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Understanding the functional consequences of synaptic specialization: insight from the *Drosophila* antennal lobe

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Synapses exhibit diverse functional properties, and it seems likely that these properties are specialized to perform specific computations. The *Drosophila* antennal lobe provides a useful experimental preparation for exploring the relationship between synaptic physiology and neural computations. This review summarizes recent progress in describing synaptic properties in the *Drosophila* antennal lobe. These studies reveal that several types of synapses in this circuit are highly specialized, and that these specializations are in some cases under tight regulatory control. These synaptic specializations can be understood in terms of the computational features they confer on the circuit. Specifically, many of these properties appear to promote odor detection when odor concentrations are low, while promoting adaptive gain control when odor concentrations are high.

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Introduction

Synapses in different regions of the nervous system have diverse functional properties [1–3]. Thus, it is logical to imagine that synapses are adapted to the computational function of the neural circuit they are embedded in. However, we do not have a systematic understanding of how the properties of particular synapses might aid (or constrain) the computations performed by the circuits that contain those synapses.

There is a practical reason why this gap in our knowledge exists. Synaptic properties are most easily studied *in vitro*, whereas the study of neural coding often requires an intact organism. Thus, experimental preparations that blur the line between *in vitro* and *in vivo* are often the most useful for this purpose.

Two circuits that fit the bill are the vertebrate retina and the crustacean stomatogastric ganglion. Both circuits can perform their functions in the context of a semi-reduced preparation. And, in both cases, it is easy to target recording electrodes to neurons having defined connectivity within the circuit. Studies in the retina have taught us that synapses can be specialized to reliably transmit weak intermittent signals while filtering out continuous noise [4]. Studies in the stomatogastric ganglion have taught us that neuromodulators can rapidly change synaptic strength and thereby reshape the dynamics of circuit output [5].

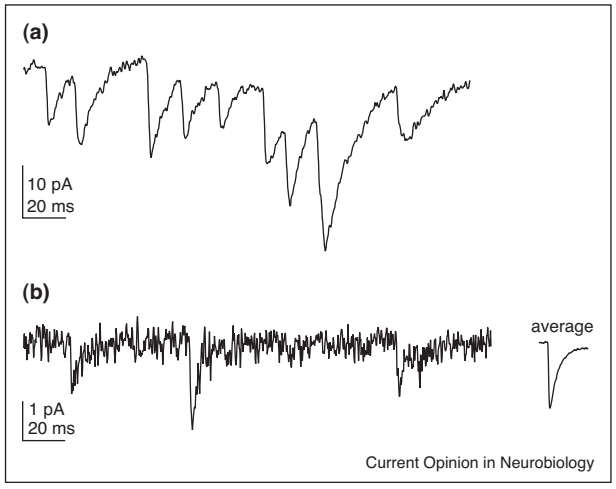
Recently, another experimental preparation has joined this list: the *Drosophila* antennal lobe. The antennal lobe is the insect analog of the vertebrate olfactory bulb. Like the bulb, it is divided into an orderly and stereotyped array of neuropil compartments called glomeruli, where each glomerulus corresponds to an odorant receptor in the periphery [6]. It is feasible to make whole-cell patch-clamp recordings from *Drosophila* neurons *in vivo* [7] or in semi-intact preparations [8–10]. Moreover, it is comparatively easy to genetically label and manipulate specific neurons [11,12]. These features make the *Drosophila* antennal lobe a useful preparation for exploring the relationship between synaptic properties and neural computations.

This review summarizes recent progress in describing synaptic properties in the *Drosophila* antennal lobe. Ultimately, the goal of all these studies is to elucidate the functional consequences of these synaptic properties for olfactory processing. In doing so, one hopes to learn fundamental lessons about the relationship between synaptic and computational phenomena.

