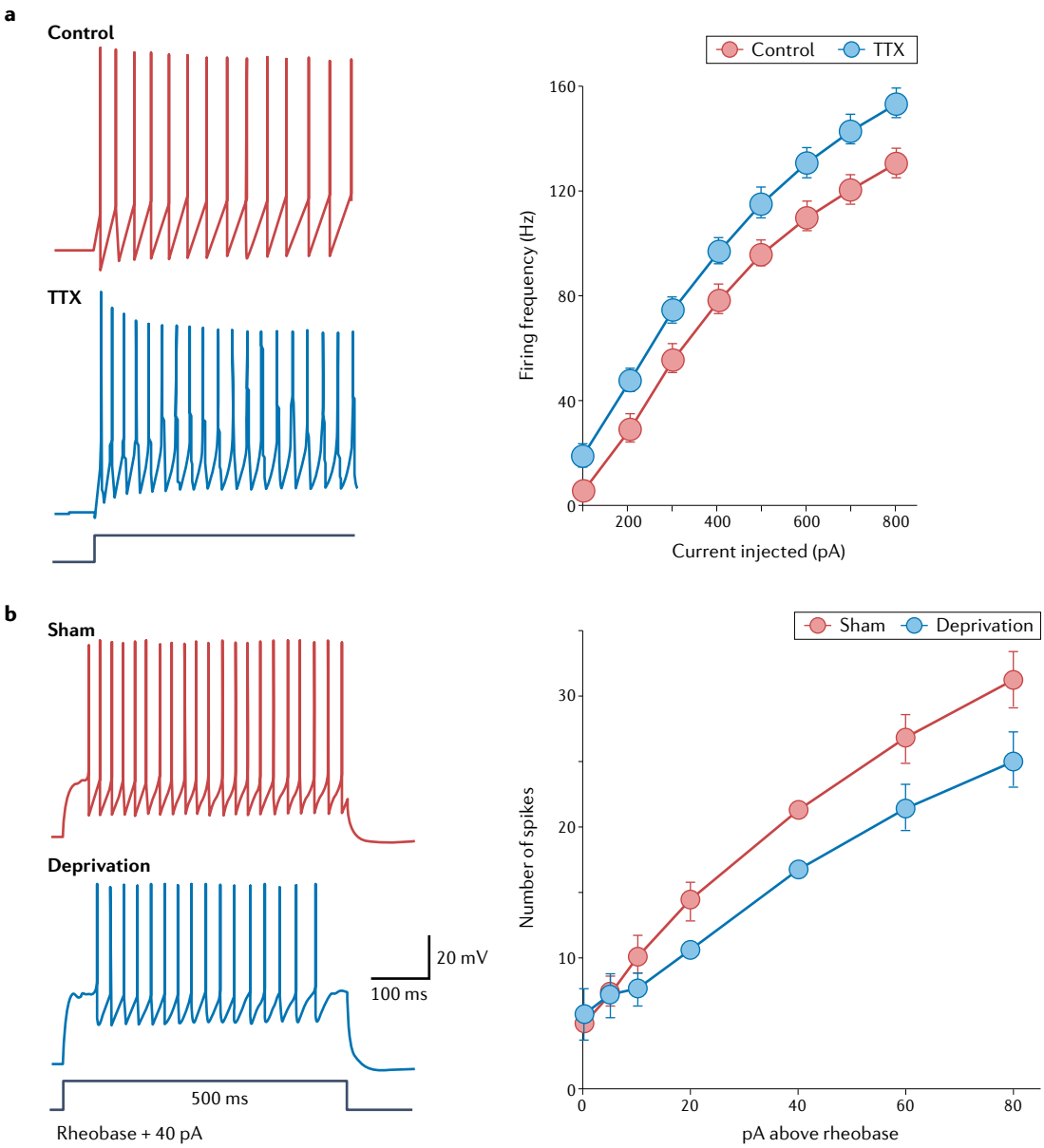


Fig. 3 | Opposing forms of IN intrinsic plasticity. Intrinsic plasticity denotes changes in the excitability of a neuron depending on overall activity levels. Surprisingly, similar activity manipulations can increase or decrease interneuron (IN) excitability[123,156]. **a**, In somatosensory cortex organotypic slice, blocking spiking activity in vitro for 2.5 days with tetrodotoxin (TTX) revealed higher layer 2/3 (L2/3) SST$^+$ IN excitability compared with controls[123]. Thus, completely abolishing activity with TTX increased SST$^+$ IN-mediated inhibition in a seemingly non-homeostatic manner, because this increase further inhibited already inactive pyramidal cells (PCs). **b**, Using 24-h whisker deprivation to reduce barrel cortex

