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REVIEW

Functions and dysfunctions of neocortical inhibitory neuron subtypes

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Neocortical inhibitory neurons exhibit remarkably diverse morphology, physiological properties and connectivity. Genetic access to molecularly defined subtypes of inhibitory neurons has aided their functional characterization in recent years. These studies have established that, instead of simply balancing excitatory neuron activity, inhibitory neurons actively shape excitatory circuits in a subtype-specific manner. We review the emerging view that inhibitory neuron subtypes perform context-dependent modulation of excitatory activity, as well as regulate experience-dependent plasticity of excitatory circuits. We then review the roles of neuromodulators in regulating the subtype-specific functions of inhibitory neurons. Finally, we discuss the idea that dysfunctions of inhibitory neuron subtypes may be responsible for various aspects of neurological disorders.

In adult neocortical circuits, inhibition is thought to be balanced with excitation. Usually this refers to the observation that the level of cortical inhibition generally scales with the amount of excitation. However, compelling evidence suggests that, instead of passively reflecting excitatory activity, inhibitory networks can also actively modulate excitatory activity in a context-dependent manner and shape the excitatory circuits during experience-dependent plasticity and learning.

The heterogeneity of inhibitory neurons (INs) facilitates their active shaping of cortical networks. Distinct subtypes of INs carry out different functions based on their distinct morphological, electrophysiological, connectivity and molecular properties. In particular, non-overlapping parvalbumin (PV)-, somatostatin (SOM)- and vasoactive intestinal peptide (VIP)-expressing INs have been extensively studied in recent years[1–3]. INs of a given subtype usually share inputs[4–7] and are electrically coupled[4] (**Fig. 1a**). PV-INs and SOM-INs mostly target perisomatic and distal dendritic regions of postsynaptic excitatory neurons, respectively, and this distinct subcellular targeting underlies their distinct inhibitory effects on excitatory neurons[3,8]. In contrast, VIP-INs mostly disinhibit excitatory neurons through inhibition of other IN subtypes[3]. Although IN groupings based on single molecular marker expression may oversimplify the complexity of cortical networks, these subtypes provide opportunities to use genetic tools to dissect cell-type-specific functions. In this review, we mainly discuss the roles of the three IN subtypes in context-dependent cortical activity modulation and in regulation of experience-dependent plasticity, and the manner in which their abnormality might lead to pathological conditions. We will not focus on control of passive sensory responses[1,3,8] or further subdivisions of IN types[3,9].

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Context-dependent shaping of excitatory activity by inhibitory subtypes

Cortical sensory responses do not solely depend on bottom-up sensory inputs: the behavioral context in which sensory inputs are received profoundly modulates cortical activity and perception. We suggest that IN subtypes can alter the operation modes of cortical circuits depending on the context[1–3,9–14], flexibly adjusting the way by which a given sensory stimulus is processed.

Behavioral contexts such as locomotion, task engagement and attention alter excitatory neuron response gain. For instance, locomotion enhances visual response of excitatory neurons in the primary visual cortex (V1) while maintaining their tuning properties[15]. This gain increase may be partly mediated by differential activation of local IN subtypes. Locomotion activates VIP-INs in V1 in an acetylcholine-dependent manner while heterogeneously modulating SOM-INs, leading to the proposal that VIP activation during locomotion causes disinhibition of excitatory neurons by inhibiting SOM-INs[16]. However, these recordings were performed in the darkness. In the presence of visual stimuli, these IN subtypes all increase visual responsiveness during locomotion[17,18] (**Fig. 1b**), challenging the simple disinhibitory model. To determine how V1 IN subtypes mediate effects of locomotion, selective suppression of each IN subtype during locomotion and visual stimulation will be required.

In contrast to that in V1, the net effect of locomotion in the primary auditory cortex (A1) is suppression of excitatory neuron activity[19–21]. At the beginning of locomotion bouts, long-range projections from premotor cortex activate PV-INs[20]. This initial increase in PV-IN activity likely reduces recurrent excitation in A1, after which excitatory and inhibitory inputs to excitatory neurons are both reduced in a balanced manner[21], leading to decreased activity of excitatory neurons. However, long-range inputs to A1 also recruit VIP-INs, which could have disinhibitory effects[22]. The neural mechanisms underlying the difference in locomotion-related modulation between V1 (amplification) and A1 (suppression) have yet to be resolved. The balance of

