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Review

Circuit mechanisms for cortical plasticity and learning

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ABSTRACT

The cerebral cortex integrates sensory information with emotional states and internal representations to produce coherent percepts, form associations, and execute voluntary actions. For the cortex to optimize perception, its neuronal network needs to dynamically retrieve and encode new information. Over the last few decades, research has started to provide insight into how the cortex serves these functions. Building on classical Hebbian plasticity models, the latest hypotheses hold that throughout experience and learning, streams of feedforward, feedback, and modulatory information operate in selective and coordinated manners to alter the strength of synapses and ultimately change the response properties of cortical neurons. Here, we describe cortical plasticity mechanisms that involve the concerted action of feedforward and long-range feedback input onto pyramidal neurons as well as the implication of local disinhibitory circuit motifs in this process.

1. Introduction

In his seminal work, Donald O. Hebb proposed that the brain's capacity to learn and memorize lies in the neuronal network's ability to change the strength of its synapses, which for each neuron is dependent on the concurrence of pre- and postsynaptic activity [1]. Even though Hebb's 'fire together, wire together'-plasticity rule has been well established, it may be insufficient for explaining how cortical neurons readily adjust the strength of their synapses in intricate processes that are necessary for improving an organism's behavioral performance. More specifically, changes in synaptic weights need to be continuously re-evaluated, not only for their ability to drive synchronous activity in neuronal pairs but ultimately for their efficiency in eliciting favorable behavioral activity. To serve these dynamic functions, the cortical architecture is endowed with feedback motifs that inform the feedforward modules about the outcome of their activity. The aim of this article is to provide an overview of the insights we have gained into circuit mechanisms of cortical plasticity and learning, and in particular how the feedforward and feedback signals interact to drive those changes.

2. Cortical function and plasticity

The neocortex consists of a vast recurrent network that is characterized by highly lateralized local connectivity in which distinct feedforward and feedback inputs from other brain areas are integrated. Glutamatergic excitatory cells account for 80% of the cortical neuron population. They are divided into multiple classes with a spatially uneven distribution, which brings about the cortex's characteristic layered and columnar architecture. Typically, granular layer (L) 4 and parts of pyramidal cell L5 receive bottom-up inputs from long-range connections (e.g. from thalamus), and in turn projects to the supra-granular L2/3. This stream of feedforward information is then distributed to other cortical areas as well as to sub-granular L5 and 6, which provide output to subcortical regions. GABAergic interneurons account for the remaining 20%. They form mostly local connections with principal cells or other interneurons. On top of the inter-laminar connectivity of principal cells, the intra-laminar connectivity of each cell class is also highly structured, with an overrepresentation of bidirectionally connected pairs of neurons [2,3]. As a consequence of this structured connectivity, each cortical area contains multiple interdigitated subnetworks of interconnected principal neurons that are often referred to as neuronal assemblies, which share similar response properties [4,5].

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At a larger scale, the cortex is organized in a hierarchical fashion [6]. Initially, the sensory information from a natural scene propagates to primary sensory areas, recruiting activity of neuronal assemblies that encode the lower-order sensory features of the scene. The activity continues to propagate in a feedforward manner to higher-order and associated cortical areas that encode more complex and contextual features. Activity finally reaches motor and executive centers to elicit a selected activity pattern that induces a specific action. At all stages in this processing stream, activity feeds back, in a top-down manner, either to update the lower-order network about the subsequent higher-order activity it elicited, or to inform the lower-order network about expected inputs [7–11]. These feedback signals may transiently modulate the response properties of lower-order neurons and tag synapses for plasticity that ultimately optimize the information stream needed for the execution of the desired action [12]. Depending on the outcome of the executed behavior (i.e. whether it was rewarding or penalizing), specific neuromodulators that relate to the state of the organism might be released in the cortex. They may strengthen or weaken the 'tagged' synapses, i.e. steering the plasticity that was gated through the feedback signals [13,14]. Several neuromodulators, such as dopamine, encode the so-termed reward prediction error (RPE), whereby the outcome of an action is evaluated as being better or worse than expected [15,16]. Thus, the combined action of feedback and RPE-related modulatory signals determines which synapses on a given neuron will undergo an update of their weight or strength [9,17]. Below, we will elaborate on the circuit mechanisms that may underlie feedback-mediated cortical plasticity.

