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## The good, the bad, and the hungry: How the central brain codes odor valence to facilitate food approach in *Drosophila*

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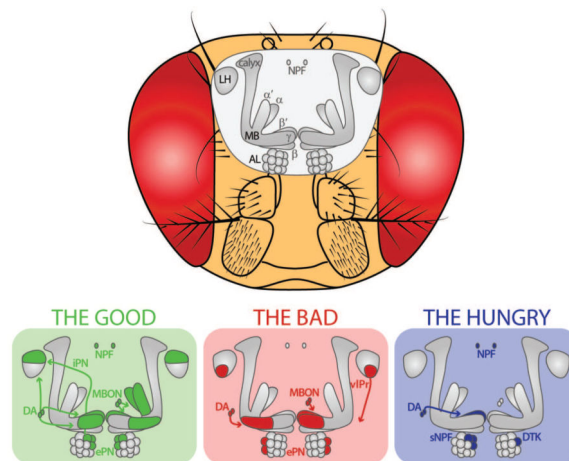
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### Abstract

All animals must eat in order to survive but first they must successfully locate and appraise food resources in a manner consonant with their needs. To accomplish this, external sensory information, in particular olfactory food cues, need to be detected and appropriately categorized. Recent advances in *Drosophila* point to the existence of parallel processing circuits within the central brain that encode odor valence, supporting approach and avoidance behaviors. Strikingly, many elements within these neural systems are subject to modification as a function of the fly's satiety state. In this review we describe those advances and their potential impact on the decision to feed.

### Graphical Abstract



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## Introduction

Accurate and timely appraisal of potential food resources is critical to survival. Prior to initiating feeding, neural systems must integrate food cue information from the external environment with information about internal satiety state to initiate motor programs that drive the search for food [1–3]. Odors are among the primary cues guiding such foraging behavior. Significant advances are being made in understanding how metabolic state alters the sensitivity of primary neurons along the olfactory axis, promoting foraging behavior [4,5\*,6]. Yet comparatively little is known about how downstream elements of olfactory circuits shape this received sensory information and their effects on the locomotor behaviors that support eventual food acquisition. In recent years an increasing number of neural pathways were characterized that support the detection, categorization and evaluation of potential food sources. Here we focus on how central pathway components contribute to the hedonic classification of olfactory food cues and how an animal's needs adaptively shape activity along the pathway length, thereby promoting exploration, approach or avoidance.

### Initial representations of olfactory food cues

Food sources emit different types of odor cues that evoke attraction behavior while certain key odorants signal danger and induce strong aversion in flies [7–9\*]. All these olfactory cues are detected first by olfactory receptor neurons (ORNs) housed in different sensilla on the fly's olfactory organs, the antennae and the maxillary palps [10] and it is long-established that most ORNs are strongly activated by food odors and that many food odors activate multiple ORNs [11] (Figure 1). In contrast to the combinatorial code of complex food odor cues, odorants that indicate spoiled food are detected and mediated through highly selective and dedicated information pathways as shown for the odor geosmin, which is emitted by toxic microbes [8], and acids [12], often emanating from rotten food or unripe fruit (Figure 2). Additionally, potential food sources emit further discrete olfactory cues that drive behaviors other than feeding (Box. 1).

Even at this initial stage of processing, satiety state affects odor representation (Figure 3). Starvation increases on one hand the sensitivity of ORNs to food odors through neuromodulatory mechanisms [4,6]. Short neuropeptide F (sNPF), which is expressed in ORNs, facilitates synaptic transmission in specific ORNs, while the expression level of the sNPF receptor is increased by a reduction of insulin signaling [4]. Both mechanisms lead to robust food-search behavior. In addition to sNPF, the neuropeptide receptor CCHamide1 is involved in starvation-induced modulation at the ORN level [6]. On the other hand, food deprivation reduces avoidance behavior to innately aversive odors [15] and increases the tolerance for noxious stimuli [16]. The reduction of aversive odor sensitivity during starvation has been shown to occur at the first olfactory synapse driven by the tachykinin receptor [5\*]. Hence, diverse neuropeptide signaling systems act in opposing directions on olfactory attraction and aversion to adjust food approach to the satiety state of the fly [5\*].

