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## Review

## Cortical disinhibitory circuits: cell types, connectivity and function

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**The concept of a dynamic excitation/inhibition balance tuned by circuit disinhibition, which can shape information flow during complex behavioral tasks, has arisen as an important and conserved information-processing motif. In cortical circuits, different subtypes of GABAergic inhibitory interneurons are connected to each other, offering an anatomical foundation for disinhibitory processes. Moreover, a subpopulation of GABAergic cells that express vasoactive intestinal polypeptide (VIP) preferentially innervates inhibitory interneurons, highlighting their central role in disinhibitory modulation. We discuss inhibitory neuron subtypes involved in disinhibition, with a focus on local circuits and long-range synaptic connections that drive disinhibitory function. We highlight multiple layers of disinhibition across cortical circuits that regulate behavior and serve to maintain an excitation/inhibition balance.**

**Disinhibition in neuronal circuits**

The study of disinhibition in neural circuits has a long tradition. Over 50 years ago, for example, John Z. Young proposed a model for learning that implies circuit disinhibition, according to which learning requires the removal of inhibition in a circuit in which neurons are connected by inhibitory collaterals [1]. Early evidence of circuit disinhibition was collected in studies of the basal ganglia and the thalamus, which, among other functions, control the initiation and suppression of movements [2]. It was shown that  $\gamma$ -aminobutyric acid (GABA) administration to tonically active neurons in the substantia nigra blocks their discharge and results in elevated thalamic activity (Figure 1A, top and middle). Moreover, glutamate injections into the striatum activate inhibitory projections to the substantia nigra and block substantia nigra tonic discharge, with a concomitant elevation of thalamic activity (Figure 1A, bottom) [2]. Subsequent studies revealed that disinhibition is a common circuit mechanism that operates not only in the basal ganglia but also in different brain circuits where subsets of GABAergic interneurons disinhibit principal cells via inhibition of other interneurons. For example, multiple disinhibitory microcircuits were identified in the olfactory bulb (OB), where interneurons in the granule cell layer increase OB output via inhibition of GABAergic granule and periglomerular cells [3,4]. In a study using paired two-photon-guided intracellular recordings in OB slices to examine inhibition of granule cells by Blanes cells, activation of sensory input pathways was shown to elicit persistent firing in Blanes cells (Figure 1B) [5]. This provides an inhibitory brake mechanism that is presumed to be involved in the encoding of short-term olfactory memory [5], synchronization of gamma oscillations [6], and odor learning [7]. Nevertheless, for several decades the mechanistic details of circuit disinhibition remained largely unstudied, partly because of a lack of selective experimental tools for investigating cell type-specific circuit composition and function.

Recent developments in genetic and optical technologies have allowed selective targeting of different populations of interneurons to understand their network and behavioral functions. Building on these technological advances, several laboratories have explored inhibitory connectivity motifs in different cortical regions. A growing literature indicates the presence of multiple local

**Highlights**

In neural circuits, disinhibition (or inhibition of inhibition) commonly operates in the form of two inhibitory neurons connected to one another in series. Disinhibition requires an inhibitory neuron in an active state such that the activity of this neuron can be inhibited.

Across cortical brain regions, synaptic connections between GABAergic inhibitory interneurons create multiple opportunities for circuit disinhibition, which are determined in part by the activity state of the connected interneurons.

Although interneurons that express VIP have been largely considered to be disinhibitory, they are a heterogeneous cell population in which distinct subtypes likely participate in distinct inhibitory and disinhibitory microcircuits.

A key disinhibitory circuit motif that has been documented across cortical areas implicates inhibition of the interneurons that innervate the distal dendrites of principal cells, such as hippocampal oriens-lacunosum moleculare cells and neocortical Martinotti cells.

Mechanistic studies linking cell types to function will be necessary to further clarify the roles of distinct disinhibitory circuits in cortical computations and cognitive functions.

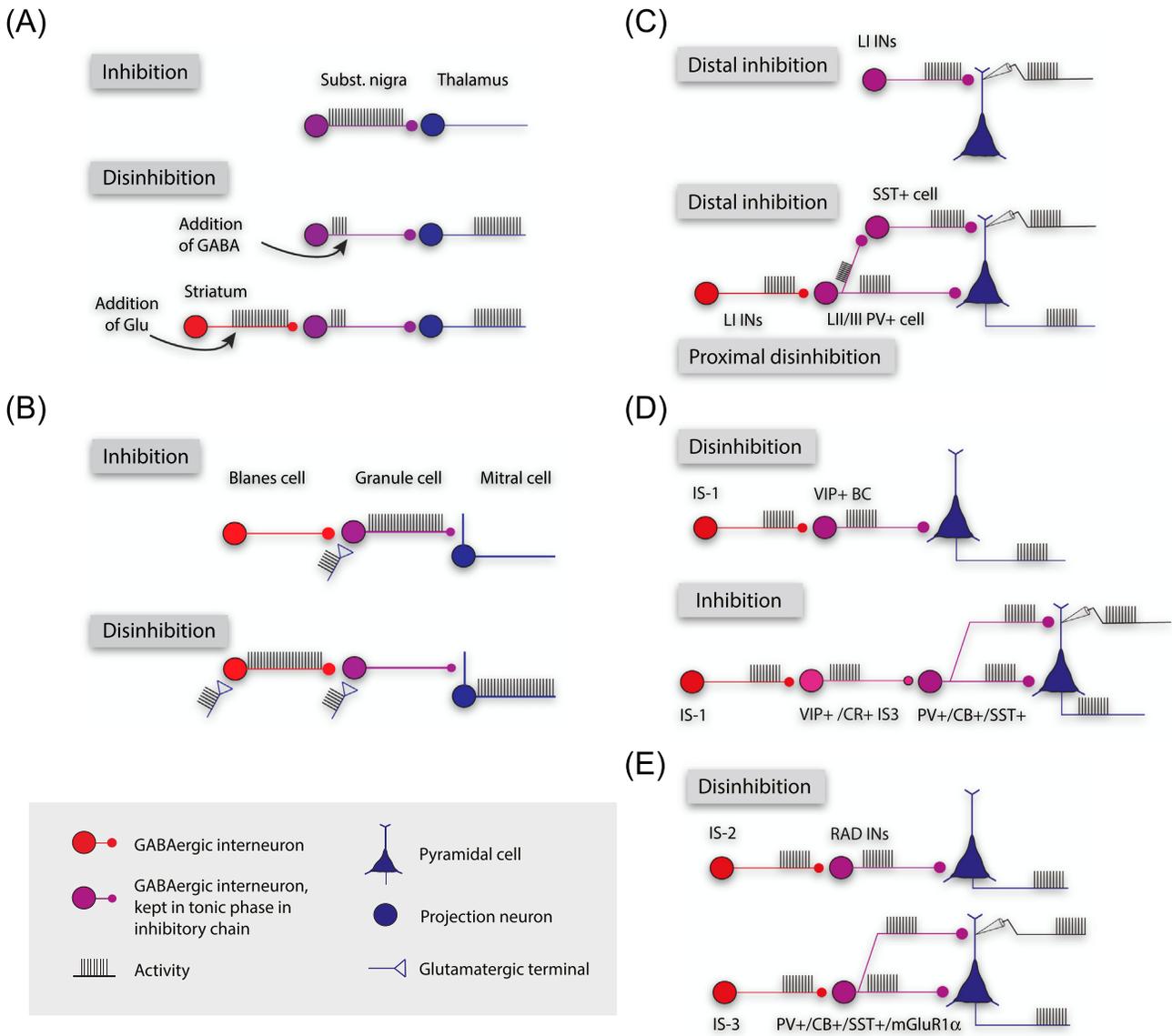
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interneuron-to-interneuron connections that result in network disinhibition and are important for a palette of cognitive functions [8–16]. Therefore, a broad question of interest is whether cortical disinhibition may represent a widespread mechanism for information selection, modification, and transfer. We discuss here recent progress in research on interneuron types that can engage in cortical disinhibition, with a particular focus on the diversity of connectivity motifs and the function of disinhibitory circuits under behaviorally relevant conditions.

