

Studying small brains to understand the building blocks of cognition

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Cognition encompasses a range of higher-order mental processes, such as attention, working memory, and model-based decision-making. These processes are thought to involve the dynamic interaction of multiple central brain regions. A mechanistic understanding of such computations requires not only monitoring and manipulating specific neural populations during behavior, but also knowing the connectivity of the underlying circuitry. These goals are experimentally challenging in mammals, but are feasible in numerically simpler insect brains. In *Drosophila melanogaster* in particular, genetic tools enable precisely targeted physiology and optogenetics in actively behaving animals. In this article we discuss how these advantages are increasingly being leveraged to study abstract neural representations and sensorimotor computations that may be relevant for cognition in both insects and mammals.

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Introduction

Insects use their relatively small brains to produce stunning behavioral complexity. The full sophistication of their actions is sometimes obscured by the rapidity with which they unfold. In fact, whether it is dragonflies capturing prey or flies escaping looming predators, there is mounting behavioral evidence that insects rely on internal models for their sensorimotor prowess [1*,2]. More generally, the capacity for complex computation has been demonstrated in behavioral and physiological studies across a wide range of insects. Insects show signatures of selective visual attention [3,4,5*], modulate their responses to sensory stimuli based on context and past associations [6–8], and bridge the gap between sensory processing and action using working memory [9–11]. They acquire and use navigational information [12] and some, like honeybees, communicate that knowledge to conspecifics [13,14]. The

weight of such experimental evidence suggests that important aspects of cognition require neither a cortex nor a large brain [15–17]. Here we focus primarily on recent experimental studies in discussing how insects might contribute to our understanding of internal representations that provide a foundation for cognition.

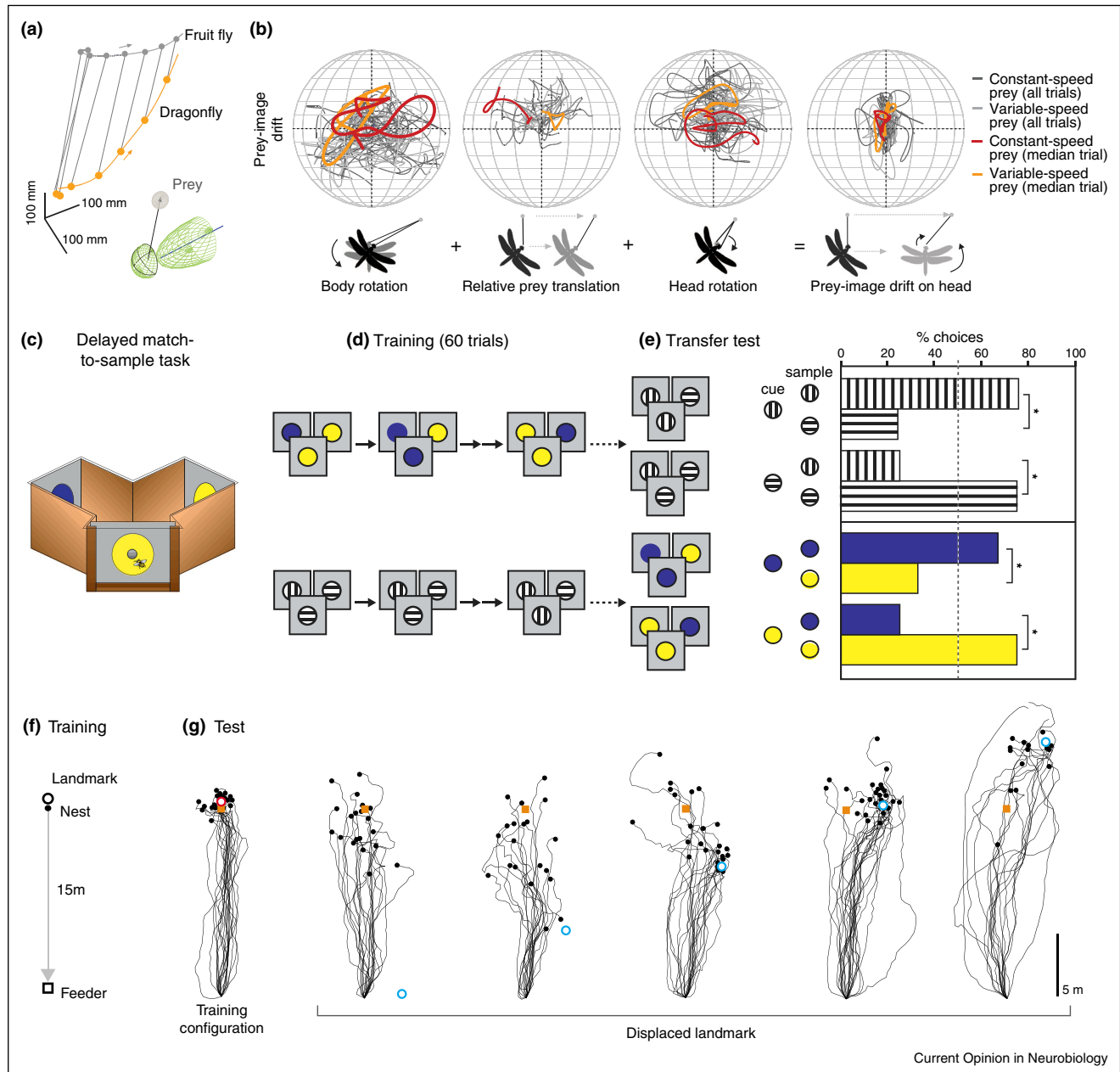
Behavioral evidence for complex internal representations in insects

