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From circuit motifs to computations: mapping the behavioral repertoire of cortical interneurons

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Abstract

The exquisite architecture of cortex incorporates a myriad of inhibitory interneuron types. Until recently, the dearth of techniques for cell type identification in awake animals has made it difficult to link interneuron activity with circuit function, computation and behavior. This situation has changed dramatically in recent years with the advent of novel tools for targeting genetically distinct interneuron types so their activity can be observed and manipulated. The association of different interneuron subtypes with specific circuit functions, such as gain modulation or disinhibition, is starting to reveal canonical circuit motifs conserved across neocortical regions. Moreover, it appears that some interneuron types are recruited at specific behavioral events and likely control the flow of information among and within brain areas at behavioral time scales. Based on these results we propose that interneuron function goes beyond network coordination and interneurons should be viewed as integral elements of cortical computations serving behavior.

Introduction

Devoted to the idea that “nature delights in repeating itself”, Cajal developed the notion that cerebral cortex may be composed of stereotypic patterns, repeated with a large diversity of specific variations [1,2]. His research initiated the search for canonical circuit motifs: cortical sub-networks that are repeated across areas and presumably support similar computational functions. This line of research led to the discovery of the “cortical column”, a vertical structure of neurons sharing similar receptive field properties in sensory cortices [3,4] and its proposed anatomical substrate, the “cortical module” [5]. The perplexing variety of cell types within cortex long appeared an “impenetrable jungle” [1] until recently developed technologies for cell-type-specific targeting enabled the field to probe how

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distinct interneuron types participate in cortical circuits and what computations these circuits support during behavior.

The main focus of our review will be on recent work that uses genetic targeting to access specific cortical interneuron subtypes. First, we will provide a brief historical overview of research leading to the conclusion that interneurons are central to cortical computation. Next, we discuss two faces of interneuron function; under what conditions are they activated (“recruitment”) and how do they affect the local circuit (“impact”). Novel techniques for cell type identification and manipulation have finally enabled the investigation of these questions and begun to reveal the function of interneurons in cortical computations and behavior.

Do interneurons compute? Insights from hippocampus and visual cortex

The neuronal operations that transform the inputs to a cortical area into its outputs are referred to as ‘cortical computations’ and were traditionally investigated in terms of principal cell function, leaving open questions about the role of interneurons. The potential involvement of inhibitory neurons in computations has been investigated and debated mainly in the hippocampus and the primary visual cortex (V1), two regions with well-established single neuronal tuning properties: place cells (i.e., cells that fire in a particular physical location) in the hippocampus and orientation and direction tuned cells of V1. In these studies, interneuron identity was mostly inferred from high firing rate and narrow spike width, features likely corresponding to parvalbumin (Pv) expressing basket cells [6–8].

Most place cells are sharply tuned to one or a few locations of the environment, while inhibitory cells often have more complex, multimodal tuning properties [9,10]. The spatial firing maps of hippocampal interneurons were initially interpreted as mere reflections of their local presynaptic pyramidal inputs [11–13], arguing against computational roles. Later it was discovered that hippocampal interneurons have both “on” and “off” fields, spatially localized increases and decreases in activity, with information content comparable to that of principal cells [9,10]. Furthermore, interneurons not only exhibit positive spatial correlation with place cell firing, suggestive of a place cell to interneuron direction of information flow, but sometimes also strong negative correlations [14]. Thus interneurons could contribute to place-specific firing with “on” fields that suppress out-of-field excitation [10] and “off” fields that allow spatially restricted excitatory input [9]. These results lead to the suggestion that hippocampal interneurons play critical roles in determining the spatial tuning of principal cell [10].

A parallel line of studies attempted to elucidate whether and how interneurons in sensory cortices influence receptive field properties of principal cells. Interneurons in the visual cortex exhibit heterogeneous tuning properties; many show broad or even no tuning, whereas other inhibitory cells are as narrowly tuned as pyramidal cells [15–18]. Most of the principal cells receive inhibition tuned to their preferred orientation, but in a large subset the inhibitory input is tuned to non-preferred orientations [19]. Whether inhibitory interneurons actually participate in shaping tuning in V1 in specific ways can be probed using optogenetic manipulations. Two recent studies showed that Pv interneurons provide different forms of gain control: Atallah et al. found Pv cells perform a linear transformation

on pyramidal cell input-output curves involving both subtractive and divisive components [20], whereas Wilson et al. found Pv cells primarily divisive [21]. In contrast, Lee et al. showed that Pv cells sharpen tuning and thus improve perceptual discrimination [22]. These and other studies also probed the role of somatostatin (Som) expressing interneurons in V1. They showed that Som interneurons provide subtractive inhibition, shifting the tuning curves of pyramidal cells [21]. In addition, Som interneurons appear to be involved in surround suppression, the attenuation of responses at the center of a neuron's receptive field by stimulation of the receptive field surround [23,24].

