did not explain the firing rate dynamics in the RSG task.

How can the data be explained? Jazayeri and Shadlen [3] modelled a number of possibilities to find out which system best accounts for observed firing rate dynamics of LIP neurons. The alternatives included anticipation of events that could drive LIP firing, for example, anticipation of the Set cue, anticipation of reward for completing the task accurately, or anticipation of the expected time of reward. Another possibility was that LIP firing reflected a Bayesian estimate of the sample time interval. The model that best explained the data, however, was one based on their analysis of the firing rate dynamics and referred to as 'preplanning'. In this model, the firing rate around the Set cue is tied to the build-up rate during the production interval.

This led to the proposal that the firing rate of LIP neurons during the measurement phase encodes information that is used to reproduce the time interval. Essentially, this means that information is not only encoded about the sample time interval during the measurement phase. Information is encoded too about a motor reproduction of the sample interval to be performed in the near future. Hence, Jazayeri and Shadlen [3] propose that there is a direct link between sensory and motor timing that is set up during the sensory phase of the RSG task.

How might this work? A simple explanation would be that both the sensory and motor information remained stored in the firing of the LIP neurons. Jazayeri and Shadlen [3] found, however, that the firing rate of LIP neurons equalizes soon after the beginning of the reproduction phase. So, it is not clear how firing rates could continue to store information needed to complete the reproduced time interval. It remains possible that the information is stored in LIP neurons in another form. Alternatively, information about reproducing the time interval may not be stored in LIP neurons and, hence, may need to be imported when needed. Further experiments will be needed to elucidate these issues.

Jazayeri and Shadlen's [3] study shines some light on the neural basis for how perception of time is integrated with our actions. Their work propels us on the way to an understanding of the neural basis perception of time and how time can contribute to dynamic adjustment of activities, which benefit from rhythm, such as dancing and speech.

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Insect Olfaction: Telling Food from Foe

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The same sensory signal can be interpreted differently according to context. A new study in *Drosophila* uses cell-type-specific tools to identify neural circuits that integrate context during olfactory processing and surprisingly implicates memory-recall neurons.

For an olfactory driven creature like a fruit fly, living in a cluttered and smelly world, the ability to classify odors into meaningful percepts is crucial. Objects may have overlapping odor profiles despite possessing vastly different values for the insect. For the fruit fly, CO_2 can signal either food or danger, as it is both a by-product of yeast respiration and an avoidance signal produced by stressed adults [1]. In order to choose the appropriate behavioral response, whether to feed or flee, the fly brain must thus somehow take into account the context and modify CO_2 processing accordingly. But how does such contextual modulation of behavior work on a circuit level? The impressive neurogenetic arsenal of *Drosophila melanogaster* makes it possible to answer this question and crack the circuits involved. In a recent *Current Biology* paper, using a combination of precise neuronal manipulations, *in vivo* imaging and behavioral experiments, Lewis *et al.* [2] build on previous work to map out the neural substrates of how the fly distinguishes food from foe.

The fly olfactory system is one of the best-characterized sensory model systems and ideal to study context-dependent sensory processing. Olfactory

