

## Interglomerular communication in olfactory processing

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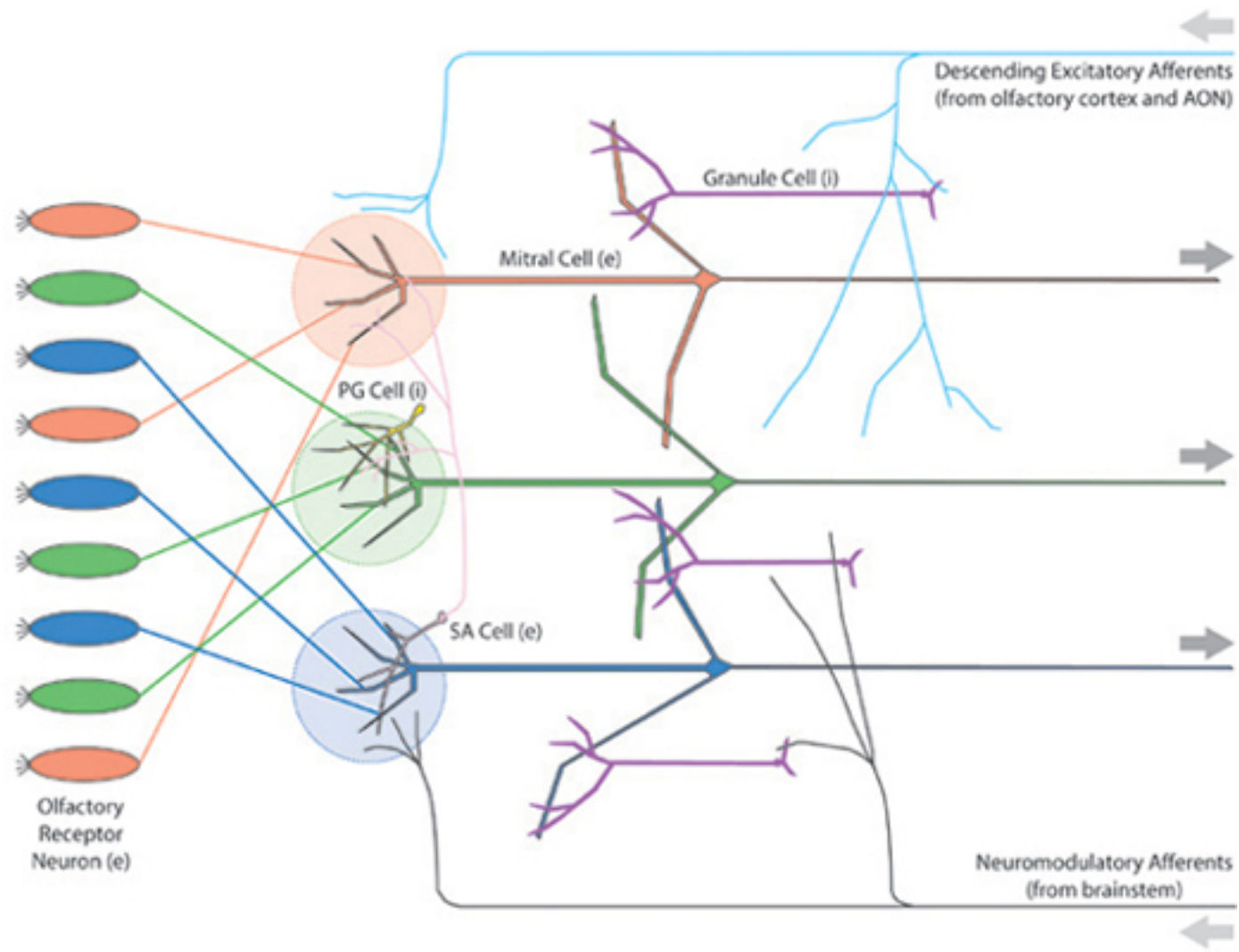
**A recent publication reports a series of findings demonstrating a network of inhibitory connections between antennal lobe glomeruli in the *Drosophila* olfactory system. These connections include a GABA-mediated presynaptic inhibition that suppresses transmitter release from olfactory receptor neuron terminals. This presynaptic inhibition is organized on an interglomerular basis, such that the inhibition scales with the global sensory input the antennal lobe, rather than with local inputs to specific glomeruli. This functional organization suggests that the inhibition may serve as a general gain control for olfactory input. These inhibitory connections were also shown to narrow the range of odorants to which the corresponding principal neurons respond, thus improving the efficiency of the neural code for odors. The *Drosophila* antennal lobe thus shares important organizational features with the mammalian olfactory bulb.**

