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A blanket of inhibition: functional inferences from dense inhibitory circuit structure

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Abstract

The function of neocortical interneurons is still unclear, and, as often happens in biology, one may be able to draw functional insights from considering the structure. In this spirit we describe recent structural results and discuss some potential functional implications. In particular, many GABAergic interneurons appear to innervate nearby pyramidal neurons very densely and without any apparent specificity within their immediate vicinity, as if they were extending a "blanket of inhibition", contacting them often in an overlapping fashion. While it is clear that subtypes of interneurons specifically target subcellular compartments of pyramidal cells, and they also target different layers selectively, they appear to treat all neighboring pyramidal cells the same and innervate them en masse. We explore the functional implications and temporal properties of dense, overlapping inhibition by four interneuron populations.

Introduction

Although functional inhibition was discovered more than half a century ago [1], there is still vigorous debate as to what exactly inhibitory neurons (INs) do. Even for the paradigmatical example of a clearly defined IN population, the chandelier cells, it is still unclear whether they are actually inhibitory [2] or excitatory [3], or whether their function could be a mixed one, depending on the state of the network [4].

To make this problem more complicated, GABAergic interneurons belong to many different subtypes, and their function is unlikely to be homogeneous or simple. However recent data suggest that some INs project densely to nearby principal cells (PCs). To gather information that could constrain hypotheses about IN function we review recent studies on network the connectivity of five IN populations that together encompass ~85% of all neocortical INs: 1) Parvalbumin containing INs (PVs) are virtually always fast spiking cells (FSs), with particularly rapid action potentials. Due to the high overlap between FS and PV groups [5–8], we use only the term PV for simplicity. 2) Chandelier cells (ChCs), also known as axo-axonic cells [9] [10,11]. 3) Neurogliaform cells (NGFCs) [12,13], 4) Somatostatin containing INs (SOMs) [14] and 5) vasoactive intestinal peptide containing INs (VIPs) [15].

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Of these five populations PVs, NGFCs, SOMs and VIPs show virtually no overlap with each other [15–17], while some ChCs contain parvalbumin [11]. All studies reviewed here were performed in rats or mice.

Blanket inhibition

This term describes the dense and unspecific innervation of local PCs by INs, i.e., restricted to immediate intralaminar territories covered by their axons. PVs and SOMs project densely to PCs within an 200 μm radius (Figure 1). This dense innervation pattern was demonstrated in living IN-GFP brain slices across multiple cortical areas and developmental stages using two-photon glutamate uncaging [18,19]. The connection probabilities decayed with distance but at peak, at around 100 μm intersomatic distances, were ~80% for both IN types and in some recordings all INs within 200 μm of a PC were connected to it demonstrating highly overlapping inhibitory connectivity. Given that many axons are cut in slice, we expect these INs project to essentially every PC around them in the intact brain. Since these studies showed that a given PC receives inhibitory input from most PVs and SOMs around it, it stands to reason that any PV or SOM inhibits most PCs around it unspecifically. Prior to these studies, compatible but less comprehensive results had been reported, using paired electrical recordings [20].

The connectivity between INs is less well understood. Some studies report a high degree of connectivity between PVs, from PVs to SOMs and SOMs to PVs [21–23] (but see [5] and [24] for smaller estimates of PV->PV and PV->SOM). Thus the dense inhibitory blankets from PVs and SOMs to PCs might extend to INs too, with the clear exception that SOMs virtually never inhibit each other.

A recent study of ChCs found that within their local axonal cloud they also project densely to local PCs [10]. Nearly 50% of AISs within 200 μm from a ChC soma were apposed by a cartridge. This could be a significant underestimate of the real connectivity because of the technical caveats and stringent analysis methods employed (discussed in detail in [10]). Indeed, some areas within the ChC axonal fields had cartridges apposing nearly every AIS. Consistent with the lack of selectivity, an average of 4 ChCs were estimated to innervate any given AIS, indicating an overlapping pattern of inhibition. Dense innervation of virtually every PC AIS by ChCs in piriform cortex has also been observed [25]. Thus, ChCs appear similar to PVs and SOMs in terms of their local blanket inhibition. It would be important to study ChC connectivity with a similar method used on PVs and SOMs [18,19] to reveal the functional density of this blanket inhibition.