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Trends in Neurosciences

**Figure 1. Disinhibition in neuronal circuits.** (A) Schematic of experiments providing evidence of a disinhibitory chain in the basal ganglia and thalamus [2]. (B) Schematic of inhibitory and disinhibitory circuit motifs involving Blanes cells and granule cells in the olfactory bulb [5]. (C) Inhibitory and disinhibitory chains involving LI-INs, PV+ cells, and SST+ cells [8,17,18,20]. (D,E) Disinhibitory and inhibitory circuit motifs involving hippocampal CA1 IS-1 cells (D), and IS-2 and IS-3 cells (E) [23,26]. Spikes on the schematic axon denote activity. Color code: red, inhibitory cells; purple, inhibitory cells second in the chain of inhibition that are kept in an active state; blue, excitatory principal cells. Note that the shift in the timing of firing of different circuit elements depends on their connectivity and activity patterns. Abbreviations: BC, Blanes cells; CB, calbindin; CR, calretinin; Glu, glutamate; IN, interneuron; IS-1 to IS-3: type 1–3 interneuron-specific (IS) GABAergic cells; LI-INs, neocortical layer I interneurons; PV, parvalbumin; RAD, stratum radiatum; SST, somatostatin; Subst. nigra, substantia nigra; VIP, vasoactive intestinal polypeptide.

### Disinhibitory circuits involving layer I and parvalbumin-expressing interneurons

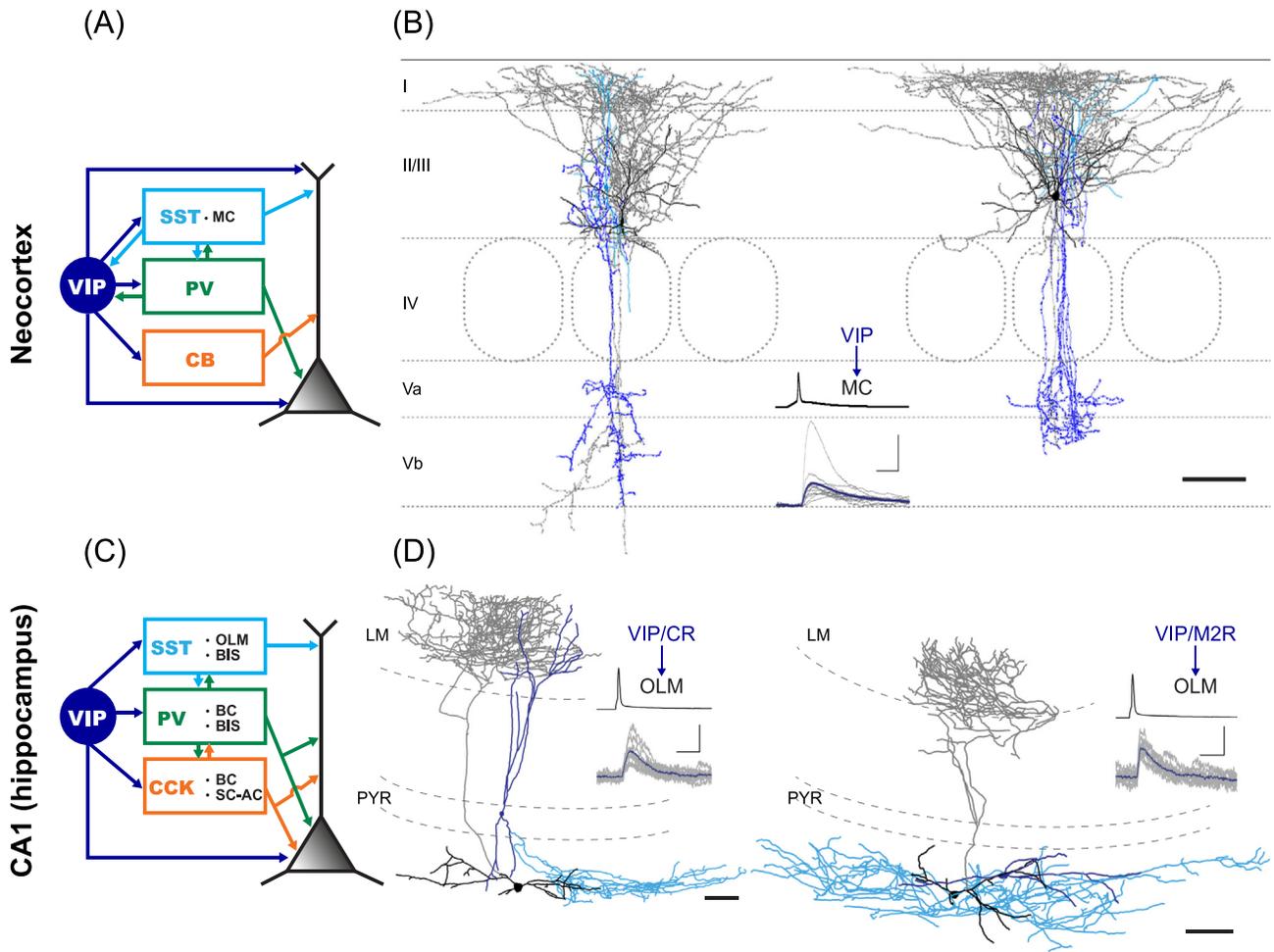
In cortical circuits, GABAergic inhibitory interneurons are often connected to each other, thus creating multiple opportunities for disinhibition of pyramidal neurons (PYRs). Neocortical layer I interneurons (LI-INs) were among the first identified to be engaged in circuit disinhibition [8]. Whole-cell recordings and morphological reconstructions in brain slices revealed two major types of LI-INs: elongated neurogliaform and single-bouquet cells, which target dendrites of the layer II/III (LII/III) PYRs (Figure 1C, top) and different types of LII/III interneurons, respectively, including parvalbumin-positive (PV<sup>+</sup>) cells involved in perisomatic inhibition of PYRs [8,17–19]. Therefore, LI-IN input to PV<sup>+</sup> interneurons can result in perisomatic disinhibition of PYRs (Figure 1C, bottom).