ORN processes converge in the fly brain on glomeruli at the level of the antennal lobe and there synapse with second-order projection neurons (PNs) [17]. Here the representation of

odor valence begins to spatially segregate, with attractive and aversive odor cues activating predominantly medial- and lateral-projecting PNs, respectively [18,19].

## Hedonic processing in the lateral horn

PNs form two classes, excitatory and inhibitory, and send spatially distinct processing pathways to the higher brain [20]. Excitatory PNs are uniglomerular and relay the odor information from the antennal lobe to the mushroom body, a center long-studied in learning and memory [21], and the lateral horn, a brain region assumed to be involved in innate olfactory behavior [22]. Inhibitory PNs, on the other hand, integrate odor-induced activity of several glomeruli, bypass the mushroom body, and innervate the lateral horn exclusively. Together, these PN populations process information on dual olfactory pathways [20,23]. Considering the axonal projections of PNs in the lateral horn, excitatory PNs spatially segregate in regions responding to pheromones or food odors [22], as well as attractive amines or aversive acids/CO<sub>2</sub> [24]. Inhibitory PNs target the posterior-medial part of the lateral horn, which is tuned to attractive odors only, and have been shown to be necessary for odor attraction behavior [25\*\*] (Figure 1). The anterior-lateral area of the lateral horn is innervated by third-order neurons that further innervate the ventrolateral protocerebrum and are responsive to aversive odors [25\*\*] (Figure 2). A third region in the lateral horn, also targeted by inhibitory PNs, mediates odor intensity independent of valence [25\*\*]. Hence, the lateral horn represents a feature-based, spatially segregated activity map decoding opposing hedonic valences and odor intensity. Notably, pheromone-responsive inhibitory PNs do not target a spatially separate area in the lateral horn as observed for excitatory PNs, but terminate together with PNs encoding attractive odors [25\*\*]. This finding seems plausible, since pheromones also induce attraction behavior in both male and female flies [26]. However, inhibitory PNs reveal a differential inhibition onto third-order neurons which are selective for food odors and pheromones [20].

These data suggest that odor identity might be lost at the level of the lateral horn and odor information seems to be categorized according to their behavioral relevance. An alternative hypothesis has also been proposed: both odor features are still present at the lateral horn level, but are processed separately by the two PN pathways. Excitatory PNs encode odor identity and mainly determine innate odor discrimination, whereas inhibition from inhibitory PNs, which scales with olfactory stimulus strength, enhances the contrast between closely related odors by stretching the distance between overlapping odor representations of excitatory PNs [27].

## Food cue processing along the lateral horn pathway

Arborizing within the lateral horn region [28\*], neurons expressing *Drosophila* Neuropeptide F (NPF) are anatomically positioned to exploit the odor valence information encoded by the lateral horn. NPF is the functional homolog of mammalian orexigenic Neuropeptide Y (NPY), and both of these peptides are long-understood to play a critical role in regulating motivational aspects of food consumption [29–32]. NPF-positive neurons also respond specifically to food odors, and these responses are increased by hunger, indicating that these neurons integrate signals relating to both olfactory food cues and appetite control

[33\*\*] (Figures 1 and 3). Further, the level of activity observed in NPF neurons shows a strong correlation with foraging behavior: the greater the food odor-evoked NPF neural response, the greater the attraction to that odor. Strongly driving NPF neurons is sufficient to flip the valence of an odorant from aversive to attractive [33\*\*]. Overall these results suggest that NPF neurons, rather than simply coding for hunger, play a key role in signaling the appetitive strength of food odors.

The activity of NPF neurons is not only necessary for food odor-induced foraging [33\*\*] but also for food-odor stimulated *feeding* [28\*]. Brief exposure to a banana-like odor leads to impulsive feeding in larvae. Both NPF neurons and neurons expressing its receptor NPFR1 are essential for the expression of this behavior [28\*]. Interestingly, this effect occurs only in the presence of a palatable, readily available food source, indicating that it is not simply a reflexive feeding response, but an effect in the sensitivity to trigger an extant behavior. This may, at least in part, be explained by changes in gustatory sensitivity that accompany stimulation of NPF neurons. Activating NPF cells enhances sugar sensitivity, increasing the acceptance of lower concentrations of sweet tastants, in fed flies while leaving bitter sensitivity unchanged [16].