Somatic whole-cell recordings *in vivo*

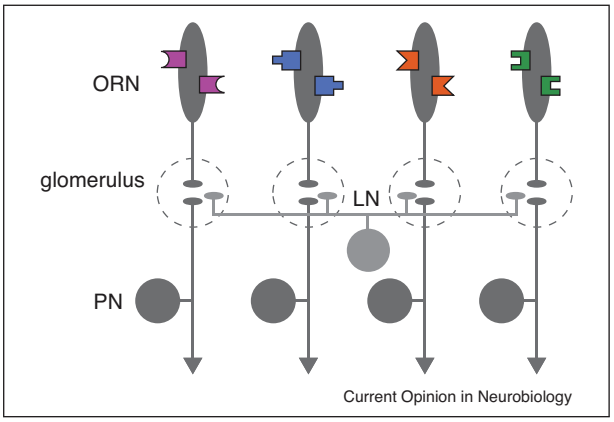
A curious feature of insect brains is that neuronal somata are excluded from the core of the brain, and are instead segregated onto the brain surface. The classical approach of insect neurophysiologists is to penetrate the neuropil core of the brain using a sharp microelectrode, thereby impaling dendrites and axons. However, this is not feasible for most *Drosophila* neurons because their neurites are very small, and because movements of the brain make it difficult to hold a sharp microelectrode in such a tiny neurite. Rather, achieving a stable recording generally requires performing a whole-cell patch-clamp recording at the cell body [7]. This is convenient because the somata are on the surface of the brain, and are thus easily

Figure 1



In vivo whole-cell patch-clamp recording from Drosophila neurons. **(A)** Spontaneous EPSCs in a *Drosophila* antennal lobe PN. **(B)** Miniature EPSCs in a *Drosophila* antennal lobe PN. Adapted from Kazama and Wilson [15•].

Figure 2



Organization of the *Drosophila* antennal lobe circuit. All the ORNs that express the same odorant receptor project to the same glomerulus in the antennal lobe. There, they make excitatory synapses with PNs. Glomeruli are also interconnected by LNs. Because most odor stimuli elicit activity in multiple ORN types, the odor response of a PN may reflect both direct input from its cognate ORNs and lateral input from other glomeruli.

visible with the conventional optics found on a typical brain-slice patching rig.

However, the strange morphology of insect neurons means that the soma is also a rather passive witness to electrical events. The soma is simply a ball of membrane which is connected by a single neurite to the rest of the cell. Synapses are distant from the soma [13], and the spike initiation zone may also be distant [14]. Given this unusual anatomy, it is worth asking whether synaptic signals can be measured at high resolution in somatic recordings.

Fortunately, the answer is yes, at least for the principal neurons of the *Drosophila* antennal lobe. Although postsynaptic sites are located about a length constant away from the cell body [14], synaptic currents are easily visible [15•] (Figure 1A). Indeed, when action potentials are blocked with tetrodotoxin, miniature excitatory postsynaptic currents (EPSCs) can be readily resolved in these recordings [15•,16] (Figure 1B). Thus, somatic whole-cell recordings can provide a detailed picture of synaptic signals in these neurons.

Properties of unitary afferent synapses

Afferent input to the antennal lobe comes from olfactory receptor neurons (ORNs). Like most Drosophila neurons, ORNs are cholinergic [17]. Each ORN expresses one (or occasionally) two odorant receptor genes, and all the ORNs that express the same gene project to the same glomerulus [6] (Figure 2). There they make nicotinic synapses with projection neurons (PNs), which in turn send axons to higher brain regions [17]. Most PNs are postsynaptic to a single glomerulus.

Synapses from ORNs onto PNs are remarkable in several respects [15•]. First, these synapses are quite strong: unitary excitatory synaptic potentials (uEPSPs) arising from these synapses measure 5–7 mV at the soma. Second, these synapses are also quite reliable, with an average coefficient of variation of 0.16. Together, these observations imply that each spike releases many vesicles of neurotransmitter onto each postsynaptic cell. Consistent with this, multiple probability fluctuation analysis reveals that each unitary synapse contains dozens of release sites, each with a basal release probability of ~0.8.

