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# Cortical inhibitory interneurons control sensory processing

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Inhibitory and excitatory neurons form intricate interconnected circuits in the mammalian sensory cortex. Whereas the function of excitatory neurons is largely to integrate and transmit information within and between brain areas, inhibitory neurons are thought to shape the way excitatory neurons integrate information, and they exhibit context-specific and behavior-specific responses. Over the last few years, work across sensory modalities has begun unraveling the function of distinct types of cortical inhibitory neurons in sensory processing, identifying their contribution to controlling stimulus selectivity of excitatory neurons and modulating information processing based on the behavioral state of the subject. Here, we review results from recent studies and discuss the implications for the contribution of inhibition to cortical circuit activity and information processing.

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## Role of interneurons in sensory processing

A fundamental quest of sensory neuroscience is to link a specific function in sensory processing to an identified circuit within the sensory pathway. One of the most striking aspects of neuronal morphology in the sensory cortex is the astonishing diversity of inhibitory interneurons. This diversity is thought to underlie the brain's ability to process and respond to complex and varied everyday sensory environments. By exhibiting differential patterns in their connectivity to excitatory and other types of inhibitory cells within and across cortical layers, interneurons contribute to the formation of a variety of microcircuits supporting potentially complex sensory processing functions. Over the last few years, there has been considerable progress in understanding of the role of different interneurons in sensory processing.

Cortical inhibitory interneurons are comprised of a vastly diverse population, with cells differing both morphologically and physiologically. Whereas up to several hundred inhibitory neuronal subtypes can be recognized [1–5], the inhibitory neurons have been grouped into three predominant classes based on molecular markers: parvalbumin-positive (PVs), somatostatin-positive (SOMs) and vasoactive intestinal polypeptide-positive interneurons (VIPs) [3,6]. The most common class of the three in the sensory cortex are PVs, which include the 'basket cells', which target excitatory neuronal cell bodies [7]. As such, they are thought to provide global inhibition to excitatory neuronal populations [8]. SOMs, the second most common class, contain a large population of Martinotti cells [9], which target the distal dendrites of excitatory neurons, and thus could exert a more specific effect of modulating excitatory neuronal responses to stimuli [10]. VIPs in the cortex preferentially target SOMs [11–13,14••,15] and to a lesser extent PVs [14••]. Since SOM and PV interneurons target excitatory cells, VIP interneurons are ideally placed to modulate cortical activity through disinhibition of excitatory cells via inhibition of SOM interneurons [13]. A fundamental question for systems neuroscientists studying sensory processing has been to understand whether and how the diversity in morphological cell types of interneurons corresponds to specific functions during stimulus discrimination.

Over the last few years, optogenetic techniques led to significant progress in identifying the function of distinct interneuron types in sensory processing [16–18,19••,20–22,23••]. A specific subset of neurons can be driven to express an opsin, which, when stimulated by light, leads to depolarization or hyperpolarization of the neuron that expresses it. Optogenetic techniques allow measuring the effects of suppressing or activating a particular neuronal cell type while the animal is presented with a stimulus or engaged in a perceptual task and to be coupled with recording of ongoing neuronal activity [14••,23••,24–26]. Below, we review recent studies in which these approaches were used to modulate the activity level of specific subtypes of interneurons while measuring the

tuning curves of excitatory neurons, in order to determine their function in stimulus selectivity, or manipulating the inhibitory neuronal activity during perceptual tasks performed by the subjects to assay the contribution of specific interneuron cell types.