Glossary

Anti-Hebbian
A rule that disobeys Hebb's postulate, such as synaptic strengthening resulting from asynchronous firing in connected cells or, conversely, coincident firing eliciting synaptic weakening.

Coincidence detection
A process by which a neuron or a neuronal circuit can detect the occurrence of temporally close but spatially distributed input signals to form associations between distinct events.

Disinhibition
Reduction of inhibitory drive onto an excitatory neuron.

E→I plasticity
Plasticity at synapses from excitatory to inhibitory cells.

E/I balance
The relative contributions of excitatory and inhibitory synaptic input to an individual neuron or in a local circuit.

Excitatory postsynaptic potential (EPSP)-spike potentiation
The ability of long-term potentiation (LTP) to additionally increase the potentiated input's capacity to drive postsynaptic spiking by altering postsynaptic excitability.

Expression of plasticity
The mechanisms that alter the strength of a synaptic connection, such as the addition or removal of neurotransmitter receptor channels postsynaptically, or changes of release probability presynaptically.

Homeostatic plasticity
The capacity of neurons to regulate their own excitability and synaptic drive slowly over many hours in the face of changes in network structure and activity.

I→E plasticity
Plasticity at synapses from inhibitory to excitatory cells, which has often been called inhibitory long-term potentiation (LTP) or inhibitory long-term depression (LTD).

Induction of plasticity
The processes that trigger the expression of long-term plasticity; typically a repeated activity pattern, but could also be chemical or pharmacological.

Miniature excitatory postsynaptic current
A depolarizing current elicited by excitatory neurotransmitters such as glutamate that promotes spiking in the postsynaptic neuron.

Miniature inhibitory postsynaptic current
A hyperpolarizing current elicited by inhibitory neurotransmitters such as GABA that reduces spiking in the postsynaptic neuron.

Negative feedback
A mechanism that acts similar to a thermostat to keep a parameter such as temperature or activity within reasonable bounds by reducing it if too high and increasing it if too low.

Positive feedback
A mechanism that achieves run-away regenerative events, such as voltage-dependent sodium channels driving action potential rise; the more they depolarize, the more they open and promote further depolarization.

Quantal amplitude
The release of one synaptic vesicle containing a stereotyped amount of neurotransmitter — a quantum — elicits a postsynaptic response of one quantal amplitude.

Reversal potential
The membrane potential at which an ion channel current reverses its sign.

Rheobase
The minimal current amplitude needed to be injected into a cell to elicit an action potential. It is a measure of membrane potential excitability.

Synapse type-specific plasticity
The activity requirements that determine plasticity depend on the synapse type, which in turn is related to the presynaptic and the postsynaptic cell types.

Theta burst stimulation
(TBS). Short bursts of stimulation at high frequency, typically 100 Hz, with the bursts themselves applied at 5–8 Hz, to mimic hippocampal theta rhythm and to achieve pre-priming disinhibition, which yields more long-term potentiation (LTP) while improving biological realism.

activity in the network. Regardless, PV^+ IN intrinsic plasticity[152,154,156,157] should profoundly impact cortical critical period plasticity[5] because activity determines the maturation of perisomatic BC-mediated inhibition[164].

Similarly, a diminished discharge rate of PV^+ INs in supragranular auditory cortex occurs in the gerbil developmental conductive hearing loss model[159,165]. Here, decreased PV^+ IN activity was also associated with increased spike adaptation although the action potential half-width was unaffected[159].

Taken together, these findings support the principle that diverse forms of activity suppression in vivo — including tactile or sensory[152,154,156], motor[157] and auditory[159] deprivation — homeostatically downregulate PV^+ IN intrinsic excitability. However, further research is necessary to reveal whether this principle applies to all IN types, because there are apparent disagreements in the literature (for instance, see refs. 123,156). Candidate explanations for these observed differences in intrinsic plasticity include IN type specificity, mode and duration of activity manipulation, developmental stage and experimental paradigm[123,156] (Fig. 3).