A high basal release probability means that synaptic vesicles should be easily depleted from this synapse. Thus, it is not surprising that this synapse shows strong short-term depression [15•]. Short-term depression is linearly correlated with a change in the $1/CV^2$ (CV, coefficient of variation) of uEPSC amplitudes, consistent with a presynaptic locus.

Interestingly, the properties of this synapse are regulated to produce a stereotyped, large uEPSP amplitude, regardless of the identity of the PN [15•]. This is notable because different PNs have dendritic arbors of different sizes. It turns out that uEPSC sizes are several-fold larger in PNs having large dendritic arbors, as compared to PNs having small dendritic arbors. Presumably, large uEPSCs compensate for lower dendritic input resistance in these cells to produce a standard uEPSP amplitude which is uniform across PNs.

These results suggest that a homeostatic process controls uEPSC amplitude in PNs. This hypothesis would predict that changing PN input resistance should produce a compensatory change in uEPSC amplitude. Indeed, if PNs are engineered to overexpress an inwardly rectifying potassium channel, their input resistance falls by half, but unitary EPSCs are correspondingly potentiated [15•]. Thus, the properties of ORN-to-PN synapses are not only specialized, but also under tight control.

Connectivity at afferent synapses

On average, each glomerulus contains the axons of ~50 ORNs and the dendrites of several PNs [17]. These are sometimes called 'sister' ORNs and sister PNs. In principle, sister PNs might receive input from nonoverlapping populations of sister ORNs. Alternatively, each PN might receive input from every ORN that projects to its glomerulus.

The answer to this question can be deduced by recording spontaneous synaptic currents simultaneously from sister PNs. ORNs fire spontaneously even in the absence of odors. Because the ORN-to-PN synapse never fails, each ORN spike reliably produces a synaptic event in every postsynaptic PN. This means that the fraction of ORN inputs that are shared among sister PNs can be inferred from the fraction of spontaneous EPSCs that occur synchronously in the two cells.

As it turns out, virtually all spontaneous EPSCs occur synchronously in sister PNs [18]. This means that each PN receives convergent input from all sister ORNs. Conversely, it also means that each ORN axon branches to contact every sister PN in its target glomerulus. Given that the strength of these synapses is also evidently tightly regulated, this result implies a high degree of precision in the developmental wiring of this circuit.

Functional consequences of afferent synapse properties

ORN-to-PN synapses clearly have specialized properties, and these properties are regulated rather than accidental. What, then, are these synapses specialized for?

It might be argued that the most challenging task in sensory perception is simply detecting the stimulus in conditions where the stimulus is weak. Just as retinal synapses are specialized to transmit information about single photons [4], ORN-to-PN synapses in the *Drosophila* antennal lobe may be specialized to transmit information about encounters with weak odor stimuli. It is not difficult to see how the properties of ORN-to-PN synapses would favor detection. Maximal convergence of afferents and high quantal content should together mean that each ORN spike produces a reliably large depolarization in each sister PN. Homeostatic control of uEPSCs may confer robustness on this connection, thereby ensuring that the synapse is strong enough.

Of course, the problem is not to detect ORN spikes per se, but rather to detect odor-evoked spikes on a background of noisy spontaneous ORN spikes. Here, the convergence of sister ORNs is important. About three synchronous ORN spikes are needed to drive a PN above threshold [14], but synchronous ORN spikes are relatively rare in the absence of odors [18]. By pooling input from a large number of ORNs having uncorrelated spontaneous spikes but correlated odor-evoked spikes, PNs should be able to maximize their signal-to-noise ratio [19].

Short-term depression at ORN-to-PN synapses also has important functional consequences. First, it means that PN spike trains disproportionately emphasize the onset of odor encounters [20]. Because of this, the PN response can actually peak earlier than the ORN response [20]. In this sense, the PN response is speedier. This type of speeding also occurs in the retina [4], where it helps explain why visual perception is fast although phototransduction is slow.