2.1. The role of feedback

In a typical sensory-motor operation, as previously described, the top-down information stream from motor to sensory regions is important for the proper perception of the environment. During active sensing, top-down efference copies of a motor program are thought to play a role in updating sensory cortices about self-generated movements and cancel sensory activity that results from it [8]. For example, feedback activity from the motor cortex in mice reflecting whisker angles and movements [18–21] allows the primary somatosensory cortex (S1) to make the distinction between a static and a moving object, and hence help to form coherent whisker-related percepts [18,22,23]. Secondary sensory and associative cortical areas provide feedback to primary sensory cortices. For instance, feedback projections from the secondary visual cortex in humans were shown to play a role in context-mediated modulation of activity in the primary visual cortex (V1) [24]. The secondary somatosensory cortex in mice is known to send feedback information to S1 that relates to a behavioral decision [25] by comparing past to present experience [26].

Feedback signals do not exclusively originate from the cortex but can also be mediated by the thalamus [6,11]. The thalamus contains many sectors that are topographically organized along with the various motor and sensory modalities, of which the sensory regions are composed of two distinct sub-regions: a first-order nucleus that represents the principal relay of sensory information and a higher-order nucleus that relays information to higher-order cortical areas as well as feedback to lower-order sensory cortices. The higher-order thalamus might play a variety of roles in cortical processing [27–30]. This view is in part motivated by the observation that higher-order regions of the thalamus such as the visual lateral posterior nucleus (LP) and the somatosensory posteromedial nucleus (POm) are in turn subdivided into regions that have projections with distinct morphologies differentially targeting cortical areas and layers [31–34]. The role of the higher-order thalamus for cortical processing is still poorly understood, but a rapidly growing number of experimental efforts are starting to provide insights. For example, the activity of LP in mice has been shown to carry feedback signals to V1 that relate to mismatches between body movement and the visual flow [35]. Within the predictive coding framework, this finding indicates that the higher-order thalamus may provide a selective attention signal to incongruent information [36,37]. Another example comprises studies of POm-mediated feedback to sensory cortices, which have highlighted its modulatory role for sensory processing [28,38–40]. In this context, it is worth noting that POm activation drives persistent long-lasting depolarizations for up to one second in L2/3 pyramidal neurons [41,42]. These correlate well with the late depolarizations that have been shown to causally contribute to increased L2/3 pyramidal neuron firing, and to sensory perception [43]. Moreover, the elevated activity of POm during wakefulness, which is absent during anesthesia [44], is necessary for the coupling of feedforward and cortical feedback onto pyramidal neurons [45]. Higher-order feedback may therefore be paramount to consciousness and attention [45–47]. Together, these recent studies are starting to indicate that higher-order feedback circuits from the thalamus constitute important motifs for optimizing cortically-driven perceptual decision making [10,48].

2.2. Learning-associated plasticity of neuronal response properties

By modulating the activity of cortical neurons during learning, top-down information streams are thought to have the ability to promote plasticity and change how sensory information is encoded by neuronal assemblies. Pioneering work by Merzenich and colleagues showed that the cortical representation of a monkey's digit with which it learned to solve a frequency discrimination task, was significantly greater in size and complexity than the representation of the same digit on the non-trained hand [49]. This work demonstrated that sensory cortical representations can change in association with learning and that their size correlates with behavioral performance. The level by which neurons change their response properties is likely to reflect the amount of cognitive processing and/or motor skills that need to be employed to solve a particular behavioral task. Usually, tuning properties are not completely remodeled, but only altered in such a way that learning increases the contrast of the responses between the various stimuli that are detected during the task [50–53]. In the primary visual, auditory and, somatosensory cortices, neurons increase their selectivity for task-relevant stimuli [52,54–61]. Moreover, discrimination learning of closely related sensory inputs enhances the contrast of neuronal assemblies' activity (Fig. 1). This is illustrated in studies where mice used their whiskers to sense different textures and learned to associate one of them with a reward. By tracking the activity of primary somatosensory neurons using longitudinal imaging of calcium signals, these studies revealed that the improvement in behavioral performance is closely associated with an overall increase in neuronal selectivity of task-relevant stimuli [52,62]. Similar selectivity tuning has been observed in V1 of mice and monkeys in which neurons start to discretely encode objects with nearly similar orientations during visual discrimination learning [55,59,61,63,64].