Internal representations of relevant aspects of the external world or of an animal's own actions allow it to make predictions and to select appropriate actions. Neural processing that relies on such internal models is likely to underlie dragonfly prey capture [1*], a behavior that typically unfolds over an interception flight lasting only a few hundred milliseconds. High-speed video recordings of their flight paths revealed that, rather than just reactively following prey movements, dragonflies steer using a prediction of prey trajectory that is likely based on their initial observations of prey movement (Figure 1a, [1*]). Further, their head movements precisely compensate for expected changes in body orientation during flight maneuvers, allowing them to maintain prey foveation throughout the flight (Figure 1b). Thus, dragonflies may use visual input of prey position during the flight only to make corrections to an existing internal representation.

Internal representations that outlast the sensory cues that produced them can also allow animals to orient towards salient landmarks when they are temporarily obscured. Such short-term orientation memory can be seen in walking flies tracking visual landmarks. The flies appear to store the angular position of a targeted landmark after extended exposure to it and retrieve this information when the landmark disappears [11].

The strongest behavioral evidence that insects must use abstract internal representations comes from honeybees, which display behaviors akin to deliberative decision-making. Foraging honeybees can be trained to memorize a pattern shown at the entrance of a Y-maze and to use this cue to predict the location of food in the maze by comparing it to two sample patterns shown at the maze's arms (Figure 1c, d and f, [10,18]). In this bee version of a delayed-match-to-sample task, animals are able to learn abstract association rules such as 'sameness' or 'difference' of the cue and sample pattern. This capacity for flexibility, abstraction and generalization in learning indicates a high degree of sophistication in the underlying internal representations.

Figure 1



Evidence for sophisticated internal representations from behavioral studies across insect species. Dragonfly (*Plathemis lydia*) prey interception relies on internal models of prey movement and of the dragonfly's own body mechanics (a–b). Honeybees (*Apis mellifera*) form conceptual memories in a delayed-match-to-sample task (c–e). Homing desert ants (*Cataglyphis fortis*) navigate by flexibly combining path-integration and visual landmarks (f–g). (a) A reconstructed flight trajectory of a dragonfly (orange) chasing a fruit fly (grey). The bottom schematic illustrates prey foveation by the dragonfly. (b) In addition to following the prey, dragonflies actively align their body to the prey's flight path and make predictive head movements that cancel self-motion-induced drift of the prey-image on their retinæ. (a–b) adapted with permission from [1]. (c) Honeybees were trained in a Y-maze with a sugar reward randomly located in one of the two arms. A bee is presented with a visual cue at the maze entrance and, after entering the maze, two samples at the end of each maze arm. (d) Over the course of 60 training trials, bees learn abstract rules such as 'sameness' to predict the location of food in the maze by comparing the cue to the two samples. (e) In a transfer test, bees trained with colors apply the learned rule to patterns of vertical and horizontal stripes and vice versa to correctly predict food location in 70–80% of trials. (c–e) adapted with permission from [18]. (f) Ants from a colony, whose entrance was marked by a black cylinder, were trained to collect food at a feeder 15 m south of the nest and then return home along an approximately straight path. (g) Trained ants were studied for how they combined path-integration and landmark guidance. They were captured at the feeder at the beginning of their homebound path, that is, with a path integration vector pointing north towards their nest, and released in a distant test site. At the test site, a landmark (red circle) was either placed at a location consistent with the training configuration at the expected location of the nest (orange square) or in a location where the landmark-based guidance would conflict to varying degrees with the path-integration vector (blue circles). (f–g) adapted with permission from [23].