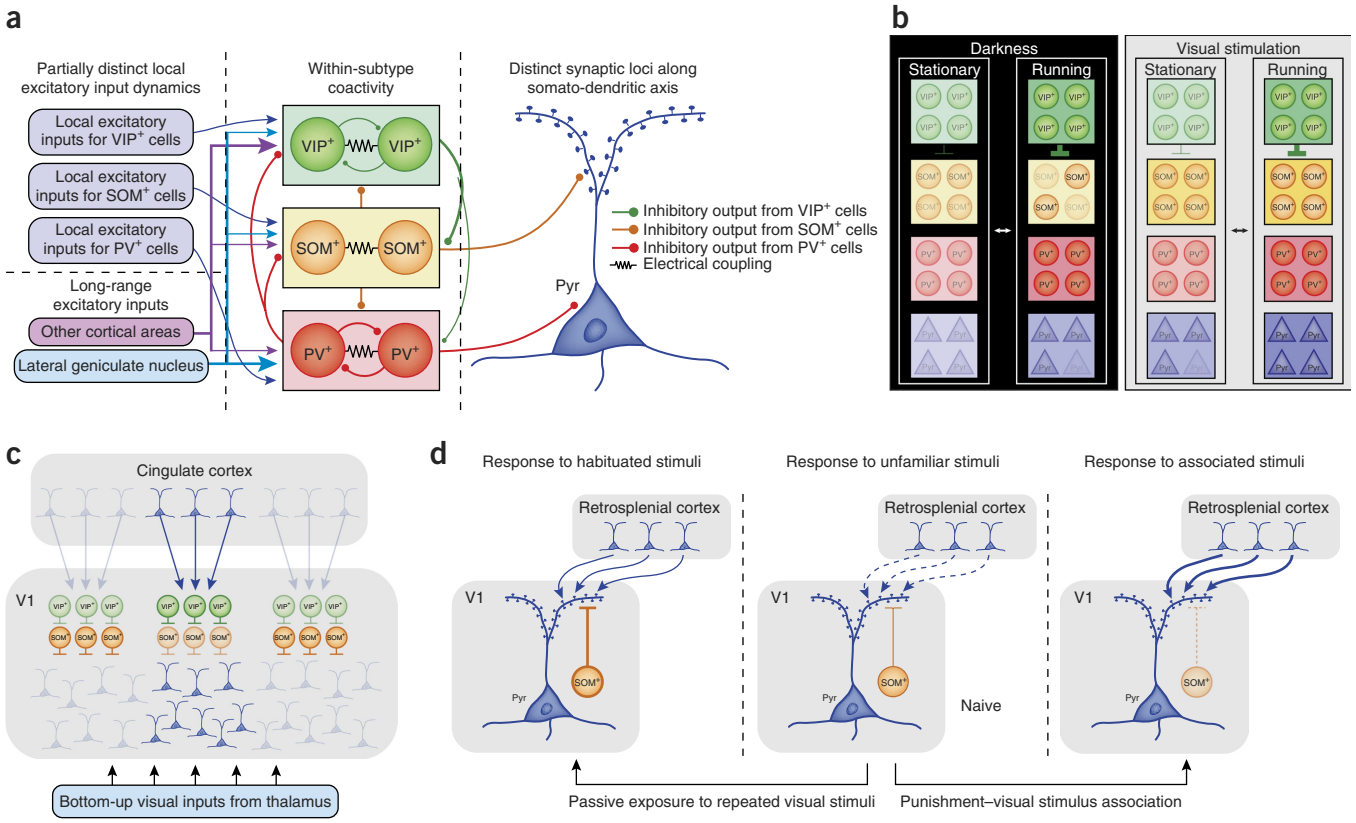

Figure 1 Context-dependent modulation of V1 by IN subtypes. (**a**) A wiring diagram illustrating differential excitatory inputs, local inhibitory connectivity and inhibitory outputs in V1 (refs. 4–7,23). (**b**) Locomotion-dependent modulation of IN activity in the presence or absence of concurrent visual inputs[16–18]. In the darkness, locomotion activates both PV-INs and VIP-INs, but SOM-INs and pyramidal neurons are heterogeneously modulated. With visual stimuli, locomotion activates all IN subtypes and pyramidal neurons. Increasing color saturation represents increasing activity relative to activity during stationary state in darkness. (**c**) Top-down projections from cingulate cortex to specific retinotopic site in V1 in mouse induce local disinhibition by preferentially recruiting VIP-INs. In contrast, SOM-INs increase their activity at surrounding areas and cause surround suppression. To our knowledge, it has not been determined whether the cingulate neurons projecting to different V1 locations are intermingled or topographically organized, as in the frontal eye field that mediates attentional modulation in primate visual cortex[28]. (**d**) Context-dependent gating of top-down inputs from retrosplenial cortex by SOM-INs[37]. Visual responses in SOM-INs increase after passive exposure to repeated visual stimuli. In contrast, visual responses in SOM-INs decrease when the mouse learns an association between the visual stimulus and tail shock, permitting strong top-down modulation of visual response in excitatory neurons by retrosplenial cortex. Line thickness and color saturation reflect the connectivity strength and the activity, respectively.

the strengths between inhibitory and disinhibitory pathways may be different across brain areas, resulting in variable locomotion effects. These examples point to a larger challenge for the coming years: to determine how feedback projections, microcircuit connectivity and synaptic weight structure differ among cortical regions.

The effect of locomotion is relatively homogeneous within each brain area. However, there is growing evidence of bidirectional modulation of excitatory neuron activity, such that some neurons are suppressed while others are activated, during task engagement or attention across sensory modalities[23–27]. In visual attention tasks, top-down modulation by higher brain areas such as the prefrontal cortex (PFC) is likely to play a critical role[28–30]. Long-range excitatory projections from cingulate cortex in PFC to V1 exert top-down influence on sensory perception in mice[23,31]. Optogenetic activation of this long-range projection amplifies visual responses in V1 and improves behavioral performance in a visual discrimination task[23]. These long-range projections preferentially recruit local VIP-INs[23] within the relevant retinotopic region of V1, which then disinhibits excitatory neurons via SOM-INs[23,32]. At the same time, SOM-INs in the surrounding areas increase their activity[23], likely due to increased drive from excitatory neurons in the disinhibited area[33–36], and suppress the activity of excitatory neurons within surrounding areas (**Fig. 1c**). Thus, cingulate cortex can generate center-disinhibition/surround-inhibition of specific retinotopic sites in V1, providing a potential basis for spatially selective visual attention.

Bidirectional modulation also extends to other sensory regions, including auditory[25,26] and somatosensory[27] cortices. In A1, task engagement coactivates PV, SOM and VIP-INs in parallel, triggering broad suppression and selective facilitation of excitatory neurons[25]. Direct recording of subthreshold inputs to excitatory neurons showed that task engagement alters inhibition more than excitation. IN subtypes are critical for the bidirectional modulation, such that PV and SOM-INs directly suppress some excitatory neurons while VIP-INs disinhibit others[25]. The potential benefits of bidirectional modulation in A1 remain unknown. One possibility is that inhibitory networks serve as a gateway for top-down and neuromodulatory signals that suppress task-irrelevant neurons while amplifying task-relevant neurons. In this model, suppression is a global response that may share mechanisms associated with locomotion. In parallel, sounds that have behavioral salience recruit a subnetwork of task-relevant neurons via disinhibition. Such a model necessitates specific connectivity of a subset of INs onto task-relevant excitatory neurons and specific inputs to those INs, which remains to be demonstrated.