A final case for a “blanket” inhibitory innervation can be made for NGFCs, which mediate a spatially extreme form of blanket inhibition by forming presynaptic boutons that are not directly opposed to postsynaptic densities of other cells and secrete GABA into the neuropil some micrometers away from the functionally postsynaptic cells. This innervation strategy, showering cortical circuits with GABA, presumably accounts for the 87% connection probability observed from NGFCs to nearby neurons within 100 μm [13]. NGFCs additionally modulate synaptic transmission within their axonal field [13] and inhibit cells with more distant somata that have distal dendrites within the NGFC axonal fields [26].

Working through presynaptic $GABA_B$ receptors, NGFCs can decrease the effect of repetitive synaptic events [13]. A high degree of connectivity was observed in another recent study on layer 4 NGFCs, although presynaptic modulation of synaptic transmission upon thalamic stimulation was found only on PV-to-PC synapses but not on excitatory synapses formed by thalamocortical afferents which also contain presynaptic $GABA_B$ receptors [12]. This discrepancy might be simply due to presence of the whole PV somato-dendritic domain within the NGFC axonal cloud, rather than spatial specificity in the distribution of release sites within the NGFC axonal field.

Early and late blanket inhibition

Subtypes of INs have different temporal properties in their firing and synaptic dynamics and also target separate subcellular compartments of PCs. Due to dynamic changes and variance of synaptic weights [27], blanket inhibition is unlikely to invariantly shut down all PC activity in a region. PCs might rather be varyingly inhibited depending on the timing, synaptic weights and the position of the IN contact (Figure 1).

Two lines of evidence suggest that PVs are specialized for a fast and transient inhibition while SOMs deliver slow-onset, lasting inhibition. Firstly, both the excitatory input synapses and inhibitory output synapses of PVs vs SOMs, have consistently different dynamics [22,28–34]. Synapses on and from PVs are virtually always depressing: postsynaptic potentials peak in the beginning and then decrease dramatically during a high frequency train of action potentials. In contrast, synapses on and, sometimes but not always, from SOMs are facilitating, meaning that they are almost silent in response to a single action potential but subsequent postsynaptic potentials increase by several fold during a high frequency spike train. Dynamics of inhibitory synapses between PVs and SOMs are determined accordingly by the presynaptic cell [31].

Secondly, the amount of monosynaptic feedback inhibition within the populations is dramatically different between subtypes, in terms of synaptic connections between individual cells within the groups [22,23,31] as well as autaptic connections [35]. Individual PVs readily form synapses onto each other and themselves, while SOMs virtually never inhibit each other [22,24,31,36] allowing them to sustain persistent firing [37]. In addition some data suggest that PVs/FSs more often than non-FSs, form reciprocal connections to the local PCs that excite them, forming direct feedback inhibition loops [38–41] (however, see [19,21,42,43]). Moreover, SOMs disinhibit layer 4 through powerful inhibition of PVs [44]. Thus we expect that during lasting high frequency neocortical activity, such as is seen spontaneously and in response to sensory stimuli in vivo [45,46], there is a rapid-onset, transient blanket of inhibition by PVs which is later replaced by a slowly recruited, persistent blanket mediated by SOMs.

ChCs, like other PV cells, appear to have a fast, early action on local PCs [47]. To the best of our knowledge there is currently a lack of information about the detailed dynamics of ChC firing and synapses in the neocortex. However their output synapses might be depressing like PV synapses (see Fig. 4c in [47]) as is the case in hippocampus [48,49].