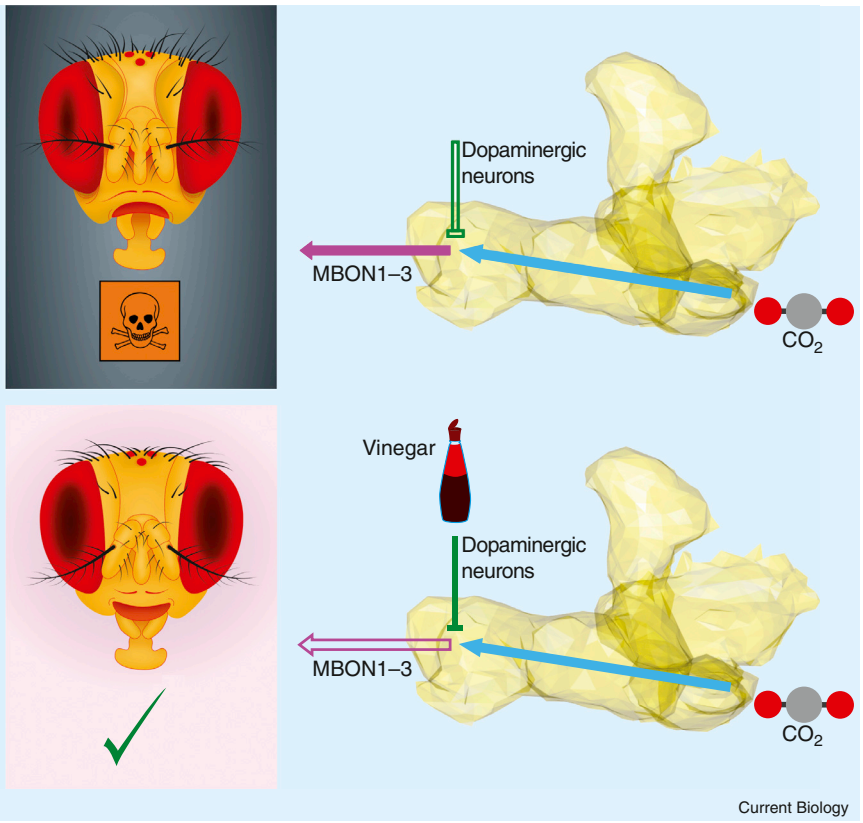

Figure 1. A model of context-dependent olfaction in starved flies.
CO_2 information is sent from the antennal lobe via projection neurons to both the mushroom body and lateral horn (not shown). These projection neurons synapse onto Kenyon cells in the mushroom body whose axons are divided into compartments. We focus here on the β'2 compartment, which has both dopaminergic input to the Kenyon cell axons and the dendrites of the Mushroom Body Output Neurons class 1–3 (MBON1–3). In the presence of CO_2, the dopaminergic neurons are silent and MBON1–3 neurons respond strongly to this stimulus, resulting in robust avoidance of CO_2. The presentation of both CO_2 and vinegar results in decreased activity in MBON1–3, perhaps due to suppression by the dopaminergic inputs which are strongly activated by vinegar. Silencing MBON1–3 neurons prevents flies from avoiding the odor mix and hence exhibiting a context-dependent switch in olfactory behavior. Illustration by Leo Hillier.

receptor neurons send their axons to the antennal lobe where they form synapses with both local and projection neurons [3]. These projection neurons transmit odor information to two higher brain regions, the mushroom body and the lateral horn [3]. The current view is that the lateral horn performs the computations necessary for innate behavior [4,5] while the mushroom body stores and executes olfactory memories [5–7] (but see [8]). In addition to its role in memory, the mushroom body is involved in a myriad of other behaviors, such as sleep, decision-making and locomotion [9]. One major experimental advantage of the fly olfactory system is the ability to manipulate circuit elements, especially the neurons of the mushroom body, in a very specific manner by using genetic tools [10].

Prior studies have used combinations of CO_2 and vinegar (a by-product of fruit fermentation) to model context-dependent behavior (Figure 1). Pure CO_2 is powerfully aversive to both hungry and satiated flies who avoid this danger signal across a wide variety of concentrations [1,11,12] while the smell of vinegar is a well-established appetitive stimulus [12]. A mixture of both odors crudely mimics the fly's favorite food source, yeast on rotting fruit. Satiated animals maintain their avoidance to this mixture but hungry flies do not display this aversion and approach. These observations show that a fly's response to CO_2 can depend both on sensory context (presence of an additional, appetitive odor) and a change in internal state [11].

This behavior is the starting point for Lewis *et al.* [2], who perform a large behavioral screen of the outputs of the mushroom body using a new set of cell type-specific drivers [13]. Starved flies were tested for CO_2 avoidance while different subsets of mushroom body output neurons were systematically silenced. Four cell types showed a reduction in CO_2 avoidance, three of which (termed MBON1–3 [13]) transmit information from the same specific region of the mushroom body further into the brain. Activating these neurons in the absence of any odor stimulation could produce avoidance.

A recent high-resolution anatomical study has revealed the basic ground plan of the mushroom body [13] and Lewis *et al.* [2] leverage these insights to gain a deeper understanding of the CO_2 circuit. The mushroom body is a large array of third-order olfactory neurons, the Kenyon cells. During associative olfactory learning, the best-studied function of the mushroom body, different classes of input converge on different domains. Direct olfactory inputs connect with Kenyon cell dendrites (the mushroom body calyx) while modulatory dopaminergic neurons conveying reward or punishment project to their axon terminals (the mushroom body lobes). Furthermore the lobes are divided into discrete compartments, each coordinately innervated by the dendrites of mushroom body output neurons and axons of modulatory dopaminergic neurons [13,14].

As three of the four output neurons with CO_2-processing phenotypes all send their dendrites to the same β'2 compartment, Lewis *et al.* went on to identify the dopaminergic neurons whose axons target this same domain. With both double labeling and GFP reconstitution across synaptic partners (GRASP) [15], a molecular genetic tool to identify membrane contacts between two nearby cells, Lewis *et al.* [2] confirmed this anatomical motif, demonstrating that the output, dopaminergic and Kenyon cells are all close enough to make synaptic contacts. However, detailed electrophysiology will be required in the future to tease apart the exact organization of this circuit.

Using a second suite of cell-type-specific lines, this time labeling subsets of dopaminergic neurons that send axons into the β'2 compartment, the authors investigated the role of dopamine signaling in this behavior. Activating these dopaminergic neurons led to decreased CO_2 aversion, suggesting a possible role in modulating the CO_2 signal in the brain. Activating the same set of neurons in the absence of any experimental odors resulted in attraction, as if the flies were smelling something they liked.