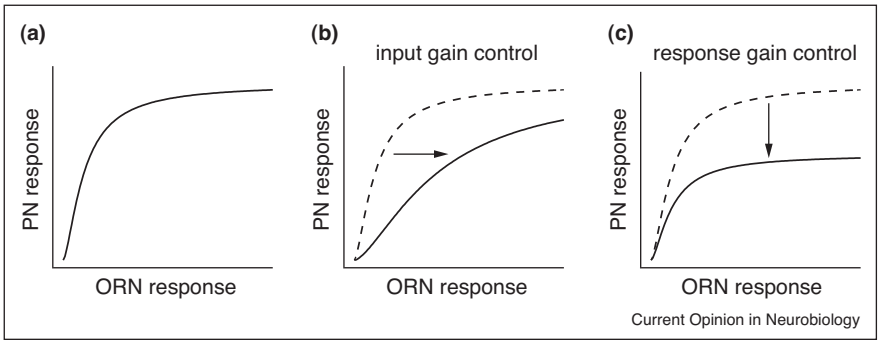
Another functional consequence of short-term depression at ORN-to-PN synapses is that it creates a so-called 'compressive nonlinearity' in the relationship between ORN and PN firing rates (Figure 3A). Because the ORN-to-PN synapse is strong, and because many ORNs converge onto each PN, this relationship has a high gain when ORN firing rates are low. Conversely, because the ORN-to-PN synapse depresses at high spike rates, this relationship has a low gain when ORN firing rates are high (Figure 3).

This compressive nonlinearity is potentially useful because it allocates PN coding space disproportionately to weak ORN responses. Weak ORN responses are more common than strong ORN responses [21]. Thus, it makes sense to allocate the lion's share of the PN dynamic range to encoding weak ORN responses. Disproportionately high gain in this regime should accentuate the subtle differences among weak ORN odor responses, thereby improving stimulus discrimination even after these responses are contaminated by noise in higher brain regions [20]. Indeed, implementing this compressive nonlinearity in a model improves the ability of a linear classifier to discriminate between different odor stimuli in the context of noise, where the inputs to the model are the recorded spiking responses of ORNs [22,23].

Properties of synaptic inhibition

PNs are not the only neurons in the antennal lobe. Antennal lobe glomeruli are also interconnected by a network of local interneurons (LNs), most of which are GABAergic [24–29]. LNs lack an axon and so exert their effects through dendrodendritic synapses [17].

Figure 3



The relationship between ORN and PN responses. These curves schematize the relationship between the odor-evoked firing rate of an ORN, and the firing rate of its postsynaptic PN in response to the same odor stimuli. **(A)** When only one ORN type is active, the response of postsynaptic PNs rises steeply and saturates at moderate levels of ORN input. This is thought to be due, at least in part, to short-term synaptic depression at ORN-to-PN synapses. **(B)** When many ORN types are active, lateral inhibition decreases the strength of ORN-to-PN synapses. This disproportionately inhibits PN responses to weak levels of direct ORN input. This makes it more difficult to drive PNs to saturation, without changing the level at which their responses saturate. This process is termed 'input gain control'. **(C)** In principle, gain control might instead uniformly decrease the responses of PNs to all levels of afferent input. This form of gain control is termed 'response gain control'. Adapted from Olsen et al. [23].

One target of synaptic inhibition is the PN dendrite. PNs express both GABA-A and GABA-B receptors, and are inhibited by GABA [24]. Paired whole-cell recordings from LNs and PNs reveal reciprocal connections between these neurons. LNs inhibit PNs via GABAergic synapses, and conversely PNs excite LNs via cholinergic synapses [7,30•,31•]. PN recordings also sometimes show membrane potential oscillations suggestive of oscillatory GABAergic inhibition [32].

However, inhibitory control of PN dendrites appears to be relatively weak. Instead, the major locus of synaptic inhibition in this circuit seems to be the ORN axon terminal. Evidence for this comes from experiments where ORN connections are selectively removed from just a few PNs. In this situation, when ORN input to a PN is absent, it is difficult to detect almost any lateral inhibition from surrounding glomeruli. By contrast, when ORN connections onto the same PN are active, lateral inhibition from surrounding glomeruli is robust [33•]. This argues that the major locus of inhibition is presynaptic, not postsynaptic.