In summary, a new consensus is emerging according to which interneurons actively participate in cortical computations by influencing the receptive field properties of principal neurons [20–25]. However, determining which specific transformations are performed by which interneuron types will require further investigation.

What are the canonical inhibitory circuit motifs?

Cortical interneurons differ in the expression of protein markers (e.g. parvalbumin), in the neuromodulators they co-release (e.g. somatostatin), in their firing patterns in response to current injections and in many other ways [26,27]. While a discrete classification of interneurons based on any single marker is not possible, many markers do map to anatomically relatively homogeneous neuronal classes and can provide systematic access to genetically homogeneous populations [26]. The identity of cells recorded *in vitro* was traditionally revealed only post hoc in the course of morphological or immunocytochemical evaluation. This made studying interneuron types tedious and characterizing rare subtypes remained a subject of a great deal of serendipity. Recently, targeted *in vitro* recordings, enabled by cell type specific expression of fluorescent markers in new transgenic rodent models [28], allowed high-yield and more easily repeatable experiments on interneuron connectivity. Furthermore, bidirectional optogenetic manipulations provided a powerful tool for probing circuit functions of various interneuron types. These technological improvements were exploited by a series of novel studies, greatly advancing our understanding of cortical interneuron circuits.

Cortical inhibitory interneurons are classically divided into two major categories. Perisomatic interneurons synapse on the somata and proximal dendrites of pyramidal cells and are thus strategically positioned to control their output. Dendrite-targeting interneurons, on the other hand, send projections to the distal dendrites of the pyramidal cells, thus gating the incoming information [27,29]. The two most prominent representatives of these classes are the Pv and Som expressing interneurons (Fig. 1a–b). Perisomatic Pv cells are heavily interconnected by chemical synapses and electric coupling promoting synchronous activity [8,30–33]. Pv-expressing interneurons with basket morphology form recurrent loops with pyramidal neurons, thought to be important substrates of feedback inhibition [34]. A recent study showed that the other major basket cell type, interneurons that express cholecystokinin (Cck), provide strong feed-forward inhibition recruited by incoming fibers in the hippocampus [35]. A third type of perisomatic interneurons, the chandelier cells, are defined by their extreme target specificity [36]. Because they exclusively target the spike initiation zone of pyramidal cells they were long proposed to serve to ‘veto’ output spikes. However,

recent studies showed that their effect on pyramidal neurons may be excitatory [37]. Determining the exact area-specific contingencies under which they provide inhibition, excitation or shunting [37–40] will require further studies. A novel developmental genetic approach to selectively target chandelier cells holds great promise for better understanding their network and behavioral function [41]. As opposed to Pv neurons, the dendrite-targeting Som interneurons largely lack within-type synaptic connections providing more asynchronous parallel pathways onto other interneuron types as well as pyramidal cells [8,31,32,42]. A subset of Som interneurons, Martinotti cells projecting to layer 1, participate in local pyramidal cell–interneuron–pyramidal cell circuits by mediating disynaptic inhibition from one principal cell to its excitatory neighbors [43,44]. Som interneurons were also shown to be capable of exerting highly focal, compartmentalized control over individual dendritic spines [45]. A subpopulation of Som expressing interneurons in layer 4 mediates disinhibition of local principal cells via Pv interneurons [46]. While these studies suggest specific connectivity patterns within the cortical circuit, a recent report found non-selective, nearly all-to-all connectivity from Som interneurons to local pyramidal cells in the mouse frontal cortex [47].

Interneurons make up almost all the neurons in layer 1 and recent *in vivo* work demonstrated that a major fraction disinhibits layer 2/3 pyramidal cells via Pv neurons in auditory cortex [48]. *In vitro* work showed that anatomically defined cell types of layer 1 differentially affect layer 5 pyramidal cells in sensorimotor cortices: neurogliaform cells inhibited whereas single-bouquet cells disinhibited them [49].