Of course, extrapolating directly from complex behavior to complex internal representations can be dangerous [19]. Foraging desert ants, for example, display impressive navigational skills, including memorizing long, stereotypic foraging routes, path integration and the ability to flexibly combine route-guiding cues across different sensory modalities [20–23] (Figure 1f and g illustrate a combination of path integration and landmark-based navigation). However, this complex behavior may rely on simpler internal representations of spatial information than those employed by many mammals. Navigating desert ants may not form an explicit representation of their environment in the form of a cognitive map, but may instead rely on implicit knowledge. This could be in the form of directions, such as a homing vector [24], or as templates of visual scenes along the path that can be used to compute and maximize familiarity metrics [25]. Distinguishing higher-order internal representations from those with less flexibility can be challenging, particularly when the only readout available is behavior.

Neurophysiological strategies to probe internal representations

Physiological recordings in immobilized animals have provided many examples of high-level internal representations in insects [26,27,28*] and revealed the existence of synaptic plasticity that is likely used to associate high-level sensory representations with appetitive or aversive experiences [28*,29,30,31*]. However, a comprehensive assessment of the nature of internal representations and their potential role in cognitive processing requires that such recordings be performed in actively behaving animals. Understanding the neural basis of the remarkable navigational behavior of bees and ants, for example, may require monitoring the activity of specific neural circuits in foraging animals. Further development of extracellular recording techniques in freely behaving large insects [32–35] may eventually enable such experiments, although identifying and targeting the relevant neurons remains a challenge. A different physiological strategy, which has been the mainstay of primate research for decades, is to record neural activity during head-fixed behavior. Head-fixation constrains behavioral output, but allows for the sensory environment to be carefully controlled. This strategy has been employed in bees to study how olfactory representations are affected by learning [36] and how visual-stimulus-evoked local field potentials are modulated by behavioral choices [3], and it has been applied in many other insects to examine sensory representations in the context of orienting [37–40]. Head-fixed recordings have also been used with success to probe internal representations in a smaller insect with a distinct set of technical advantages.