## Role of interneurons in stimulus selectivity

Behavioral discrimination of sensory stimuli is thought to rely on sensory tuning, or selectivity, of neuronal populations. Neurons in the sensory cortex typically exhibit selectivity for specific aspects of sensory stimuli — for example, neurons in the auditory cortex exhibit frequency tuning with elevated responses to tones of particular frequency [27–29]. This stimulus selectivity arises through the combination of excitatory and inhibitory inputs to neurons (Figure 1a), which themselves have stimulus tuning [29–31]. Several theories for the contribution of inhibition to stimulus selectivity rely largely on the differences or similarities in tuning profiles of excitatory and inhibitory inputs (Figure 1) [32–34]. By providing co-tuned input, inhibition can enhance selectivity in a multiplicative fashion [29]. Alternatively, by providing broadly tuned uniform inhibition, inhibitory neurons can increase selectivity through a linear offset to the excitatory neuronal responses, such that the relative strength of the offset increases with distance from the receptive field center [35]. In another scheme, the differences in timing between excitatory and inhibitory neurons can lead to sharpening or broadening of the tuning of excitatory neurons [36]. These models were previously supported by results from studies measuring relative contribution of excitatory and inhibitory currents to receptive fields of excitatory neurons or using pharmacological tools to suppress inhibition. For example, in the auditory cortex, experimental evidence from pharmacological experiments and intra-cellular recordings has supported either of these schemes [29,32–37] providing a contradictory view of the function of inhibition in sensory tuning. However, given the wide range of inhibitory neuron subtypes, an emerging possibility is that the different types of inhibitory neurons differentially shape the tuning properties of excitatory neurons.

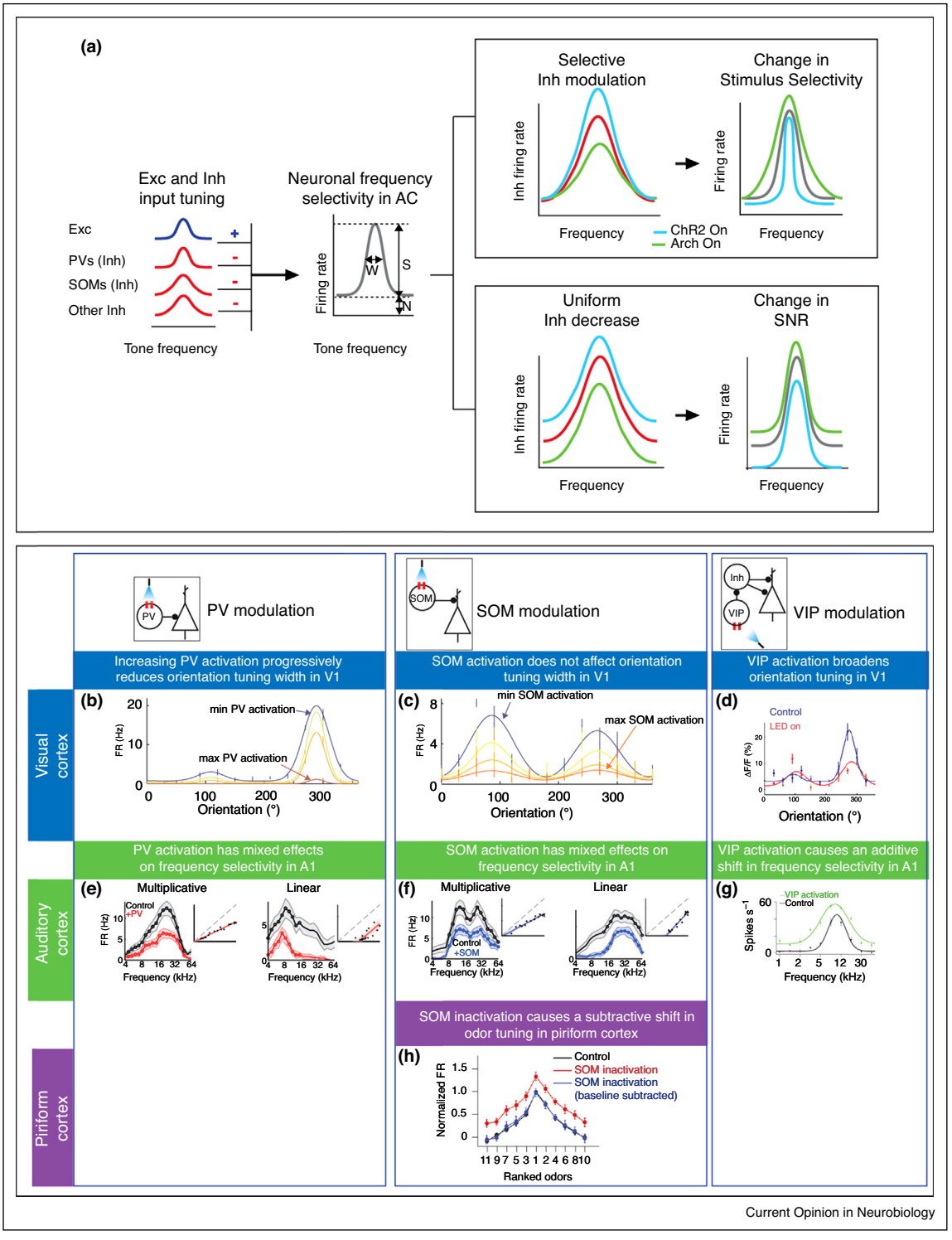
In primary visual cortex, studies testing how PV activity affected excitatory neuronal responses to oriented gratings provided mixed results. Activating channelrhodopsin-expressing PVs with high intensity light decreased the firing rate and sharpened the orientation tuning of excitatory neurons in one study [19••,38], whereas activating or suppressing PVs with light of lower intensity linearly shifted the responses of excitatory neurons without affecting their stimulus sensitivity [39••]. This suggested that PVs contributed to visual selectivity (Figure 1b) through a mechanism that shifted the excitatory tuning both linearly and multiplicatively. Modulation of SOMs yielded more specific modulatory effects, producing changes in responses that were stimulus-dependent through surround suppression release [40,41]. These results are consistent with broad uniform inhibition provided by SOMs (Figure 1c), as measurements of SOM response properties found that SOMs respond to larger stimuli that encompass the surround at shorter response latencies than to smaller stimuli [42].