In primary sensory cortices, neuronal selectivity may not be solely bound to lower-order stimulus features. This was demonstrated by experiments in which mice that had learned a whisker-based texture discrimination task were confronted with a reversal of the reward contingencies. This caused dramatic changes in the selectivity of a large fraction of L2/3 pyramidal neurons in the barrel cortex [52,65]. Interestingly, most of the selectivity that emerged in one group of neurons during the initial texture discrimination learning period was lost upon reversal learning, while selectivity emerged in yet another group of neurons. In addition, among the neurons that exhibited selectivity in both the initial and the reversal learning phases, some encoded the behavioral choice or the value associated with the stimulus. These results demonstrate that profound cortical remapping may occur as the result of a simple change in the relevance of a stimulus. This implies that the information encoded in primary sensory areas is very diverse and that incoming information can reach a high level of integration even at the early stages of cortical processing. It remains to be determined how the encoding of higher-order stimulus features (e.g. the reward value) in the early stages of cortical processing contributes to the animal's

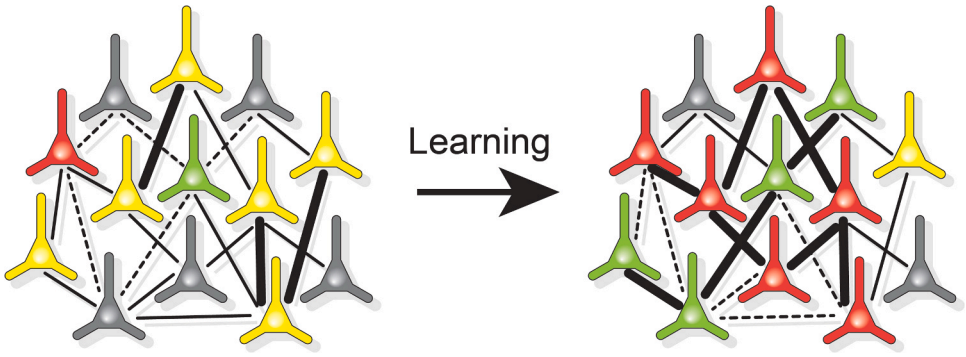

Fig. 1. Learning correlates with the reshaping of cortical representations. Two closely related stimuli may exhibit cortical representations that are largely overlapping (Left, only a few neurons are selective for one or the other stimulus [red and green neurons] whereas a large fraction of neurons respond equally to both stimuli [yellow neurons]). Changing the behavioral relevance of one of these stimuli improves the discretization of the cortical representations during learning (Right, after discrimination learning, more neurons are selective for one or the other stimulus). Lines indicate the strength of the synaptic connections between pairs of neurons, and changes thereof may be driven by learning. These plasticity mechanisms are thought to underlie the learning-mediated changes in cortical representations (figure design inspired by [5]).

behavior.

Changes in response properties do not only affect the early stages of processing such as primary sensory cortices but can also alter the tuning properties of higher-order cortical neurons [66–68]. During fear conditioning, neurons of the medial prefrontal cortex integrating sensory and emotional signals, change their response properties to form fear memory traces [69]. In another study, learning of a motion discrimination task in monkeys induced minimal changes in the motion-evoked responses in the middle temporal area, which encodes the location and direction of moving objects, whereas neurons in the lateral intraparietal area, which is important for decision-making, increase their response during learning [70].

