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# State-dependent plasticity of innate behavior in fruit flies

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Behaviors are often categorized into innate or learned. Innate behaviors are thought to be genetically encoded and hardwired into the brain, while learned behavior is a product of the interaction between experience and the plasticity of synapses and neurons. Recent work in different models show that innate behavior, too, is plastic and depends on the current behavioral context and the internal state of an animal. Furthermore, these studies suggest that the neural circuits underpinning innate and learned behavior interact and even overlap. For instance, hunger modulates several innate behaviors relying in part on neural circuits required for learning and memory such as the mushroom body in the fruit fly. These new findings suggest that state-dependent innate behavior and learning rely on functionally and anatomically overlapping and shared neural circuits indicating a common evolutionary history.

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## Introduction

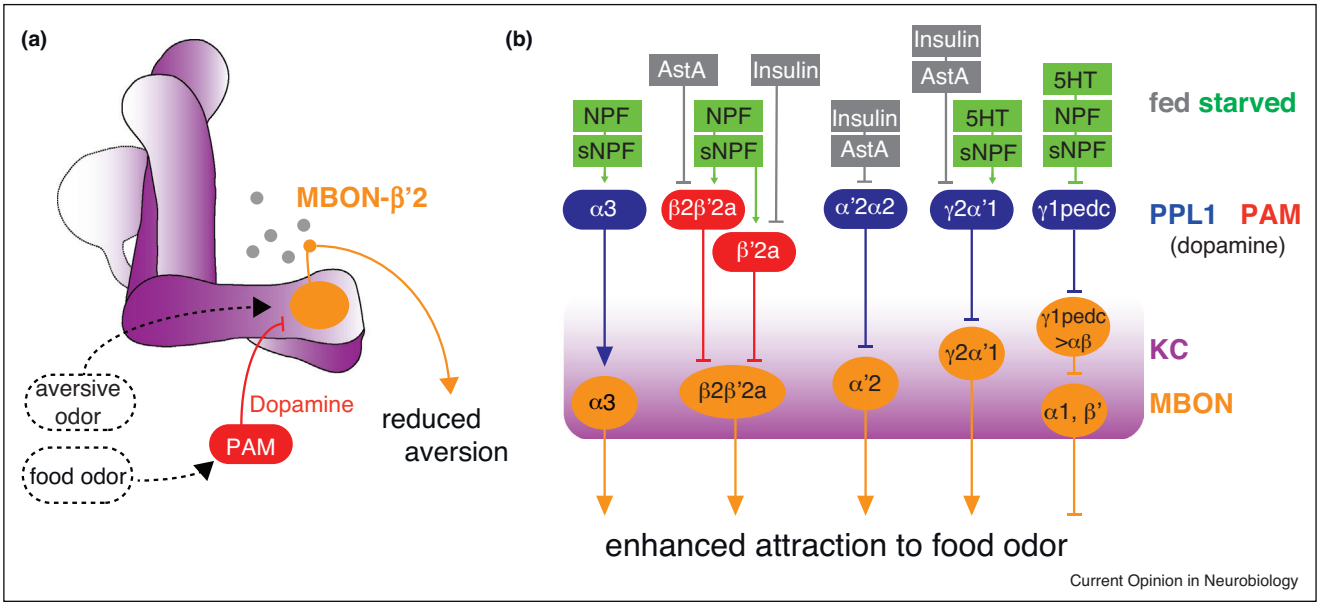
Arguably one of the key roles of a brain is to prioritize the sensory information most relevant at a given moment and convert it into a percept to guide behavior. How sensation is translated into perception is a long-standing question in psychology and neuroscience. The signals and neurons shaping these percepts also remain largely unknown.

Clearly, learning contributes to the perception of sensory information. A neutral stimulus such as an odor can be perceived as threatening if once experienced in the context of a fearful event. However, not only prior experiences matter, also ongoing experience, behavioral and internal state shape how sensory information is perceived at a given moment without necessarily changing perceptions in the long-term. Therefore, it is not surprising that even innate reactions to a stimulus are under such context- and state-dependent regulation. Here, I will review studies in *Drosophila* focusing on mechanisms underpinning plasticity of innate behavior. These mechanisms are, nevertheless, by no means exclusive for innate behavior, but rather expose the continuum between an innate and a learned behavior.