These studies have investigated general suppression or disinhibition at the level of individual excitatory neurons. In addition, recent studies indicate that certain operational modes of IN networks can selectively alter the effective weights of different inputs to excitatory neurons depending on context. For example, when mice are passively and repeatedly exposed to visual stimuli, the responses of excitatory neurons, PV-INs and VIP-INs in V1 gradually decreases in parallel with a specific enhancement of SOM-IN responses[37,38]. In contrast, when mice learn to associate the visual stimulus with subjectively important context such as punishment, SOM-INs gradually decrease their visual response, disinhibiting excitatory neurons at apical dendrites[37]. The dendritic disinhibition by SOM-INs occurs concurrently with increased activity of top-down projections from retrosplenial cortex arriving at the apical dendrites[37], allowing top-down inputs to strongly modulate excitatory neuron activity (**Fig. 1d**). Notably, these IN changes are stimulus specific, indicating that the circuit operation modes controlled by IN subtypes can switch rapidly and reversibly. Similar pathway-specific gating mechanisms have been also found in hippocampus and amygdala during fear learning, where SOM-INs disinhibit specific inputs in amygdala[39] but inhibit specific inputs in hippocampus[40]. The context-dependent gating of specific input pathways in V1 is consistent with the notion that response to familiar or behaviorally salient stimuli is under the strong influence of internally generated information. Also supporting this notion, V1 inherits internal representations of visual scenes through top-down projections from other areas such as anterior cingulate cortex[31].

The examples above suggest an emerging view that IN subtypes can reversibly switch the operation modes of sensory cortex, such that sensory cortex processes an identical sensory stimulus differently depending on behavioral context. Context impinges on cortical IN subtypes in multiple and overlapping ways; IN subtypes express receptors for a wide range of neuromodulators while also receiving long-range excitatory inputs from frontal regions. How do IN networks integrate these various signals and negotiate between potentially competing inputs? Future modeling studies will instruct targeted manipulations to test mechanistic hypotheses. Furthermore, the notion that each subtype has unique and dedicated functions is overly simplistic. For example, SOM-INs in barrel cortex are heterogeneously modulated during whisking behavior due to different levels of inhibition from VIP-INs in different lamina[41]. Moreover, VIP-INs can disinhibit other INs, but they also inhibit excitatory neurons[22,42,43], and the relative contributions of disinhibitory and inhibitory effects by VIP-INs may not be fixed.

Regulation of excitatory neuron plasticity by inhibitory subtypes

In addition to contextual modulation of excitatory neuron activity, INs can actively control the synaptic plasticity of excitatory circuits. This mechanism was first described in studies of critical periods, developmental windows during which plasticity is enhanced. The maturation of PV-INs is thought to determine critical-period onsets and durations[44,45]. Classically, occluding one eye during the critical period for ocular dominance leads to expansion of the spared eye representation. Recently, it has been shown that this plasticity is mediated by transient disinhibition due to a decrease in the excitatory inputs to PV-INs[46,47]. This disinhibition is followed by recovery of PV-IN responses[46,47] and potentiation of PV-IN outputs[48,49] within a few days. Manipulations of PV-IN activity demonstrated that the transient perisomatic disinhibition by PV-INs is necessary for the critical-period plasticity of excitatory circuits[46] (**Fig. 2a**, top).

Disinhibition opens a window of enhanced plasticity even in adulthood[50]. In V1 during passive experience, deprivation-induced plasticity in adulthood primarily involves dendritic disinhibition[46,51–56], in contrast to the predominant role of PV-INs in critical period (**Fig. 2a**, middle). The degree of experience-dependent plasticity in V1 is more limited in the adult than in the critical period, but certain behavioral contexts in adulthood can enhance plasticity. For example, locomotion enhances speed and degree of recovery from amblyopia in adult V1 (refs. 57,58). It has been suggested that suppression of SOM-INs by VIP-INs is responsible for this locomotion-dependent enhancement of V1 plasticity[58] (**Fig. 2a**, bottom). Suppression of SOM-INs, in turn, results in disinhibition of excitatory neurons at their dendrites, which correlates with enhanced spine dynamics in V1 (refs. 52,54,55). The dendritic disinhibition by SOM-INs can be recruited in a number of other contexts, such as attention[23] and associative learning[2,37], and therefore SOM-INs may play a pivotal role in controlling excitatory neuron plasticity based on the context in which animals receive sensory inputs.

Another line of evidence supporting the role of INs in controlling excitatory neuron plasticity comes from studies on primary motor cortex (M1) during motor learning. In a forelimb lever-press task, spine formation increases specifically on distal dendrites of excitatory neurons during the initial learning phase, followed by elimination of some spines that existed on the distal dendrites before learning[59,60]. The spine dynamics on pyramidal neurons occurs in parallel with elimination of SOM-IN synapses onto dendrites of excitatory neurons[60] (**Fig. 2b**, top). Activation and suppression of SOM-INs respectively increase and decrease spine elimination on apical dendrites and impair learning[60], supporting their critical role in controlling spine dynamics. In contrast, PV-IN synapses on the perisomatic region transiently increase during learning[60], which might act to equalize the excitatory/inhibitory input ratio onto pyramidal neurons to prevent hyperactivity[61].