The spatially extreme NGFC inhibitory blanket is also temporally extreme, in that the slow $GABA_B$ receptor-mediated postsynaptic event, elicited by a single action potential in a NGFC, reaches its peak well over 100 ms later [50–52]. Also the $GABA_A$ receptor-mediated component of NGFC inhibition is slower and longer lasting than with PVs [50].

Functional relevance of blanket inhibition

In rodents INs form a minority, ~15% [53,54], while PCs constitute the majority (~85%) or neocortical neurons. Despite variance in input strength, every neuron receives both inhibitory and excitatory inputs [55,56] and PCs target only ~10% of the neurons around them [53]. Given these numbers one could infer that blanket inhibition serves to balance excitation and prevent epilepsy. However, more detailed functional roles of inhibition in cortical networks can be divided into five (partially overlapping) hypotheses: sharpening tuning of stimulus response relation through lateral inhibition [57]; generation/pacing of network oscillations through feedback inhibition [58,59]; normalization of input through feed-forward inhibition [56,60], modulation of stimulus-response gain of PCs [61] and computational discrimination of inputs into self-organizing maps [62]. Some of these hypotheses have been recently reviewed elsewhere [29,63], so we will not discuss them in detail but solely focus on some aspects of these hypotheses where the impact of the blanket configuration of inhibition is evident. As a related aside, the blanket configuration might reveal a principle for how cortical circuits are wired up during development and a further impetus to build a disinhibitory network to sculpt specificity into the blanket (Box 1), alongside the PC-specific synaptic weights.

The sharpening of excitatory responses by lateral inhibition is a traditional function of inhibitory circuits and one that seems to be at work throughout the sensory systems of the brain [57]. Any given excitatory input, by firing neighboring inhibitory interneurons, themselves connected to all neighboring excitatory cells, will achieve essentially a “winner take all” strategy, and enable the sole excitation of the desired target (Figure 2A). The design of blanket inhibition goes hand in hand with this functional logic, since one would want a uniform and unspecific inhibitory connectivity. This will assure that all excitatory inputs are subject to a similar degree of local filtering and thus prevent biases in the propagation of signals. An intriguing hypothesis, based on neural network theory, is the possibility that inhibitory circuits serve to separate in a multidimensional vector space similar patterns of excitatory inputs [64]. In fact, a learning rule with a local inhibitory spatial flanks can spontaneously generate self-organizing maps [62], helping to explain the common occurrence of functional maps in most regions of the brain. A local blanket of inhibition is critical for this function, since it will enable a circuit to orthogonalize inputs automatically, and this could be a critical aspect to enable sensory areas of the brain to enhance the discrimination among similar inputs.

A blanket inhibitory design is also ideal for feedforward inhibitory circuits to linearize or extend the dynamic range of PCs (Figure 2B). Otherwise some cells could escape this normalization and saturate with increasing excitatory inputs. This would essentially inactivate them from the network, defeating the purpose of this mechanism.

The role of inhibitory circuits in the generation of oscillations and synchronization could be equally well served by a blanket inhibitory design, although the functional implications are more complicated. As a result of the dense blanket inhibition PCs near each other experience synchronous inhibitory postsynaptic events from common presynaptic INs [65], and this could in principle serve to synchronize their spiking [58]. At the same time, electrically or synaptically coupled interneuron groups in slice can synchronize sustained spiking under some experimental manipulations [36,66]. On the other hand, recent work shows that interneuron spiking in neocortical brain slices is largely uncorrelated spontaneously during UP-states or after thalamic stimulation [65]. However, in vivo, the subthreshold membrane potential changes and spiking of some INs tend to be synchronized [67] and sensory evoked responses are apparently similar within cell groups [29]. Moreover, in apparent contradiction to the role of INs in generating oscillations [59], recent work suggests that inhibition can actually decorrelate firing of PCs [65,68,69]. In principle, from an information theoretic aspect both synchrony and decorrelated firing of neurons are useful – the prior for effective transmission and the latter for unambiguous representation of information for example. Perhaps a compromise can be reached by neuronal networks where irregular firing and population level rhythmicity coexist [70]. If this is the case, interneurons could be involved in generating both synchrony and irregular firing, depending on the exact state of the circuit. Future work needs to examine the exact role of INs in synchronizing or decorrelating PCs.