Sensory systems typically operate by transducing a stimulus using a large number of detector elements that vary in their sensitivities or physical position and then analyzing the resulting neural signals across these many parallel channels. The processing of these signals serves to extract higher level information about the stimulus and ultimately to synthesize an integrated representation of the external environment. Understanding how neural information is combined across different sensory input channels is thus fundamental to understanding sensory system function. A recent study of inhibition between olfactory glomeruli in the fruit fly antennal lobe has yielded exciting new insights into the nature of this cross-talk

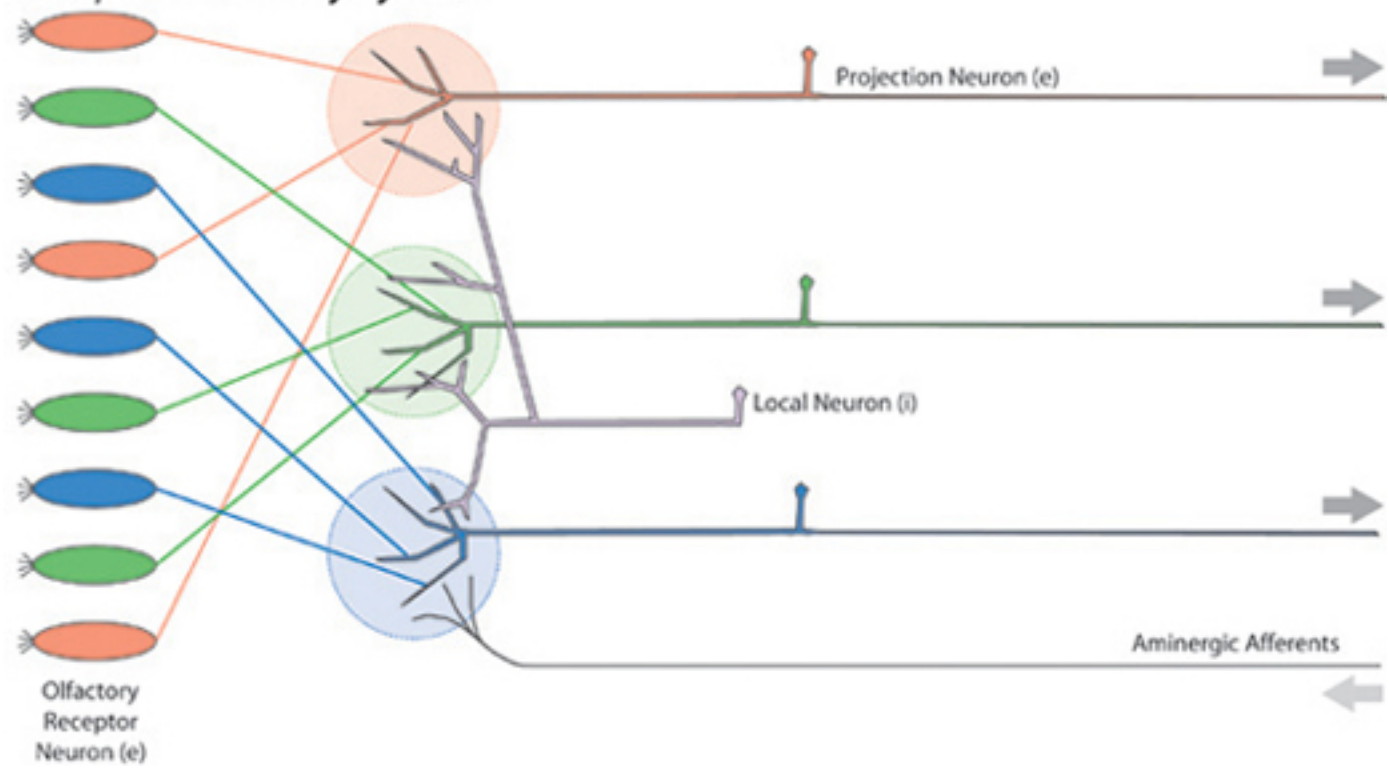
(Olsen & Wilson, 2008).