Furthermore, as reported across different cortical areas, PV<sup>+</sup> interneurons, in addition to inhibiting PYRs, can inhibit the somatostatin-expressing (SST<sup>+</sup>) interneurons (Figure 1C, bottom). For example, in the primary visual cortex (V1) of adult mice, a large-amplitude PV<sup>+</sup> input to SST<sup>+</sup> cells, mainly from basket cells to Martinotti cells (MCs) within LII/III and layer V (LV), was identified using simultaneous octuple recordings and morphological analyses [17]. In addition, a strong inhibitory input from PV<sup>+</sup> interneurons to MCs within LII/III was found using optogenetic stimulation and paired recordings in the barrel cortex [20]. Together, these findings indicate that, in addition to fast perisomatic inhibition of PYRs, cortical PV<sup>+</sup> interneurons engage in distal dendritic disinhibition. Such connectivity patterns may be required for the input-specific integration and plasticity that is necessary for associative learning [8,18,21]. In fact, targeted single-unit recordings *in vivo* revealed that the tonic firing of LII/III PV<sup>+</sup> cells observed under baseline conditions is suppressed by foot shocks during the auditory fear-conditioning paradigm because of the activation of LI-INs via cholinergic projections [8]. Thus, the LI-IN and PV<sup>+</sup> interneuron disinhibitory circuit motifs may guide associative learning via compartmentalization of inhibition and disinhibition in different subcellular domains of PYRs.

### Interneuron-specific interneurons in the hippocampal CA1 area

In hippocampal area CA1, interneuron-specific (IS) GABAergic cells, which innervate GABAergic interneurons selectively [22–27], engage in disinhibition of CA1 PYRs. Three types of IS cells have been identified using morphological and ultrastructural analyses of VIP- and calretinin (CR)-immunolabeled cells. Type 1 IS (IS-1) cells have a cell body located in the stratum oriens, stratum pyramidale (Str. Pyr), or stratum radiatum (Str. Rad). These cells express CR and innervate calbindin-expressing (CB<sup>+</sup>), CR<sup>+</sup>, and VIP<sup>+</sup> interneurons, and can be therefore involved in both disinhibition (Figure 1D, top) and inhibition (Figure 1D, bottom) of PYRs. Type 2 IS cells have a cell body located in the stratum lacunosum moleculare (LM) and express VIP. These cells contact interneurons located in the Str. Rad (Figure 1E, top). Type 3 IS (IS-3) cells have soma located primarily in the Str. Pyr or Str. Rad and coexpress VIP and CR. They have a bipolar orientation of dendrites and an axon projecting to the oriens–alveus (O/A), to contact SST- and metabotropic glutamate receptor 1a-immunopositive oriens–lacunosum moleculare (OLM) cells as well as other interneuron types (Figure 1E, bottom), as revealed by paired whole-cell recordings [26]. Recently, a fourth IS type was added to this population, namely the VIP- and muscarinic receptor 2 (M2R)-coexpressing cells whose soma and dendrites reside in the CA1 O/A and axons innervate the CA1 and subiculum (Figure 2D, right) [27,28]. Paired whole-cell recordings together with two-photon photostimulation in hippocampal slices revealed the region-specific target preference of these long-range projecting VIP<sup>+</sup> (VIP-LRP) cells, where interneurons are the preferential targets in CA1, but both interneurons and PYRs are targets in the subiculum.

The functional role of hippocampal IS cells remains elusive. Two-photon imaging in combination with local field potential recordings in VIP-Cre mice running on a treadmill followed by *post hoc*



Trends in Neurosciences

**Figure 2. VIP<sup>+</sup> inhibitory and disinhibitory microcircuits in neocortex and hippocampal area CA1.** (A,C) Schematic representations of synaptic connections between VIP<sup>+</sup>, SST<sup>+</sup>, PV<sup>+</sup>, CB<sup>+</sup> and CCK<sup>+</sup> interneurons and PYRs in neocortex (A) and CA1 (C). It should be noted that some of PV<sup>+</sup>, SST<sup>+</sup>, VIP<sup>+</sup>, and CCK<sup>+</sup> interneurons can coexpress CB, indicating that CB<sup>+</sup> targets of VIP<sup>+</sup> cells may represent a fairly mixed population of different interneuron types. (B) Examples of connected pairs of presynaptic VIP<sup>+</sup> cells and postsynaptic MCs in LI/III barrel cortex. Scale bars: 100  $\mu$ m. The inset illustrates average unitary inhibitory currents (uIPSCs) evoked by single spikes in the corresponding MCs (different cells, grey; grand average, blue). Scale bars: 20 pA, 50 ms. Color code: VIP dendrite, blue; VIP axon, light blue; MC dendrite, black; MC axon, grey. Figure adapted, with permission, from [20]. (D) Examples of connected pairs of postsynaptic OLM cells with a presynaptic VIP<sup>+</sup>/CR<sup>+</sup> cell (left) and a presynaptic VIP<sup>+</sup>/M2R<sup>+</sup> cell (right). Scale bars: 100  $\mu$ m. Insets illustrate uIPSCs (10 individual traces and average trace) evoked by a single spike in a corresponding OLM. Scale bars: 20 pA, 50 ms. Color code: VIP dendrite, blue; VIP axon, light blue; OLM dendrite, black; OLM axon, grey. Adapted from [26,27]. Abbreviations: BC, Blanes cell; BIS, bistratified cell; CB, calbindin; CCK, cholecystokinin; CR, calretinin; LI–III, cortical layers II–III; LM, stratum lacunosum moleculare; MC, Martinotti cell; M2R, muscarinic receptor 2; OLM, oriens–lacunosum moleculare; PV, parvalbumin; PYR, pyramidal neuron; SC-AC, Schaffer collateral-associated cell; SST, somatostatin; VIP, vasoactive intestinal polypeptide.

immunolabeling revealed that IS-3 cells are mostly active during locomotion and may fire during the rising phase and peak of theta oscillations, but are silent during sharp-wave ripples [29]. By contrast, VIP-LRP cells are strongly recruited during quiescent states and exhibit decreased activity during locomotion and theta oscillations [27]. Similar findings were obtained using large-scale 3D two-photon imaging of molecularly identified CA1 interneurons [30] where all IS cells, with the exception of the VIP<sup>+</sup>/M2R<sup>+</sup> subtype, showed a positive correlation with animal running speed. Together, these findings reveal cell type-specific differences in activity and likely function of IS cells, where the majority of these cells are recruited during locomotion and theta oscillations, and are likely involved in memory encoding. In fact, chemo- and optogenetic silencing of the VIP<sup>+</sup>

population impairs spatial learning in freely moving mice [31] as well as reward-location remapping by place cells in head-restrained animals [16]. Furthermore, VIP<sup>+</sup>/M2R<sup>+</sup> cells that are preferentially active during quiescent states [27,30] may provide correlated spontaneous activity during the intrinsic mnemonic processes associated with memory consolidation.

#### VIP<sup>+</sup> cells: selective providers of cortical disinhibition?

GABAergic interneurons expressing VIP have long been considered to be instrumental in providing disinhibition in cortical circuits [9–11,13,17,22,23]. Multiple experimental lines of evidence obtained using genetically targeted recordings from specific types of cortical interneurons, as well as optogenetic activation of VIP<sup>+</sup> cells *in vitro* and in awake mice during behaviorally relevant tasks, revealed that, by inhibiting interneurons preferentially, VIP<sup>+</sup> cells act as specialized circuit players that facilitate the information flow and allow the integration and top-down modulation of sensory information [9,12,15,32–35] and different types of goal-oriented behaviors and learning [11,16,36–38]. However, this enticing view of VIP<sup>+</sup> cells as a circuit moderator is largely complicated by the cellular diversity and complex connectivity motifs of this interneuron type that require detailed discussion.

