



HHS Public Access

Author manuscript

Neuron. Author manuscript; available in PMC 2018 August 03.

Published in final edited form as:

Neuron. 2015 July 15; 87(2): 247–248. doi:10.1016/j.neuron.2015.06.041.

Parvalbumin interneurons: All forest. No trees

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Abstract

There has been a surge of interest in how inhibitory neurons influence the output of local circuits in the brain. Here, Scholl et al. provide a compelling argument for what one class of inhibitory neurons actually does.

Main text

What is cortical inhibition good for? Recently, the answer to this question is remarkably similar to one of those questions on “Family Feud”, where there’s a survey of opinions, and the top 10 answers are all correct. Fortunately, the results from Scholl et al in this issue, add enough new data to tip the scales in favor of one simple answer.

In the neocortex, inhibitory neurons are a fairly small minority, comprising roughly 20% of all cortical neurons. Historically, this has made it difficult to find these cells and to record from them in the intact brain. Even more maddening, this small population is subdivided, very roughly, into 3 groups (and more likely a dozen), based on their interaction with excitatory neurons (Kawaguchi and Kubota, 1997). Parvalbumin (PV)-expressing interneurons fire rapid barrages of action potentials, and are accordingly named “fast-spiking” interneurons. These innervate and inhibit the cell bodies of excitatory neurons. Somatostatin (SOM)-expressing interneurons have firing rates that are more on par with the local excitatory neurons, and are thus often referred to as “regular-spiking”. These innervate and inhibit the dendrites of pyramidal neurons. In the primary visual cortex, where these cells have been most extensively studied, both groups receive strong excitatory input. The final group of inhibitory neurons is characterized by their expression of vasoactive intestinal polypeptide (VIP). These cells appear to inhibit other inhibitory neurons and to receive neuromodulatory input from the brainstem, and are thought to regulate brain states during arousal (Hangya et al., 2014; Pfeffer et al., 2013).

Over the past half decade or so, a number of mouse lines have been developed in which expression of the gene encoding the bacteriophage tyrosine recombinase enzyme, Cre recombinase, is directed by PV, SOM, or VIP promoter/enhancer elements (Pfeffer et al., 2013). These mice have given us the ability to finally visualize and manipulate each inhibitory class.

Scholl et al provide new data supporting a view that the computational heavy lifting in the cortex is done by the excitatory neurons, whereas PV cells seem to leave a lot of potentially very useful information on the table. Rather than integrating specific cortical inputs to create complex receptive fields that extract higher order information from the visual scene, as

excitatory neurons do (Cossell et al., 2015), PV cells simply integrate inputs from the local network without specificity (Figure 1). Being uniformly connected to the local excitatory neurons makes PV cells well suited to a different role – monitoring and regulating the total activity of the local network, also known as gain control.

To reach this conclusion, they imaged the activity of large numbers of excitatory and PV neurons in mouse primary visual cortex using 2-photon excitation of the calcium indicator Oregon Green BAPTA. PV cells in these mice selectively expressed the red fluorescent protein tdTomato, which was used to identify these cells and separate their signals. Many earlier studies found that PV cells are less interested in the particular orientation of a visual stimulus than are excitatory neurons. This response promiscuity could be restricted to orientation selectivity, or it could be a general property of PV cells. Scholl et al examined this by measuring ocular dominance and binocular disparity in PV and excitatory neurons. Because excitatory neurons in the binocular zone of visual cortex receive inputs from both eyes, they can be sensitive to binocular disparities and respond optimally when the visual stimuli delivered to each eye are slightly out of phase. This binocular disparity gives rise to a perception of the world in three dimensions.

What they found is quite remarkable, while at the same time quite consistent with other investigators. Despite having far stronger responses to binocular stimulation than excitatory neurons, PV cells appear to discard the binocular disparity information that comes with it. That is, they don't seem to participate much in the process of extracting depth information. Instead, these inhibitory cells simply sum all of the information from the surrounding network of neurons residing within 100 microns or so of their position.

If this same local and linear integration model applies to carnivore and primate visual cortex, where neurons with similar orientation preference are clustered into columns of orientation and ocular dominance, then, as the authors point out, PV cells in these brains would find themselves surrounded by excitatory neurons of like tuning (Anderson et al., 2000). These PV cells would then be expected to show similarly sharp orientation and ocular dominance tuning, in stark contrast to what has been reported in mice where such columns do not exist. Should this be true, it would call into question the idea that broad tuning seen in PV cells acts to sharpen excitatory tuning (Lee et al., 2012; Liu et al., 2011). Instead, the authors argue, as others have done (Bock et al., 2011; Kerlin et al., 2010), that by simply integrating information from nearby neurons, PV cells are taking a moment-by-moment pulse of network activity and acting on this information to modulate cortical response gain (Atallah et al., 2012; Wilson et al., 2012). That is, PV cells are not altering the computations performed by local excitatory neurons, but altering their firing rates.

Gain control is not simply there to prevent seizures. An emergent model, based on results from many labs, is that PV cell-mediated gain control is tremendously important for, perhaps, the most interesting aspect of cortical processing: Learning (Figure 1). In juvenile cortex, a prolonged drop in sensory input to cortex drops excitatory firing rates. The most rapid anatomical and physiological plasticity that occurs to compensate is a loss of feed-forward input to PV cells (Kuhlman et al., 2013). This severe reduction in PV cell responsiveness in turn drops local inhibition of excitatory networks, enabling them to be

more responsive to whatever sensory input remains. This form of experience-dependent plasticity is simply gain control by another name. By working to re-establish normal excitatory firing rates PV cells set the conditions necessary for slower, more permanent changes in the excitatory wiring of local networks.

In adults, too, PV cell-mediated gain control is a central part of learning (Hangya et al., 2014). In mice trained to associate a tone with a foot shock, PV cells in primary auditory (Letzkus et al., 2011) and dorsomedial prefrontal cortex (Courtin et al., 2014) are phasically inhibited during fear expression, whereas PV cells are phasically activated when mice transition out of a reward zone (Hangya et al., 2014).

For years our understanding of inhibitory neocortical circuitry has been limited by our ability to access specific cell subclasses. The emergence of transgenic animals, coupled with the ability to express proteins in specific cell types, is revealing the underlying rules of circuit connectivity, both at the functional and anatomical levels. Instead of playing a game of Jeopardy, where answers are questions, we are moving towards Wheel of Fortune, where the individual letters, or cortical motifs, are being uncovered.

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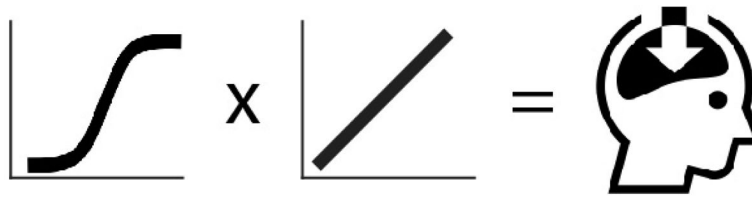


Figure 1. PV cell-mediated gain control and learning

(Left), Pyramidal neurons non-linearly integrate broad synaptic input to produce sharply tuned spiking output. (Middle), PV interneurons simply sum their inputs linearly. (Right), The resulting broad inhibition acts to alter firing rates of pyramidal neurons, which underlies learning.