Cross-talk between sensory processing channels (*i.e.* lateral interactions) can be excitatory or inhibitory, and the nature of this cross-talk can have different functional consequences for information processing. For example, lateral excitation can create circuits that detect temporal coincidences, selectively respond to certain stimulus features, or pool input across channels to increase sensitivity. Lateral inhibition can serve to enhance contrast between similar inputs, to detect temporal sequences of interactions, and to generate patterns of oscillations that synchronize information transfer throughout a circuit. In the olfactory system, new techniques have permitted the exploration of the circuit-level organization of glomeruli in the mammalian olfactory bulb and its insect analog, the antennal lobe. These results are now beginning to elaborate which of these circuit motifs are operative in early olfactory processing and what role they play in odor coding (Aungst *et al* 2003; McGann *et al.* 2005; Olsen *et al.* 2007; Shang *et al.* 2007).

In the olfactory system of both mammals and insects, the primary sensory neurons express only one (or two; see Goldman *et al.* 2005) of a large suite of odorant receptors. These olfactory receptor neurons (ORNs) project their axons to the olfactory bulb (in mammals) or antennal lobe (in insects), where each ORN selectively innervates a specific glomerulus corresponding to the odorant receptor it expresses (see **Figure 1**). Within the glomerulus, each ORN axon synapses onto the dendrites of the principal output neurons for that structure, which are the mitral cells of the olfactory bulb and the projection neurons (PNs) for the antennal lobe. Each odorant receptor thus has a dedicated feed-forward processing channel composed of the population of ORNs that express it, the glomerulus to which they project, and the projection neurons that receive the ORNs' synaptic output and send their axons on to other structures. The unique segregation of olfactory information channels into discrete glomeruli has permitted a rich environment for the investigation of the neural circuitry at this early stage of sensory processing. In both mammals and insects, there are large populations of interneurons that interconnect neurons across these channels. In the mammal, there is a complex network of local interneurons (LNs; including periglomerular cells, external tufted cells, and short axon cells) in the glomerular layer and a second network of LNs (including granule cells, Blane's cells, and others) interconnecting the mitral cells (see **Figure 1**). The insect antennal lobe likewise contains a large number of LNs that interconnect glomeruli (**Figure 1**).



### *Drosophila* Olfactory System



**Figure 1. Circuitry of the rodent and *Drosophila* olfactory systems.** Both the rodent (top) and *Drosophila* (bottom) olfactory systems include a population of olfactory receptor neurons (ORNs) that each express a single odorant receptor. These neurons project their axons to specific glomeruli (shaded circles) in the olfactory bulb (rodent) or antennal lobe (fly) that correspond to the odorant receptor they express. In the glomerulus, they make synapses onto mitral cells (rodent) or projection neurons (fly), which send their axons on to higher processing centers (dark arrows). Within the glomerulus of the rodent, input from ORNs is modulated presynaptically by uniglomerular interneurons like periglomerular (PG) cells, and a network of multiglomerular short axon (SA) cells connects across glomeruli postsynaptically. In the fly, input from ORNs is modulated presynaptically across glomeruli by local neurons. Glomeruli in both species receive neuromodulatory descending input from higher brain centers (black lines; light arrows). The rodent olfactory system also includes a second level of inhibitory processing, mediated by the granule cells, and a second form of descending inputs, from the olfactory cortex and anterior olfactory nucleus (light blue lines; light arrow). Cell types are identified as excitatory (e) or inhibitory (i).