VIP<sup>+</sup> cells originate in the caudal ganglionic eminence and, in mice, reach their destination by postnatal day 4 [39]. The VIP<sup>+</sup> population is composed of cells that express a large diversity of molecular markers [22,27,28,40–43] and can be subdivided into multiple transcriptomic subtypes [44–47]. Adding to this immense molecular diversity of VIP<sup>+</sup> cells, morphological and electrophysiological studies of VIP<sup>+</sup> cells have identified cell subpopulations with distinct properties (Box 1). Recently, a combined morphoelectric and transcriptomic analysis of mouse neocortical GABAergic neurons using a patch-seq technique in acute slices revealed a correlation between the morphophysiological features and the transcriptomic profile of a given type of interneuron, including VIP<sup>+</sup> cells [47], thus paving the way toward an integrated classification of interneuron subtypes in the cortical milieu.

Regarding the interneuron target selectivity of VIP<sup>+</sup> cells, multiple simultaneous patch-clamp recordings or optogenetic stimulation experiments in acute slices showed that the main connectivity motif that is conserved across different neocortical areas is the contact between VIP<sup>+</sup> and SST<sup>+</sup> cells, including the MCs (Figure 2A,B) [9,10,15,17,20,33,38]. Similarly, paired

#### Box 1. Molecular, morphological, and intrinsic firing properties of VIP<sup>+</sup> cells

The VIP<sup>+</sup> population is composed of cells that exhibit different combinations of molecular markers, with most cells expressing the 5-HT<sub>3</sub> receptor and calretinin (CR<sup>+</sup>), and some expressing proenkephalin, acetylcholine transferase, cholecystokinin (CCK<sup>+</sup>), neuropeptide Y, muscarinic receptor 2, and calbindin [22,27,28,40–43]. A large molecular diversity of VIP<sup>+</sup> cells was reported in a recent transcriptomic analysis, which revealed five transcriptomic types in the mouse neocortex [44] and at least seven in the CA1 region of hippocampus [45]. An even larger transcriptomic diversity of VIP<sup>+</sup> cell types is reported in human neocortical areas, where nearly 20 types were identified [46].

Across different neocortical areas, the most superficial LII/III VIP<sup>+</sup> cells have vertically oriented dendrites that reach layer I and an axon confined within a single cortical column [132,133]. The deeper LV and LVI VIP<sup>+</sup> cells have axons that establish horizontal collaterals across two to three columns [132,133]. Furthermore, anatomical and functional studies in acute slices from 5HT3a–GFP mice revealed VIP<sup>+</sup> cells interspersed among the white matter of the corpus callosum. These cells resemble the cells named by Ramon y Cajal as white matter interstitial cells, and they send long-range projections to distant regions [134]. Bipolar/bitufted VIP<sup>+</sup> cells represent the most common type in the superficial layers of neocortex and in hippocampal area CA1 [29,132,133]. Studies combining anatomical, molecular, and physiological analyses in both neocortex and CA1 revealed that bipolar VIP<sup>+</sup> cells typically fire at an irregular frequency but can also show regular spiking, rapidly adapting, and bursting firing patterns [25,26,39,43,84,85,135,136]. Moreover, although bipolar VIP<sup>+</sup> cells often coexpress CR, CR<sup>−</sup> subtypes within this morphological type have also been reported in the neocortex [43], thus supporting the existence of subtypes within the bipolar VIP<sup>+</sup> cell type. Furthermore, the neocortical double-bouquet, small basket, and arcade VIP<sup>+</sup> cells can coexpress CCK [84], which is also coexpressed by VIP<sup>+</sup> basket cells in the CA1 area [26]. Like bipolar VIP<sup>+</sup>/CR<sup>+</sup> cells, the VIP<sup>+</sup>/CCK<sup>+</sup> cells exhibit a range of firing patterns [26,84,85], suggesting additional functional diversity within this VIP<sup>+</sup> type.

recordings in CA1 revealed that VIP<sup>+</sup> cells contact OLM cells, bistratified cells (BIS), and oriens-oriens interneurons (which may include SST<sup>+</sup> LRP cells) (Figure 2C,D) [26,27]. Across neocortical regions, VIP<sup>+</sup> cells also target LII–VI CB<sup>+</sup> and PV<sup>+</sup> cells (Figure 2A), with a highly variable degree of innervation [48–51]. Similarly, as shown using paired recordings and optogenetic stimulation in the CA1, VIP<sup>+</sup> cells also connect to cholecystokinin-positive (CCK<sup>+</sup>) cells (Figure 2C) [27]. Interestingly, the density of innervation provided by VIP<sup>+</sup> to PV<sup>+</sup> cells in the hippocampus is upregulated by experience, such as spatial navigation [36]. In most cases, VIP<sup>+</sup> cells provide dendritic inhibition and therefore are suited to control the integration of excitatory inputs and dendritic spike initiation in interneurons, but these putative mechanisms require further investigation. Strikingly, ultrastructural studies of VIP<sup>+</sup> targets in the neocortex using electron microscopy revealed that up to 80% of VIP<sup>+</sup> contacts are onto GABA-immunonegative dendrites [52]. Specifically, in LI–IV of the barrel cortex, most VIP<sup>+</sup> inputs contact GABA-immunonegative dendrites, with the LV exhibiting the highest proportion of VIP<sup>+</sup> boutons on GABA-immunopositive dendrites and the LVI showing frequent somatic synapses on both GABA and non-GABA neurons. In summary, these anatomical data indicate that, in addition to disinhibition, VIP<sup>+</sup> cells provide an important source of inhibition to PYRs. This observation consolidates previous functional studies using paired recordings or optogenetic activation of VIP<sup>+</sup> cells in V1 and barrel cortex that revealed connections between VIP<sup>+</sup> cells and PYRs [9,10,17,53], pointing to the involvement of different VIP<sup>+</sup> cell subtypes in parallel inhibitory and disinhibitory circuits (Figure 2A,C) [9,11,53–55].

Regarding the inputs to VIP<sup>+</sup> interneurons, the current prevalent viewpoint is that VIP<sup>+</sup> cells are preferentially driven via long-range excitatory and neuromodulatory projections [9,12,13,56,57]. Anterograde tracing of thalamic projections and VIP immunolabeling in the rat barrel cortex combined with correlated light- and electron-microscopy revealed that LII/III and LIV VIP<sup>+</sup> cells receive the ventroposteromedial lemniscal input [56]. Moreover, genetically targeted recordings from LII VIP<sup>+</sup> cells in the barrel cortex combined with optogenetic stimulation revealed a direct input from the primary motor cortex [9] and the paralemniscal pathway (POm) [57] to VIP<sup>+</sup> cells. In addition, a recent study combining anatomical tracing with optogenetics and whole-cell recordings from S1 *ex vivo* revealed that long-range projections from different cortical areas engage distinct sets of GABAergic interneurons in a cell type-specific manner, and that VIP<sup>+</sup> cells are preferentially driven by motor-related information [58]. Similarly, optogenetic activation of projections from the motor cortex [13] or from the cingulate region of the frontal cortex [12] recruited VIP<sup>+</sup> cells in V1 during locomotion and attention. Together, these data provide evidence for the possible role of VIP<sup>+</sup> cells in top-down modulation of sensory processing.

