filtering can, when combined with diverse forms of neuronal physiology, synapse heterogeneity, and circuit wiring, lead to unexpected patterns of emergent network activity.

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Forward and Back: Motifs of Inhibition in Olfactory Processing

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DOI 10.1016/j.neuron.2010.07.023

The remarkable performance of the olfactory system in classifying and categorizing the complex olfactory environment is built upon several basic neural circuit motifs. These include forms of inhibition that may play comparable roles in widely divergent species. In this issue of *Neuron*, a new study by Stokes and Isaacson sheds light on how elementary types of inhibition dynamically interact.

Inhibition is ubiquitous in neural circuits and is often manifest in two motifs: feedforward and feedback. These motifs have different characteristics that may be further shaped by the plastic, time-dependent, dynamic properties of the circuit. Feedforward inhibition usually involves more than one brain area. It occurs when excitatory neurons directly activate inhibitory neurons that reach forward to inhibit neurons of another (downstream) area. These downstream neurons may also receive input from the original excitatory neurons. By casting inhibition forward, this motif permits control over the way downstream neurons respond to input. Feedback inhibition, on the other hand, usually involves neurons all within the same brain structure. It occurs when excitatory neurons drive activity in inhibitory interneurons, which, in turn, inhibit further output from those excitatory cells, holding their firing to stable, or oscillatory activity. A new study by Stokes and Isaacson (2010), in this issue of *Neuron*, provides a clear and interesting example of a circuit that generates a dynamically changing interplay between feedforward and feedback inhibition in the olfactory system, a context that offers the promise of understanding the circuit's information-processing functions.

Information about the olfactory environment enters the vertebrate brain through the nose, where waves of sniff-driven odorants elicit patterns of action potentials from olfactory receptor neurons. The receptor neurons then drive the circuitry of the olfactory bulb, which includes inhibitory and excitatory neurons that engage reciprocally in cycles of activity. Excitatory mitral and tufted cells project the olfactory bulb's distributed and temporally patterned output through the lateral olfactory tract to several brain areas, including the piriform cortex. There, mitral and tufted cells reach into superficial layer 1a, where they synapse onto the distal, apical dendrites of pyramidal cells, whose somata reside deeper in the cortex in layer 2/3. These pyramidal cells are known to interact with two populations of local inhibitory interneurons. The more superficial population, in layer 1a, receives afferent input from the mitral and tufted cells, and then feeds inhibition forward onto the apical dendrites of the pyramidal cells. The deeper population, in layer 2/3, receives its input from the

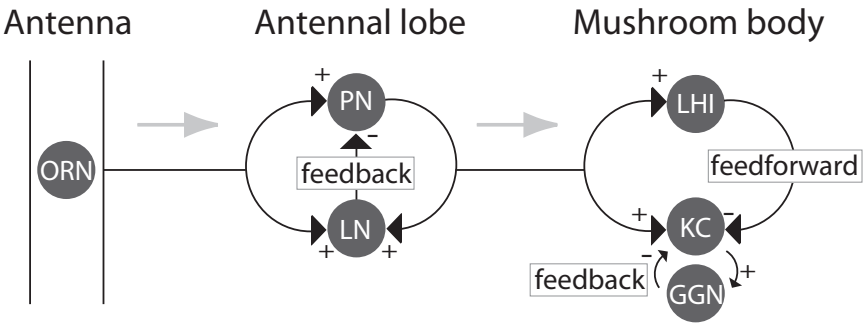

Figure 1. As in the Vertebrate, Feedforward and Feedback Inhibition Play Important Roles in the Insect Olfactory System

Afferent volleys from olfactory receptor neurons (ORNs) activate the antennal lobe (analogous to the vertebrate olfactory bulb), where excitatory projection neurons (PNs) interact with inhibitory local neurons (LNs). The oscillatory and synchronized spiking output is transmitted to the mushroom body (analogous to the piriform cortex), where Kenyon cells (KCs, analogous to pyramidal cells) receive direct excitation from PNs, feedforward inhibition from lateral horn interneurons (LHIs), and feedback inhibition from the giant GABAergic neuron (GGN). See the text for details.

pyramidal cells, and then feeds inhibition directly back to those pyramidal cells (Neville and Haberly, 2004).