Finally, another potential function of inhibition could be to leave a temporal mark in the circuit, as a refractory trail for the spread of further excitatory patterns (Figure 2C). Inhibition, in particular by the facilitating SOMs and the $GABA_B$ receptor-triggering NGFCs, can remain in a given cortical circuit after the excitatory neurons that recruited the INs have ceased firing (see e.g., disynaptic inhibition traces in [30,33,60]). This could result in a transient trail of inhibition left behind by a passing wave of excitation, possibly causing a network level refractory period akin to that associated with the action potential in an axon. Like the latter allows action potential propagation in only one direction along an axon, the inhibitory trail might, to some extent, enforce directionality of spread of activity seen for example across the cortical surface during sensory stimulation [71]. The blanket configuration would be ideal for this function, and infact early and late “blankets” could differentially re-channel excitatory activity into different circuits, enabling a novel type of fast circuit plasticity that does not require the slower Hebbian learning rules.

Since the possible functions of INs are so many, it might be useful to comprehensively study, through simulations and experiments, whether realistic networks can actually perform multiple roles simultaneously.

Conclusions

Blanket inhibition is a general feature of most inhibitory connections to principal cells in the cortex, except for VIP cells which appear to make holes in the blankets. Blanket inhibition exists in different temporal domains and could be critical to implement different functional roles of inhibitory neurons.

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Highlights

- Key inhibitory interneurons innervate pyramidal neurons densely and unspecifically.
- Timing of inhibition is different across interneuron populations.
- Dense inhibitory network structure should inform hypotheses of function.
- Disinhibitory interneurons can make holes in the dense inhibitory “blanket”.

Box 1: "Making holes in the blanket: VIPs as disinhibitory specialists"

In contrast to the dense blanket inhibition of PCs by INs discussed here so far, VIPs do not connect to most PCs within their reach [24,72,73]. VIPs specifically target SOMs and, to a lesser extent, PVs [24,72,73]. Two recent papers [72,73] show inhibition of SOMs by VIPs during behaviorally triggered excitation of VIPs, by whisking in somatosensory cortex and by aversive feedback stimuli in auditory and prefrontal cortices. This would disinhibit the PCs under SOM blanket inhibition. Given the horizontally restricted extent of VIP axons [72,74,75], activation of a limited number of VIPs could make holes in the blanket of inhibition, selectively disinhibiting PCs in some regions while leaving others under the blanket (Figure 3). These disinhibitory holes might be expected to be the size of the axonal fields of a few SOMs, and to occur at times of behaviorally relevant activation of VIPs [72,73] as well as spontaneously due to the high resting membrane potential and excitability of these neurons. Alternatively, if many or all VIPs can be activated by a stimulus, this would briefly disable the whole SOM blanket, possibly allowing for spread of excitation into an unusual direction (see "Functional relevance of blanket inhibition"). Given that VIPs could be activated by higher cortical feedback [72,73], these holes in the blanket might serve to recall past experiences.