Recently, three papers converged on a circuit motif controlled by cells expressing vasoactive intestinal polypeptide (Vip; Fig. 1c) [32,50,51]. Vip expression demarcates a small population of interneurons (~10–15%), located mostly in the supragranular cortical layers, that are distinct from the two major interneuron populations defined by Pv and Som expression. These neurons – as also suggested by earlier anatomical studies [52–54] – preferentially target other types of inhibitory neurons, potentially providing disinhibitory control by releasing pyramidal cells from inhibition. All three studies agreed that the major target of Vip interneurons are the Som-expressing interneurons. VIP inhibition onto Pv-expressing interneurons was found to be either comparable to [32], stronger [50] or weaker [51] than that onto pyramidal cells but always weaker than onto Som interneurons, suggesting that the strength of these connections may vary slightly across different cortical areas. The Vip to Pv connection in the hippocampus and motor cortex was shown to undergo substantial experience-related plasticity, which likely increases the variability of connection strength [55]. Importantly, Pi et al. provided the first *in vivo* demonstration that Vip interneurons generated disinhibition, impacting a functionally defined, strongly tone-responsive subset of pyramidal cells in the auditory cortex. Taken together, the three studies described very similar connectivity patterns for Vip interneurons in four functionally and cytoarchitecturally different regions of the neocortex: three sensory areas, the auditory [50], visual [32] and somatosensory [51] cortices and the prefrontal cortex [50]. Thus, the Vip-controlled disinhibitory circuit appears to define a canonical cortical circuit motif (Fig. 2).

Mapping the behavioral repertoire of cortical interneurons

Cortical neurons tend to show great heterogeneity in response properties during behavior (e.g. [56–59]). For instance, even neighboring neurons in prefrontal cortex encode distinct combinations of sensory, motor and other features with unique temporal dynamics, resulting in the vexingly complex “cortical response zoo”, which greatly complicates the interpretation of extracellularly recorded neural activity during behavior [56,59,60]. Similarly puzzling response diversity has been reported in sensory and motor cortices [57,58]. Indeed, such representational heterogeneity can have computational benefits [60–63]. However, it is not known whether response diversity is a property of a defined cortical population, or if part of this heterogeneity can be attributed to cell-type diversity within the recorded population. This question is particularly relevant for inhibitory interneurons because of the large diversity of subtypes each with distinct connectivity and intrinsic properties [27,64].

In the previous section we reviewed evidence for well-defined network functions associated with interneuron classes; however, network function does not necessarily imply behavioral correlates. It is conceivable, that interneuron function can only be understood with reference to the circuit they are embedded in; for instance, by referencing interneuron activity to local principal cells using a cross-correlation approach or registering interneuron spiking to local field potential oscillations [29,65–68]. In this case, aligning interneuron activity to behavioral events may not uncover specific moments of recruitment.

Recent technical developments have enabled testing these ideas [8,69–76]. For instance, optogenetics-assisted identification of genetically defined cell types enables mapping the behavioral correlates of rare neuron types [8,75,76]. Briefly, a defined population of neurons is rendered light-sensitive by cell-type specific expression of a light-sensitive cation channel (variants of channelrhodopsin; [77]) via viral delivery or transgenic approaches [28]. Neurons from the targeted cell type are then identified in extracellular recordings based on their short latency light-evoked responses.

Applying this optogenetic tagging method, P_v- and Som-expressing interneurons were recently investigated in the anterior cingulate cortex (ACC) of freely behaving mice (Fig. 1d–g) [8]. Mice were trained to perform a foraging task in which they had to shuttle back and forth between a distant trigger location and a dedicated reward zone. P_v and a subset of Som interneurons, characterized by narrow action potentials (NS-Som), showed strong behavioral correlates of the foraging decisions: NS-Som neurons uniformly suppressed their activity when the mice entered the reward zone (Fig. 1f–g), whereas P_v neurons, again as a homogenous population, became phasically active when the animal left the reward zone (Fig. 1d–e). In addition, the activity increase of P_v cells was correlated with the time the animal had spent in the reward zone before deciding to leave. In another study, prefrontal P_v-expressing interneurons were investigated in mice during auditory fear conditioning [78]. P_v neurons were suppressed during freezing and fear expression was causally dependent on this effect.

Pv-expressing interneurons have been also recorded with the juxtacellular technique in head restrained behaving rats [74]. This study showed that while pyramidal neurons in the forelimb area of the motor cortex have diverse behavioral correlates in relation to motor preparation, initiation and execution, identified Pv neurons are mostly active during the expression of voluntary movements, constituting a homogeneous group. Similarly, Lapray et al. demonstrated that hippocampal Pv-expressing basket cells are mostly active during movement as opposed to quiet wakefulness in freely moving rats [71].