For both food odor-stimulated feeding and increased gustatory sensitivity, NPF cells act upstream of dopamine-positive neurons [16,28\*]. Stimulating NPF cells is not sufficient to increase sugar sensitivity when dopamine receptors expressed in sugar-sensing gustatory receptor neurons [34] are absent [16] and food odor stimulated feeding is reduced after NPFR1 knockdown on dopamine-positive cells [28\*]. Odor-driven feeding can also be elicited by activation of a small number of dopaminergic neurons, DL2-LH, so-named given their putative synaptic connectivity with the lateral horn. DL2-LH neurons also respond to the banana-like odor that drives impulsive feeding and knocking down NPF receptors on these cells attenuates this effect [28\*] (Figure 1).

## Hedonic and food cue processing along the mushroom body pathway

In addition to the lateral horn, olfactory information from the excitatory PNs is directly transmitted to the mushroom body which is thought to code for odor identity rather than valence [33\*\*,35]. The approximately 2000 intrinsic neurons, so-called Kenyon cells, of the mushroom body converge onto a total of only 34 output neurons (MBONs) [36]. Unlike the highly stimulus-specific Kenyon cells and the stereotyped odor response properties of PNs [17,35], MBONs are broadly- and uniquely-tuned across animals with their response profiles likely dependent on experience [37]. Indeed, learning does support changes to the Kenyon cell-MBON odor drive [38–40].

Although Kenyon cells don't appear to carry a representation of odor valence (but see [41]), photoactivation of individual MBON types induces robust attraction or aversion behavior (Figures 1 and 2). Furthermore, the type of behavioral response triggered by different MBONs is related to the neurotransmitter each uses: activating glutamatergic MBONs elicits aversion while activating either GABAergic or cholinergic MBONs elicits attraction [42\*]. In line with this observation, a small subset of glutamatergic MBONs (projecting from  $\gamma 5\beta'2a$  and  $\beta'2mp$ ) are necessary to mediate aversion behavior to CO<sub>2</sub> [43\*\*]. CO<sub>2</sub>,

generally repellent to the fly [44], is also a byproduct of fermenting fruit, a strong natural attractant and food source for the fly. A good deal of evidence describes how the olfactory periphery can accommodate the integration of these opposing signals [3] but higher order neural circuits also play a role [15,43\*\*]. Overlapping with the same region of the mushroom body as the CO<sub>2</sub>-responsive glutamatergic MBONs [43\*\*], are a subset of vinegar odor-responsive mushroom body-projecting dopamine-positive PAM neurons that when activated support attraction behavior. The responses of these PAM neurons are heightened with hunger and provide a mechanism by which to depress the activity of CO<sub>2</sub>-responsive MBONs [43\*\*] (Figures 1 and 3). This local circuit provides a means to reconcile conflicting olfactory food cues and demonstrates that the mushroom body pathway is not limited to learning and memory processing.

There is further evidence for context-dependent modulation of neural activity at the level of the mushroom body. Mushroom body-innervating dopamine-positive cells display spatially-segregated patterns of activity to aversive and appetitive stimuli [45\*]. Electric shock heightens the activity of dopamine cells targeting  $\gamma 2/\gamma 3$  and depresses activity in those targeting  $\gamma 4/\gamma 5$ . The reciprocal pattern is observed in response to sugar feeding. Intriguingly, even in the absence of overt external stimulation similar patterns are observed [45\*]. When the fly is idle, dopamine responses mimic the sugar-feeding state. Conversely, during spontaneous expression of an escape-like behavior, patterns look like those elicited by electric shock [45\*]. The compartmentalized nature of dopamine's mushroom body modulation provides a means to differentially shape MBON activity in accordance with the fly's behavioral state. When taken together [42\*,43\*\*,45\*], there emerges a complementary segregation of the actions supported by mushroom body-projecting dopamine neurons and MBONs. On the whole, avoidance behavior is supported by dopamine-positive cells targeting the heel to the midline of the horizontal mushroom body lobes while avoidance-related MBONs cover the midline to the tip (Figure 2). The converse is true for approach behavior (Figure 1). It is also important to note that driving combinations of MBONs produces the strongest behaviors, be they approach or avoidance, supporting the idea that ultimate behavioral output results from the combination of multiple valence-specific signals [42\*] even at this late level of processing. While MBONs and the dopamine neurons that modulate their activity clearly support the production of approach and avoidance behaviors [42\*,45\*], their response specificity for food odor cues and how elements of such cues might be integrated with satiety information to generate state-appropriate behavior remains unknown.