Similar disinhibition has been suggested for PV-INs in M1 during rotarod motor learning, which may be subserved by increase in VIP-IN synapses on PV-INs[62] (**Fig. 2b**, bottom). The increased inhibition of PV-INs likely results in perisomatic disinhibition of excitatory neurons and promotes excitatory neuron plasticity. Interestingly, after the initial learning, VIP-IN synapses decrease and excitatory synapses increase on PV-INs[62]. As a result, PV-IN activity at the post-learning stage may be even higher than in the pre-training period. Similar dynamics of disinhibition followed by hyperinhibition has been reported in human visual cortex during learning of orientation detection task[63]. Such hyperinhibition at the post-learning stage is consistent across species[62–64] and may prevent excessive circuit reorganization and protect learned skills[65].

These studies on sensory and motor cortices have established disinhibition as critical to excitatory neuron plasticity. Subtype-specific disinhibition can potentially control the spatiotemporal specificity of cortical critical periods or other epochs of heightened plasticity. Perisomatic disinhibition would increase the global excitability of target excitatory neurons and lower the threshold for excitatory inputs to evoke sufficient postsynaptic activity for Hebbian or spike-timing-dependent plasticity. Dendritic disinhibition, by contrast, may lower the threshold for Ca^{2+} spikes locally on dendrites and can selectively potentiate specific excitatory input pathways (**Fig. 2c**). Each dendrite-targeting IN may indiscriminately disinhibit all dendritic branches or may be able to selectively disinhibit a specific dendritic branch or even a subregion within a branch. In M1, for example, excitatory inputs for different motor skills cluster on different dendritic branches[65,66]. Elimination of SOM-IN synapses on selective dendritic regions may allow formation of new synaptic inputs specifically on the disinhibited

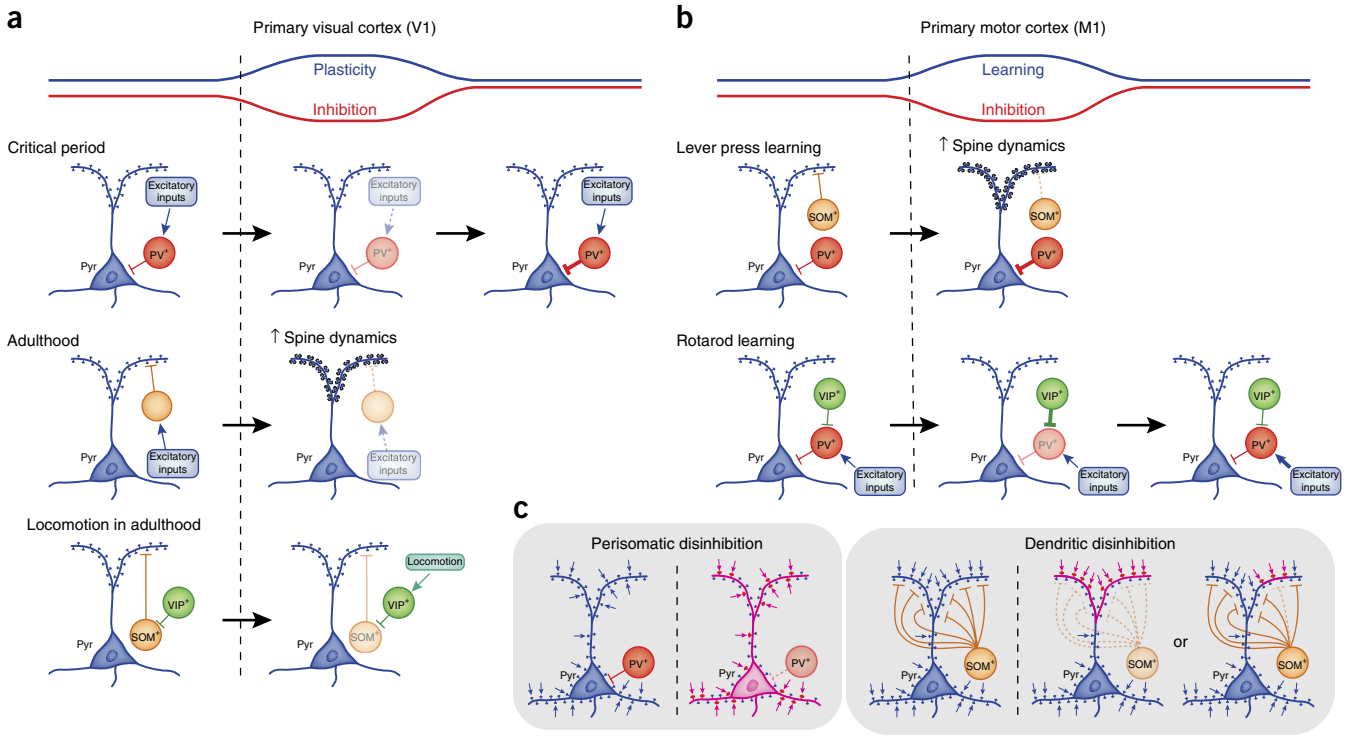

Figure 2 Relationship between disinhibition and excitatory neuron plasticity in sensory and motor cortex. (**a**) Monocular deprivation reduces PV-IN-mediated perisomatic inhibition in V1 during the critical period[46,47] (top) whereas it induces a reduction only in dendritic inhibition in adulthood[46,51–56] (middle). In both cases, the transient disinhibition permits the plasticity of excitatory circuits. The plasticity in adulthood can be enhanced by locomotion, at least partially through activation of VIP-INs[57,58] (bottom). (**b**) Lever press motor learning (top) reduces SOM-IN-mediated dendritic inhibition in M1, which permits structural plasticity of dendritic spines on excitatory neurons[60]. In contrast, PV-IN-mediated perisomatic inhibitory synapses increase in density to maintain the net excitatory/inhibitory input balance in pyramidal neurons[60]. Another study with rotarod learning reported transient increase of VIP-IN-mediated inhibitory synapses on PV-INs during learning[62] (bottom). As the learning performance saturates, the putative perisomatic disinhibition is terminated by decreased VIP-IN-mediated inhibitory synapses and increased excitatory synapses on PV-INs. (**c**) Hypothetical consequences of subtype-specific disinhibition. Perisomatic disinhibition by PV-INs may lower the threshold of plasticity induction over the entire neuron. By contrast, dendritic disinhibition by SOM-INs would lower the threshold locally at dendrites. Each SOM-IN may control plasticity of all targeted dendritic branches equally or may gate plasticity at a narrow dendritic branch region selectively.

branch. Future studies should test whether disinhibition is specific to task-related excitatory neurons and/or dendritic branches.