The responses of Vip-expressing interneurons were probed in auditory cortex during an auditory discrimination task [50]. Many Vip neurons showed auditory tuning but the surprising observation was that they were most strongly and uniformly recruited by reinforcement signals: with rapid phasic activation after punishment (air puff or foot shock) and somewhat weaker but more sustained response after water reward (Fig. 1h–i) [50]. Vip interneurons have similar circuit functions across four distinct cortical regions, which shows they play analogous roles in distinct cortical circuits [32,50,51]; therefore, it will be interesting to determine if they also have similar behavioral correlates across regions.

These new data, combined with our knowledge of cortical interneuron circuits, allows one to speculate about the network and behavioral function of interneuron types. Pv neurons are likely to control the output of their cortical area. This implies that Pv neurons should be active when this output is formed, which is strongly region-specific. This may explain their activation during foraging decisions in the ACC (Fig. 1d–g) [8] and their elevated firing during movement expression in the motor cortex [74]. On the other hand, Som interneurons are in a position to control the input to cortical pyramidal cells. Interestingly, NS-Som cells are uniformly silent in the ACC during the exact period when incoming information might be integrated to form a leaving decision in the foraging task [8]. In line with this proposed role in inhibitory gating, Som neurons in the barrel cortex are suppressed during passive and active whisker sensing [51,79]. Vip interneurons express fast ionotropic receptors for serotonin and acetylcholine [80–83], putting them in an optimal position to rapidly relay long-range neuromodulatory signals [84] as well as other long-range input [51]. By disinhibiting pyramidal cells via Som interneurons, they provide a switch by which other cortical and subcortical areas can engage cortex. These data support a new model of interneuron function: interneurons may exert a precise control over cortical information flow by selectively gating distinct input and output channels governed by the requirements of ongoing behavior.

Concluding remarks

Until recently, it has been unknown whether interneurons form canonical circuit motifs across different cortical areas. Similarly, it has been unclear whether specific types of interneurons have signature behavioral correlates or their function can only be explored in terms of circuit function and oscillations. New transgenic mouse lines, optogenetic tagging and awake juxta/intracellular recording techniques enabled a series of recent studies that have already revealed a great deal about interneuron network and behavioral functions. The contours of a canonical cortical microcircuit are already becoming visible, revealing different cortical interneuron subtypes in critical positions. Moreover, it appears that

interneurons have functions beyond network coordination and certain subtypes can be recruited at specific behavioral events. As the behavioral repertoire of different interneurons is becoming clearer it appears that they serve to control the flow of information. These recent breakthroughs foreshadow a deeper understanding of the logic of the cortical network guided by studies of identified cortical cell types.

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Highlights

- Inhibitory interneurons actively participate in cortical computations
- Cortical interneurons form canonical circuits
- Cortical interneurons are recruited under specific behavioral contingencies