In other sensory modalities, modulating activity of PVs and SOMs similarly drove heterogeneous effects on stimulus-driven responses. In the auditory cortex, activating PVs resulted in narrowing of the receptive fields of excitatory neurons and an increase in the strength of their tone-evoked responses [23••,43], whereas their suppression led to opposite effects [23••]. Suppressing or activating SOMs increased or decreased the firing rate of excitatory neurons respectively [21,44•], but the effect was more often multiplicative when SOM activity was reduced as compared with PVs, whose suppression provided both multiplicative and linear shifts in excitatory neuronal responses to tones. Activation of PVs or SOMs also produced a mixture of multiplicative and linear shifts in excitatory neuronal responses to tones (Figure 1e–f). By contrast, in the piriform cortex, SOM inactivation caused a predominantly additive shift in odor tuning and reduced neuronal discriminability (Figure 1h) [45•].

A third class of interneurons, VIPs, also contributed to stimulus selectivity in the visual cortex, providing facilitation specific to the receptive field center, but not the surround, of excitatory cells [41]. Manipulating VIP activity affected spatial and orientation tuning. Specifically, activation of VIP interneurons increased preferred spatial frequency, while inactivation decreased preferred spatial frequency, and both manipulations decreased orientation selectivity (Figure 1d) [46•]. This finding of increased spatial resolution with VIP activation could in fact be a substrate mechanism of how VIP activation can improve performance in behavioral tasks [41]. By contrast, in the auditory cortex, VIPs had a differential effect, consistent with disinhibition of excitatory neurons: activation of VIPs caused a positive shift in tone-evoked excitatory responses (Figure 1g) [14••]. More specifically, activating cholinergic inputs to VIP interneurons broadened the tuning of excitatory cells to tones of different frequencies by decreasing responses to the preferred frequency and increasing responses to the less preferred stimuli [47].

These heterogeneous effects of modulation of interneuron activity point to the complexity of the underlying circuits: even a simple model that represents recurrent excitatory and neuronal populations through mean activity level has demonstrated that elevating inhibitory activity can yield diverse, and potentially paradoxical effects, either suppressing or enhancing activity of excitatory neuronal populations [48]. A model of responses of excitatory and inhibitory neurons demonstrated that a similar mechanism may appear as a linear or a multiplicative

**Figure 1**




Sensory tuning of neurons in the cortex (example: frequency tuning in the auditory cortex) is shaped by the interactions of excitatory (Exc) inputs (blue), and inhibitory (Inh) inputs (red) from several neuronal cell types, including PVs and SOMs, which themselves exhibit stimulus selectivity. **(a)** Suppression (green) or activation (cyan) of inhibitory interneurons selectively (top right) or uniformly (bottom right) modulates responses of inhibitory neurons, which control frequency selectivity and signal-to-noise ratio of responses of excitatory neurons. Modulation of selective inhibition can affect tuning width, whereas broad inhibition modulation can affect signal-to-noise ratio. Both of these effects can change the sensitivity of neuronal populations to stimuli. S: signal, N: noise; W: tuning width; SNR: signal-to-noise ratio. **(b)** Example neuron showing increasing levels of PV activation in visual cortex decreases firing rate and orientation tuning width in putative excitatory cells. Adapted from [38].