In a recent publication (2008), Olsen and Wilson report a series of experiments that demonstrate a network of inhibitory connections between antennal lobe glomeruli that can dramatically shape patterns of odorant-evoked neural activity. They took advantage of the separation of *Drosophila* ORNs into two physically distinct peripheral clusters (90% on the antenna and 10% on the maxillary palp) to investigate the lateral interactions – mediated by LNs - between olfactory processing channels. They found that removing the antennae increased odor-evoked neural responses (measured by patch-clamp recordings) in PNs receiving sensory input from the maxillary palp, suggesting that sensory input from the antenna normally exerts an inhibitory effect on PNs innervating the palp glomeruli. After removing the antennae, PNs innervating palp glomeruli also exhibited odor responses to a broader range of odorants, suggesting that one function of this lateral inhibition may be to effectively narrow the tuning of a glomerulus to different odorants. Such an effect would increase the contrast between the response spectra of different glomeruli, removing redundant responses in the neural code and improving the system's efficiency in representing odorants.

Previous reports had demonstrated a lateral excitatory circuit between glomeruli in the antennal lobe (Olsen *et al.* 2007; Shang *et al.* 2007; Root *et al.* 2007) by showing that even after removing the antenna (and thus the primary sensory input), PNs innervating antenna glomeruli exhibit an odorant-evoked depolarization. Olsen and Wilson replicated this result, but they noted that because antennal ORNs are normally spontaneously active, ablating them confounds the experiment by eliminating a potential substrate for a lateral inhibition that could exist in parallel with the lateral excitation. To avoid this confound, they performed a separate

experiment in which they recorded from PNs receiving input from palp ORNs, but with the palp covered during presentation. This new approach isolates the lateral inputs to palp PNs (by shielding them from direct sensory input), without eliminating the spontaneous activity of palp ORNs. In this configuration, they found that the odorant-evoked activation of ORNs on the antenna induced a dramatic presynaptic inhibition of the spontaneous synaptic output from ORNs on the palp, with a consequent hyperpolarization of PNs innervating palp glomeruli. This inhibition was shown to be mediated by the neurotransmitter  $\gamma$ -amino-butyric acid (GABA), acting at both GABA<sub>A</sub>-like and GABA<sub>B</sub>-like receptors. Curiously, the activation of either GABA receptor population was sufficient to induce lateral presynaptic inhibition, as the pharmacological blockade of either receptor individually was much less effective at eliminating the observed inhibition than the simultaneous blockade of both receptors at once.

Interestingly, the magnitude of the lateral inhibition evoked by an odorant was well-correlated with the total activity that odorant evokes across all ORNs in the antennal lobe. This finding is interesting because it suggests that - in this case - lateral presynaptic inhibition does not serve as a glomerulus-specific tuning mechanism (as it might in a classical contrast enhancement circuit, where the inhibition is strongest between nearest neighbors), but rather may serve a global gain control or normalization function. As the authors suggest, by maintaining the PN population in the middle of their dynamic range, where differences in odorant binding produce the biggest changes in neural activity, the global gain control provided by this lateral inhibition may indirectly serve to improve neural coding of odor identity by increasing the range of different activity levels across PNs. The anatomical basis for this widespread inhibition has yet to be identified, but may be a population of LNs with extensive projections throughout the glomeruli of the antennal lobe or alternatively could be mediated by feedback from descending aminergic projections from higher structures (see **Figure 1**). Whether more localized lateral inhibitory interactions occur between specific glomeruli also has yet to be determined.