Mechanisms of intrinsic plasticity

Mouse barrel cortex L2/3 PV^+ INs express the delayed rectifier Kv1.1 voltage-gated K^+ channel at the axon initial segment, a location that enables Kv1.1 to strongly influence PV^+ IN excitability by regulating the action potential threshold[166]. PV^+ INs derive from the medial ganglionic eminence[167], where the transcription factor Er81 is prominently expressed[168]. Interestingly, Er81 can regulate PV^+ IN intrinsic excitability by controlling Kv1.1 expression[155]. Increased network activity downregulated Er81 expression to lower the action potential threshold and increase excitability. Conversely, decreased network activity upregulated Er81 expression, which raised the action potential threshold and decreased excitability. The bidirectional Er81–Kv1.1 regulatory pathway[155] suggests mechanistic underpinnings for the findings discussed above that whisker trimming reduces PV^+ IN excitability[156]

and Schaffer collateral tetanization upregulates PV$^+$ IN intrinsic excitability[146].

Neuregulin 1 (NRG1) is a neurotrophic factor that acts via the ErB family of tyrosine kinases, including ErbB4. Endogenous ErbB4 expression is enriched in PV$^+$ INs but expressed in only a fraction of PCs and other IN types[169,170]. Similar to Er81, the NRG1–ErbB4 path directly regulates the excitability of PV$^+$ INs by modulating the action potential threshold through Kv1.1 channel regulation[171]. NRG1–ErbB4 signalling can also act bidirectionally, as exogenous NRG1 lowered the action potential threshold whereas specific deletion of ErbB4 reduced the intrinsic excitability of PV$^+$ INs, leading to increased seizure susceptibility[171]. In addition to Kv1.1-delayed rectifier K^+ channels, A-type K^+ channels have also been implicated in PV$^+$ IN intrinsic plasticity by spike threshold modulation[154,156].

These Kv1.1 channels exert profound control of the action potential threshold by virtue of their specific localization at the axon initial segment. This implies a lack of input specificity (Box 2), as Kv1.1-mediated intrinsic plasticity affects a cell's propensity for spiking output[146] (Box 4). However, the intriguing possibility exists that the dendritic structure of INs can allow localized changes in intrinsic excitability — alterations in the density and properties of ion channels could be constrained to a subset of dendritic compartments[14,15]. For example, excitatory postsynaptic potential (EPSP)-spike potentiation in CA1 PCs[172] can be enhanced or reduced by modifying channel expression to alter input–output function following the induction of synaptic plasticity[173–175]. However, it remains unclear to what extent local activity-dependent changes in dendritic excitability occur in the diverse inhibitory IN subtypes. Still, intrinsic plasticity can never confer the same degree of input specificity as synaptic plasticity (Box 2). This implies that the information storage capacity due to intrinsic plasticity must be considerably smaller than that of synaptic plasticity[172]. However, the contribution of IN intrinsic plasticity to learning and memory is not negligible, as both non-synaptic and synaptic modifications might contribute[160,176]. More research is needed to clarify how synaptic and intrinsic forms of plasticity interact to achieve learning while maintaining balanced activity in cortical circuits.

Conclusions

In this Review, a central observation is that there is a massive diversity of IN plasticity learning rules that have varied roles in key aspects of brain function. For example, IN plasticity in development can stabilize synapses but can also render circuits more malleable. However, a seemingly constant emerging principle is that IN plasticity serves to maintain the E/I balance in the healthy brain, which can explain aberrant circuit rewiring and performance after pathological activity. We also explored how disinhibition is associated with wakefulness and learning. Finally, INs have a clear role in activity homeostasis, but IN plasticity extends beyond this essential function to help facilitate other key processes, such as re-routing circuits.