Studying internal representations in head-fixed behaving *Drosophila*

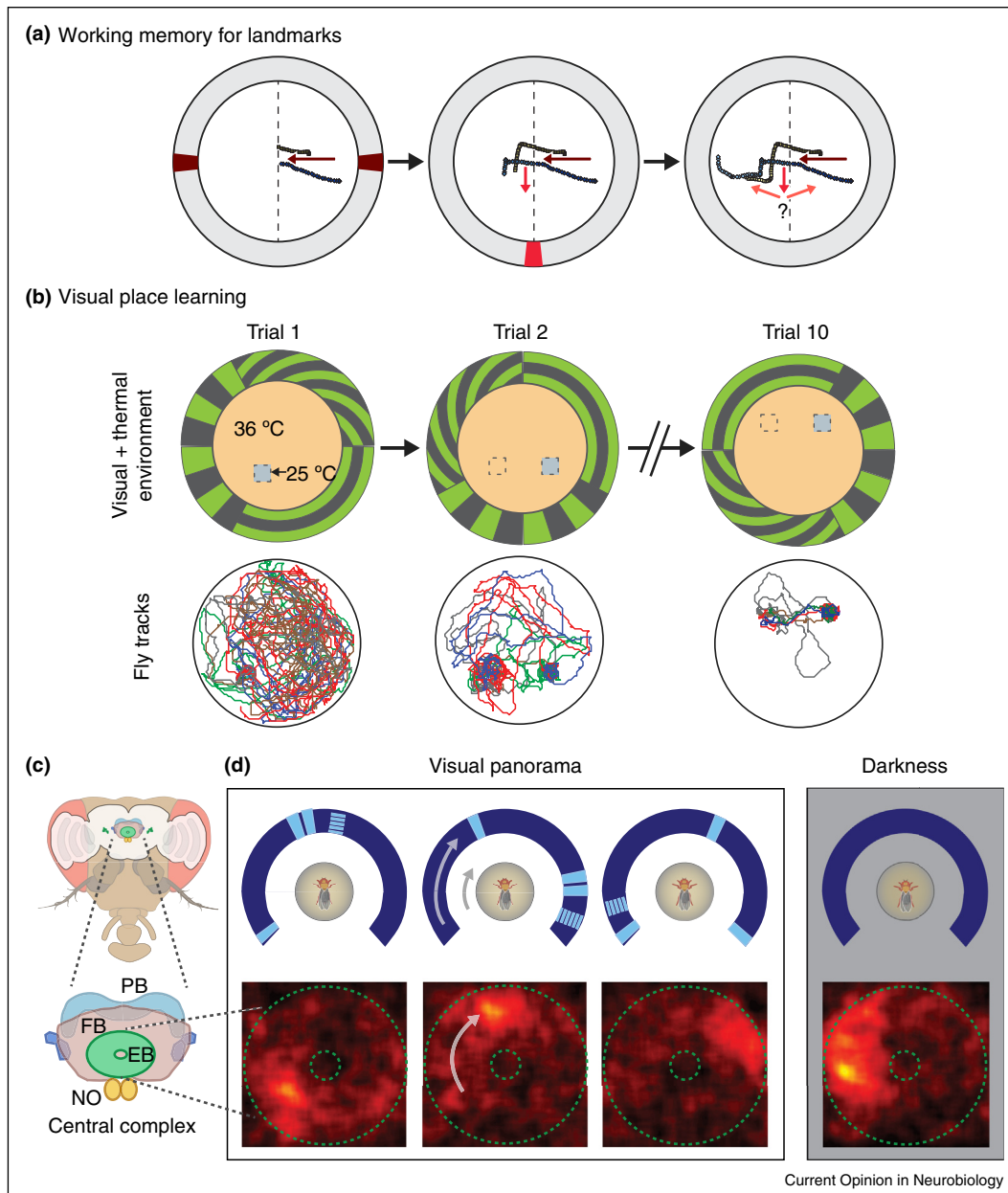
In adult *Drosophila*, the development of head-fixed behavioral paradigms has allowed the combination of powerful

genetic tools with whole-cell patch clamp recordings and two-photon imaging with genetically encoded calcium indicators [41,42]. The fly's small brain size allows physiological access to the entire central brain with a minimally invasive preparation. Comprehensive anatomical and behavioral genetics studies [43,44*,45] help to target the search for cellular correlates of specific internal representations. Repeatable access to these genetically identified cell types permits precisely targeted perturbation and monitoring of neural activity during behavior. Overall, the ability to reliably access the same sets of identified neurons across trials and animals enables rigorous and mechanistic circuit analysis.

A recent study [46*] investigated the cellular basis of the suppression of optomotor reflexes — compensatory head and body movements in response to wide-field optic flow — during voluntary turns. Such selective suppression establishes a distinction between sensory signals elicited by voluntary movements from those caused by external influences. This can be achieved by efference copy [47] and related corollary discharge mechanisms [48], which filter sensory input by subtracting an internally generated prediction of the self-generated signal from the observed signal, that is, by implementing a so-called forward model. In the study [46*], optic-flow processing neurons in the fly visual system were found to receive turn-direction-specific feedback with the appropriate sign and latency to suppress self-generated sensory input. The amplitude of the feedback signal scaled with the visual drive, which depends not only on the turn speed but also on the structure of the visual environment. Investigations into how the flexible scaling of the motor-related feedback signal is achieved should clarify the level of sophistication of the underlying internal models.

Compelling direct evidence for an abstract internal representation comes from recent work on spatial orientation in walking flies [49*]. The work focused on the computational role of neurons in the fly central complex, a conserved brain region that has been implicated in motor control, orientation and navigation behavior in various insect species [27,50*,51,52]. In flies, the central complex is required, among other tasks, for short-term orientation memory ([11], Figure 2a) and visual learning ([53,12], Figure 2b). Simultaneously imaging a complete population of genetically defined neurons in the central complex (Figure 2c) while the fly was walking in either darkness or in a simple visual virtual reality environment [49*] revealed that flies possess an internal representation of their angular orientation. This abstract internal representation, which is stable across visual environments, is updated by both self-motion signals, and, if available, visual cues (Figure 2d). Interestingly, the representation of the fly's orientation persists even when the fly is standing in place in darkness, that is, in the absence of visual or motor information. A variety of theoretical