Altogether, this large body of work suggests that learning stabilizes the population of neurons that represent task-specific stimuli [54]. In this process, neuronal responses to stimuli that previously possessed overlapping cortical representations are increasingly discretized [61, 71]. In addition, depending on the behavioral task and sensory experience, lower and/or higher-order cortices can change their response properties. However, it is important to note that longitudinal experimental evidence for the persistency of this phenomenon is still lacking.

2.3. Is cortical plasticity causal to learned behavior?

The finding that during learning, neurons in sensory cortical areas tune their activity to become selective for particular features of a stimulus, and that during this reshaping some neurons increasingly discriminate between behavioral contingencies, suggests that cortical plasticity is causally linked to learned behavior. However, it remains challenging to experimentally establish such a link, since this requires the simultaneous recording of and interference with neuronal activity while reading out behavior. A few recent studies partially addressed this causal link by combining two-photon calcium imaging and optogenetic holographic stimulation [72]. This allowed the identification of V1 neurons that had become selective for a reward-associated visual stimulus during a discrimination learning task, and the subsequent reactivation of a subset of these neurons. Recalling the reward-stimulus-selective ensemble improved the animal's performance when only low contrast visual stimuli were used [73]. From this study, it remained unclear whether the change in the neurons' response properties during learning was a result of plasticity processes within these neurons or of dynamics in the upstream synaptic circuit. Brain-machine interface studies might help to address such questions. In this approach, electrical or optical stimulation of cortical neurons can be used to provide artificial feedback and pair it with a specific behavior or perceptual decision. Proof-of-principle experiments have been performed in monkeys, showing that the artificial pairing of activity in two locations of the wrist area in motor cortex leads to the long-term reorganization of the movement representation in this area [74]. Artificial pairing was also used to change the orientation selectivity of single neurons in mouse V1 [75] or to train mice to activate motor or somatosensory cortical L2/3 neurons in order to obtain a reward [76,77]. Together, these experiments demonstrate that cortical neurons can readily adjust their receptive field properties when provided with behaviorally-relevant, albeit artificial, feedback.

3. Plasticity at the synaptic level

Pyramidal neurons can adjust their responses upon changes in experience and during learning, which is thought to result from modifications in synapse numbers, composition, and strength [78,79]. Although, as developed in the previous section, causality between synaptic changes and the learning of new skills or improving perception has not been fully established, the large number of studies showing a close correlation between these two phenomena suggests that synaptic plasticity is very likely to be the substrate for learning and memory [9,80, 81]. Causality has been strongly corroborated by a recent study in the mouse primary motor cortex (M1), in which the memory of a learned motor skill was specifically disrupted by photoablation of the synapses that had been strengthened during learning [82]. But how and where synaptic plasticity occurs during learning is still poorly understood. A plethora of studies have investigated the cellular mechanisms of synaptic plasticity in cell cultures and brain slices, yet little is known about how these are integrated at the circuit level *in vivo*. This is in part due to the complex and perhaps non-linear interactions between pyramidal neuron inputs in the intact cortex [83–85]. Furthermore, multiple mechanisms might be at play and may operate differently depending on the cortical pyramidal neuron type (i.e. L2/3 and L5). As mentioned earlier, feedback-inputs may facilitate processes of plasticity that ultimately lead to alterations in synapses of feedforward inputs in order to optimize stimulus detection and hence the animal's behavior [9]. Below, we will summarize some of the latest insights into the cellular and circuit mechanisms for synaptic plasticity in cortical pyramidal neurons.

