The central complex and the genetic dissection of locomotor behaviour

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The central complex is one of the most prominent, yet functionally enigmatic structures of the insect brain. Recently, behavioural, neuroanatomical and molecular approaches in *Drosophila* have joined forces to disclose specific components of higher locomotion control in larvae and adult flies, such as those that guarantee the optimal length and across-body symmetry of strides and an appropriate activity.

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Abbreviations
CX central complex
nob *no bridge*
sim *single-minded*

Introduction

Insects walk through our daily existence as such a matter of course that we have stopped being amazed by their extraordinary manoeuvring capabilities. Analyses of their locomotion have been and are being made at the level of single neurons, whole neuronal networks and behaviour, primarily in larger insects such as stick insects, grasshoppers and cockroaches. This work has led to a detailed understanding of the local regulatory circuits, which on the one hand guarantee the rhythmic sequence of the stepping movement (reviewed in [1]) and on the other hand integrate information from mechanoreceptors into adaptive changes in the leg movements (reviewed in [2]).

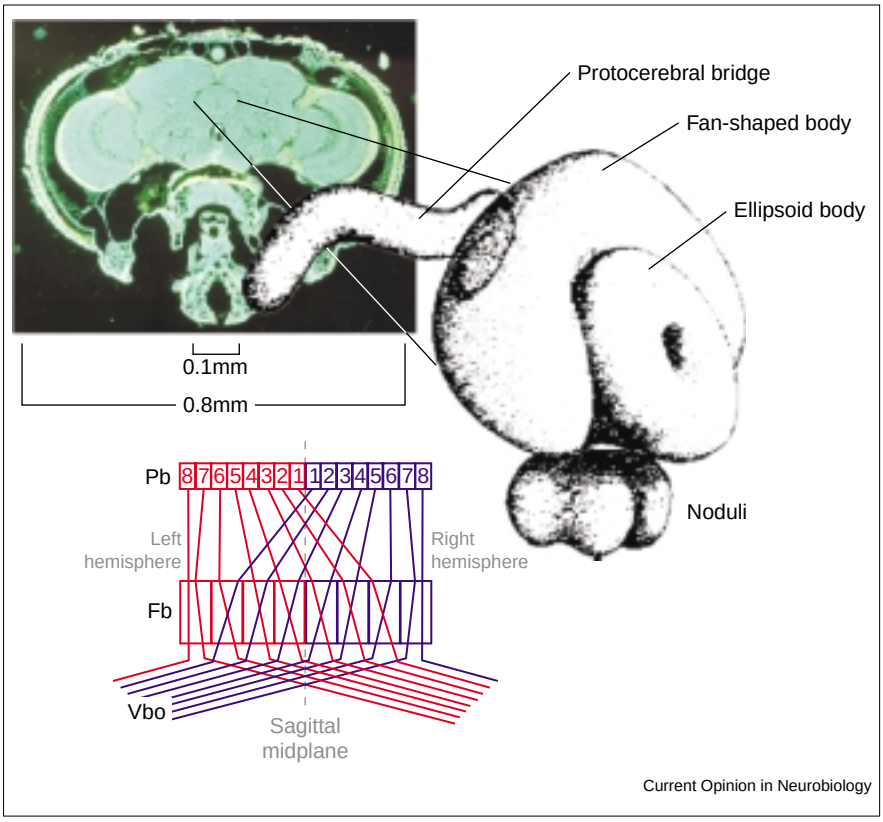
The local neuronal circuits are found in the insect thoracic ganglia, which carry out tasks remotely comparable to those performed by the vertebrate spinal cord during locomotion. For example, in decapitated fruit flies the trunk is able to coordinate its legs if the cut cervical connective is non-rhythmically stimulated with biogenic amines in place of the missing 'go' signal from the brain [3]. Until now, however, issues such as how the insect brain influences processes in the thoracic ganglia, or what kind of information about direction and speed is conveyed from the brain to the thoracic system, have not been investigated in as much depth as the local regulatory circuits.

For the functional analysis of central nervous structures, *Drosophila* neurogenetics offers a multitude of elegant experimental methods, such as the specific genetic manipulation of defined small subsets of neurons in so-called P[Gal4] enhancer trap lines (e.g. [4,5••]). In the selected P[Gal4] lines of the reviewed studies the yeast transcriptional activator Gal4 is expressed under the control of specific neuronal enhancers in small groups of neurons within a brain region under study. Initially, the yeast transcriptional activator Gal4 is jumped randomly into the genome. The lines in which Gal4 is under the control of an enhancer that groups neurons with a common genetic address (i.e. a common enhancer) are then isolated. Effector lines containing, for instance, the genetic information for a neurotoxin can be crossed to the P[Gal4] lines, so that the neurotoxin specifically blocks the few Gal4-expressing neurons. Alternatively, different mosaic techniques allow genetic defects to be confined to patches of tissue, parts of the body or regions of the nervous system (e.g. [6–8]). Mutant lines with hereditary defects are more advantageous than insects with acutely introduced lesions, because a large supply of individuals with similar failures can be generated and so the defects can be analysed at any desired depth.