Furthermore, paired simultaneous recordings or ChR2-assisted mapping in slices showed that VIP<sup>+</sup> cells in V1 and barrel cortex receive local excitatory inputs from specific subtypes of PYRs [9,17,43,59]. As such, LV PYRs with a regular spiking firing pattern do not contact VIP<sup>+</sup> cells, whereas intrinsically bursting LV PYRs can form up to four contacts with VIP<sup>+</sup> proximal dendrites, as demonstrated using *post hoc* morphological and immunohistochemical analyses of rat somatosensory neurons recorded in acute slices [60]. Nevertheless, the strength of the local input to VIP<sup>+</sup> cells is lower than that of the long-range input [9], which is in line with privileged recruitment of these cells via long-range projections.

The inhibitory input to VIP<sup>+</sup> cells originates from PV<sup>+</sup> cells [60,61]. This connectivity pattern is conserved across sensory areas, albeit at different strengths of the PV-to-VIP cell connection [10,17,60,61]. In addition, VIP<sup>+</sup> cells may receive input from neurogliaform, reelin-expressing and SST<sup>+</sup> cells, and are connected to each other via electrical and/or synaptic contacts across the cortex (Figure 2A) [10,17,29,59,62,63]. Interestingly, VIP<sup>+</sup> cells possess the self-regulatory

mechanism allowing them to tune down according to circuit state by inducing *Igf1*, an activity-regulated gene specific to VIP<sup>+</sup> interneurons that is involved in the formation of inhibitory synaptic connections [64].

Importantly, VIP<sup>+</sup> cells may receive diverse neuromodulatory inputs because they express a multitude of receptors involved in norepinephrine, dopamine, and serotonin (5-HT) signaling [28,65]. The 5-HT projections have long been thought to drive VIP<sup>+</sup> cells because some of these cells, predominantly the VIP<sup>+</sup>/CCK<sup>+</sup> subtype, express the 5HT3a receptor [10,42,66,67], the activation of which has a strong excitatory effect with maximal conductance when the membrane potential is held at  $-45$  mV. In addition, VIP<sup>+</sup> cells may express metabotropic 5-HT2 receptors [68]. They receive 5-HT projections from the median and dorsal raphe nuclei [69,70], with a so far unknown function, which is also further complicated by the large diversity of raphe neurons [71,72]. Furthermore, VIP<sup>+</sup> cells across neocortical and hippocampal regions receive cholinergic and GABAergic inputs from the diagonal band complex and the medial septum, respectively [13,70]. Although both acetylcholine (ACh) and 5-HT can switch the activity of some VIP<sup>+</sup> cells from burst to tonic firing [68], it remains unknown how these inputs instruct specific VIP<sup>+</sup> cell types that are involved in inhibitory or disinhibitory circuits.

#### Function of VIP<sup>+</sup> cells

Regarding the function of VIP<sup>+</sup> cells, most studies performed to date in neocortex were conducted on the superficial LII/III VIP<sup>+</sup> cells because they are more accessible for imaging/somatic recordings. These cells often express CR and preferentially connect to inhibitory interneurons, mainly SST<sup>+</sup> cells. Accordingly, we will focus on the VIP-to-SST disinhibitory motif, which appears to be universally engaged in the modulation of sensory processing and different types of learning [9,11–13,37,38]. In the barrel cortex, cell type-specific recordings and optogenetic stimulation revealed that VIP<sup>+</sup> cells are strongly recruited during whisking via direct excitatory inputs from the primary motor cortex [9], thus resulting in disinhibition in distal dendrites of PYRs. Accordingly, the role of the VIP-to-SST circuit motif may be to gate excitatory inputs converging onto distal dendrites of PYRs for generating regenerative activity and burst firing. In addition, paired activation of cortical and P0m inputs in thalamocortical slices showed that the VIP-to-SST circuit motif in the barrel cortex can gate the induction of synaptic plasticity by boosting the NMDA receptor-dependent sustained depolarization [73]. Together, these findings indicate that long-range inputs from the motor cortex and thalamus can use VIP<sup>+</sup> cells to coordinate the integration of sensory inputs in the barrel cortex.

VIP<sup>+</sup> cells constitute a highly heterogeneous population of distinct cell types that are apt to project to different targets and likely engage in multiple circuit motifs, with the outcome of their input being determined by the properties of the target circuits. A study along this line reported layer-specific modulation of SST<sup>+</sup> cells in behaving mice that was shaped by target-specific innervation of SST<sup>+</sup> cells by VIP<sup>+</sup> cells [33]. Specifically, during whisking, LII/III SST<sup>+</sup> MCs that inhibit LII/III PYRs were suppressed, whereas LIV–VI SST<sup>+</sup> non-MCs that preferentially inhibit PV<sup>+</sup> cells were activated. Given the differential innervation of LII/III and LIV–VI SST<sup>+</sup> cells by VIP<sup>+</sup> cells, and the distinct cholinergic drive to SST<sup>+</sup> cell subtypes, a push–pull mechanism was proposed to explain the whisking-on or -off activities of distinct SST<sup>+</sup> cell subtypes [33]. This mechanism can result in compartmentalized inhibition/disinhibition in PYRs with layer-specific excitatory input integration.

A similar VIP-to-SST connectivity motif was revealed in V1 [12,13], where VIP<sup>+</sup> cells preferentially target SST<sup>+</sup> cells, although the latter, in addition to PYRs, contact different interneuron types, including PV<sup>+</sup> cells, Tnfr813<sup>+</sup> cells, and LI-INs. Thus, like LI-INs, SST<sup>+</sup> cells in V1 can non-specifically contact different neuronal types and have been considered as master regulators of

circuit activity (also [10,17]). Importantly, this also means that SST-to-interneuron connections can result in disinhibition of PYRs over the entire somatodendritic domain, with VIP<sup>+</sup> cells likely playing a moderator role in the SST-to-PYRs dialogue. Concordantly, two-photon calcium imaging in V1 of awake mice revealed cooperating functional ensembles comprising VIP<sup>+</sup> and SST<sup>+</sup> cells with strong within-population coactivity [59], and a positive correlation between activity of LII/III VIP<sup>+</sup> cells and nearby PYRs during various brain states [14], indicating that VIP<sup>+</sup> cells in these layers modulate SST-to-PYR interactions to support high activity states. Additional studies using targeted optical recordings and manipulations, as well as computational modeling, have highlighted the role of V1 VIP<sup>+</sup> cells in novelty detection and in context-dependent modulation of visual responses, mainly via modulation of recurrent excitation [34,35]. In particular, it was found that VIP<sup>+</sup> cells respond to differences between the visual stimulus and surrounding environment, thus inhibiting SST<sup>+</sup> cells and disinhibiting PYRs [35]. In summary, the VIP-to-SST circuit motif in the sensory cortex supports sensory input discrimination, gain control, and input-specific synaptic plasticity, and may provide top-down or bottom-up modulation of sensory processing via non-sensory cortical or thalamic inputs [12,13,32,57,62,73,74]. Nevertheless, some conflicting results obtained using optophysiological recordings in primary visual and auditory cortices of awake mice [13,75–80] indicate that the role of VIP<sup>+</sup> cells in modulation of sensory encoding during different behavioral states, such as locomotion, may be determined by their region-specific properties, connectivity motifs, and context-specific interactions with SST<sup>+</sup> cell types.