3.1. Spike-timing-dependent plasticity

Spike-timing dependent plasticity (STDP) has been postulated as a powerful Hebbian learning rule. It is defined as the bidirectional modification of the strength of a synapse upon the near-coincident activation of synaptic receptors and strong local postsynaptic depolarization induced by back-propagating action potentials (bAP) [86–89]. It underlies a mechanism for the 'fire together, wire together' rule, since synaptic inputs are only reinforced if their activity has contributed with a high likelihood to the firing of the neuron. In brain slices of rodent, coincident stimulation in S1 of L4-to-L2/3 inputs and postsynaptic bAPs have been shown to induce long-term potentiation (LTP) in L2/3 pyramidal neurons [89–92]. There have also been successful attempts to

induce sensory input-mediated spike-timing-dependent LTP in the visual, auditory, and somatosensory cortex [93–95]. For example, a study in mouse S1 showed that when whisker-evoked post-synaptic potentials (PSPs) in L2/3 pyramidal neurons were repeatedly paired with precisely timed current injections that caused spikes, the subsequent sensory-driven PSPs were potentiated [88,93,95]. Similarly, the artificial pairing of a visual stimulus with neuronal spiking leads to a long-term change in its response properties *in vivo* [75,96]. Together, this suggests that STDP represents a mechanism for altering receptive field properties of pyramidal neurons during sensory learning.

The main prerequisite for STDP is that bAPs, which are generated at the axon initial segment, depolarize postsynaptic membranes to promote the opening of voltage-dependent ion channels, in particular NMDARs (N-methyl-D-aspartate receptors). In neurons with extensive dendritic trees such as L5 pyramidal neurons, a bAP reaches distal synapses with a delay as compared to proximal synapses which could significantly alter the sign of plasticity [97]. bAPs are also gradually attenuated as they propagate towards distal compartments and therefore are less likely to exert a direct depolarizing effect on synapses in the apical tuft dendrites [98,99]. Conversely, distal synapses may only have a modest capacity to generate an action potential as compared to proximal inputs, due to their large electrotonic distance to the axon initial segment [99–102]. To overcome the electrotonic dampening with distance, pyramidal neurons with long apical dendrites are equipped with a second initiation zone near the tuft that serves the generation of broad and long-lasting calcium-based action potentials, so-called dendritic spikes [103–106]. On its own, a dendritic spike may not sufficiently depolarize the soma to produce an action potential, but when this event coincides with the activation of proximal inputs, the cell may actually fire a burst of action potentials. This mechanism of apical amplification is referred to as backpropagation-activated calcium spike firing (BAC firing) [38,107]. The compartmentalized initiation of spikes in L5 pyramidal neurons is an important underpinning of cortical function [38]. A recent study showed that BAC firing is not ubiquitous across the cortex and appears to be predominantly present in L5 neurons with long apical dendrites [108]. Since feedback signals from other parts of the cortex or the thalamus arrive mostly at the distal portions of their apical dendrites in L1, these connections may act as gain controllers of the feedforward inputs predominantly located at proximal dendrites [109]. Since BAC firing is associated with cell-wide calcium events it may also promote synaptic potentiation or prevent synaptic depression, similar to bAPs (Fig. 2) [110]. Such a model is confirmed by simulations in which bidirectional changes in strength are induced in apical dendritic synapses [85]. BAC firing as initiated by feedback inputs onto the tuft may then also represent a mechanism for facilitating heterosynaptic plasticity of coincident inputs at other locations on the dendrites, including those that represent feedforward inputs. In such a model feedback input may facilitate sensory response tuning of L5 pyramidal neurons.

3.2. Plasticity induced by dendritic plateau potentials

STDP as a unifying mechanism for cortical synaptic plasticity during learning and memory has been debated. The essence of this criticism lies in some of its peculiar attributes, such as that the brief depolarization induced by bAPs *in vivo* may be insufficient to relieve the Mg^{2+} block on NMDARs. In addition, STDP requires repeated pairing of excitatory postsynaptic potentials and bAPs [111], which may not normally occur as part of behavior-relevant network activity [112,113]. Moreover, pyramidal neurons in supragranular layers of the cortex spike infrequently, both spontaneously and in response to sensory stimuli [114]. Even in awake animals, the performance of a simple tactile detection task largely evokes only short-latency subthreshold depolarizations in L2/3 pyramidal neurons without spiking [43,115,116], which is in line with sparse coding models of sensory information [117]. Together, these constraints of STDP pose a conundrum for learning-induced changes in L2/3 pyramidal neurons response properties. How does the L2/3 network strengthen synapses between weakly connected neurons when sensory or feedforward inputs to do not a priori elicit a sufficient and frequent number of action potentials?