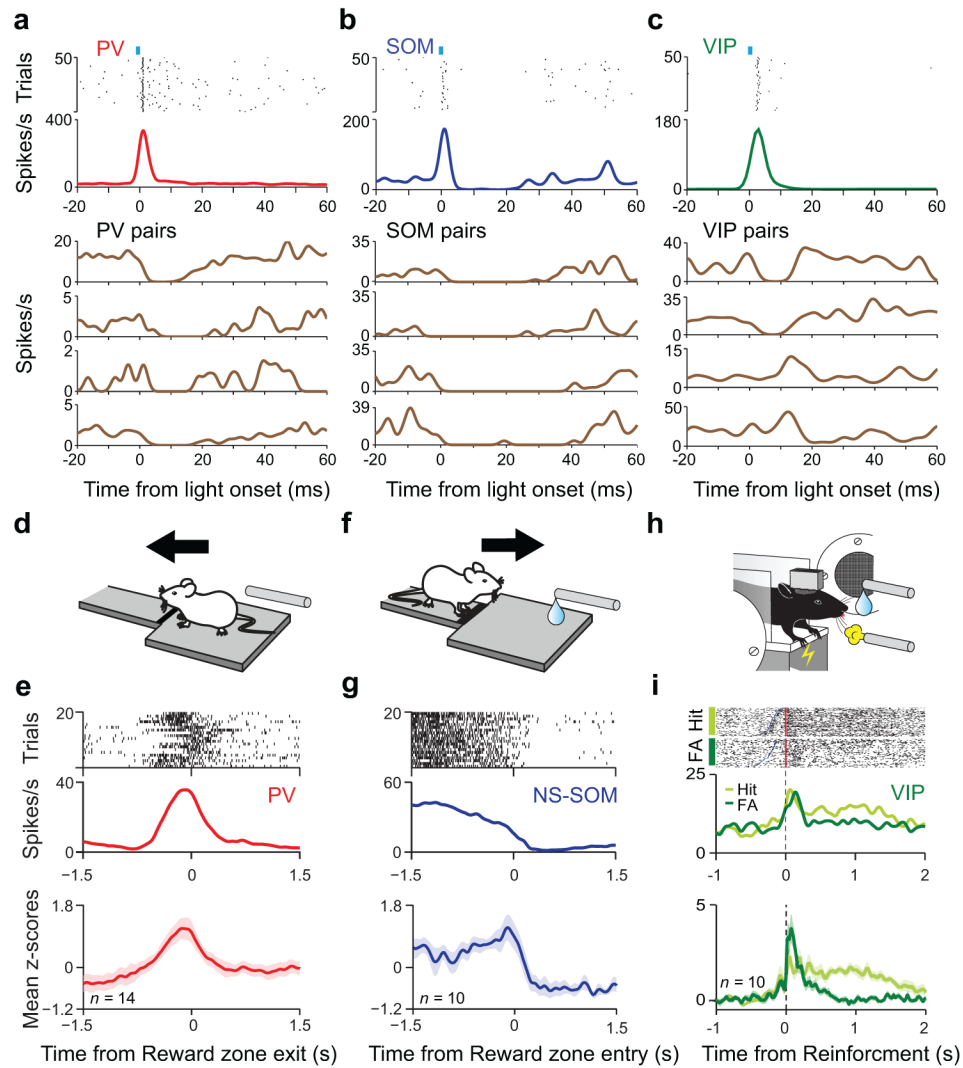


Figure 1. Network effects and behavioral correlates of identified interneuron classes
ab,c, Top, spike raster and peri-stimulus time histogram (PSTH) of Pv (a), Som (b) and Vip (c) interneurons aligned to light pulses. Bottom, PSTH of four simultaneously recorded unidentified neurons (Pv pairs, Som pairs and Vip pairs). Pv and Som pairs are inhibited after light pulses; Vip pairs are either inhibited (first and second PSTH) or show delayed activation (third and fourth PSTH), indicating disinhibition. **d**, Schematic depicting a mouse leaving the reward zone in a foraging task. **e**, Top two panels, spike raster and peri-event time histogram (PETH) of a Pv interneuron aligned to reward zone exit. Bottom, mean z-scored response of 14 PV neurons (shaded area indicates s.e.m.). **f**, Schematic depicting a mouse entering the reward zone in a foraging task. **g**, Top panels, spike raster and PETH of a NS-Som interneuron aligned to reward zone entry. Bottom, mean z-scored responses of 10 NS-Som neurons (shaded area indicates s.e.m.). **h**, Schematic of auditory go/no-go discrimination task. **i**, Top two panels, raster plots and PETHs of a Vip interneuron aligned to reinforcement (light green, reward; dark green, punishment; FA, false alarm). Bottom panel, mean z-scored responses of 10 Vip interneurons. Modified from refs 8 and 50.

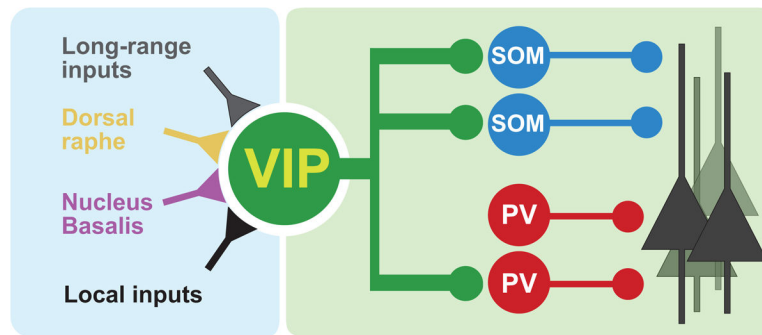


Figure 2. Disinhibitory microcircuit controlled by Vip interneurons

Vip interneurons receive long-range and local excitatory inputs as well serotonergic and cholinergic neuromodulatory projections from the dorsal raphe and nucleus basalis, respectively. They control the activity of a cortical pyramidal cell subpopulation by disinhibiting them mostly through Som interneurons.