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Divisive Normalization in Olfactory Population Codes

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SUMMARY

In many regions of the visual system, the activity of a neuron is normalized by the activity of other neurons in the same region. Here we show that a similar normalization occurs during olfactory processing in the *Drosophila* antennal lobe. We exploit the orderly anatomy of this circuit to independently manipulate feedforward and lateral input to second-order projection neurons (PNs). Lateral inhibition increases the level of feedforward input needed to drive PNs to saturation, and this normalization scales with the total activity of the olfactory receptor neuron (ORN) population. Increasing total ORN activity also makes PN responses more transient. Strikingly, a model with just two variables (feedforward and total ORN activity) accurately predicts PN odor responses. Finally, we show that discrimination by a linear decoder is facilitated by two complementary transformations: the saturating transformation intrinsic to each processing channel boosts weak signals, while normalization helps equalize responses to different stimuli.

INTRODUCTION

Sensory neurons are selective for specific stimulus features. For example, a neuron in primary visual cortex may be sensitive to both the spatial location and the orientation of a stimulus. Similarly, the preferred stimulus of an olfactory neuron is defined by the molecular features of the odors that are effective at driving that neuron. Stimuli with nonpreferred features often have an inhibitory effect on a sensory neuron. The earliest illustrations of this principle came from studies of neurons in the *Limulus* eye (Hartline et al., 1952) and vertebrate retina (Barlow, 1953; Kuffler, 1953). These neurons respond best to light at a particular spatial location, and responses to light at the best position can be suppressed by simultaneously illuminating other locations. This concept was later extended to features other than spatial location. For example, it was observed that in primary visual cortex, a neuron's response to a grating with a preferred orientation can be suppressed by superimposing a nonpreferred orientation (Morrone et al., 1982).

The idea linking these findings is that a neuron's response to a preferred stimulus feature is inhibited by adding nonpreferred stimulus features. This phenomenon can be understood as a form of "gain control," defined as a negative feedback loop that keeps the output of a system within a given range. It has been proposed that this type of gain control in the visual system works by performing a divisive normalization of neural activity (Heeger, 1992). According to the divisive normalization model, the response of a neuron to a complex stimulus is not the sum of its responses to each stimulus feature alone. Rather, the response is divided by a factor related to the total "stimulus energy," which increases with stimulus intensity and complexity. For this reason, the response of a neuron to a complex stimulus is closer to an average of its responses to each feature.

A fundamental question is how gain control alters the response of a neuron to its preferred stimuli. A neuron's response to preferred stimuli is generally nonlinear, with intense preferred stimuli driving the neuron to saturation. It is important to define whether gain control scales the input to this function (thus making it more difficult to reach saturation) or the output of this function (diminishing the strength of the saturated response). Both forms of gain control seem to occur in visual processing and attentional control (Albrecht and Geisler, 1991; Cavanaugh et al., 2002; Williford and Maunsell, 2006; Reynolds and Heeger, 2009). Another important question is what cellular and circuit mechanisms form the substrate of this process. At least in some classic examples of gain control in visual processing, there is a clear role for lateral inhibition (Kuffler, 1953; Hartline et al., 1956).

One reason why these questions have been difficult to resolve is the complexity of the underlying circuits. Ideally, one would like to selectively manipulate feedforward excitation and lateral inhibition to the neuron one is recording from. From this perspective, the *Drosophila* antennal lobe is a useful preparation because of its compartmental organization (Figure 1A). All the olfactory receptor neurons (ORNs) that express the same odorant receptor project to the same glomerulus in the brain, where they make excitatory synapses with projection neurons (PNs). Each PN receives ORN input from one glomerulus and lateral inputs from other glomeruli (Bargmann, 2006). A PN's odor responses are disinhibited by silencing input to other glomeruli (Olsen and Wilson, 2008; Asahina et al., 2009), implying that lateral interactions are mainly inhibitory. This could explain the observation that a PN's response to an odor can be inhibited by adding a second odor that is ineffective at driving that PN when presented alone (Deisig et al., 2006; Silbering and Galizia,