Figure 2



Studying the circuit mechanisms underlying visually guided navigation in walking fruit flies (*Drosophila melanogaster*). **(a)** Walking flies can keep the angular location of vertical landmarks in working memory. Flies have an innate attraction to prominent vertical stripes and readily track them. In the so-called detour paradigm a fly is first presented with two stripes on opposite sites of an arena, which stimulates the fly to walk back and forth between them (left panel). When the fly crosses the midline, both stripes disappear and a distractor stripe appears lateral to the fly (middle panel), triggering a turn towards it. One second after the fly turns towards the distractor stripe, the latter also disappears (right panel). 80% of the tested flies subsequently turned towards the location of the previously tracked, but now invisible, stripe suggesting that the fly stored its angular position. Representative trajectories of two flies are shown. Adapted with permission from [11]. **(b)** Visual place learning in a Morris water maze-like task for walking fruit flies. Over the course of 10 training trials, flies learn to use visual cues to quickly find the location of a small cool spot (grey square) in an aversively hot arena. The upper row shows schematics of the arena with the location of the cool spot and the visual panorama. Trajectories from four representative flies are shown in the bottom row. Figure adapted with permission from [12]. **(c)** Schematic of the fly brain overlaid onto a frontal view of the fly head (top), and an enlarged view of the central complex (bottom). The fly central complex is composed of four regions: the protocerebral bridge (PB), the fan-shaped body (FB), the ellipsoid body (EB), and the paired noduli (NO). **(d)** Calcium dynamics of a single, genetically identified population of neurons whose dendrites segment the ellipsoid body (bottom, dashed green line outlines the EB). Two-photon imaging was performed while the fly walked on a spherical treadmill in a visual virtual reality consisting of a multi-landmark panorama (left) and in darkness (right). Rotations of the fly on the ball induce a corresponding update of the visual panorama and are accurately tracked by a single localized calcium activity 'bump' in the ellipsoid body (illustrated by grey arrows in the second panel). This bump is also present and tracks the fly's rotational movements in the absence of visual cues. Adapted with permission from [49*].

models describing possible mechanisms for such angular path integration have been proposed in the context of vertebrate head direction cells [54]. These models make specific predictions about the connectivity of underlying circuits, but the scale of vertebrate brain circuits makes them challenging to test. In the fly, electron-microscopy-based reconstruction efforts should provide the circuit connectivity information necessary to constrain such models [55], and the ability to specifically monitor and perturb the activity of complete populations of identified neurons should enable powerful tests of their predictions.

Challenges and future directions

There is increasing evidence that insect brains rely on some of the same internal representations that are thought to underlie cognition in mammals [49*,54], but challenges remain in definitively linking physiological data to cognitive behavior. Mammals are usually trained for several weeks before they perform cognitively demanding tasks in physiological settings. Insects have shorter memories, a shorter lifespan, and only a few can be chronically implanted with recording devices. Thus, insect physiologists seldom have the luxury of training protocols that last more than a few hours. Instead, they typically rely on tasks that exploit or extend an animal's natural behavior, as for example described in the experiments in Figures 1 and 2a,b. Although the genetic tools in the fly make it an appealing system, many other insects display a richer cognitive repertoire. Mechanistic investigations of cognition in these species will be greatly aided by the development of physiological and genetic tools for these systems as well [56,57]. Finally, the biophysics of insect neurons may be key to a complete understanding of how internal representations are created and used in insects. More information about the expression and subcellular distribution of channels and receptors [58], as well as the development of high signal-to-noise voltage sensors that enable membrane potential changes to be monitored in cell bodies and processes [59,60], may pave the way forward.

Internal representations underlying mammalian cognition have been amongst the most evocative phenomenology described in neuroscience [61]. A major challenge with dissecting the mechanisms involved in generating such representations is that they are often distributed across large populations of neurons in brain regions far from the periphery [62]. As discussed above, there is now evidence that, in some of these cases, insect brains may carry out similar computations [49*]. Essential features of the implementation of specific neural computations can generalize well beyond a single system. Studies in the olfactory and visual systems, for example, have highlighted similarities between insect and mammalian sensory circuit function [63,64]. Although studies of cognitive computations in insect brains are in their early stages, these numerically simpler systems may provide a more

navigable path towards understanding some of the fundamental synaptic, cellular and circuit mechanisms underlying cognition [17].

Conflict of interest statement

Nothing declared.

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