shift, depending on the parameters of optogenetic manipulations [44•]. An inhibitory-excitatory circuit rate model found that a small change in connection parameters between inhibitory and excitatory neurons as well as stimulation parameters can yield differential effects on neuronal network behavior [22,23••]. To bring the disparate findings together, future studies need to investigate perturbations under variable light intensities, and combine the results with computational analysis for identifying the differential contribution of interneuron cell types to sensory processing in a coupled neuronal circuit [49]. Further specific targeting of opsins to interneuron subtypes within the broad interneuron classes as well as layer-specific studies for inhibitory-excitatory interactions [3] will help understand the degree of complexity of the interactions.

## Role of interneurons in behavioral state modulation

Inhibitory interneurons are also involved in modulation of sensory responses by the behavioral state of the subject across sensory modalities. A striking example of this modulation is provided by locomotion. Locomotion has been predicted to affect sensory processing, for example by activating visual processing pathways dedicated to processing of rapidly changing stimuli; or by suppressing activity that would be due to locomotion artifact.

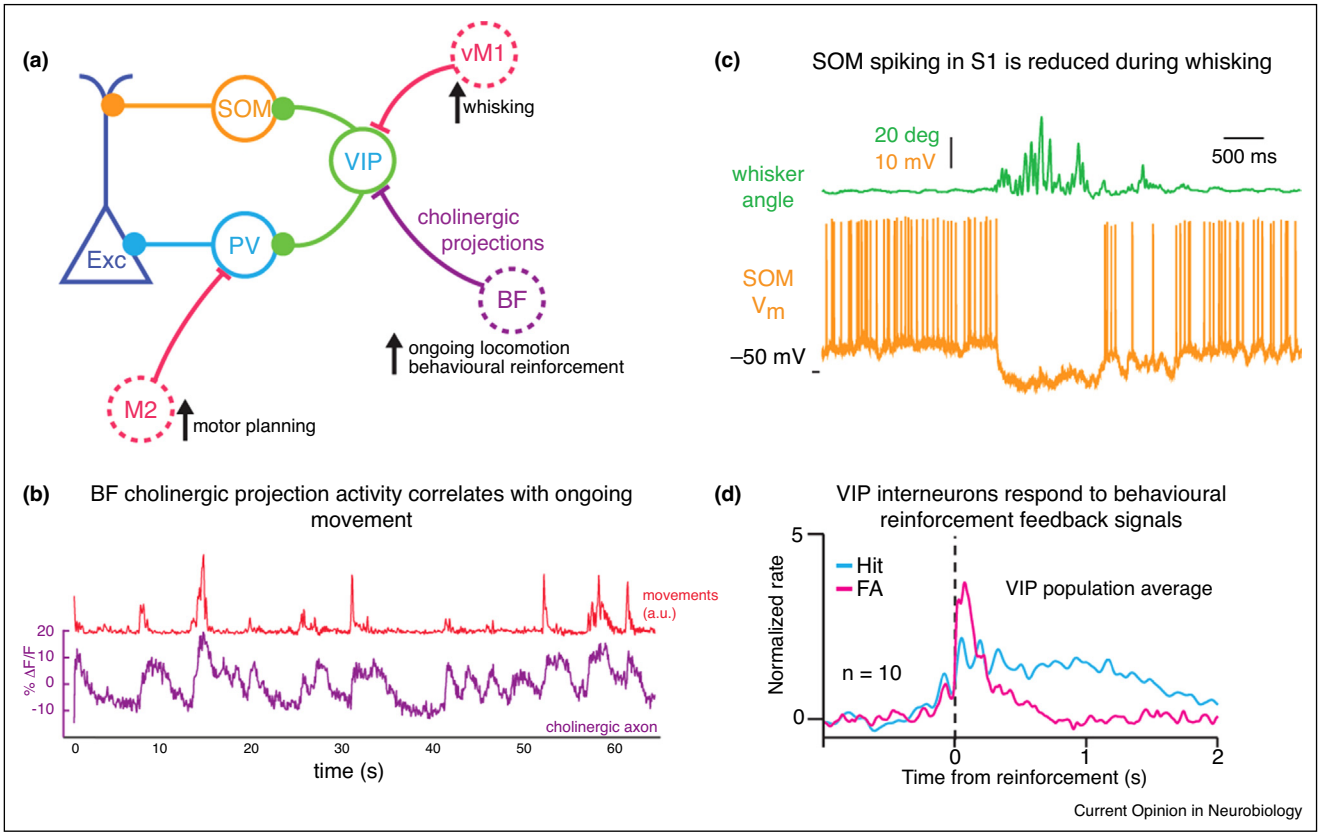
In visual cortex, locomotion was found to increase excitatory activity [50•,51,52]. Recent recordings from VIP interneurons found that they also increase their firing rate during locomotion [52–54], while the firing rate of SOMs decreases [52,53]. These findings suggest that increased stimulus-driven responses of excitatory neurons observed in V1 during locomotion could be caused by inhibition of SOM activity through activation of VIPs [53]. However, when combined with stimulus presentation, SOM interneurons increased their stimulus-driven firing rate during locomotion [51]. Recording activity of VIP, SOM and PV interneurons during still periods or locomotion in darkness or with visual stimulation revealed differential effects of locomotion on neuronal responses depending on the presence of visual stimulation [55]. During visual stimulation, interneurons from all three interneuron classes increased their responses with locomotion, challenging the generality of the VIP disinhibitory network as the mechanism underlying increases in stimulus driven excitatory responses during locomotion, and suggesting that the action of VIPs may be both stimulus and behavioral-state dependent.