An important question is how plasticity can be controlled by disinhibition without compromising the ongoing circuit operation. Disinhibition would render the postsynaptic excitatory neuron hyperactive, so some type of homeostatic processes is necessary to ensure proper circuit functions. Excitatory neurons on their own have homeostatic mechanisms to prevent hyperactivity[67], but IN subtypes can also compensate for disinhibition to maintain the general activity level of the circuit, as shown in the case of PV-INs during motor learning[60]. Another remaining issue is the mechanisms behind subtype-specific disinhibition. Top-down signals and neuromodulatory inputs may modulate each IN subtype and excitatory neurons differentially during learning to instruct subtype-specific disinhibition. However, for disinhibition to achieve cellular and subcellular specificity (for example, disinhibition only on task-related neurons and/or dendritic branches), finer-scale mechanisms must be in place. One potential mechanism for inhibitory synapse plasticity with synapse specificity is spike-timing-dependent plasticity[68]. Furthermore, postsynaptic excitatory neurons may have intrinsic mechanisms to instruct subcellular specificity of disinhibition. For example, environmental enrichment triggers the expression of Npas4, which cell-autonomously redistributes inhibitory synapses from dendrites to soma in hippocampal excitatory neurons[69].

Neuromodulatory control of inhibitory networks

The circuit mechanisms that enable inhibitory plasticity during context-dependent activity and associative learning are starting to be understood, with advances in imaging, molecular genetics and intracellular recordings in behaving animals. Neuromodulation seems to be critical for induction of inhibitory and excitatory synaptic modifications during development and adulthood. Although the effects of a given neuromodulator can be quite complex[70,71] and include changes to pre- and postsynaptic excitability, synaptic transmission, glial responses and blood flow, one common theme that has emerged is that many neuromodulators directly alter GABA release[50,72,73]. In long-term plasticity, for example, neuromodulators such as acetylcholine and oxytocin initiate disinhibition to enable excitatory neuron plasticity. Here we discuss recent results that help connect modulation, inhibition, disinhibition, plasticity and behavior for four different neuromodulators: acetylcholine from the basal forebrain[25,74–77], norepinephrine from the locus coeruleus[78–80], serotonin from the dorsal raphe nuclei[81] and dopamine from the ventral tegmental area[82]. In addition to these canonical modulators, we also note that other neurochemicals such as adenosine[72], estradiol[83] and oxytocin[73,84] have been reported to directly decrease cortical inhibition, potentially gating behaviorally relevant plasticity in target circuits. There is a large literature for each of these neurochemicals, particularly in regards to effects on spiking activity or sensory perception and cognition,

beyond the scope of this review. Here we will focus on newer studies that examine how each modulator affects inhibitory networks *in vivo* in a behavioral context.

Acetylcholine. Cholinergic signaling has been postulated to promote plasticity and control brain state by directly working through cortical IN networks. Cholinergic neurons in basal forebrain are rapidly recruited by reward and punishment, and the magnitude of their activation is scaled by the unexpectedness of the reinforcement signals[74]. These cholinergic neurons innervate diverse cortical areas, including sensory cortex. In sensory cortex, reinforcement signals are paired with concurrent sensory inputs and provide opportunities for association learning. For example, pairing nucleus basalis stimulation with auditory input can enhance responses to the paired auditory stimuli in A1. If this pairing is repeated for several minutes, a long-lasting enhancement of the cortical representation of the paired sound is induced[85,86]. This plasticity seems to act through disinhibition[87]. Nucleus basalis stimulation leads to cortical muscarinic receptor activation, which reduces inhibitory inputs onto excitatory neurons elicited by the paired sound. Acetylcholine also reduces GABA release and disinhibits excitatory cells in mouse barrel cortex[72]. Reduction of inhibition is followed by a shift in excitatory synaptic tuning due to long-term potentiation of paired inputs and then a fine-scale rebalancing of inhibition to match excitation. The shift in excitatory synaptic tuning also involves a reduction in excitatory and inhibitory synaptic responses to the unpaired, original best frequency. Together, these adjustments of synaptic strength lead to translations in spiking responses and tuning curve peak along the *x* axis while conserving total synaptic strength[87].

This plasticity of cortical representations has also been linked to changes in auditory perception. In associative fear conditioning experiments, recent work has begun to reveal circuit elements that implement disinhibitory computations[88]. During acquisition of auditory fear conditioning, foot shocks recruit cholinergic inputs that activate layer 1 INs and possibly deeper layer VIP-INs, which inhibit their target INs, including SOM-INs and PV-INs[22,88]. This disinhibition is required for the fear learning, suggesting the cholinergic control of cortical plasticity and learning via disinhibition. Nucleus basalis pairing can also improve performance on a target detection or recognition task, with rats showing transient or lasting enhancements in response rates to paired stimuli depending on how many days of pairing occur[87,89]. Interestingly, changes at the level of tonotopic maps seem to recover, with the original map structure returning weeks after pairing although behavioral performance remains high[89]. This suggests that tonotopic map plasticity may not be the most relevant feature linking neural changes to behavior. Alternatively or in addition, improved behavioral performance after prolonged training periods might be supported by the auditory striatum[90], as associative learning induces potentiation of field potentials in this region[91].