To link these discoveries, the authors use these specific lines to express GCaMP for calcium imaging while exposing flies to different odors. Recordings from the dopaminergic input neurons revealed a large calcium response (a proxy for neuronal activity) to vinegar and some appetitive odors but no response to CO_2. In contrast the output neurons responded strongly to CO_2 but depressed in response to the mixture of CO_2 and vinegar. This leads to a simple model: in the presence of CO_2, the dopamine neurons are silent while the output neurons respond strongly, resulting in avoidance. By contrast when flies are exposed to the mixture, vinegar activates the dopaminergic inputs suppressing the MBON1-3 neurons (Figure 1). This results in reduced avoidance and potential approach to the mixture. The imaging data elegantly connect the two contexts — danger and food — with the behavioral phenotypes and suggests that this may be a function of a discrete compartment of the mushroom body. Future studies will need to confirm this hypothesis by directly manipulating the dopaminergic inputs while recording from the output neurons.

One major task for the field is integrating all the available data into a coherent model of mushroom body function and the insect olfactory system. Two recent studies [14,16] have demonstrated that manipulating individual outputs (including MBON1–3) can produce changes in behavior that are not seen when the whole mushroom body is silenced. The activation of different combinations of output neurons can lead to avoidance or approach, and these effects sum when different outputs are activated simultaneously [14]. It has been proposed that changing individual mushroom body outputs unbalances the assembly and produces either avoidance or approach behavior [14], as opposed to silencing them all by inhibiting signaling in the mushroom body. A previous paper from the Kadow lab has demonstrated the mushroom body is only required for CO_2 avoidance when the fly is starved [11] and indeed the effects of silencing MBON1–3 in Lewis *et al.* [2] (reduced CO_2 avoidance) are greater in starved flies compared to fed controls. If this context-dependent circuit is only engaged during starvation, it raises the fascinating question of how internal state modulates the significance of mushroom body output. Somewhat surprisingly, Lewis *et al.* [2] observe no effect of starvation on calcium responses in these output neurons.

The MBON1–3 neurons have also been implicated in the recall of olfactory memories [16,17], suggesting that context-dependent olfaction uses the same circuitry as memory recall to produce behavioral flexibility. This is important because traditionally there is considered to be a strict dichotomy of function between these two higher olfactory brain regions, the mushroom body and the lateral horn [3]. The results of Lewis *et al.* [2] suggest that the presumed functions of the mushroom body (learning) and lateral horn (innate) in the fly higher brain are an oversimplification. However, it is important to note that these experiments do not rule out a role for the lateral horn in context-dependent olfaction.

Even for a single odor, however, the interplay between starvation and satiety may be the tip of the iceberg. Other paradigms have demonstrated the exquisite sensitivity of the CO_2 response to social context [18], behavioral state [19], sensory modality [20] and even sex [12]. It's exciting to wonder if the circuit identified by Lewis *et al.* [2] could also integrate these contexts to fine-tune the fly's behavior and if these same neurons perform this function generally for other odors and contexts. Regardless, the results of this study demonstrate that the higher olfactory regions of the insect brain do not easily divide into innate and learned. This has important implications for our understanding of how olfactory processing, context and internal state interact.

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Neuroplasticity: Unexpected Consequences of Early Blindness

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A pair of recent studies shows that congenital blindness can have significant consequences for the functioning of the visual system after sight restoration, particularly if that restoration is delayed.

Cataracts cause one third of all cases of blindness worldwide [1]. Although nowadays cataracts are readily treated surgically (and potentially in the near future even using eye-drops [2]), these techniques are not equally accessible worldwide. The case of Claude Monet, who went blind late in life, illustrates the debilitating consequences of cataracts (Figure 1). Was Monet genetically predisposed to be the originator of impressionism, or was his pioneering role as a painter influenced by a critical period of visual development? What would he have painted if he had been blind during childhood? Disentangling the respective contributions of biological constraints and experience and their neural bases are important challenges for neuroscientists.

The visual system has long been used as a model to study this so-called nature–nurture debate: is one born an impressionist master or can this be learnt? Two recent studies [3,4] in *Current Biology* addressed precisely how early-life blindness reorganises the brain and influences the ability to see again after corrective surgery. Which functions are innate, which require early-life experience, and which can be (re)trained at any time in life?

McKyton *et al.* [3] show that, while sight-restored individuals can see, they do not always perceive occlusion between objects. Thus, certain visual functions rely on the integrity of sight during early life and seem to not be restored even after sight recovery (unless, possibly, following specialised training; see below). Collignon *et al.* [4] demonstrate how hearing recruits otherwise visual brain regions following just short-term loss of vision during early life. Their findings show that early crossmodal reorganisation can persist into adulthood, years after vision has been restored. Together, these studies not only provide new insights regarding optimal times for developing brain functions, but also emphasise how brain plasticity extends across canonical boundaries between the senses.

Part of Hubel and Wiesel's Nobel prize-winning research revealed that 'critical periods' — time intervals beyond which a function is either never acquired or, if it is