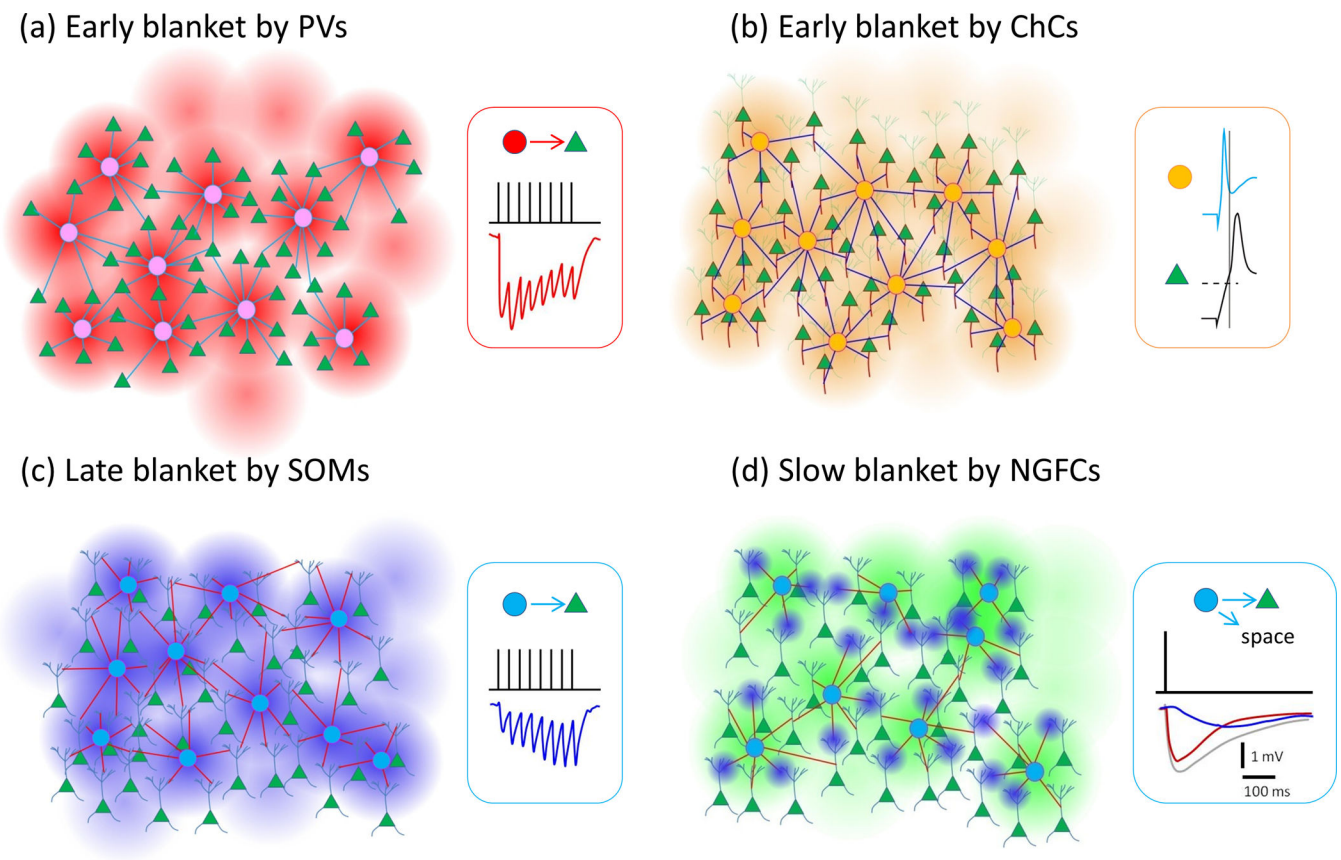

Figure 1.

Blanket inhibition by the different subtypes of interneurons. (a) Early blanket inhibition by PVs. (b) Early Blanket inhibition by ChCs. Right panel shows early activation of ChCs compared to PCs after layer 1 stimulation (copied with permission from [4]). (c) Late blanket inhibition by SOMs. (d) Slow blanket inhibition by NGFCs. Inset: Gray trace represents total inhibitory current while blue is a $GABA_B$ receptor component and red is the difference. Green triangles represent PCs, and circles in each panel represent INs projecting to PCs. Traces shown in (a), (c), and (d) represent responses of PCs to IN inputs.

