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

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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.

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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 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 [6,7,8••].

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 [20,21•,22–25]. 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. Peri-somatic 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 (Figure 1a,b). Perisomatic Pv cells are heavily interconnected by chemical synapses and electric coupling promoting synchronous activity [8••,30,31,32••,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, is 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 [37–39,40•] 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