The Olsen and Wilson results thus illustrate a system in which both lateral excitatory and lateral inhibitory circuits appear to be operating in parallel at the earliest level of sensory processing. It is intriguing that these systems appear to be actually competing with each other, and that 'spontaneous' or tonic neural activity in the ORN terminals themselves appears to be the primary determinant of whether the excitatory or inhibitory drive dominates the PN's firing pattern. Though it was beyond the scope of the study, it is appealing to imagine that the spontaneous activity of the ORNs might be in some way modulated by the fly's environment, such that in odorant-poor environments the tonic activity is reduced, leading to

signal amplification and perhaps pooling by lateral excitation between glomeruli, while in odorant-rich environments the tonic activity is elevated, driving a global lateral inhibition.

The results of the Olsen and Wilson model suggest a number of further lines of experimentation. Foremost, it should be possible to directly test the global gain control hypothesis they propose by comparing both the input-output functions and odorant selectivities of PNs before and after the blockade of that inhibition with GABA receptor antagonists. If their model is correct, blocking the lateral inhibition should both reduce the effective dynamic range of the PNs and increase the number of odorants to which they respond. It will also be interesting to explore the functional consequences of the unusual combination of ionotropic GABA<sub>A</sub> and metabotropic GABA<sub>B</sub> receptors in mediating this inhibition.

The *Drosophila* and mammalian olfactory systems share a striking similarity in the initial steps of odor transduction and the projection of ORNs into receptor-specific glomeruli (**Figure 1**). Olsen and Wilson's results illustrate that sensory processing in the *Drosophila* antennal lobe shares important features with that of the mammalian olfactory bulb. First, both appear to involve lateral inhibitory interactions between different input channels. Second, both systems involve a GABA<sub>B</sub>-mediated presynaptic inhibition of transmitter release from ORNs which may provide adaptive gain control on sensory input (Aroniadou-Anderjaska *et al.* 2000; Wachowiak *et al.* 2005). Species-specific differences are apparent in the details of how each of these features is implemented, however. For example, the functional organization of presynaptic inhibition in the mouse olfactory bulb appears qualitatively different than the interglomerular presynaptic inhibition they have shown in *Drosophila*. Recent experiments in the mouse have shown that the GABA<sub>B</sub>-mediated presynaptic inhibition is a strictly *intraglomerular* phenomenon, with strong effects within a glomerulus but little evidence for lateral presynaptic inhibition between glomeruli (McGann *et al.* 2005; Pirez & Wachowiak 2008). In the mouse, odorant-evoked excitation of neighboring glomeruli does not modulate synaptic input to glomerulus, nor does it alter the relative pattern of synaptic input across glomeruli as it clearly does in *Drosophila*. Despite this difference, there is strong evidence for lateral inhibitory interactions between glomeruli of the mammalian OB, occurring *post-* rather than pre-synaptic to the ORNs. In this case, the lateral inhibition is thought to be mediated by excitatory LNs known as short axon cells, which make extensive lateral connections between glomeruli and excite other, GABA-ergic LNs in the glomerular layer (Aungst *et al.* 2003; Wachowiak & Shipley 2006). Finally, additional inhibitory cross-talk between different input channels in the mammalian olfactory bulb is mediated by inhibitory LNs that

connect different olfactory bulb projection neurons in sub-glomerular layers. The overall effect of either of these circuits could be similar to that described by Olsen & Wilson.

Despite these broad similarities, the mammalian system appears more complex than its *Drosophila* counterpart, not only in its greater number of odorant receptors, but also because it includes multiple levels of processing between input channels and because it includes strong reciprocal connections with higher-order olfactory structures (such as olfactory cortex and the anterior olfactory nucleus) as well as massive centrifugal inputs from modulatory centers (see **Figure 1**). We speculate that just as the similarities in ORN function and glomerular structure may be a remarkable example of evolutionary convergence, the differences in the circuitry underlying cross-channel sensory processing between the two organisms may reflect their relative evolutionary pressures – physical space is at a premium in the airborne *Drosophila*, thus favoring an organization that compresses cross-channel analyses into the earliest part of the processing circuit, while greater processing demands and cognitive capacity in mammals may favor an architecture that features multiple stages of cross-talk and a more extensive descending control of sensory processing.

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