Consistent with this, ORN axon terminals are immunopositive for GABA-B receptors [34•]. GABA potently inhibits evoked EPSCs at ORN-to-PN synapses, and this is associated with an increase in the paired-pulse ratio, implying a presynaptic locus [33•]. Odor-evoked release of GABA from LNs has the same effect on evoked EPSCs [33•]. Moreover, GABA suppresses calcium influx into ORN axon terminals [34•]. Finally, selective knockdown of presynaptic GABA-B receptors disinhibits odor-evoked PN spiking activity and alters olfactory behavior [34•]. Together, these results demonstrate a major role for presynaptic inhibition in this circuit, although they do not argue against a (comparatively smaller) role for postsynaptic inhibition. Interestingly, both presynaptic GABA-A receptors and presynaptic GABA-B receptors mediate presynaptic inhibition at this synapse [33•].

LNs can also produce presynaptic inhibition in other ways. ORNs express receptors for tachykinin, and some LNs are immunopositive for tachykinin [35]. Bath application of tachykinin suppresses calcium influx into ORN axon terminals, and a fluorescent indicator of synaptic vesicle release shows that release from ORNs is also suppressed. Knockdown of ORN tachykinin receptors potentiates ORN release and alters olfactory behavior. LNs express a diverse collection of neuroactive peptides [36], and so peptidergic presynaptic inhibition may be an important mechanism for controlling the gain of ORN-to-PN synapses.

An interesting open question is whether different LN subtypes serve different functional roles. LNs have diverse morphologies, diverse intrinsic electrophysiological properties, and express diverse neurochemical markers [26–29,37,38]. Some LNs selectively innervate just a subset of glomeruli [26–29,38]. One LN subtype type innervates only the core region of each glomerulus, avoiding the rind, where ORN axons terminate [27,32,37]. Conditional inactivation of another LN subtype suppresses field potential oscillations in higher brain regions, suggesting a special role in synchronizing PN spikes [32]. In future, it will be interesting to learn whether more LNs play specialized functional roles, and if so, what these might be.

Functional consequences of synaptic inhibition

The existence of inhibitory LNs that interconnect glomeruli predicts that activity in one glomerulus should

tend to suppress activity in other glomeruli. Consistent with this, PN odor responses are suppressed when other glomeruli are coactivated by the same odor stimulus [23,39,40]. Conversely, PN odor responses are disinhibited when other glomeruli are silenced [33•].

Many LNs arborize in most or all glomeruli [26–29,38], and so are likely to pool input from most ORN types. These pan-glomerular (or nearly pan-glomerular) LNs also have presynaptic specializations in all the glomeruli they innervate [27,28]. Thus, we would expect that the level of inhibition in each glomerulus should mirror the level of activity in all glomeruli. Indeed, lateral inhibition grows nearly linearly with the magnitude of total network activity [23,33•]. Lateral inhibition thus represents a form of 'gain control', defined as a negative feedback loop that keeps the output of a system within a given range.

What is the functional consequence of the fact that lateral inhibition is mainly presynaptic? Recall that the ORN-to-PN transformation exhibits a compressive nonlinearity (Figure 3). This is thought to be due (at least in part) to intrinsic short-term synaptic depression at ORN-to-PN synapses due to vesicle depletion [15•]. Presynaptic lateral inhibition decreases release probability, and thus should make it more difficult to deplete vesicles from ORN terminals. However, if the synapse is driven vigorously, it should still be possible to dump the entire readily releasable pool. Thus, we would expect that lateral inhibition should increase the level of direct ORN input that is needed to drive a PN to saturation, without changing the level at which PNs saturate.

As it turns out, this precisely what is observed [23]. In these experiments, direct ORN input and total ORN input were manipulated independently using carefully chosen odor stimuli. When total ORN input was low, PNs were easily driven to saturation by activating their presynaptic ORNs. When total ORN input was high, it required substantially higher levels of direct ORN input to saturate PNs.

