similar clinical manifestations, suggesting that these two proteins operate through common mechanisms[10]. Laforin is a phosphatase that interacts with PTG[11] and has a functional carbohydrate-binding domain. Malin is a ubiquitin ligase that causes ubiquitination and proteasome-mediated degradation of laforin[12].

In a series of elegant experiments, Vilchez *et al.*[7] brought the pieces of the puzzle together. They showed that the massive induction of glycogen synthase activity and of abnormal glycogen deposition induced in neurons when PTG is overexpressed is abolished by the concomitant overexpression of both laforin and malin. (Overexpressing either one alone had no effect.) They also demonstrated that the malin-laforin complex markedly decreases PTG and glycogen synthase protein levels, thus inactivating the glycogen-synthesizing machinery, through a mechanism mediated by activation of the ubiquitin-proteasome pathway. If a form of malin containing a mutation observed in individuals with Lafora disease is cotransfected in neurons with laforin instead of the wild-type malin, the inhibitory effect on PTG and glycogen synthase expression and activity is lost.

These results provide an explanation for previous puzzling observations of glycogen synthase in neurons *in situ*[13], although glycogen could not be observed in these cells in the adult brain. Vilchez *et al.*[7] report that neurons have the capacity to synthesize glycogen. However, glycogen spells trouble for neurons as it triggers a proapoptotic program. Accordingly, neurons have effective and redundant mechanisms for inhibiting glycogen synthesis. The first mechanism is to keep glycogen synthase in a phosphorylated (inactive) state. The second is to degrade PTG and glycogen synthase in a tonic, proteasome-dependent manner involving the malin-laforin complex. Mutations in the genes encoding these enzymes are found in individuals affected by Lafora disease, a condition that is histopathologically characterized by the presence of glycogen-like deposits in neurons. Thus it appears that neurons have an ambivalent relationship with glycogen; they benefit from it as long as it is localized in astrocytes and so long as they are provided with energy substrates deriving from it, most likely lactate. Increasing astrocytic glycogen has a neuroprotective effect in experimental stroke[5,14]. However, when synthesized inside of neurons, glycogen acts as a Trojan horse, triggering mechanisms that lead to neuronal dysfunction and eventually death.

Although Vilchez *et al.*[7] bring some new insights to the regulation of brain glycogen metabolism, this report raises several questions. For example, through what mechanism(s) does accumulation of abnormally branched glycogen trigger apoptosis? Why are astrocytes 'immune' to the destructive effects of glycogen accumulation? The actual link between glycogen accumulation in neurons and the clinical phenotype of Lafora disease still remains to be elucidated. Most curiously, why are neurons endowed with the potential for glycogen synthesis, but then activate complex protein-protein interaction mechanisms to keep this potential inhibited? Paradoxically, this inhibitory mechanism is likely to consume energy. One possibility raised by the authors is that glycogen synthase has other, yet undiscovered, roles in neuronal functions. This article is likely to bring a renewed attention to the study of glycogen regulation in the brain, a field that has evolved in a low-key but steady fashion over the last 25 years and is likely to still bring surprising insights into neuron-glia physiology and pathology in the years to come[3].

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A step toward optimal coding in olfaction

L F Abbott & Sean X Luo

Receptor neurons may not encode sensory information in an efficient manner. A new paper supports the idea that the brain achieves optimal encoding downstream of sensory transduction through additional processing.

Sensory information is converted into neural activity by receptor neurons and then shaped by subsequent processing stages into a neural representation that can direct behavior. Our understanding of early steps along this pathway has been guided by the concept of optimal coding. Receptor neurons, having to handle the complexities of sensory transduction, may not be able to respond in ways that optimally encode information for particular tasks. According to the idea of optimal coding, subsequent processing may involve a transformation to a more efficient representation. In this issue, Bhandawat *et al.*[1], reporting on the *Drosophila* olfactory system, provide strong support for this idea and also raise interesting questions.

In the fly olfactory system, sensory transduction takes place in olfactory receptor neurons (ORNs), and olfactory signals are relayed in the antennal lobe (the insect analog of the olfactory bulb) through glomeruli that receive direct sensory input from ORNs that all express the same olfactory receptor gene[2,3]. Output from the antennal lobe is carried by projection neurons that each receive their input from a single glomerulus. Intrinsic projection-neuron response characteristics, properties of the synaptic connections made by ORNs and projection neurons, and features of the circuitry in and between glomeruli can all contribute to making projection neurons respond differently than ORNs (**Fig. 1a**). However, ORNs not directly connected to a given projection neuron can only influence that projection neuron through interglomerular connections within the antennal lobe. Recent studies[4–7] have revealed interesting features of interglomerular interactions, but their functional role has remained unclear. Bhandawat *et al.*[1] provide

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new insights by comparing and contrasting responses to a variety of odorants at both the ORN and projection neuron levels.

Neural circuits downstream of the antennal lobe must differentiate between the patterns of activity that are generated by different odorants if the fly is to discriminate between odors. Conversely, discrimination will be impossible if the firing rates evoked by a pair of odors are too close to each other for these circuits to distinguish between them. Discrimination performance across a whole spectrum of odors is limited by the extent to which olfactory responses cluster into indistinguishable groups. Responses across an array of odors can be characterized by a response distribution, reflecting the probability that randomly selected odorants evoke various firing rates. Using a simple model of detection, the optimal distribution of firing rates for discrimination is one with no clusters: that is, a flat distribution with equal probability for firing rates to fall anywhere within their allowed ranges.