Acetylcholine, however, also acutely modulates cortical activity and is implicated in controlling brain state and context-dependent activity. Locomotion and arousal modulate the responses of cortical neurons; in V1, for example, neurons show increased stimulus-evoked responses when animals are running[15]. These effects are mediated by inhibitory networks. In V1, cholinergic activity excites VIP-INs, which increases pyramidal spiking via disinhibition[16]. In A1, engaging in a stimulus-recognition go/no-go task leads to significant modulation of excitatory output[25]. Most excitatory neurons are suppressed but a select group are enhanced by task engagement. A recent study[25] dissected this phenomenon and showed that cholinergic activity is elevated during task engagement. In A1, acetylcholine activates all major IN subtypes, including PV-INs, SOM-INs and VIP-INs, to create a balance of inhibition and disinhibition in the network that enables both suppression and facilitation of excitatory output[25,92]. It should be noted, however, that IN subtypes exhibit different sensitivity to acetylcholine, with VIP- and SOM-INs being most sensitive[25,93,94] and PV-INs showing complex and potentially region-specific sensitivity[25,72]. A theoretical model could only recapitulate this outcome if neuromodulation activated all three inhibitory subtypes in parallel, ruling out inhibition or disinhibition as the sole relevant computation[25]. Going forward, it will be useful to incorporate insights gleaned from experimental data and network models into integrated behavioral models that account for the effects of different neuromodulators on decision-making processes[95].

Overall, cholinergic activity in the cortex supports behavior both by promoting plasticity in a phasic manner through disinhibition and by providing contextual signals by acting on both inhibitory and disinhibitory circuit elements. How can these two functions of the cholinergic system—reduction of inhibition for plasticity and coactivation of cortical INs during behavior—be reconciled? We speculate that there may be different operation modes that might vary as a function of cholinergic neuron firing rate, duration of activation, connectivity and muscarinic versus nicotinic sensitivity. For example, during task engagement, cholinergic neurons may fire at a low to moderate rate, leading to general recruitment of INs. But during initial learning phases or episodes of heightened reward, cholinergic neurons might fire at higher rates, similarly to what is seen during classic pairing experiments, producing a disinhibition permissive for long-term synaptic modifications. These hypotheses remain to be tested.

Noradrenaline. There is also a long literature supporting a role for noradrenergic signaling in attention, arousal, behavioral performance, and synaptic modulation or plasticity[79,80]. Norepinephrine is released from neurons in a number of brainstem nuclei, including the locus coeruleus. The locus coeruleus has extensive projections throughout the brain[78,96,97], and locus coeruleus stimulation or norepinephrine iontophoresis can have complex effects on sensory cortical neurons. In primary somatosensory cortex, noradrenergic activation can enhance evoked activity while decreasing spontaneous activity[98]. In rat A1, noradrenaline and locus coeruleus stimulation can bidirectionally modulate evoked responses via α-adrenergic receptors[99,100]. In V1, noradrenergic projections have been shown to connect to cortical interneurons including SOM, neuropeptide Y and VIP interneurons[101].

Noradrenaline can also act as a disinhibitory neuromodulator in rat A1, but in a different manner than acetylcholine. When a pure tone is repetitively paired with electrical or optogenetic locus coeruleus stimulation, responses to all tones are dramatically increased for minutes, up to tenfold in strength. This is due to a reduction in tonic (spontaneous) inhibition, in contrast to the reduction in phasic (tone-evoked) inhibition. Gradually, responses recover in amplitude, leaving tuning curves shifted to the paired input as with nucleus basalis pairing. Thus noradrenergic modulation first produces transient changes in overall response gain on the *y* axis to any incoming stimulus, before leaving enduring changes to specific paired tones. These changes have an important impact on behavior: locus coeruleus stimulation enhances detection of auditory cues and accelerates reversal learning[99]. While the physiological and behavioral effects of a few minutes of nucleus basalis pairing last only for several hours, the effects of brief locus coeruleus pairing can last for days to weeks[99]. This long-lasting response enhancement is due to plasticity

within the locus coeruleus itself. Locus coeruleus neurons can start directly responding to conditioned stimuli[99,102], potentially enabling this system to come online during task engagement for state- or context-dependent modulation[103].

Dopamine. There are two main sources of dopamine in the mammalian brain, the ventral tegmental area (VTA) and the substantia nigra. Axons from dopaminergic neurons in these areas densely innervate striatum and PFC but also have more sparse connectivity to other neocortical regions. Dopamine can bidirectionally regulate synaptic events: D1-type receptors enhance excitatory and inhibitory events while action through D2-type receptors reduces these events[104]. Pairing VTA stimulation with pure tones can bidirectionally adjust cortical representations, depending on the relative timing between sensory input and VTA activation[105]. The synaptic mechanisms by which dopamine controls this reorganization remain unknown.

The strongest evidence supporting a link between dopamine and inhibitory networks is from studies of the PFC. Inhibition is thought to shape task-related activity in the PFC[106–109], a major site of dopaminergic innervation. Experiments in reduced preparations strongly support dopaminergic modulation of inhibitory networks[110,111]. Dopamine enhances the excitability of fast-spiking INs (putatively PV-INs)[112] while still depressing GABA release through direct inactivation of presynaptic terminals[104]. In contrast, dopamine enhances inhibitory transmission from non-fast-spiking INs, likely via postsynaptic action[104]. These cell-type-specific effects of dopamine suggest a complex function for dopaminergic modulation of inhibitory networks during behavior. A recent study in the hippocampus, for example, implicates dopaminergic modulation of PV-INs as a proximal mechanism for long-term consolidation of memories[113].