Physiologically relevant spike-independent LTP has been described *ex vivo* in the hippocampus [112,118–120]. Similar mechanisms may be at play in the cortex *in vivo*. For example, rhythmic whisker stimulation was shown to efficiently induce synaptic LTP in L2/3 pyramidal neurons in the absence of somatic spikes [41]. The plasticity instead depends on the occurrence of NMDAR-mediated long-lasting dendritic depolarizations, which bear similarities to dendritic plateau potentials [41, 83,84,121,122].

In the sensory-evoked LTP study, long-lasting NMDAR-mediated depolarizations were elicited by feedback signals originating in the POm of the thalamus [41,123]. Using electrical and optical stimulation in brain slices, it was demonstrated that the simultaneous activation of L4 and POm-originating circuits, i.e. feedforward and feedback circuits, was sufficient to induce the LTP [123]. Thus, repeated coincident arrival of feedforward and feedback inputs may not only instantaneously enhance cortical processing [39,45], it may also increase the sensitivity of pyramidal neurons to future sensory stimuli (Fig. 2). In addition, when mice experience whisker sensory deprivation, functional cortical

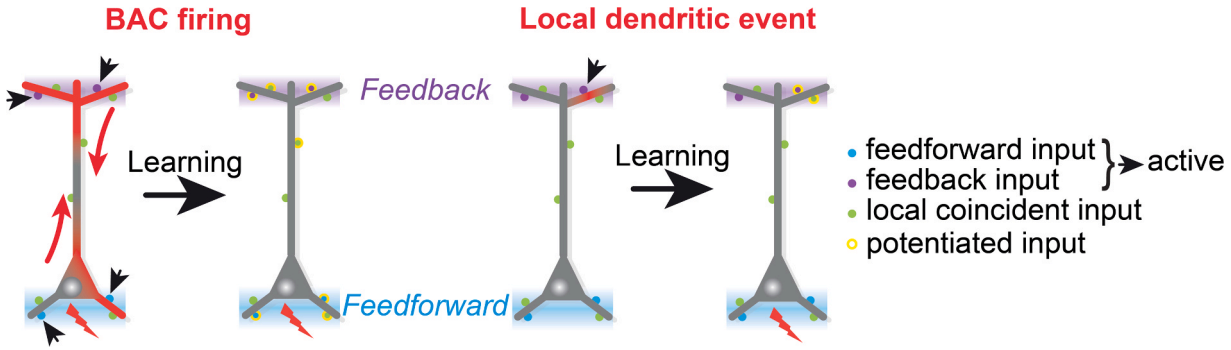

Fig. 2. Feedback-mediated plasticity in pyramidal neurons. Several mechanisms of signal integration might be implicated to mediate the plasticity of synaptic inputs on cortical pyramidal neurons. (Left) Feedforward and feedback inputs on pyramidal neurons are highly segregated on basal and apical dendrites respectively, such that the activation of one of these pathways alone cannot drive action potentials. When the two pathways are activated coincidentally, strong depolarizations at the soma and the apical tufts may generate calcium spikes that result in bursts of activity (red flash). This global activity (BAC firing) may promote plasticity of coincident feedforward, feedback and local inputs. (Right) Strong activation of feedback inputs can also produce local dendritic spikes that remain subthreshold at the somatic level for the generation of action potentials. Nonetheless, these potentials may cause a calcium influx and that drives synaptic plasticity in dendritic branch-selective manner. This mechanism may promote changes in the response properties of neurons without the necessity for a sensory input to evoke action potentials. It would allow the 'silent' recruitment of neurons to an assembly (figure design inspired by [38]).

remapping occurs within a few days, which is facilitated by an increase in POm-driven plateau potentials [124]. Furthermore, spike-independent or plateau potential-mediated plasticity may also drive plasticity of feedback circuits themselves. For example, during home-cage sensory-associated training, thalamocortical POm inputs to L5a and L2 were shown to be potentiated [125].

