Dispatches

Visuomotor Control: *Drosophila* Bridges the Gap

Fruit flies with genetic lesions disrupting the structure of a brain region known as the protocerebral bridge fail to aim their movements correctly when crossing gaps, implicating this central brain neuropile in the visual control of goal-directed behaviour.

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Insect nervous systems have been models for understanding motor control for several decades. Much of this work has focussed upon neurons in the ventral nerve cord that process mechanosensory information and control limb or wing movements [1]. Behavioural studies of insects, however, have demonstrated that they are capable of producing sophisticated motor control involving co-ordination between limbs [2,3] and requiring the integration of visual and/or mechanosensory information from the compound eyes and antennae, respectively, with mechanosensory information from leg sense organs to navigate through complex environments [3–6]. Locusts walking on ladders, for example, use visual information and local mechanosensory inputs to target their forelimbs [4].

The need for integration between sensory information acquired by the compound eyes and/or antennae with that from the legs is emphasised by the behavioural paradigm of gap crossing. Walking insects encountering a gap in the substrate undertake a series of co-ordinated behaviours to locate firm footholds on the opposite side [5,6]. Several insects, including the fruit fly *Drosophila melanogaster*, have been studied using the gap crossing paradigm [5]. Walking flies that detect a gap estimate its width from vertical edges on the opposite side using parallax motion generated during the approach (Figure 1). If the gap is judged to be surmountable, flies initiate co-ordinated leg movements to reach the opposite side [5].

Studying the neurons that generate and co-ordinate gap-crossing behaviour is challenging, because the fly is freely moving. Electrophysiological techniques for recording neural activity require that the fly is restrained, preventing it from undertaking gap-crossing behaviours and, although anatomical techniques can identify potential structures involved, they cannot provide information about neural activity. With *Drosophila*, genetic techniques offer the possibility of identifying neurons involved in generating a particular behaviour and of manipulating their activity, for example using the light-activated channel protein channelrhodopsin. In a study published in this issue of *Current Biology*, Triphan *et al.* [7] have used genetic tools to identify structures in the *Drosophila* brain involved in gap crossing.

Triphan *et al.* [7] investigated the effect of mutations *tay bridge*[1] and *ocelliless*[1], which affect the structure of the protocerebral bridge — a neuropile that is part of the central complex (Box 1 and Figure 2). The rationale behind this was based on

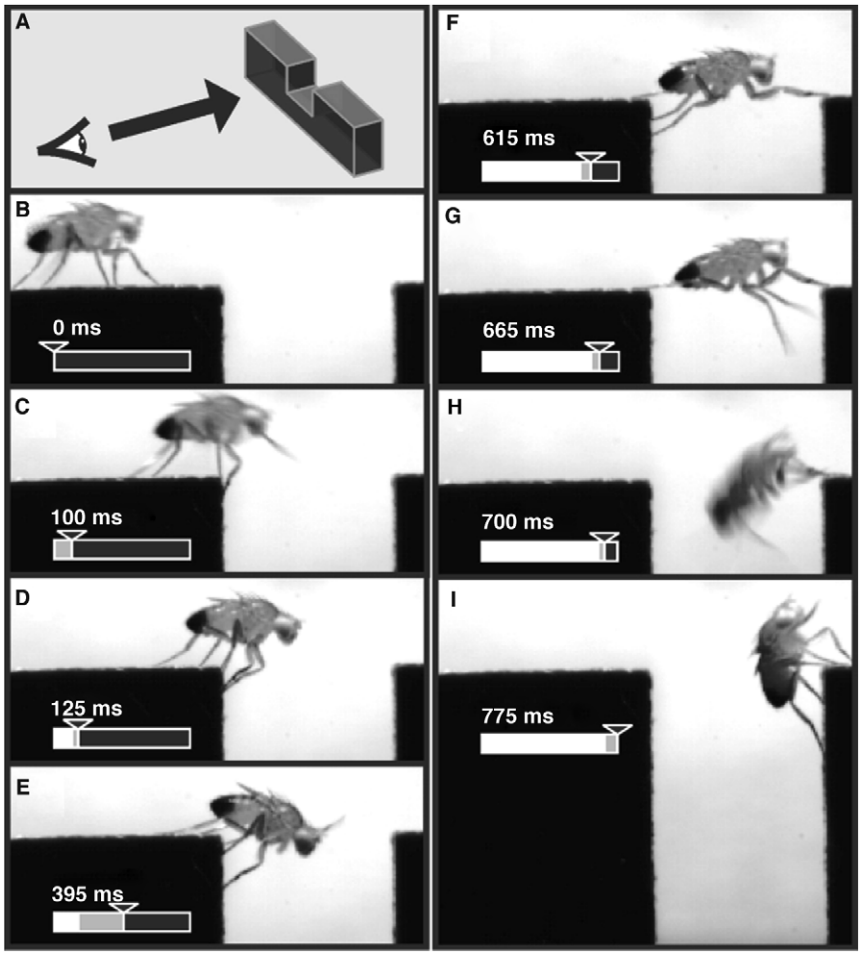

Figure 1. A high-speed video sequence showing a male fruit fly crossing a 3.5 mm gap in the substrate.