Serotonin. Serotonin (5-hydroxytryptamine; 5-HT) is released from neurons located in the brainstem dorsal raphe nuclei. Serotonergic signaling is thought to regulate mood, appetite and reward-related behaviors but also modulates cortical activity[114] (particularly in PFC), potentially acting through inhibitory networks. The PFC is highly enriched in 5-HT receptors, including suppressive 5-HT1aRs and excitatory 5-HT2aRs. Both receptors reside on fast-spiking INs; most such neurons are inhibited via the 5-HT1aR[115] but some are enhanced by the 5-HT2aR[114]. Similarly, serotonin reduces GABA release from fast-spiking INs onto excitatory cells in primary somatosensory cortex, consistent with a role in disinhibition[72]. One major class of cortical INs includes those that express the ionotropic serotonin 5-HT3A receptor (5-HT3aR), including VIP-INs. Whether and how serotonin interacts with cortical circuits during behavior via INs remains to be determined.

Inhibitory network contribution to neurological disorders

Inhibitory networks play a key role in many neurological disorders, from schizophrenia[116] to Alzheimer's disease[117,118]. What are the circuit mechanisms by which INs may mediate disease pathogenesis? Here, we outline three general ways that INs contribute to pathological conditions: hyperexcitability, network oscillations and structural degradation of GABAergic synapses.

Loss of inhibitory control leading to hyperexcitability. INs provide cortical networks with the ability to balance spontaneous and evoked excitatory drive. This balance helps to prevent runaway excitation. A large body of work suggests that insufficient inhibition promotes epileptiform activity in a cell-type-specific manner. PV-INs provide strong feedforward inhibition in the thalamocortical relay; disruptions to this feedforward inhibition can lead to runaway excitation and are implicated in generalized absence epilepsy in several mouse models[119–121]. The precise mechanisms that govern changes in feedforward inhibition via PV-INs are a potent target for therapeutic intervention. The activity of PV-INs can be modulated by voltage-gated calcium channels[122] and sodium channels[123]. Moreover, direct activation of PV-INs has been used in mouse models to ameliorate epileptic activity[121]. SOM-INs stand out for their role in providing local feedback, as opposed to feedforward, inhibition to excitatory neurons. Partial deletion of SOM-INs results in epileptic behavior in mice[121], suggesting that feedback inhibition is also critical for maintaining normal levels of excitation. VIP-INs contribute to excitatory activity mainly via disinhibition. Genetic removal of VIP-INs or blockade of VIP-IN activity leads to a marked reduction in seizure activity[121,124].

In epilepsy, the therapeutic challenge is no longer to generically increase total amounts of inhibition, but rather to selectively scale the appropriate type of inhibition for the particular form of epilepsy being treated. This strategy may apply to other diseases in which abnormal inhibition is implicated, such as Alzheimer's disease, schizophrenia, autism and Rett syndrome. For example, Rett syndrome is a developmental disorder caused by loss of methyl CpG binding protein 2 (MeCP2) functions, and rodent studies suggested that loss of MeCP2 function in INs is responsible for many of the symptoms including seizures[125–127]. Interestingly, loss of MeCP2 in either PV-INs or SOM-INs causes non-overlapping Rett-syndrome-like phenotypes in mice[127]. Selectively targeting therapeutic agents at specific IN subtypes may therefore have a rational basis. Gene therapy using new cell-type-specific viruses may provide one therapeutic approach for particularly intractable conditions[128].

Disruptions of gamma activity. Cortical and hippocampal brain regions exhibit striking rhythmic activity resulting from synchronicity of neuronal populations[129]. These oscillations occur in specific frequency bands, including theta (4–8 Hz), alpha (8–13 Hz) and gamma (30–80 Hz). Gamma power in the cortex and hippocampus has been shown to increase during attention, memory and demanding behavioral tasks[130] and has been causally associated with cognition[131,132]. Synaptic inhibition plays a fundamental role in the generation of these oscillations[129,133,134]; for example, manipulating the firing rate of PV-INs fundamentally changes gamma band synchrony[131]. Now evidence suggests that disruptions to oscillations may be a proximal cause of a wide range of neuropsychiatric and neurological disorders[135].

In schizophrenia, patients exhibit reductions of gamma power during performance of cognitive tasks[135]. This has been linked to deficits in PV-IN activity. Schizophrenia-like behavioral symptoms and disruptions to gamma band oscillations have been observed in numerous mouse models in which aspects of PV-IN function have been impaired[132,136–138], and stimulation of INs in PFC at gamma frequency can restore certain aspects of cognitive flexibility in a mouse model[138]. IN-related changes to gamma band synchrony have also been observed in Alzheimer's disease. Transgenic mice with expression of human amyloid precursor protein exhibit abnormalities in gamma power that result from changes to the intrinsic properties of fast-spiking PV-INs[118]. These mice show reduced expression of a specific voltage-gated sodium channel, Nav1.1; deficits in gamma band oscillations and behavior are restored in these mice by increasing Nav1.1 levels[118]. Gamma power is also affected by changes in apolipoprotein (Apo) E4, the main genetic risk factor for Alzheimer's disease. ApoE4 knock-in mice exhibit a reduction in slow gamma activity that can be partially restored by elimination of ApoE4 in

INs[139]. Furthermore, stimulation of PV-INs at gamma frequency is sufficient to reduce amyloid-β in a mouse model of Alzheimer's disease[140]. Across diseases, the potential role of IN-mediated disruptions in gamma power suggests that this may be a convergent mechanism ripe for therapeutic intervention.