Plasticity is specific to cell[34,103,118] and synapse[24] type, leading to a large multiplicity of plasticity learning rules (Fig. 4). Therefore, it is not enough to solely map E → E plasticity, because it does not act in isolation, but in concert with E → I, I → E and I → I plasticity. To understand how brain circuits rewire in healthy development[4–6] as well as in pathological scenarios such as epilepsy[21–23] or amblyopia[177], we need a relatively complete database of plasticity learning rules across synapse types, cell types and brain regions. Although there are also different excitatory neuron types, this effort will require specific attention to the many IN types[26]. A relatively complete plasticity database is a plasticitome[25] (Fig. 4).

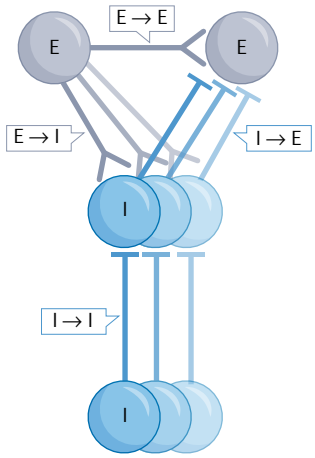


Fig. 4 | The plasticitome. To elucidate how neuronal circuits learn and store information, a comprehensive collection of plasticity learning rules — the plasticitome — is required. This is because the functional effects of synaptic plasticity at excitatory and inhibitory connections between excitatory and inhibitory cell types are distinct. For instance, excitatory to excitatory cell (E → E) plasticity supports Hebbian learning, excitatory to inhibitory (E → I) plasticity alters inhibitory drive, I → E plasticity modifies the brakes on activity and I → I plasticity gates learning. Furthermore, phenomenology and mechanisms differ dramatically across cell and synapse types[24] (shades of blue/grey). Classically, long-term potentiation (LTP) and long-term depression (LTD) have been studied at E → E connections, presumably because Hebb[8,11] postulated that memories are stored when assemblies of neurons are bound together by strengthening E → E synapses. Plasticity at E → I and I → E synapses has been less well explored, yet these connections also impact information storage[18,41,82,83]. Disinhibitory I → I synapses might gate learning in local circuits, yet there is a paucity of information on I → I plasticity[67,79]. Although interneuron (IN) plasticity is relatively poorly studied, it is well established that IN plasticity influences E → E plasticity[18,41,67,79,82,83,182]. Finally, Hebbian E → E plasticity[8,11] and spike timing-dependent plasticity (STDP)[3,42,43] are local two-factor learning rules that cannot easily account for overall circuit performance (Box 3), which would instead require that network errors be fed back to modify individual synapses accordingly[204–206,208], a process IN plasticity might be able to facilitate. Thus, to understand information storage and computations in neuronal circuits, it makes poor sense to focus experiments on E → E plasticity at the expense of E → I, I → E and I → I plasticity. Consequently, establishing the plasticitome[25] is a key next step in plasticity research. For clarity, intrinsic plasticity, homeostasis, autapses, different excitatory cell types and neuromodulation are not illustrated, but are also important.

The plasticitome will, for each synapse type[24], require detailed description of long-term plasticity phenomenology such as its dependence on factors such as rate, timing[178] (Box 1), depolarization[61], homosynaptic or heterosynaptic location (Box 2) and neuromodulation[179] (Box 3), including intrinsic plasticity (Box 4). In addition, key mechanistic underpinnings will help to classify plasticity learning rules into categories depending on the need for NMDARs[14,15,88], CP-AMPARs[20,98,99], mGluRs[107–109], endocannabinoids[117–119] or other factors, much as genetic markers such as PV, SST and VIP help to classify INs[21–23,34]. The presynaptic versus postsynaptic locus of plasticity expression will also aid in categorizing plasticity learning rules and has computational implications, because presynaptic expression and postsynaptic expression affect information processing differently[54,55]. Furthermore, phenomenology and mechanism often change with development so will need to be accounted for; for example, the need for presynaptic NMDAR

signalling in visual cortex E → E LTD disappears at the end of the critical period[94,95,180,181].