Furthermore, studies in frontal cortices of behaving animals using cellular-resolution calcium imaging or optically targeted electrophysiological recordings and manipulations have shown that VIP<sup>+</sup> cells engage in complex tasks that permit associative and motor skill learning [11,38] as well as working-memory-guided, goal-directed, and avoidance behaviors [37,51,81,82]. In particular, the VIP-to-SST disinhibitory circuit motif is important for the sequential activation of LII/III PYRs in mouse primary motor cortex during motor skill learning [38] and for neuronal coding of action plans in the prefrontal cortex (PFC) of mice performing a working-memory task [37]. In addition, in the PFC of freely moving rats performing a delayed cue matching-to-place task, the firing of PV<sup>+</sup> basket cells correlated well with the amount of VIP<sup>+</sup> input received [51]. Interestingly, basket cells can fire during different working memory-related tasks and can easily adapt to the task [51]. Such flexibility in firing is likely a feature of all cortical interneurons, with VIP<sup>+</sup> cells being instrumental in the on-demand coordination of interneuron firing and, subsequently, of cortical network oscillations. For example, by modulating the theta-phase coupling of basket cells in the PFC, VIP<sup>+</sup> cells can increase hippocampus–PFC theta synchrony, which is important for working memory-guided and avoidance behaviors [82]. Furthermore, optogenetic activation of hippocampal CR<sup>+</sup> cells, which correspond to IS-1 and IS-3 cells, revealed that, by controlling the firing rate and timing of OLM cells, they can pace OLM activity at theta frequency [26]. Moreover, the layer-specific innervation of neocortical SST<sup>+</sup> cells by VIP<sup>+</sup> cells is important for the recruitment of SST<sup>+</sup> cells in delta (1–5 Hz) and gamma (40–100 Hz) oscillations [33]. Surprisingly, however, decreasing the glutamatergic input to VIP<sup>+</sup> cells by targeted *ErbB4* deletion can result in a reduced phase-coupling of regularly spiking PYRs during gamma oscillations [83], thus highlighting the overly complex effects of different types of VIP<sup>+</sup> cells on PYR activity and network oscillations.

#### OLM cells and MCs: mediators of disinhibition?

Hippocampal OLM cells and neocortical MCs are the preferential target of VIP<sup>+</sup> cells; therefore, they can directly mediate cortical disinhibition (Figure 2B,D). OLM cells are located within the stratum oriens and send prominent axonal projections to the LM. Similarly, MCs, which are sometimes referred to as the OLM cell of the neocortex, are multipolar neurons defined by their ascending axon collaterals to LI, where they target distal dendrites of PYRs. Both OLM cells and MCs have been marked and studied based on their expression of SST [84–87]. Although these cell types

have long been considered as a well-defined interneuron type that provides distal dendritic inhibition to PYRs, recent work has highlighted further diversity within the OLM and MC populations, with intriguing connectivity motifs that, in addition to inhibition, may result in the disinhibition of PYRs.

OLM cells receive excitatory input from local PYRs, and in turn inhibit the distal apical dendrites of PYRs, thus providing feedback inhibition. At the soma of a PYR, the inhibitory postsynaptic potential from a single OLM cell has a small amplitude and slow kinetics [88], but is presumably several-fold larger at the input site at the distal dendrite compared to the soma. About 80 OLM synapses are found on each PYR [89]; thus, OLM-mediated inhibition is an important regulator of the excitatory inputs onto the PYR distal dendrite. Importantly, electrophysiological recordings combined with *post hoc* anatomical identification show that OLM cells also target neurogliaform cells, basket cells, Schaffer collateral (SC)-associated cells, and perforant path-associated cells in the LM [90]. In turn, they are inhibited by PV<sup>+</sup>, IS-3, and VIP-LRP cells [25–27,91,92], thus mediating local circuit disinhibition.

Like OLM cells, SST<sup>+</sup> MCs receive facilitating excitatory connections from nearby PYRs. It is estimated that ~10 PYRs converge onto each MC [93]. MC output connections are predominantly formed onto PYR distal dendrites and mediate recurrent lateral inhibition [94–96]. Moreover, optogenetic experiments as well as simultaneous multiple whole-cell recordings of neocortical interneurons followed by morphological reconstruction showed that SST<sup>+</sup> cells, including LV MCs, connect to each other and can inhibit different types of interneurons including PV<sup>+</sup> and VIP<sup>+</sup> cells (Figure 2A) [15,17,59,97], thus mediating circuit disinhibition. Genetically, guided single-unit recordings in the PFC of awake mice revealed that the activity of SST<sup>+</sup> cells, which include MCs, is increased during social fear expression and, via inhibition of PV<sup>+</sup> cells, may gate social memory behavior [98].

OLM cells form a heterogeneous population [99–101] that is composed of three transcriptomically distinct subtypes (Box 2) [45], with some cells expressing *Chrna2*, the gene encoding the nicotinic  $\alpha 2$  receptor ( $\alpha 2$ -nAChR). *Chrna2* expression is specific to OLM cells in the ventral CA1 hippocampal region [102,103] and subiculum [104], and to layer V MCs in the neocortex [105]. MCs are also molecularly and morphologically diverse [84–87,106–108], and only some express *Chrna2* (Box 2). Because *Chrna2* is currently one of the most specific genetic markers available for LV MCs and OLM cells in CA1, we focus on the MCs <sup>$\alpha 2$</sup>  and OLMs <sup>$\alpha 2$</sup>  subpopulations.

The MC <sup>$\alpha 2$</sup>  and OLM <sup>$\alpha 2$</sup>  populations exhibit low-threshold spiking (LTS) and are excited by ACh through nicotinic receptors [109,110], although SST<sup>+</sup> cells in neocortical LII/III and LV can be