This form of gain control is sometimes known as 'input gain control' (Figure 3B). Its essential feature is that it suppresses postsynaptic responses to weak inputs more than it suppresses responses to strong inputs. This makes it more difficult to saturate postsynaptic responses, while still preserving the full dynamic range available to the postsynaptic neuron. The alternative scenario is that lateral inhibition would uniformly suppress all postsynaptic responses (Figure 3C). This is sometimes known as 'response gain control'.

The computational consequences of lateral inhibition in this circuit have been examined in theoretical studies. Input gain control that scales with total ORN activity improves the ability of a linear classifier to discriminate between different odor stimuli [22,23]. This is because it tends to normalize the response of a PN population, such that the total number of spikes in the population is more equal across stimuli. This improves performance because it prevents classifiers from generating false positive responses to off-target stimuli.

By contrast, response gain control (Figure 3C) produces poorer performance [23]. This is because response gain control compresses the PN dynamic range when the total level of ORN input is strong, and so strong stimuli elicit weak responses in all glomeruli. This makes it difficult for classifiers to generate correct hits while also minimizing false positives. Whereas it is easy to see how a presynaptic mechanism can produce input gain control, theoretical considerations suggest that postsynaptic mechanisms are more likely to produce response gain control [41]. Thus, the presynaptic or postsynaptic locus of inhibition can potentially have important consequences for the computational capacity of a circuit.

Synaptic mechanisms of lateral excitation

Although most LNs are immunopositive for GABA, some are instead immunopositive for choline acetyltransferase [25,28]. These interneurons are termed 'excitatory LNs' (eLNs). They form reciprocal synapses with PNs, GABAergic inhibitory LNs (iLNs), and other eLNs [30•,31•].

Notably, eLNs make specialized synapses with iLNs and PNs. Synapses from eLNs onto iLNs are mixed chemical–electrical synapses. By contrast, synapses from eLNs onto PNs are essentially purely electrical [30•,31•]. There are other examples in the literature of a presynaptic neuron forming specialized synapses onto different types of postsynaptic cells [42], and this is particularly striking example of this phenomenon.

The eLN network is thought to serve two functions. First, it spreads excitation between PNs in different glomeruli. This should slightly and transiently move all PNs nearer to their spike threshold when odor is present. Indeed, a mutation in a gap junction subunit (*shakB*) that eliminates eLN synapses onto PNs substantially weakens some PN odor responses [31•], implying that eLN can provide substantial excitatory drive to PNs. In addition, eLNs might help synchronize PN spikes. As a result, the eLN network could improve odor detection when stimuli are weak.

The second proposed function of the eLN network is to excite iLNs. It should be noted that iLNs also receive excitatory drive from PNs and ORNs [7,30•,31•]. However, eLNs are evidently an important source of excitation to iLNs, because genetically eliminating eLN-to-iLN synapses impairs the recruitment of GABAergic inhibition onto PNs [31•]. Thus, eLNs may have a role

in making sure that inhibition keeps pace with rising afferent excitation.

What is the functional relevance of the finding that eLNs form purely electrical synapses onto PNs? Recurrent excitatory circuits are dangerous because they can easily produce runaway excitation. Electrical connections can help prevent this, because electrical synapses are both inhibitory and excitatory. An electrical connection acts as a shunt which diminishes the effect of a synaptic current on the membrane potential of the cell that receives that synaptic input. Thus, the electrical connections between PNs and eLNs should shunt current away from PNs that are receiving relatively more ORN input, toward PNs that are receiving relatively less ORN input. The redistributive nature of this network may help prevent runaway excitation of the PN population.

Conclusions

These studies reveal a considerable degree of specialization in the properties of *Drosophila* antennal lobe synapses. Moreover, it is clear that these specializations have implications for the computations this circuit performs. In future, it will be important to harness the power of *Drosophila* genetics to make more direct causal links between the properties of these synapses, the computational function of this circuit, and the olfactory behaviors of the organism.

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