## Conclusions

The conventional wisdom that olfactory information leaving the first brain relay bifurcates to form neural systems that separately code for odor identity and odor valence, along the mushroom body and lateral horn pathways respectively, needs to be revisited in light of recent discoveries. Within the central brain, valence-coding neurons that promote approach or avoidance behavior appear in both these parallel processing streams [19,25\*\*,28\*,33\*\*,42\*,43\*\*,45\*]. Indeed, food odor responsive neurons that promote attraction or feeding are present downstream of both the lateral horn and mushroom body [28\*,33\*\*,43\*\*]. In light of decades of research solidifying its role in learning and memory [21], it is perhaps

unsurprising that neurons downstream of the mushroom body appear more favorably tuned to alter their response properties as a function of acute learning [37–39,42\*,45\*]. Plasticity along the lateral horn axis remains to be determined.

Additionally, nearly every element within both of these neural pathways faces some form of modification as a function of satiety state [4,5\*,6,15,16,28\*,33\*\*,43\*\*,45\*]. Emerging evidence for the existence of neurons that directly detect nutrient quality [46–48] and those responsible for coding hunger more generally [49] leaves open the question of how and where this information is integrated with external sensory cues, such as food odors, to flexibly promote the appropriate expression of food approach behavior. It is also interesting to note that while the satiety state of the animal can alter sensitivity to external cues, influence appears to be bidirectional. Exposure to food odors concomitantly elicits changes in metabolic pathways controlling food intake [50]. Given the critical nature of food resource determination in the life of any animal, the fly being no exception, it makes sense that there exist multiple controls governing the discrimination between good and bad food odor cues. The accessibility of the *Drosophila* nervous system continues to provide fertile ground in understanding how neural systems process such cues and dynamically alter their representation as a function of state and experience.