#### Box 2. Transcriptomic profile of OLM and Martinotti cells

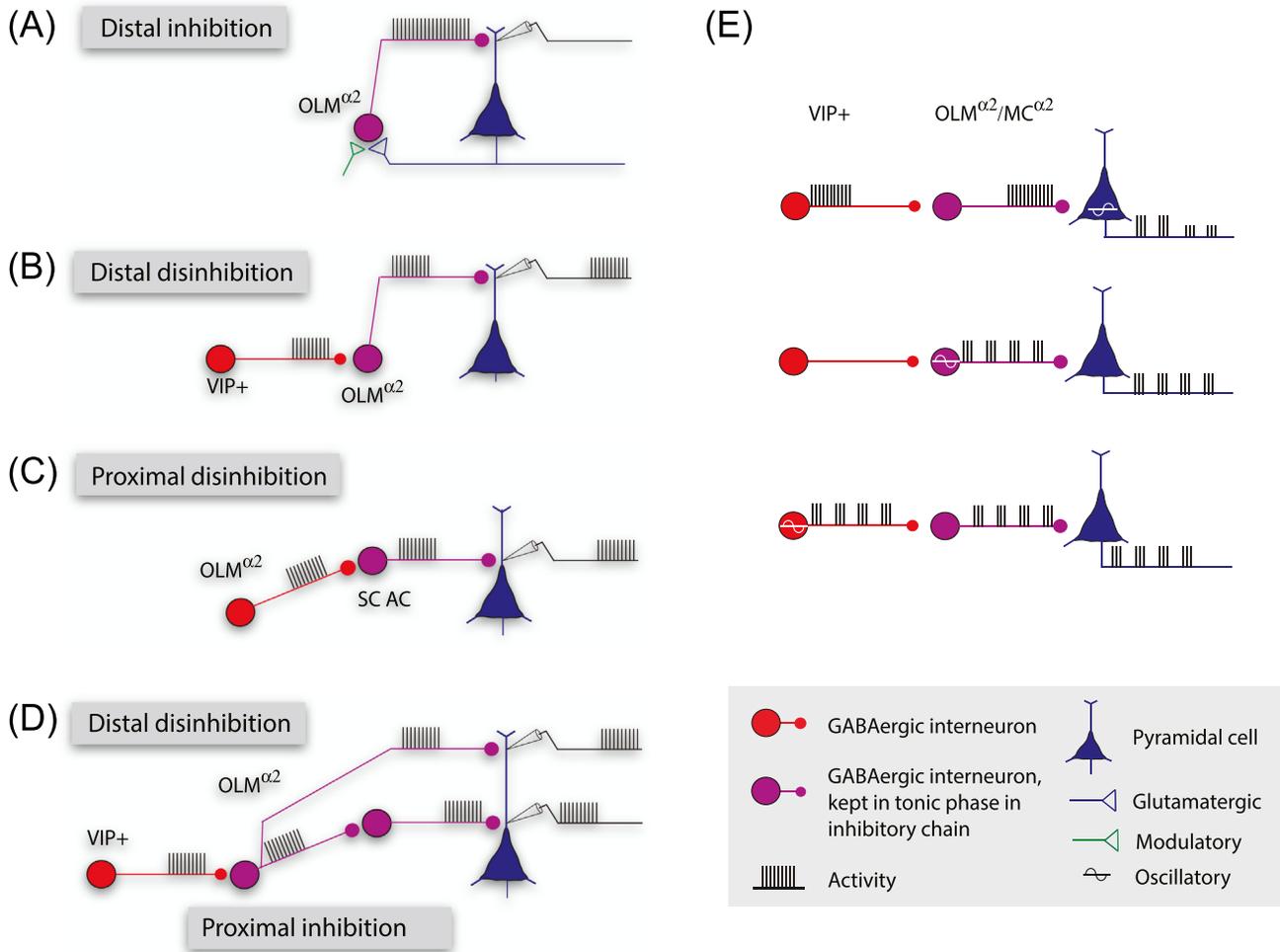
OLM cells in the hippocampus, traditionally labeled by their expression of SST, form a genetically heterogeneous population [99–101]. Some OLM cells express PV [99,119,120,122]; a single-cell RNA sequencing study found consistent expression of *Npy* gene in OLM interneurons [101] and another study identified selective *Chrna2* expression in OLM cells located in the ventral and intermediate CA1 hippocampal region [102]. Analysis of data from a large-scale RNA sequencing study of CA1 interneurons [45] led to the identification of 12 clusters of *Sst*-expressing cells, of which three are subclasses of OLM cells. Two of these contain *Pvalb*, whereas the third OLM subclass is *Pvalb*-negative and expresses *Chrna2* and *Calb1* [45].

Similarly to hippocampal OLM cells, MCs in the rodent neocortex express *Npy* [137], *Calb1* [84,85,138], and *Chrna2* [105]. Mouse neocortex single-cell RNA sequencing data identified 20 clusters of SST<sup>+</sup> cells and confirmed *Chrna2* as one of nine distinct molecular markers for identifying SST<sup>+</sup> cells in the neocortex [44]. Moreover, the study identified the presence of both *Calb1* and *Chrna2* in two subtypes, which were further subdivided into two separate populations based on their discrete patterns of gene expression. Although these findings are intriguing and suggest additional diversification in cortical interneuron populations, it remains to be established whether such molecularly defined subpopulations also differ in morphology, connectivity, and functionality.

modulated by both carbachol, the nicotinic and muscarinic receptor agonist, and muscarine, the agonist for the muscarinic receptors [111–113]. Moreover, oscillations at different frequencies, in which MCs participate, are regulated by cholinergic modulators [114]. Furthermore, in OLM cells, genetic deletion of  $\alpha 2$ -nAChR eliminated the facilitation of nicotine-induced long-term potentiation and led to memory impairment [115]. The activation of muscarinic receptors in OLM cells resulted in increased AP firing, longer-lasting plateau depolarizations, and higher sensitivity to the theta-patterned input [116,117]. Moreover, although muscarinic receptors in OLM cells promote transient theta generation,  $\alpha 7$ -nAChR activation facilitates future theta generation, as revealed using pharmacological and genetic manipulations in freely moving mice [118]. Therefore, both MCs and OLM cells show state-dependent activity which can be tuned by ACh [102,113,119,120], and therefore result in state-dependent modulation of inhibition to PYRs and target interneurons.

The functional role of OLM <sup>$\alpha 2$</sup>  cells in potential disinhibitory circuits is on at least two levels. First, although the primary role of OLM cells is to provide inhibition to the PYR distal dendrites (Figure 3A), distal disinhibition of PYRs may occur when upstream interneurons connected to OLM cells (e.g., VIP<sup>+</sup> cells) are activated (Figure 3B). Second, OLM <sup>$\alpha 2$</sup>  cells participate in disinhibition of the proximal dendritic sites of PYRs to facilitate SC input integration in ventral CA1 [102]. This disinhibitory circuit motif can arise from OLM cell connection to multiple interneuron subtypes within LM, including SC-associated cells (Figure 3C) [90]. In fact, electrophysiological recordings in slices obtained from the ventral hippocampus showed that optogenetic activation of OLM <sup>$\alpha 2$</sup>  cells resulted in reduced activity of Str. Rad interneurons, accounting for the disinhibition of the proximal PYR dendrites [102]. This creates a complex circuit that balances the inputs to PYRs from CA3 and entorhinal cortex via SCs and the temporoammonic pathway, where both pathways are under disinhibitory regulation. Such balanced processing between hippocampal inputs was found in functional studies of OLM <sup>$\alpha 2$</sup>  cells in the intermediate hippocampus *in vivo*, where optogenetic activation of OLM <sup>$\alpha 2$</sup>  cells impairs object- and fear-related memory encoding, and inactivation improves object memory encoding, in accordance with two counteracting circuits [121]. OLM <sup>$\alpha 2$</sup>  cells also participate in PYR synchronization that is essential for rhythmogenesis. In freely moving animals, OLM cells preferentially fire in theta oscillations (4–12 Hz), with no observable coupling to the gamma rhythm (30–80 Hz), whereas the firing of BIS cells is phase-locked to gamma oscillations [120,122]. Within the OLM <sup>$\alpha 2$</sup>  population, dorsal and ventral cells have different resonance frequencies – dorsal cells are faster, possibly because of a larger hyperpolarization-activated current ( $I_h$ ) [123]. Evidence from optogenetic activation of OLM <sup>$\alpha 2$</sup>  cells suggests that ventral cells can drive the slower frequency, ACh-dependent, type 2 theta oscillations in the ventral hippocampus, which was also directly related to increased risk-taking behavior [124]. In summary, OLM <sup>$\alpha 2$</sup>  cells may play significant roles in driving rhythmogenesis in the ventral hippocampus and in the control of cognitive and emotional information processing.