As we work towards elucidating the IN plasticitome, we must consider what all these different forms of IN plasticity are good for. In the traditional Hebbian view on learning and memory[8], E → E LTP serves to bind excitatory neurons into an assembly that together code for a percept[11], hence the notion that cells that fire together wire together[9,10]. Although Stent subsequently argued that inhibitory synapses play no less important a role in Hebbian learning than excitatory connections[182], inhibition was not needed in Hebb's original framework[8,11,182]. Whereas immature GABAergic neurotransmission is typically depolarizing[183] and may drive circuit-sculpting activity in early development[184–186], GABA is generally hyperpolarizing in mature circuits (but see refs. 187,188). Therefore, IN plasticity must be understood in the context of excitatory neuron plasticity, as the former impacts the latter[189]. As a simple illustration, any impact of I → I plasticity in a I → I → E disinhibitory motif is contingent on excitatory drive of the intermediate IN[67,68,79] and, consequently, on its E → I plasticity. We must therefore take a circuit-level rather than synapse-centric view to understand the diversity of IN learning rules[189] (Fig. 4).

For instance, taking a circuit-level view, distinct plasticity learning rules operating at different connection types[24] together could solve the credit assignment problem[190] in the brain, which consists of deep multilayered biological neuronal networks[191,192]. In the credit assignment problem, a multilayered neural network has an output error that must be corrected to achieve a specific outcome[190], for example to convert letters to spoken phonemes[193] or to recognize handwritten digits[194]. To minimize the error, individual synapses across different network layers are tweaked up or down during learning to improve overall network performance, with these individual tweaks constituting the assignment of credit.

In the artificial neural network community, the credit assignment problem is typically solved using the error backpropagation algorithm[195], by which network output error travels backwards across layers to adjust individual synaptic connections, thereby assigning credit to each connection. As real biological brains are also many layers deep, they too presumably need to accurately tweak synapses in different layers during learning, and so they are also likely to be faced with the credit assignment problem[25]. Although two or three-factor plasticity rules (Box 3) might be able to assign credit in specific scenarios[196–200], Hebbian plasticity and STDP might not generally do so, because these local two-factor rules do not consider global network output error. Yet for decades, the dogma has been that biological neural networks cannot implement error backpropagation[201–203]. Crick[201], for example, argued that biological synapses cannot signal backwards.

Theoretical work[204–206] has generated an exciting counterargument to Crick: let feedback pathways contribute the error signal. These models typically combine excitation and inhibition to approximate the backpropagation algorithm, as controlled by certain forms of IN plasticity[191,192,207,208]. Therefore, these models can make specific predictions about the plasticity that is required at different synapse types. Experimental studies showing how INs gate local plasticity and learning[209–212] lend support to this idea. However, the specific mechanistic details of credit assignment in deep biological networks remain unclear. Thus, the plasticitome is needed to test specific credit-assignment model predictions.

In this Review, we have focused on long-term plasticity. However, short-term plasticity also depends on synapse type[54]. For example, PC → MC connections short-term facilitate, but PC → BC synapses short-term depress[213]. A neocortical short-term plasticitome has been published[214], which will be crucial for understanding processes such as computations and information flow in local cortical circuits. However, all forms of plasticity together — including short-term, long-term, homosynaptic, heterosynaptic, intrinsic and homeostatic plasticity — are simultaneously needed to achieve functional goals such as memory formation and retrieval in the brain[57]. Thus, the long-term plasticitome is a key next challenge (Fig. 4).

Unfortunately, long-term plasticity experiments are slow and painstaking. Therefore, an important future direction in IN plasticity research is the development of novel methods by which long-term plasticity of many dozens of inputs can be monitored in parallel, for a much higher throughput[25]. Elucidating the plasticitome will probably require a combination of different techniques, such as patch robots[215,216], electrode arrays[45], multiple simultaneous patch clamp recording[217–219] and optogenetics[220,221].

Finally, primary research on IN plasticity is needed to understand and treat neuropathologies such as epilepsy, a devastating disease in which hyperexcitability leads to seizures in the brain. We might be able to harness IN plasticity in novel treatments to control the hyperexcitation that causes epileptic seizures[70,222,223]. IN dysfunction has also been implicated in other complex pathologies such as autism[224–227] and schizophrenia[224,228–230]. In other words, there is a dire need to understand the diversity of IN plasticity to pave the way for novel therapies to treat major neuropathology. In conclusion, the plasticity of inhibition is currently particularly exciting.

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Competing interests
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Additional information

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