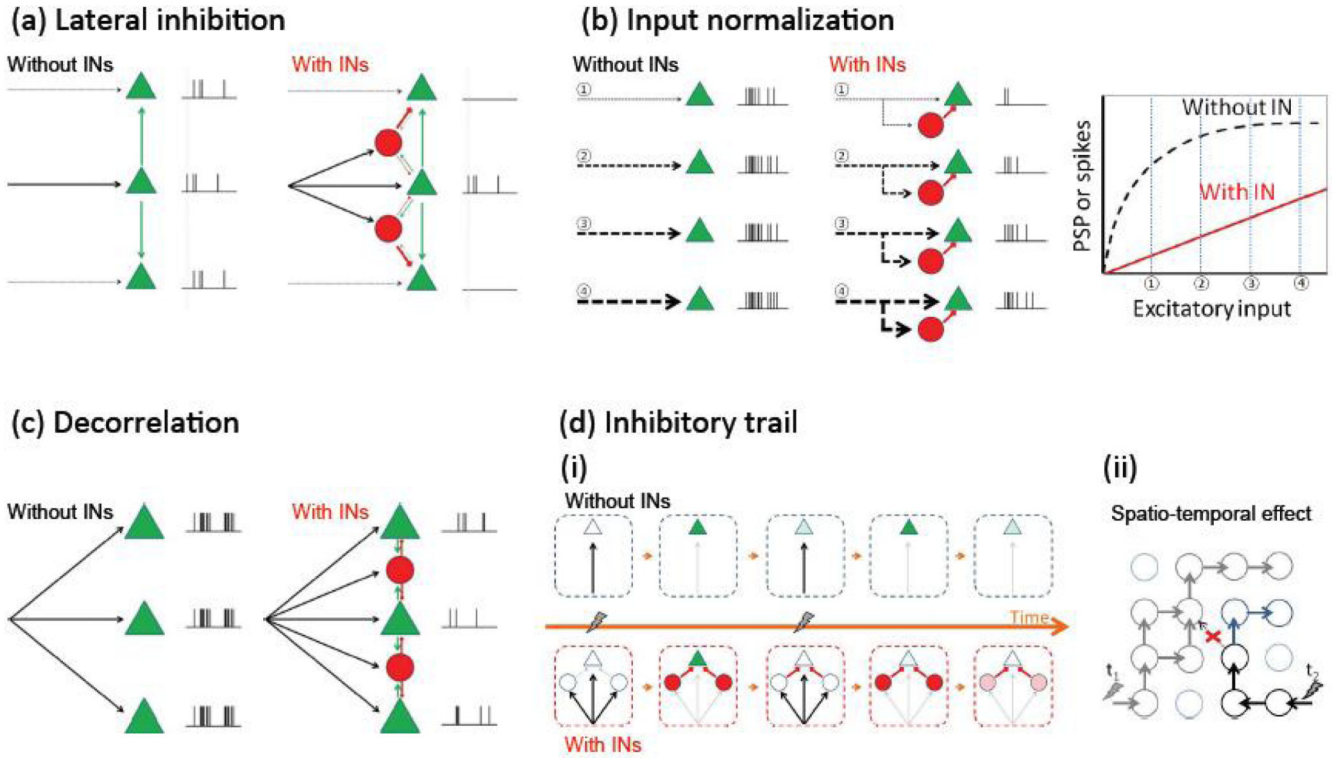

Figure 2.

Functional roles of INs. (a) Lateral inhibition. (b) Input normalization. (c) INs decorrelate PC spiking. (d) Inhibitory trail reduces response to a second input. Lightning symbols indicate input along arrows. (ii) Simple temporal effect. Green triangles represent PCs and red circles represent INs. (ii) example of spatio-temporal effect. Here circles represent modules containing both INs and PCs, and arrows the spread of excitation; because of the inhibitory trail stimulation of a pathway at t_1, shortly before stimulation of another path at t_2 blocks the progress of the latter activity at the red cross and directs it instead to the blue direction.