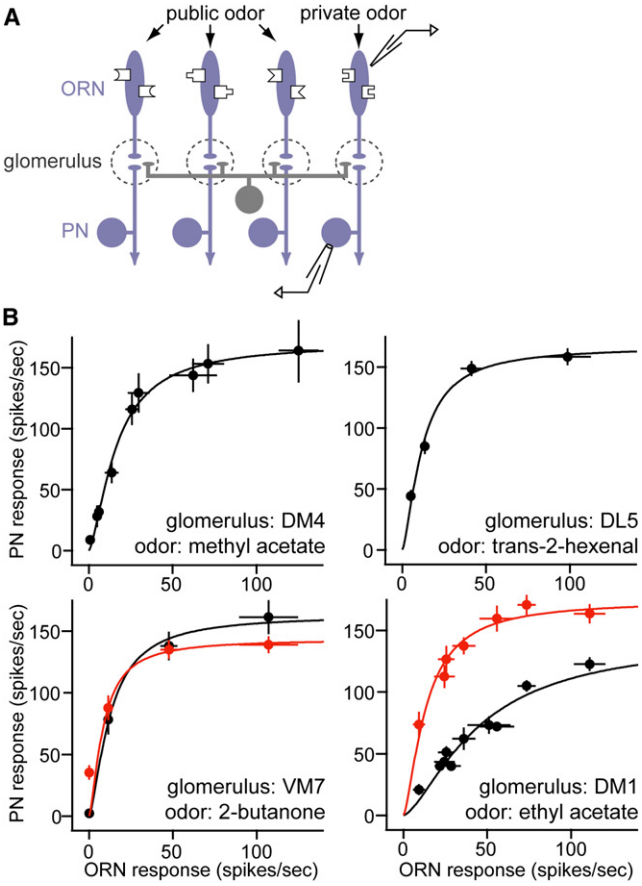

Figure 1. A Generalized Intraglomerular Transformation

(A) Experimental design. Varying the concentration of a private odor stimulus activates one ORN type to varying degrees. Recordings are performed from both these ORNs and their cognate PNs. In this figure, we use only private odors. In the experiments that follow, we will blend in a public odor that activates other ORNs (but not the cognate ORNs of the PNs we are recording from). This allows us to manipulate direct and lateral input independently.

(B) Intraglomerular input-output functions for four glomeruli. Within a graph, each point is a different concentration of the same private odor. GABA receptor antagonists (5 μM picrotoxin + 10 μM CGP54626) increase the gain in DM1 but not VM7 (red). All values are means of 6–12 recordings, ± SEM. Curves are best fits to Equation 1. Concentrations are as follows: methyl acetate 0, 10^{-11}, 10^{-10}, 10^{-9}, 3×10^{-8}, 7×10^{-8}, 10^{-7}, 10^{-6}, 10^{-5}; trans-2-hexenal 10^{-9}, 10^{-8}, 10^{-7}, 5×10^{-7}; 2-butanone 10^{-7}, 10^{-6}, 10^{-5}, 10^{-4}; ethyl acetate 0, 10^{-14}, 10^{-13}, 10^{-12}, 10^{-11}, 10^{-10}, 10^{-9}, 10^{-8}, 10^{-7}, 10^{-6}.

2007). Similar mixture suppression effects occur in the vertebrate olfactory bulb (Kang and Caprio, 1995; Giraudet et al., 2002; Tabor et al., 2004).

The aims of this study are to understand how lateral inhibition alters the response of a PN to its presynaptic ORNs and how this type of gain control affects PN population codes for odors. Previous studies have used odor stimuli that activate multiple ORN types, thereby driving both direct and lateral input to a PN. Instead, here we begin with "private" stimuli, defined as stimuli that activate only one ORN type (Figure 1A). By mixing private stimuli with varying concentrations of "public" stimuli (defined as stimuli that selectively activate a population of other glomeruli), we measure how increasing activity in other glomeruli suppresses the response of a PN to its presynaptic ORNs.

RESULTS

A Uniform Intraglomerular Transformation

Based on a previous study (Hallem and Carlson, 2006), we identified four likely private odors and their cognate ORN types (Table S1). We sampled randomly from many ORNs of other types in order to confirm that these odors do not activate non-cognate ORNs (Figure S1). Moreover, where mutations were available in the cognate odorant receptors for these odors, we verified that they virtually abolish the response of the ORN population (Figure S1).

For each of the four associated glomeruli, we recorded the responses of both ORNs and PNs to a range of concentrations of their private odor. Responses were quantified as spike rates over the 500 ms stimulus period. We found that the input-output relationships for three of these glomeruli were very similar (Figure 1B). In all these cases, weak ORN inputs were selectively boosted and strong inputs saturated. In the fourth glomerulus, the relationship between PN and ORN responses was shallower, but when GABA receptor antagonists were added, this relationship reverted to the typical steeper shape. The antagonists had no effect on a more typical glomerulus (Figure 1B).

These results suggest that all glomeruli perform a similar transformation on their inputs, although in some cases this transformation is modified by GABAergic inhibition. We can formalize this by fitting all these input-output relationships with the same equation:

$$PN = R_{max}\left(\frac{ORN^{1.5}}{ORN^{1.5} + \sigma^{1.5}}\right) \quad (1)$$

where *PN* is the response of an individual PN to a private odor stimulus, and *ORN* is the response of an individual presynaptic ORN to the same stimulus. R_{max} is a fitted constant representing the maximum odor-evoked response, and σ is a fitted constant representing the level of ORN input that drives a half-maximum response. R_{max} and σ are essentially the same for all glomeruli (10^{-10}, antagonists σ is larger for the fourth glomerulus we examined). The saturating form of this function reflects the combined effects of short-term depression at ORN-PN synapses and the relative refractory period of PNs (Kazama and Wilson, 2008). In Equation 1, the input terms are raised to an exponent of 1.5 because this produced the best fit; a similar equation describes the contrast response functions of visual neurons, and there too an exponent >1 is generally required (Albrecht and Hamilton, 1982; Heeger, 1992; Reynolds and Heeger, 2009; see Discussion).

Lateral Interactions Are Inhibitory

We next asked how activity in other glomeruli affects a PN's response to its cognate ORNs. Here we focused on two glomeruli: VM7 and DL5. In order to manipulate input to other glomeruli independently from input to these glomeruli, we used a "public" odor that activates many ORN types but not these ORNs (Figure 1A). We verified that this odor (pentyl acetate)