(A) The view of the catwalk. The behaviour is divided into eight epochs (B–I) in which the fly encounters and detects the gap (B,C), makes co-ordinated movements of the limbs to cross the gap (E–H) and then, after crossing the gap, resumes walking. (Adapted from [5].)

Box 1

The fruit fly central complex.

The central complex in *D. melanogaster* was originally described by Power [15]. It is composed of unpaired midline neuropiles found in the protocerebrum (or forebrain) of all insect species that have been studied (Figure 2A) [16,17]. The central complex consists of the protocerebral bridge (PB), central body (CB) and, in the winged insects (pterygotes), paired spherical noduli (N) located ventrally (Figure 2B). It has a modular architecture, like many other neuropiles in the insect brain, and is surrounded by glia. In flies, the PB is a narrow neuropile 'like the handlebar of a bicycle' [16] that spans the midline. It is composed of 16 glomeruli, eight on each side of the midline. The PB is located dorsally and posterior relative to the CB, which in flies can be divided into the fan-shaped body (FB) and ellipsoid body (EB). These four neuropiles (PB, FB, EB and N) are themselves composed of the input or output branches of either columnar neurons or tangential neurons [16]. Columnar neurons link the neuropiles or regions within the neuropiles (Figure 2C) whereas tangential neurons are perpendicular to the columnar neurons. Input pathways to the PB and CB originate in many neuropiles, including those of the visual system (for example, the medulla). Outputs from the central complex target many associated neuropiles, including the ventral bodies (Figure 2C), which have been implicated in descending control of motor activity.

previous experiments on *Drosophila* [8], and in other insects (e.g. [9,10]) that have implicated the central complex in visuomotor control. Mutations affecting the central complex alter the stepping pattern during walking in *Drosophila* [8]. Likewise, surgical lesions of the central complex in the cockroach affect turning [9]. The authors [7] analysed high-speed video of *tay*^{1} and *oc*^{1} mutant flies walking along a catwalk and crossing gaps (Figure 1). Despite the severe structural defects in the protocerebral bridge caused by *tay*^{1} and *oc*^{1}, flies with either of these mutations were able to initiate gap-crossing behaviour, but they could not target their attempts correctly. Instead of aiming their gap-crossing attempts towards the opposite side, the mutant flies aim a high proportion of their gap crossing attempts off the sides of the catwalk.

To confirm that disruption of protocerebral bridge structure is indeed the cause of the defects in gap crossing behaviour, Triphan *et al.* [7] performed rescue experiments using genetic constructs. A complete genomic rescue of *tay*^{1} returned the flies to the wild-type phenotype — these flies crossed the gap without the deviations associated with the *tay*^{1} mutants. Triphan *et al.* [7] then used GAL4 driver lines to induce expression of a UAS-*tay* construct in a *tay*^{1} mutant background. These driver lines induced expression in central complex neurons, including the columnar and tangential neurons of the protocerebral bridge (Box 1). By comparing the flies' ability to cross gaps, the authors showed that UAS-*tay* expression in either columnar or tangential neurons was sufficient partially to rescue the *tay*^{1} phenotype. Combined *tay* expression in both the columnar and tangential neurons (using drivers 007Y-GAL4+210Y-GAL4) was sufficient to completely rescue the *tay*^{1} phenotype. These flies are indistinguishable from wild-type flies when crossing gaps, showing that rescuing the structural defects in the protocerebral bridge is sufficient to restore gap crossing performance.

Triphan *et al.* [7] used a second paradigm, the 'diving board', to investigate the role of vision in the rescue of the *tay*^{1} phenotype. In this paradigm, the gap is modified so the vertical edges on the far side of the gap are missing. Wild-type flies are less successful on the diving board than when crossing a normal gap, but show no excess deviation. Similarly, *tay*^{1} flies show no change in their deviation. Flies with the combined 007Y-GAL4+210Y-GAL4 drivers, however, showed reduced success and increased scatter in the absence of the vertical edges of the gap. Triphan *et al.* [7] argue this shows the combined driver rescue is dependent upon a conspicuous visual cue and that, unlike wild-type flies, they cannot resort to using the top edge of the gap to target their movement, emphasising the role of the protocerebral bridge in the visuomotor control.