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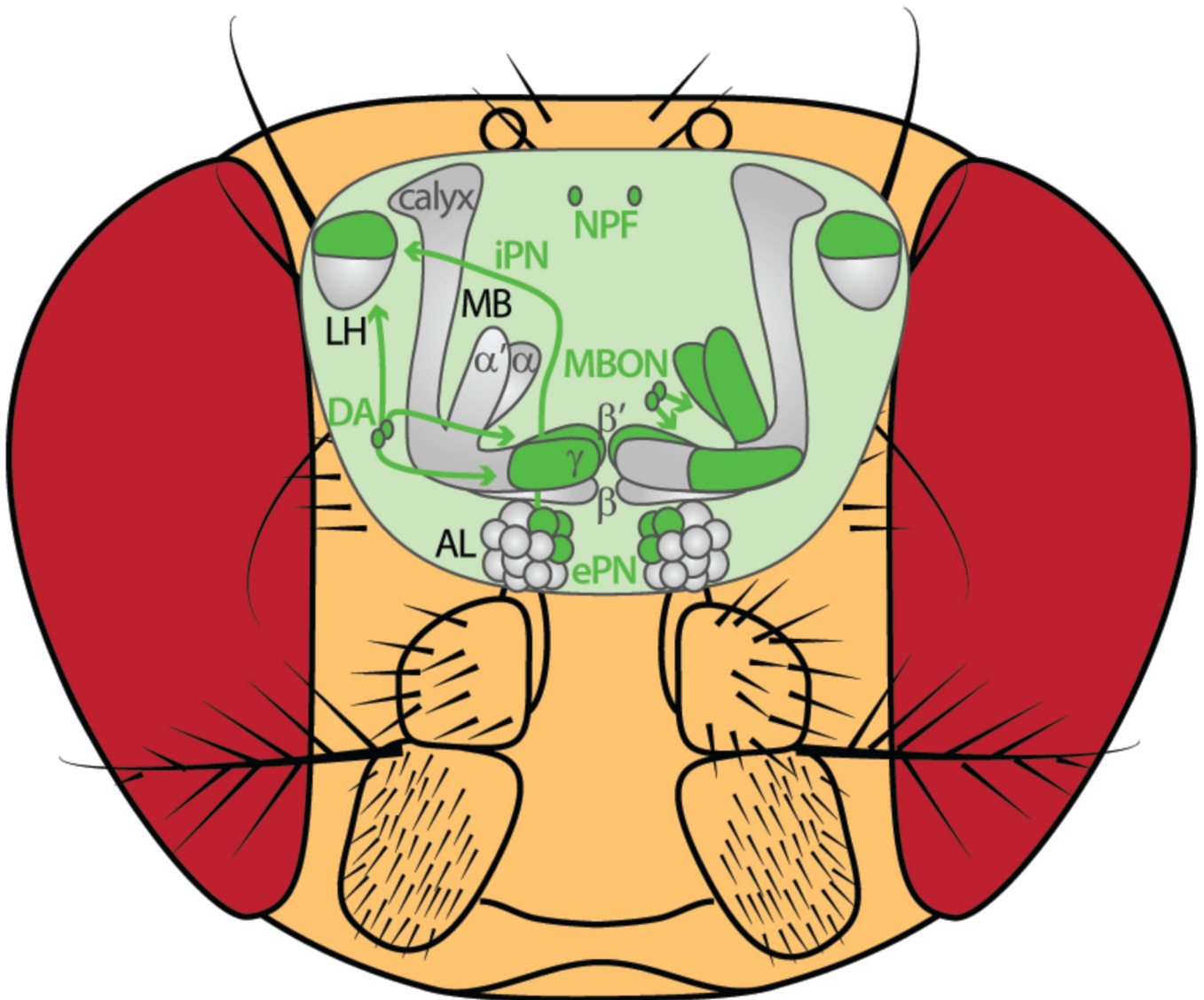
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### Highlights

- Starvation reduces aversive odor sensitivity and increases activity to food odors
- Odors are categorized according to their behavioral relevance in the lateral horn
- Dopamine and Neuropeptide F cells respond to food odors, directing approach/feeding
- State-dependent dopamine modulates mushroom body output neurons coding odor valence