Bhandawat *et al.*[1] found that ORN responses are not uniformly distributed; the majority of them are at low rates. This agrees with the distribution of the responses reported previously[8] from a larger sample of 24 olfactory receptors generating responses to 110 odors (**Fig. 1b**, left). The clustering of responses at low rates is probably an unavoidable consequence of using general-purpose receptors that are likely to bind to many molecules weakly and only a few strongly, thereby generating a clustering of responses at low firing rates. According to the optimal-coding hypothesis, the antennal lobe should change the exponential distribution of ORN responses (**Fig. 1b**, left) into a flat distribution of projection neuron responses, making downstream discrimination easier. This operation, known as histogram equalization, is exactly what Bhandawat *et al.*[1] report.

Bhandawat *et al.*[1] found that projection neuron firing rates over the odorants that they tested are much more uniformly distributed than ORN responses. Furthermore, they uncovered the mechanism for this histogram equalization, a nonlinear dependence of projection neuron firing rates on the rates of the ORNs that provide their direct sensory input. Projection neuron firing rates rise sharply as a function of the corresponding ORN rate, but soon saturate (**Fig. 1b**, center). To further support this point, if the ORN responses from the study[8] mentioned above (**Fig. 1b**, left) are passed through the nonlinear firing-rate function reported by Bhandawat *et al.*[1] (**Fig. 1b**, center), then the resulting distribution is flat (**Fig. 1b**, right). If the distribution of ORN responses recorded in these experiments is representative of responses to natural odors, something that should be checked, these results provide a notable illustration of a mechanism suggested earlier and illustrated in fly vision[9]: appropriately shaped nonlinear firing-rate curves can equalize responses to enhance neural encoding.

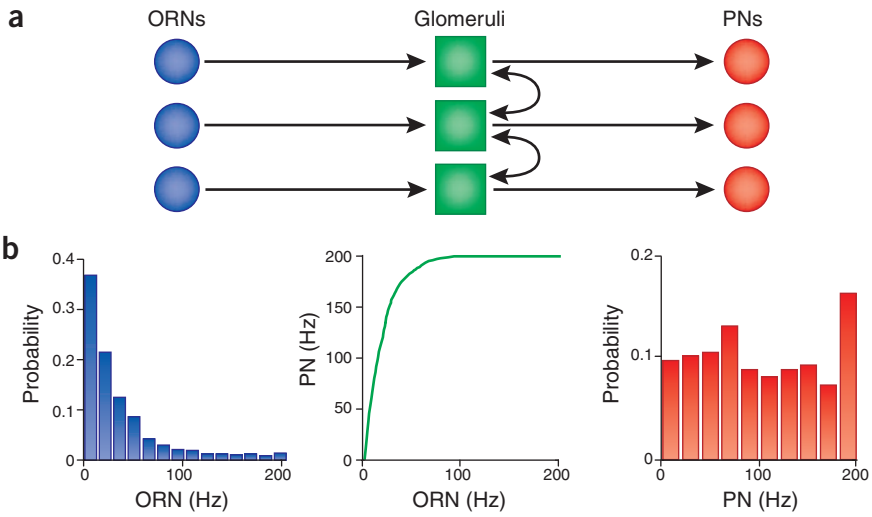

Figure 1 Transformation of olfactory responses in the antennal lobe. (**a**) Schematic of the antennal lobe circuitry. Here, each ORN provides input to one glomerulus and each projection neuron (PN) receives input from one glomerulus. Interactions within individual glomeruli (green squares) allow for single-channel processing and connections between glomeruli (curved arrows) allow for cross-channel processing. (**b**) The transformation from ORN responses to PN responses applied to data from a previous study (figure modified from ref. 8). Left, ORN responses over the ensemble of odorants are distributed in an exponential manner with most of the responses occurring at low rates. Center, the nonlinear transformation linking ORN responses to PN responses, as determined by Bhandawat *et al.*[1]. Right, the distribution of PN rates generated by the ORN rates (left), transformed by the firing rate relation (center), is approximately flat.

An uneven histogram is not the only way that responses can cluster. Even if individual projection neurons have flat response histograms, correlations between their responses can cause clustering across the projection neuron population. Because any correlation or redundancy that exists between olfactory responses makes discriminating between odors more difficult, optimal encoding demands that they be removed[10]. Unlike histogram equalization, this requires interglomerular interactions. ORN responses are correlated[1,8], which is probably another unavoidable consequence of binding odorant molecules to a family of related receptor proteins. This appears to be a problem that is not solved by the antennal lobe. Bhandawat *et al.*[1] did not find any substantial reduction in the correlation of projection neuron responses relative to those of the ORNs. As far as optimal coding is concerned, the antennal lobe does part (histogram equalization of individual projection neurons), but not all (decorrelation across projection neurons), of the job.

Decorrelation may not be as important for odor discrimination as the simple readout model that is being considered suggests, or perhaps decorrelation takes place at a later stage in the odor-processing pathway[10]. If the antennal lobe is not using its interglomerular connections to decorrelate projection neuron responses, what other functions might they have? Perhaps they are involved in adaptation or learning[11], or are a target for neuromodulation. Alternatively, the cross-channel signal carried by antennal lobe circuitry may be an overall odor intensity or salience signal, rather than identifying or representing specific odors. These issues remain to be clarified, but, at least at the single-olfactory channel level, Bhandawat *et al.*[1] have uncovered an interesting transformation generated by the antennal lobe circuitry and have provided a satisfying explanation of its role in olfactory processing.

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