By contrast, in the auditory cortex, locomotion caused a decrease in excitatory responses to auditory stimuli [56,57,58••]. This reduction in response is thought, in part, to be driven by direct corollary projections from neurons in secondary areas of motor cortex innervating auditory cortex directly immediately prior to movement (Figure 2a, b). These excitatory projections target PV interneurons in auditory cortex, thus inhibiting excitatory neurons during locomotion [57,58••]. In addition, the auditory cortex received motion-related cholinergic input alongside direct input from motor cortex; these two signals provide distinct movement-related information [47]. Cholinergic inputs from the basal forebrain target VIPs [53], SOMs [59], and excitatory cells directly [47], thereby providing information about ongoing physical activity and arousal state, whereas secondary motor cortex inputs provide top-down information about impending movement and target AC PVs and pyramidal cells just prior to movement initiation [47]. Cholinergic activity in auditory cortex increased not only during locomotion but during other small movements such as licking, paw movement, and whisking (Figure 2b) [47]. Similarly, it has been shown that cholinergic activity in the barrel cortex of mice is increased during active whisking [60]. Activity of VIPs also increased during active whisking as a result of direct input from primary motor cortex: VIPs were found to preferentially inhibit SOMs, releasing excitatory neurons from SOM inhibition [12]. This result is consistent with the finding that SOM interneurons were more active during quiet wakefulness (with no whisking) compared with other neuronal subtypes in L2/3 and were suppressed by both passive whisker deflection and active whisking (Figure 2c) [61].

Some of the effects of physical activity on cholinergic modulation of cortical neuron responses are due not simply to physical movement, but also to changes in the attentional or arousal state of the animal [62]. More generally, cholinergic activity in sensory cortex correlated with pupil size, a well-established measure of arousal state [62], feedback signals during behavioral tasks [63,64], behavioral performance [63], and behavioral context of the stimulus presentation [65•]. Cholinergic neurons in the basal forebrain are rapidly activated by feedback signals during behavioral tasks [64] and, consistent

**(Figure 1 Legend Continued) (c)** Example neuron showing increasing levels of SOM activation in visual cortex decreases firing rate, but has no effect on orientation tuning width. Adapted from [38]. **(d)** Example unit showing activation of VIP interneurons in visual cortex decreases orientation selectivity. Adapted from [46]. **(e)** Example units showing activation of PV interneurons in auditory cortex has both multiplicative and linear effects on frequency selectivity. Adapted from [21]. **(f)** Example units showing activation of SOM interneurons in auditory cortex has both multiplicative and linear effects on frequency selectivity. Adapted from [21]. **(g)** Activation of VIP interneurons in auditory cortex causes an additive shift in frequency selectivity ($n = 28$). Adapted from [14]. **(h)** Inactivation of SOM interneurons in piriform cortex causes a subtractive shift in odor tuning. Adapted from [45].