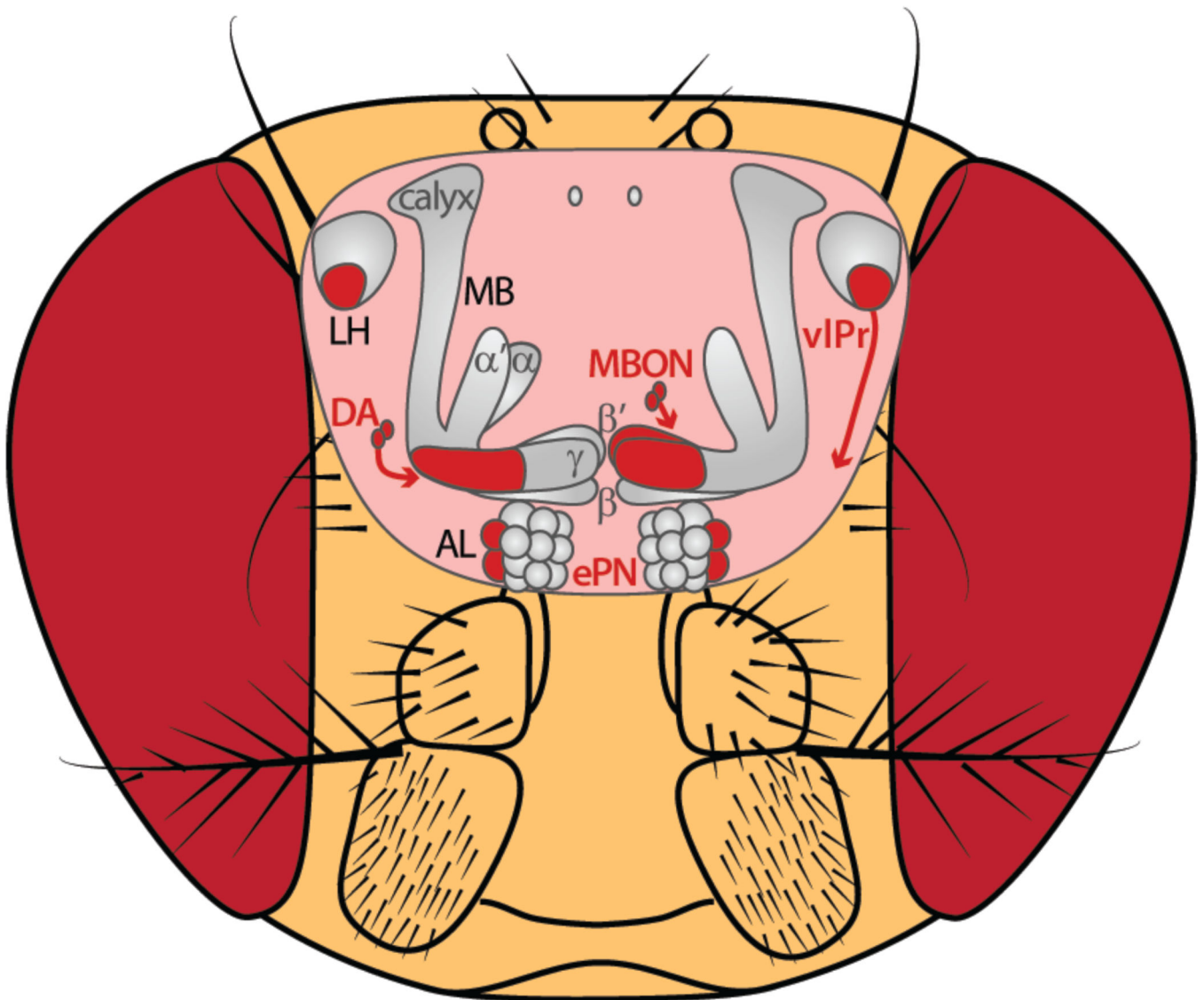
**Box 1****Feeding versus oviposition**

Food-derived odor cues do not solely indicate a food source. A mated female fly for example has to evaluate -- in addition to the nutritional value of the food -- whether this substrate represents a favorable environment where her offspring, i.e. the larvae, will be able to feed and develop. Both aspects are not necessarily combined within the same substrate. Most studies published so far have merely considered only one aspect. Flies prefer for example citrus fruits as an oviposition substrate [13] but seem not to feed on it. Flies detect terpenes which are characteristic of these fruits via a single class of ORNs, expressing the odorant receptor Or19a. These neurons are necessary and sufficient for selective oviposition. A separate olfactory pathway has recently been shown to specifically inhibit oviposition [9\*]. *Drosophila* adult females as well as their larvae avoid sites smelling of the main parasitoid enemies, *Leptopilina* wasps. This avoidance is mediated via a highly specific ORN type that is tuned to detect three odors of the parasitoid, including the wasps' sex pheromone iridomyrmecin. Also geosmin serves as an indicator for bad oviposition sites and strongly inhibits egg laying in female flies [8]. Interestingly, yeast-produced ethylphenols which are derived from dietary antioxidants represent odor cues that induce both, feeding as well as oviposition behavior [14]. Dietary antioxidants are abundant in fruits and thus constitute a significant nutritional reward. Flies are able to detect the presence of dietary antioxidants with ORNs expressing the odorant receptor Or71a. These ORNs are located on the maxillary palps and are tuned to detect ethylphenols. Activation of these neurons in adult flies induces attraction behavior, oviposition, and increases feeding [14].