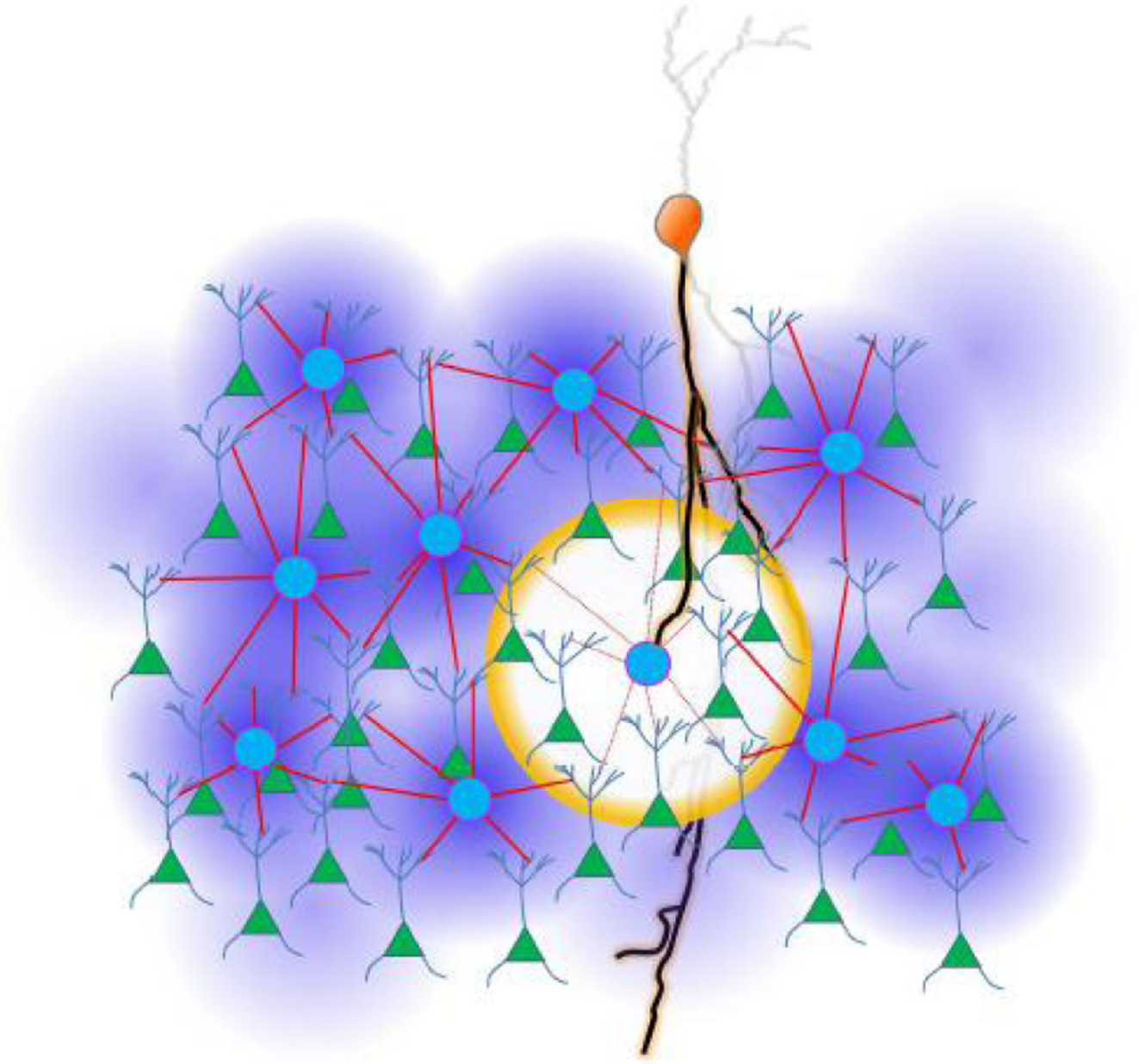

Figure 3.
Hole in inhibitory blanket. Orange cell represents a VIP disinhibiting a network through inhibition of a SOM. Green triangles represent PCs, and a light blue circles SOMs.