How does the central complex influence behaviour? Triphan *et al.* [7] propose a model for central complex function and its relationship with motor control centres. Columnar neurons from the 16 glomeruli of the protocerebral bridge make output connections in the ventral bodies (Figure 2C). They suggest these glomeruli represent the position of a visual target, glomeruli closer to the midline representing objects directly in front of the fly and the most lateral glomeruli objects at the rear of the fly. Asymmetrical activation of the glomeruli indicates an object located to the left or right of the fly. In the model, columnar neurons convey the target location from the protocerebral bridge to the ventral bodies and from there to the motor centres to activate motor neurons in the ventral nerve cord. Asymmetric activation causes an

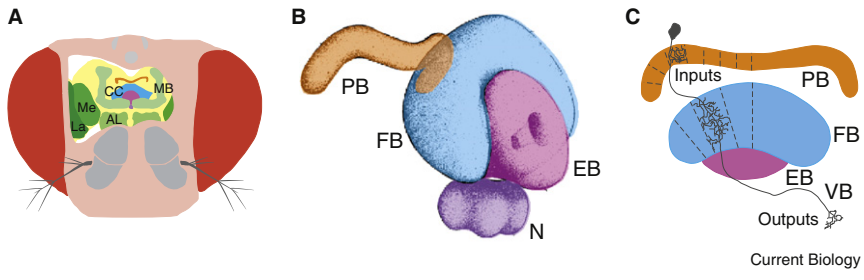

Figure 2. The central complex in the fruit fly brain.

(A) A schematic diagram of the head of *D. melanogaster* with the cuticle removed to reveal several major neuropiles within the brain: the lamina (La) and medulla (Me) of the visual system, the antennal lobes (AL), mushroom bodies (MB) and central complex (CC). (B) An enlargement of the central complex showing four substructures: the protocerebral bridge (PB, orange), the fan-shaped body (FB, blue), the ellipsoid body (EB, pink) and the noduli (N, purple). (C) An example of a single columnar neuron with branches innervating the protocerebral bridge, fan-shaped body and the ventral bodies (VB), a neuropile closely associated with the central complex. (Panels (B) and (C) adapted with permission from [16].)

increase in step size on the contralateral side of the body, turning the fly towards the target.

Although this is a model for visuomotor control, insects use a range of different stimuli to locate objects in the environment. For example, cockroaches locate obstacles using their antennal system [11]. If the protocerebral bridge does represent target locations relative to an insect, the neurons are likely to integrate visual, mechanosensory, olfactory and auditory cues. Some insects also form memories of locations — such as the site of a food source — relative to object positions [12,13]. If the model is correct, these object locations should also be represented in the protocerebral bridge glomeruli. The outputs of the protocerebral bridge would have to be modified by memories, presumably stored in the mushroom bodies, to take the insect to the food location rather than that of the target.

Protocerebral bridge glomeruli would produce a relatively coarse representation of targets in the insects' environment. With such a coarse representation of targets, the routes insects take towards a target should then cluster together. Whether this can be detected in behavioural data is uncertain because routes to targets may be initiated from different orientations and there may be considerable noise. It is also unclear how such a representation would account for the precise targeting of conspecifics or prey during flight [14]. Nevertheless, the experiments and model of Triphan *et al.* [7] offer valuable new insights into the role of protocerebral bridge during gap crossing and its function in other behaviours.

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Vesicular Traffic: A Rab SANDwich

The small GTPases Rab5 and Rab7 mark temporally distinct but sequentially connected stages in phagosome maturation, but the mechanism underlying the transition between these stages has been unclear. Recent studies in *Caenorhabditis elegans* have now uncovered a new protein complex that connects Rab5 to Rab7.

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Phagocytosis is essential for the clearance of microbes, apoptotic cells and extracellular matrix and, as a result, is a cornerstone of innate immunity, prenatal development and tissue remodeling. In some respects, phagocytosis is cell biology's version of capital punishment: it consists of the imprisonment and subsequent execution of cellular outcasts. Phagocytic cells extend pseudopods that trap and engulf target particles into a membrane-bound vacuole or phagosome. However, because it is largely derived from the plasma membrane, the nascent phagosome is unable to kill and/or digest its prey. The necessary microbicidal and degradative properties are acquired subsequently, through a complex and carefully choreographed sequence of fusion and fission events collectively known as phagosome maturation. A new study from Kinchen and Ravichandran [1] now reports insights into the regulation of a key transition during phagosome maturation.

During maturation, the nascent phagosome sequentially fuses with early endosomes, late endosomes and lysosomes, generating the early phagosome, late phagosome, and phagolysosome, respectively (Figure 1A). The early-to-late phagosome transition is a critical juncture; it is required for the acquisition of degradative hydrolases, for presentation of antigens by major histocompatibility complex class II (MHC II) molecules, and for full acidification of the phagosomal lumen. Indeed, some pathogens, like *Mycobacterium tuberculosis*, survive inside host cells and establish chronic infections by preventing this transition [2].

Two small GTPases, Rab5 and Rab7, coordinate the early-to-late phagosome transition. Rab5 associates with the early phagosome, facilitates its fusion with sorting and recycling endosomes, and regulates its conversion to the late phagosomal stage. Rab7, which is a marker for late phagosomes, promotes phagosome fusion with late endosomes and ultimately with lysosomes. Despite its importance, the mechanism whereby early phagosomes shed Rab5 to become Rab7-containing late