4. Feedback-mediated disinhibition facilitates plasticity

In the previous sections, we discussed the role of feedback circuits and pyramidal neuron dendritic mechanisms for plasticity. Recent studies have indicated that a large variety of interneurons, which are intermingled with cortical pyramidal neurons, play an important intermediary role in balancing the impact of feedforward and feedback inputs. They strongly impact not only activity but also plasticity of pyramidal neurons. A particular role is played by interneurons that target distal dendritic compartments of pyramidal neurons, such as the somatostatin (SST)-positive Martinotti cells in superficial layers of the cortex [126–128]. Their GABAergic inputs suppress the generation of NMDA spikes on apical tufts and calcium spikes on the distal apical oblique dendrites of pyramidal neurons [107,121,129,130]. Since SST interneurons have high spontaneous activity rates [131,132], they steadily decouple pyramidal neurons' distal feedback input from their perisomatic feedforward inputs [133]. Most SST interneurons are themselves inhibited by other interneurons, many of which are marked by the expression of the vasoactive intestinal peptide (VIP) [134–137]. VIP interneuron activity can transiently halt SST firing, which results in the disinhibition of pyramidal neuron apical dendrites. Hence, VIP interneurons may indirectly prompt calcium or NMDA spikes in pyramidal neurons and promote their burst firing [121,135,138–140]. This VIP-SST-disinhibitory motif is conserved across cortical regions [135–137,141,142].

VIP interneurons in the somatosensory cortex are activated during active tactile behavior [143]. They receive inputs from various sources, including the higher-order POm sector of the thalamus, M1, and subcortical modulatory centers [123,135,136,141,142,144–146]. Therefore, the activity of these cortical afferences does not only evoke monosynaptic excitatory responses in pyramidal neurons. In fact, under certain conditions they may also cause VIP-mediated disinhibition, indirectly impacting integrative processes in pyramidal neurons.

Recent experiments on S1 L2/3 pyramidal neurons have shown that VIP-mediated disinhibition as elicited by the combined activation of POm-feedback and L4-feedforward circuits is necessary for synaptic plasticity of the latter inputs (Fig. 3) [123]. Interestingly, sensory deprivation-mediated increase in pyramidal neuron synaptic plasticity and cortical map changes are facilitated by both disinhibition and plateau potentials, and plateau potentials themselves increase upon disinhibition [93,123,124]. These studies are suggestive of a mechanistic convergence of feedback-driven plateau potentials and disinhibition for pyramidal neuron plasticity. Since VIP interneurons receive inputs from M1 neurons as well, it is tempting to speculate that those feedback pathways also facilitate plasticity of S1 L2/3 pyramidal neurons via disinhibition [135,146]. In V1, nicotinic cholinergic projections from the basal forebrain that provide input to VIP interneurons are activated by running, independent of visual stimulation [141,147]. The recruitment of this VIP interneuron activity was shown to be necessary for the enhancement of visual responses in V1 and plasticity thereof [141,148,149]. Similarly, in the auditory cortex, nicotinic cholinergic inputs that project to L1 targeting VIP interneurons, provoke disinhibition of pyramidal neuron dendrites [150] and facilitate plasticity [136,151]. Auditory fear conditioning has also been shown to depend on a VIP-disinhibitory circuit motif [152]. Long-range disinhibitory motifs may play a role in plasticity too. For example, inhibitory feedback projections from the entorhinal cortex that target hippocampal cholecystokinin-positive (CCK) interneurons evoke disinhibition and plasticity of pyramidal neurons, and thereby improve the specificity of contextual and object memory encoding [153].

The common observations in the above studies are that disinhibition enhances pyramidal neuron responses to sensory stimuli and facilitates synaptic plasticity of the first-order inputs that relay relevant sensory information. During learning, these two phenomena will likely bias the disinhibited neurons to become part of a memory trace [4,154–156]. Thus, the activation of disinhibitory circuitry by feedback pathways has a unique ability to transiently modulate the excitatory/inhibitory balance of pyramidal neurons, which may be a prerequisite for heterosynaptic plasticity and ultimately underpin perceptual learning processes.