## Hunger dominates all

An energy deficit poses an imminent risk to any animal including flies. Hunger states, therefore, dominate most other needs or behaviors. For instance, a recent study has shown that innate temperature preference is regulated by the metabolic state of the fly [1•]. In mammals, hunger reduces body temperature, presumably to preserve energy. Flies and other ectotherms lack internal temperature regulation and instead regulate body temperature by moving to their preferred environmental temperature. To sense ambient temperature, flies rely in part on neurons (anterior cells, AC) in the central brain that express the temperature receptor dTrpA1 [2]. Umezaki *et al.* observed that starved flies shift their typical preference from 25 to 23 °C, presumably also in an effort to save energy. This shift is mediated by insulin-like receptor signaling in ACs, which react to insulin-like peptide 6 (Ilp-6) produced in the fly's fat body effectively lowering the AC temperature threshold by a few degrees. Nevertheless, innate temperature preference also depends on dopamine in the fly's mushroom body (MB) network, a higher brain center required for learning and memory [3–5], but which also receives hunger and temperature information [6–8]. Several recent studies have revealed that the MB integrates internal state and modulates innate behavior [9,10•,11•,12••]. The MB's intrinsic cells, the Kenyon cells (KC) receive sensory information, and pass it on to MB output neurons (MBON) tiling the MB lobes into distinct regions [13]. Dopaminergic neurons (DANs) of two broad subtypes, PPL1 and PAM, innervate these regions and synapse with KCs as well as MBONs [14•]. Whether hunger-dependent temperature preference requires the MB is not known, however, hunger modifies innate odor preference [9,11•,12••,15]. While in fed flies innate odor avoidance behavior does not require KC synaptic output, avoidance is mediated by KCs and specific MBONs (output of the β′2 lobe) upon starvation [9,11•,15] (Figure 1a). Tsao *et al.* now asked whether and how the MB network contributes to hunger-induced innate food odor attraction [12••]. The authors

**Figure 1**




Mushroom body circuits regulate metabolic state-dependent innate food seeking behavior.
**(a)** When searching for food flies are confronted with mixtures of appetitive and aversive odorants. Rotting fruit, the fly's preferred food source, emit for instance aversive $CO_2$ and attractive acidic odors. Hungry flies appear to use their mushroom body to integrate these two conflicting sensory drives. While $CO_2$ drives innate aversion through the activation of a set β'2-lobe MBONs providing output of the β'2-lobe, vinegar activates PAM DANs which instantaneously inhibit MBON output and thereby lower aversion [9,11•]. **(b)** Hunger regulates the attraction to food odor by modulating MB networks. Different neuromodulators signal hunger or satiety states to DANs, which in turn regulate the output of specific MBONs in different MB lobe regions. KCs and MBONs require the expression of the dopamine receptor DAMB to be modulated in a state-dependent manner. The combined output of at least five MBONs drives or suppresses food seeking in hungry or fed animals, respectively [12••].

showed that at least 5 MBONs (Figure 1b) mediate the hungry fly's attraction to food odors. Consistent with previous studies, odor responses of these MBONs are modulated by metabolic state through specific DANs [6,15]. Specifically, RNAi-mediated downregulation of the expression of one dopamine receptor, DAMB in KCs or MBONs, reduced food odor attraction, suggesting that DAMB signaling is required in KCs and MBONs to regulate their synaptic output or sensitivity, respectively, to odor in tune with the animal's metabolic needs [12••]. That DAMB is involved but not DopR1 led the authors to speculate about the differential roles that DopR receptor signaling might play in MB function and plasticity. While DopR1 in KCs is required for learning, DAMB could be specifically required for the maintenance of a certain synaptic configuration such as acquired or state-dependent synaptic depression or potentiation. However, KC DAMB signaling also leads to active forgetting of previously learned odor associations [16]. Regardless, different synaptic release modes might recruit different DopR types such that phasic release activates DopR1 and tonic release DAMB signaling [17] stressing the importance of careful analysis of synaptic mechanisms in the MB network. Furthermore, the response of DANs to odors, which, at least in some subtypes, depends on metabolic, behavioral state or experience [11•,18–20], appeared to be regulated through several neuromodulators including short neuropeptide F (sNPF), serotonin and insulin, signaling hunger or satiety [12••]. Perhaps the most surprising conclusion of this and previous studies is that KCs, which were shown to receive non-stereotyped odor input [21], mediate stereotyped behavior. While it is currently unclear why the system has evolved in this way, analysis by Hige *et al.*, using *in vivo* patch clamp recordings and imaging, discovered a certain degree of stereotypy with some MBONs responding more to innately aversive or attractive odors, respectively [22].

In addition to hunger, several recent studies have analyzed more specific nutritional needs and how they modulate innate feeding-related behaviors [23,24,25••,26•,27]. So-called 'protein hunger', for instance, increases dramatically upon mating in female flies [23,28]. Lui *et al.* have now identified a surprising degree of anatomical plasticity underpinning this protein-specific appetite [25••]. Protein-deprivation in males similar to mating in females switches food preference from sugar to proteinaceous food. Activation of a subset of dopaminergic neurons of the PPM2 cluster, named DA-WED, was sufficient to induce protein preference and reduce sugar feeding in males that had not been deprived of protein. Remarkably, lack of protein not only increased