Stokes and Isaacson focused on the ways these two inhibitory circuits together shape the responses of pyramidal cells. Working with slices of rat anterior piriform cortex, and mimicking the sniff-driven output of the olfactory bulb with electric shocks to the lateral olfactory tract, and with optogenetically driven input to specific pyramidal cells, they explored the response properties that emerge from variations in the circuit's projection patterns, synaptic properties, and connectivity. Notably, they found that bursts of afferent activity lead to progressive depression of feedforward inhibitory synaptic input, but facilitation of direct excitatory input. This appears to cause the piriform circuit to regulate the temporal summation of afferent spiking, filtering it to favor transmission of the relatively intense and bursty inputs generated both by the sniff cycle and by the reciprocal, oscillation-inducing circuitry of the olfactory bulb, leading the pyramidal cells to fire sparsely, and in patterns that vary with the odorant. It remains to be seen how these components of the intact olfactory system respond when activated by odorants, but Stokes and Isaacson suggest the primary outcome of these interactions is a form of contrast enhancement—only the mitral and tufted cells most strongly activated by an odorant will be able to elicit spiking from their follower pyramidal cells.

Similar motifs of feedback and feedforward inhibition appear in the olfactory systems of insects, particularly in the locust (Figure 1). There, odor-driven olfactory receptor neurons in the periphery activate excitatory and inhibitory neurons in a structure analogous to the olfactory bulb called the antennal lobe (MacLeod and Laurent, 1996). The inhibitory cells (called local neurons) provide feedback onto the excitatory neurons, leading to oscillatory, distributed, and temporally structured waves of spiking output. This output is delivered by projection neurons to the mushroom body, a structure that in many ways appears analogous to the piriform cortex. Here, projection neurons fan out broadly and synapse upon Kenyon cells (Jortner et al., 2007), which are analogous to pyramidal cells. The projection neurons also synapse upon a small population of inhibitory neurons in a structure called the lateral horn; these cells, driven by projection neurons, provide waves of feedforward inhibition to Kenyon cells. Thus, Kenyon cells receive odor-driven cycles of input, each consisting of a burst of direct excitation from specific, transiently synchronized populations of projection neurons, followed slightly by a burst of bisynaptic, globally integrated inhibition from the lateral horn (Perez-Orive et al., 2002).

These alternating inputs effectively regulate the flow of information between the antennal lobe and the mushroom body, restricting Kenyon cells to fire sparsely, much like pyramidal cells. Their constrained integration windows suggest that Kenyon cells are extremely sensitive to the timing of synchronized inputs from the antennal lobe; Kenyon cells may respond only when sufficient numbers of input spikes arrive coincidentally. The feedforward inhibition mechanism has been proposed to adjust the integration properties of Kenyon cells to preserve the sparseness of response even as odor concentration changes over wide ranges (Assisi et al., 2007). And recent work also suggests that another type of inhibitory cell, the giant GABAergic neuron, can broadly integrate excitatory input from the population of Kenyon cells and then return feedback inhibition to them, gating their responsiveness to input from projection neurons (M. Papadopoulou, G. Turner, and G. Laurent, 2009, Frontiers in Systems Neuroscience, conference abstract, 10.3389/conf.neuro.06.2009.03.106). Thus, in many respects, feedforward and feedback inhibition in insect and vertebrate olfactory systems share similar attributes, suggesting common principles for controlling information flow within the brain (Kay and Stopfer, 2006).

In the insect, these inhibitory motifs are thought to organize the timing of input to the Kenyon cells, orchestrating discrete, odor-specific, cyclic bursts of synchronized spikes that contribute to the sparse coding of olfactory information. In the vertebrate, work building on that of Stokes and Isaacson, using olfactory stimuli and intact circuits, will no doubt reveal additional ways neurons process information.

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