Structural degradation of INs. Many neurological diseases impair neural circuitry by introducing toxicity to a local region. In stroke, the loss of oxygenation leads to cell death. In Alzheimer's disease, extracellular amyloid-β and intracellular tau deposits are thought to initiate cellular degeneration pathways. In Parkinson's, α-synuclein aggregates and environmental toxins drive selective vulnerability of dopaminergic neurons. While most studies have focused on how excitatory neurons respond to these stressors, recent work is beginning to elucidate how these various insults may also affect INs.

In Alzheimer's disease mouse models, axonal segments of SOM-INs in the hippocampus have recently been shown to be particularly sensitive to amyloidosis[117]. Surprisingly, axonal atrophy does not depend on distance to amyloid plaques, suggesting that INs, unlike their excitatory counterparts, may propagate dysfunctional synaptic activity well beyond the plaque periphery. In stroke models, transient global ischemia triggers rapid changes in both excitatory and inhibitory dendritic structure[141]. Reperfusion can rapidly restore dendritic structure of both excitatory and PV-INs, but surprisingly, GABAergic synaptic network activity remains impaired much longer. This suggests that PV-IN function may be particularly sensitive to stroke. In rat models of Parkinson's disease, transplantation of embryonic medial ganglionic eminence–derived neural precursors (which would normally mature into GABAergic INs) into the adult striatum ameliorates motor symptoms[142].

Conclusions and outlook

Inhibitory control of cortical circuits remains an area of active exploration. As outlined above, significant progress has been made in uncovering the broad activity patterns of these IN subtypes in context-dependent control of activity and plasticity and in neurological disorders. This builds on a strong foundation of characterizing the functional profile of INs in reduced preparations. Going forward, we see four main areas of exploration that will become more plausible with the advent of new behavioral, molecular, physiological and optogenetic tools.

Precise role of IN subtypes during well-defined behaviors. Thus far, the functional dissection of IN subtypes has been focused on relatively simple behaviors, largely in stimulus detection, recognition and discrimination tasks. We believe that understanding how GABAergic activity shapes behavior will require a more nuanced approach to behavioral manipulations. A first step will be to obtain parametric control of contextual influences. Currently, inhibitory control of context-dependent behavior appears to be highly dependent on task design and parameters. The continuum from passive sensation to active attentional control needs to be carefully dissected behaviorally, and implications drawn about the cell-type-specific functions of different INs need to be considered with this in mind. For instance, the role of disinhibition in selective versus global attention remains a mystery. A second step will be to consider more ethological behaviors. In auditory cortex, notable work[20] has identified the possibility of motor influences on auditory cortical output. While locomotion or experimenter-defined motor-auditory tasks are a reasonable starting point, rodent vocalizations provide an ethological entry point to understanding the fundamental circuit architecture of motor-auditory interactions. A third step will be to understand how INs mediate social behaviors. For example, maternal behavior and responses to infant distress calls appear to be gated by inhibitory plasticity in mouse auditory cortex[73,143]. Future studies should dissect the cell-type-specific role of different INs during parental behaviors. Overall, a fundamental goal of neuroscience is to link neural activity to behavior. To do so not only requires molecular and genetic access to the constituent elements of neural networks but also a deeper understanding of behavioral output.

Heterogeneity and interactions between cell types. Cell-type-specific calcium imaging and electrophysiological recordings make it clear that INs, even within the same defined molecular class, exhibit heterogeneity in activity patterns. Explaining this heterogeneity will be a critical undertaking over the next years. One likely possibility is that molecular markers such as PV or SOM do not sufficiently define a neuronal subtype. In this view, greater molecular, functional or structural specificity will aid in reducing the heterogeneity[3,144]. Another possibility, not mutually exclusive from the first, is that INs within a given subtype exhibit experience-dependent differences in activity. For example, not all INs in a given class may be recruited for a particular behavior or task. Heterogeneity, in this case, would derive from recruitment of INs into task-dependent ensembles. New tools, including activity-dependent optogenetics and cell-type-specific imaging, should allow investigators to explore this heterogeneity in more detail. This includes examining interactions between cells of different types and identifying lower-level subtypes within existing classes. New transgenic approaches and intersectional genetic strategies will make it possible to examine these more elaborate molecular specifications. Simultaneous observation and/or manipulation of multiple inhibitory pools will be required to understand how inhibition sculpts cortical activity. Moreover, theoretical modeling can help provide testable hypotheses as to whether and how heterogeneity may emerge from interacting sub-ensembles.

Functional connectomics. INs exhibit broad output innervation and diverse input connectivity. How do synaptic inputs onto INs control their output activity pattern? How flexible and dynamic are these connections based on behavioral context? To answer these types of questions requires dissecting the synaptic partners of INs and the corresponding functional activity pattern of these neurons in distinct behavioral epochs and contexts. The methodological development of single-cell rabies virus tracing coupled with calcium imaging will soon make it possible to perform these types of experiments[145]. Moreover, functional characterization of neuronal activity during behavior followed by detailed structural analysis with electron and light microscopy can further help understand how structural connectivity patterns enable functional outputs.

Convergent inhibitory mechanisms in neurological disorders. Given the ability to target molecularly defined inhibitory subtypes with gene editing tools, inhibitory networks may provide powerful entry points for therapeutic intervention. Accumulating evidence suggests that inhibitory computations are complicated, and generic increases or decreases to inhibition may not be an effective strategy. The challenge for the field will be to identify ways to operationalize changes to IN activity in a way that improves cognitive symptoms. The answer may reside in both the generality of the effects (for example, multiple diseases exhibit disruptions to gamma oscillations) as well as the specific determinants (for example, ApoE4-mediated disruptions to gamma in Alzheimer's disease). To effectively intervene, we will have to titrate the cell types being targeted ("who"), the intensity of the change ("how much"), and at what stage the intervention makes sense ("when").

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