Regarding the function of MCs during behavior, most studies so far have focused on LII/III SST<sup>+</sup> cells, which showed reduced firing during sensorimotor integration in barrel cortex [33,125]. In LV, the T-shaped MCs with an LTS firing pattern inhibit the apical dendrites of LII/III PYRs, whereas the fanning-out MCs with adaptive firing inhibit the more proximal PYR dendrites [126]. The generation of spontaneous activity in MCs, that is dependent on persistent sodium currents, suggests that they play a functional role in disinhibitory circuits [127]. As discussed previously, evidence of VIP-to-MC-to-PYR disinhibition has been found in LV of the mouse barrel cortex, where T-shaped MCs become silent during whisking, whereas fanning-out MCs remain active, which may indicate that mainly T-shaped MCs are connected to VIP<sup>+</sup> interneurons [9,33]. It is unknown whether the MC <sup>$\alpha 2$</sup>  subtype belongs to the T-shaped or fanning-out category, and a goal for future studies will be to examine in detail the microcircuits involving MC <sup>$\alpha 2$</sup>  cells (see Outstanding questions). Of note, however, it has been found that MC <sup>$\alpha 2$</sup>  cells preferentially target



## Trends in Neurosciences

**Figure 3. Inhibitory and disinhibitory circuits involving OLM<sup>α2</sup> and MC<sup>α2</sup> neurons.** (A) Schematic of neuron inhibitory chain in which an OLM cell (purple) receives modulatory inputs (green) and reciprocal excitatory inputs from PYRs (blue) that support an active OLM cell state resulting in PYR distal dendrite inhibition. (B) Schematic of a distal disinhibitory chain where upstream inhibitory interneurons (VIP<sup>+</sup>) provide inhibitory input to OLM cells. (C) Schematic of proximal disinhibition because of the inhibitory input from the OLM<sup>α2</sup> cells to Schaffer collateral-associated (SC-AC) cells, which in turn inhibit the PYR proximal dendrite. (D) Schematic of distal disinhibition with simultaneous proximal dendritic inhibition. Note that temporal shifts in neuronal firing depend on their connections and activity states. (E) Possible scenarios for oscillating networks in which OLM<sup>α2</sup>/MC<sup>α2</sup> cells participate. In the upper scheme, oscillations are generated in PYRs, where disinhibition sustains PYR oscillations and tonic inhibition decreases PYR oscillatory patterns. In the middle and lower schemes, oscillations in OLM<sup>α2</sup>/MC<sup>α2</sup> or in upstream inhibitory neurons (VIP<sup>+</sup>) result in sustained or increased oscillatory activity in PYRs in phase with VIP<sup>+</sup> cell activity, and out of phase with OLM<sup>α2</sup>/MC<sup>α2</sup> cell activity. Disinhibitory VIP<sup>+</sup> cells are shown in red, inhibitory cells (purple), principal cells (blue), and activity is denoted by spikes and bursts. Abbreviations: α2, nicotinic α2 receptor; MC, Martinotti cell; OLM, oriens-lacunosum moleculare; PYR, pyramidal neuron; VIP, vasoactive intestinal polypeptide.

LV thick-tufted type A PYRs that mainly project to subcortical regions; therefore, MC<sup>α2</sup> cells most likely affect information directed toward subcortical structures [128].

Both OLM cells and MCs provide disynaptic inhibition onto distal dendrites of PYRs, which, via control of dendritic electrogenesis and burst firing in PYRs [92,129,130], can contribute to phase-locking of PYRs to ongoing oscillations. In fact, optogenetic manipulations of SST<sup>+</sup> cells of V1 in awake mice and computational modeling suggest that such a mechanism can synchronize distributed neuronal ensembles [131]. Moreover, in the primary auditory cortex, burst firing of the MC<sup>α2</sup> subtype can synchronize type A PYR firing into oscillatory patterns of activation [105]. In

CA1 of awake mice, optogenetic silencing of SST<sup>+</sup> cells, including OLM cells, increases burst firing of PYRs [130]. Whether inhibitory inputs into OLM cells and MCs (e.g., from VIP<sup>+</sup> cells) may control network oscillations remains unknown but, if so, this modulation may depend on the activity state of the connected neurons (Figure 3D). In the case of oscillatory activity in PYRs, disinhibition is hypothesized to sustain oscillations, whereas tonic inhibition from OLM cells and MCs can dampen the oscillatory behavior (Figure 3E, top). Accordingly, oscillatory activity in OLM cells and MCs, or in upstream neurons (e.g., VIP<sup>+</sup> cells), may result in sustained or increased oscillatory activity of PYRs in phase with VIP<sup>+</sup> cells and out of phase with OLMs and MCs (Figure 3E, middle and bottom). Similarly, oscillatory input from VIP<sup>+</sup> cells onto tonically active OLM cells and MCs can pace their output and therefore increase the oscillatory activity of PYRs [26]. All these scenarios are possible depending on brain-level and cellular-level states. Whether one mechanism is more common than the others warrants further investigation.

### Concluding remarks

In summary, the appealing idea of a disinhibitory model as a canonical circuit for gain modulation in cortical information processing should now be updated by placing more weight on the diversity of the cortical modules that can mediate disinhibition, with outcomes depending on the cell type involved, the microcircuit wiring diagram, and the behavioral context. Different types of interneurons not only provide temporally organized inhibitory inputs to specific subcellular domains of PYRs but are also interconnected with each other and can potentially engage in different disinhibitory microcircuits. This wiring diagram creates multiple opportunities for PYR inhibition and disinhibition depending on the actual connection that is activated and the firing output of the connected interneurons, which awaits detailed investigation. Although the activity of all neuronal types builds upon intrinsic membrane conductances, this activity is fine-tuned by synaptic and neuromodulatory inputs which fluctuate in a network- and brain state-dependent manner. These factors will determine the outcome of the activated microcircuit and the output of PYRs. Hence, complex wiring schemes and state-dependent modulation of cortical inhibitory interneurons provide both inhibition and disinhibition to achieve flexible excitation/inhibition coordination during cortical computations.

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### Declaration of interests

The authors declare no conflicts of interest.

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### Outstanding questions

VIP<sup>+</sup> cells form a heterogeneous population in which different cell types are connected to distinct postsynaptic targets, including GABAergic and glutamatergic neurons. What are the connectivity motifs and functions of specific VIP<sup>+</sup> cell types in different cortical circuits?

How do different VIP<sup>+</sup> cell types, including deep layer VIP<sup>+</sup> cells, shape LV PYR computations and cortical output?

Are particular subtypes of PYRs preferentially inhibited by VIP<sup>+</sup> interneurons, and what is the function of this inhibition?

To what extent are MC<sup>α2</sup> and OLM<sup>α2</sup> cell states driven endogenously by PYR feedback excitation and by long-range excitatory connections?

Is the cholinergic drive to MC<sup>α2</sup> and OLM<sup>α2</sup> cells via α2-nACh-containing receptor complexes distinctive, and, if so, how?

In relation to VIP<sup>+</sup> cells, what subtype of VIP<sup>+</sup> cells connect to MC<sup>α2</sup> and OLM<sup>α2</sup> neurons, and do these VIP<sup>+</sup> cells also connect to PYRs?

What is the relationship between oscillatory activity in VIP<sup>+</sup>, MC<sup>α2</sup>/OLM<sup>α2</sup>, and PYR cells?

Do the microcircuits containing a chain of VIP<sup>+</sup>, MC<sup>α2</sup>/OLM<sup>α2</sup>, and PYR cells represent a similar computational module in the neocortex and hippocampus?

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