**Figure 2**




PVs and SOMs inhibit excitatory neurons in sensory cortex **(a)** whereas VIPs in primary somatosensory cortex preferentially target SOMs. VIPs receive input directly from primary vibrissal motor cortex (vM1) during active and passive whisker movement thus decreasing SOM activity [**c** — [61]]. During ongoing locomotion, auditory and visual cortex receives input from cholinergic neurons in the basal forebrain (BF) [**b** — [47]] and auditory cortex receives input from secondary motor cortex (M2) which conveys information about motor planning. Cholinergic activity also conveys information about feedback signals during behavioral training [64] and preferentially target VIPs, VIPs thus respond to feedback signals [**d** — [14]]. (a) Simplified circuit diagram of sensory cortex, solid circles indicate interneurons (VIP, SOM and PV) which target excitatory cells (Exc) and each other. Dashed circles indicate other brain areas which project to sensory cortex. (b) Activity in cholinergic axons in auditory cortex (purple shows a single example axon) correlates with small movements (licking, paw movements etc.) of the mouse (red). Adapted from [47]. (c) SOM (yellow) spiking activity is decreased during passive and active whisker movement (green indicates angle of whisker, Vm = membrane potential). Adapted from [61]. (d) VIP interneurons respond to behavioral feedback signals. They show shallow sustained response to water rewards in hit trials (cyan) and strong, sharp response to air puff or mild shock during in false alarm trials (magenta). Adapted from [14].

with the finding that they preferentially target VIPs in sensory cortex [47,53], VIPs show activity correlated with reinforcement signals (Figure 2d) [14••]. Thus, cholinergic modulation can exhibit both direct activation and indirect disinhibition (via VIPs) of excitatory neurons, providing a rich foundation for directing cortical responses in a context-specific fashion.

Combined, these studies suggest that inhibition controls modulation of sensory responses during locomotion, attention, and behavior, with a range of effects that are at least in part facilitated through cholinergic inputs that target VIPs and differentially perturb inhibitory and excitatory connections.

## Future goals for investigation of the function of inhibition in sensory processing and perception

The development of optogenetic tools led to considerable progress in understanding the role of inhibitory interneurons in sensory processing over a relatively brief period of time. However, application of optogenetics has thus far been generally coarse, targeting a broad class of interneurons over a relatively large area. Future studies need to target specific subclasses of interneurons, which will become amenable to specific targeting as genetic understanding of the classes and subclasses of interneurons improves [66]; one recent method targets specific cells through a combination of projection-specific and

genetically identified labels [67]. Furthermore, two-photon laser stimulation techniques now allow for targeting of single or multiple specific neurons for optogenetic manipulation (e.g. [68]) as well as coupling with single cell electroporation [69], which can further help to dissect the role of specific cells within sensory cortical circuits. Activation or deactivation of specific types of cell with optogenetics is often very strong and thus it is possible that subtle changes in depolarization state of neurons that may be important in sensory processing are missed. Measuring subthreshold responses during sensory processing and mimicking these changes with optogenetics could further help to unravel the roles played by interneurons in sensory processing.

To understand the different roles of neuronal subtypes in cortical networks, sophisticated models will need to be developed that can pull together vast amounts of information gleaned from different studies on the roles of neural subtypes and provide testable hypotheses [70]. Recently, there have been attempts to make more realistic circuit models which include subtypes of interneurons [71,72]. Lee *et al.* (2017) were able to replicate multiple experimental findings, including function of distinct interneuron subtypes in 'attentional gating' as well as an explanation for differential effects of VIP/SOM activity in visual cortex [19••,41]. Interestingly, both models found that top-down driven VIP activity need not be context selective to achieve attentional gating, something which can be tested experimentally. More realistic models of cortical circuits will help in understanding heterogeneous findings from different sensory areas, whether there are distinct roles of specific subtypes of interneuron in different cortical areas and also the variation caused by different experimental conditions. It is important to know the exact conditions of experiments in order to correctly define the roles of neural subtypes (e.g. [55]) to avoid confounding effects, for example, the arousal state of the animal [62]. Furthermore, it will be important in the future to corroborate findings or compare differences with other animals, as application of optogenetic tools in other animal models improves (e.g. [73]).

## Conflict of interest statement

Nothing declared.

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