5. Conclusion

In the last decades, a tremendous amount of research has provided insights into how the cortex reshapes its response during learning and memory. Inspired by an increased understanding of the operating principles of cortical networks, classical Hebbian models of associative learning have been refined. In the latest models, plasticity of cortical pyramidal cells is not only dependent on the coincident activity of feedforward inputs but also requires the coordinated activation of long-range feedback inputs [8,9,38,64]. Nonetheless, several key questions remain to be addressed. For example, it remains unclear whether changes in the response properties of pyramidal cells during learning are causal to the increased performance. As detailed above, answers might be provided by the selective modulation of neurons that have first been observed to adjust their response properties in a learning task [73,75–77,82]. Furthermore, we still lack insights into which synapses are potentiated or depressed during learning. Some studies have suggested that feedback-driven plasticity pertains to changes in local feedforward inputs [9,41,123], which binds a given neuron to the assembly that encodes for the features of a natural scene on which the animal is trained [5]. However, we still lack insights into the precise sequence of the circuit and synaptic events that lead to the changes in neuronal

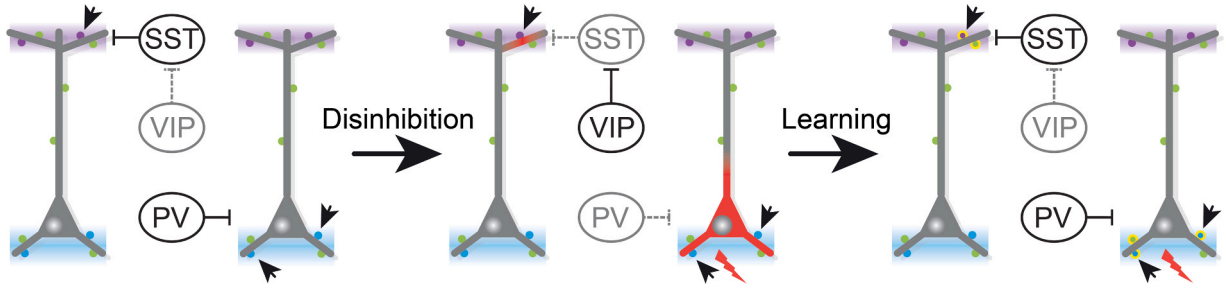

Fig. 3. Disinhibition of neuronal compartments promotes synaptic plasticity. (Left) SST and PV interneurons tonically suppress activity of pyramidal neurons in distal dendrites and at the soma respectively. (Middle) During learning, in addition to a direct excitatory role, feedback signals activate VIP interneurons that inactivate SST neurons leading to the disinhibition of the subcellular compartments of pyramidal neurons. (Right) The synaptic weights of coincidently active inputs change in the corresponding disinhibited compartments, permanently reshaping neuronal assemblies (figure design inspired by [4]).

selectivity during learning, and which of those are causally crucial. In this context, feedback inputs from different sources may also have differential, or even antagonistic effects on plasticity [157,158]. More connectivity studies will also be required to understand how synaptic inputs are topographically organized on pyramidal cells, and how inhibitory inputs affect the integration of their activity. Longitudinal synaptic mapping studies, in which the size and function of single synapses are tracked and manipulated during learning will be essential. The toolbox for such endeavors is being equipped. Intersectional viral vector and transgenic mouse technology have been customized for specific labeling of synaptic pathways *in vivo* [159–161]. In combination with live synapse tracking techniques such as mGrasp [162], SynTagMA [163], iGluSnFR [164], and synapse-targeted GCaMPs or voltage sensors [165,166], these have the potential to provide critical new insights into how experience and learning selectively alter the feedforward and feedback inputs onto pyramidal cells.

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Competing interests

Authors declare no competing interests.

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