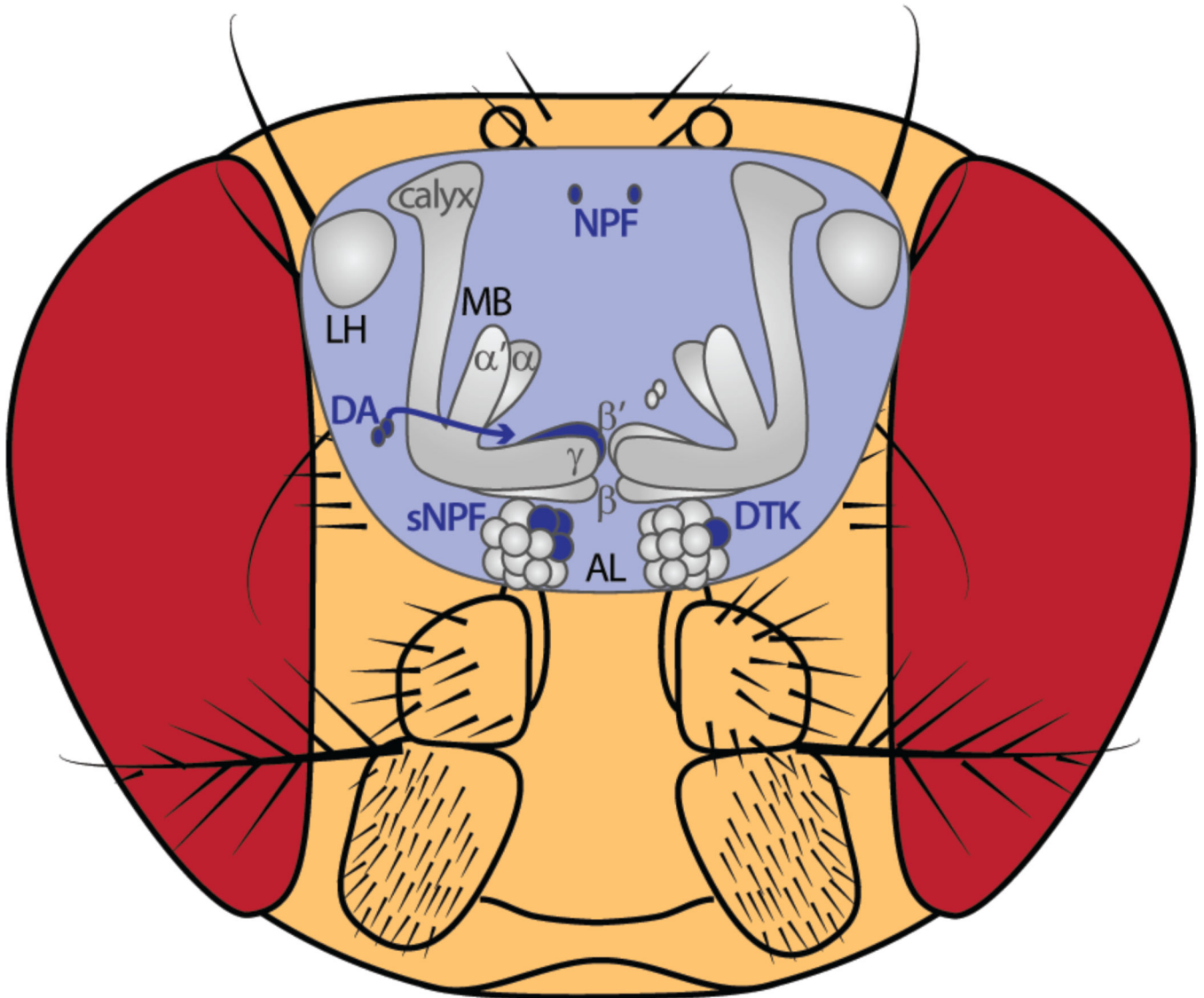
**Figure 1. The good**

Elements along olfactory neural pathways that respond to food odorants or support approach behavior when activated. AL: antennal lobe, DA: dopamine, ePN: excitatory projection neuron, iPN: inhibitory PN, LH: lateral horn, MB: mushroom body, MBON: mushroom body output neuron, NPF: neuropeptide F.



**Figure 2. The bad**

Elements along olfactory neural pathways that respond to aversive odors or support avoidance behavior when activated. AL: antennal lobe, DA: dopamine, ePN: excitatory projection neuron, LH: lateral horn, MB: mushroom body, MBON: mushroom body output neuron, vIPr: ventrolateral protocerebrum.



**Figure 3. The hungry**

Elements along olfactory neural pathways that are modulated as a function of satiety state. AL: antennal lobe, DA: dopamine, DTK: tachykinin receptor, MB: mushroom body, NPF: neuropeptide F, sNPF: short neuropeptide F.