Walking analysis in *Drosophila* strains with mutations affecting brain structure soon associated the central complex (CX; Figure 1) with functions related to higher locomotor control. In several behavioural paradigms flies from mutant strains with altered structure of the CX walk more slowly than wild-type flies, react less quickly to changing stimuli during flight and show altered orientation behaviour toward landmarks. They are either less active or quickly lose activity, or fail to start walking or flying under circumstances in which wild-type flies would readily do so ([8–10]; reviewed in [11]).

The CX, which is also called the central body in other insect species, is located centrally between the two protocerebral hemispheres in the brains of all insects. It comprises four neuropilar regions, the fan-shaped body, the ellipsoid body, the protocerebral bridge and the paired noduli, which are all interconnected by sets of columnar interneurons that form many regular patterns of projection ([12,13]; and reviewed in [11]). It receives input from most parts of the brain through large field neurons that form stacked parallel strata perpendicular to the columnar elements; however, no obvious prominent tracts either from sensory areas or to motor areas exist that might prompt an easy guess at its functions. Earlier work in various insect species on the functions and morphology of the CX (comprehensively reviewed in [14]) produced vague results concerning its behavioural significance, and the common denominator of its role at that time might have been considered to be 'the regulation of behavioural activity'.

Figure 1



Frontal sections through the head and brain of a *Drosophila* fly. Autofluorescence highlights all of the neuropils in green and the cell bodies in yellow. The central complex (CX) is located in the middle, between the protocerebral brain hemispheres. It comprises four interconnected neuropilar regions: the fan-shaped body, the ellipsoid body, the protocerebral bridge and the paired noduli. Columnar neurons in the CX form many ordered projection systems that seem most suitable to overlay, compare and balance neuronal information from both sides of the brain. For example, the lower line diagram shows a representation of the horizontal fibre system, which connects the two by eight glomeruli of the protocerebral bridge (Pb) with the eight fans of the fan-shaped body (Fb) and exits the CX towards one of its paired accessory areas called the ventral bodies (Vbo). For detailed accounts of the CX anatomy, see [12,13].

The present article reviews the progress in our understanding of specific CX functions in the control of insect locomotion, which has been achieved predominantly in the fruit fly *Drosophila melanogaster*. The article concentrates on the time period after the comprehensive review by Heisenberg [11].

Walking behaviour of *Drosophila* and a screen for locomotor mutants

On a smooth horizontal surface, fruit flies that are walking fast use an alternating tripod gait. They deviate increasingly towards a tetrapod coordination as the frequency decreases from a maximum of 17 steps to 6 steps per second for each leg [15]. On average, high stepping frequencies are associated with long strides and short swing-phase durations, whereas low frequencies are associated with short strides and long swing-phase durations [15]. Turning is achieved by lowering the step size on the inside of the curve [16]. Flies can also turn rapidly on the spot by making sideways and backwards steps with some legs [15,16]. Studies of leg placement on rough terrain show that placement is achieved predominantly by tactile and not visual control [17,18]. Placement information is conveyed from the anterior to the posterior legs. Visual orientation towards a distant landmark results in larger strides even if they are less appropriate for a given regular arrangement of stepping stones.

The evaluation of step-resolved walking data in wild type or mutant flies has been automated [19]. A thin sheet of laser light projected immediately above the surface of a glass plate illuminates only the tips of those legs that are in contact with, or nearly contacting, the plate. Video cameras and a computer extract the pertinent spatial and temporal information. This method made it possible to carry out an extensive screen for locomotor mutants, which has identified 230 X-chromosomal lines from almost 11,000 candidate flies [20].

Many of the new lines and several previously existing mutant lines could be classified into seven distinct classes of aberrant walking that predominantly affect (1) the temporal pattern of swing phases, (2) the spatial placement of legs, (3) the proper initiation and maintenance of step length, (4) the across-body symmetry of step length, (5) the range of stepping frequencies, (6) the swing phase duration, and (7) the swing speed of legs ([19]; and R Strauss, unpublished data). The first mutant from this screen to be molecularly and functionally studied is *highwire*, which has exuberantly growing synapses at the neuromuscular junctions [21]. Notably, 30 of the 230 locomotor defective lines show structural defects in the CX. This large fraction (13%) further emphasises the importance of the CX in walking control. Basic leg coordination problems were not found to be associated with the brain in this screen.

The central complex and the across-body symmetry of locomotion

The mirror-symmetrical architecture of the CX seems suited to exchange and to adjust neuronal information from both the brain and body halves. Consequently, 'right–left bargaining' has been among the suggested general functions of this neuropil that spans the sagittal midplane [11]. The suggestion has been supported by recent reports on flies that circle during free walking.

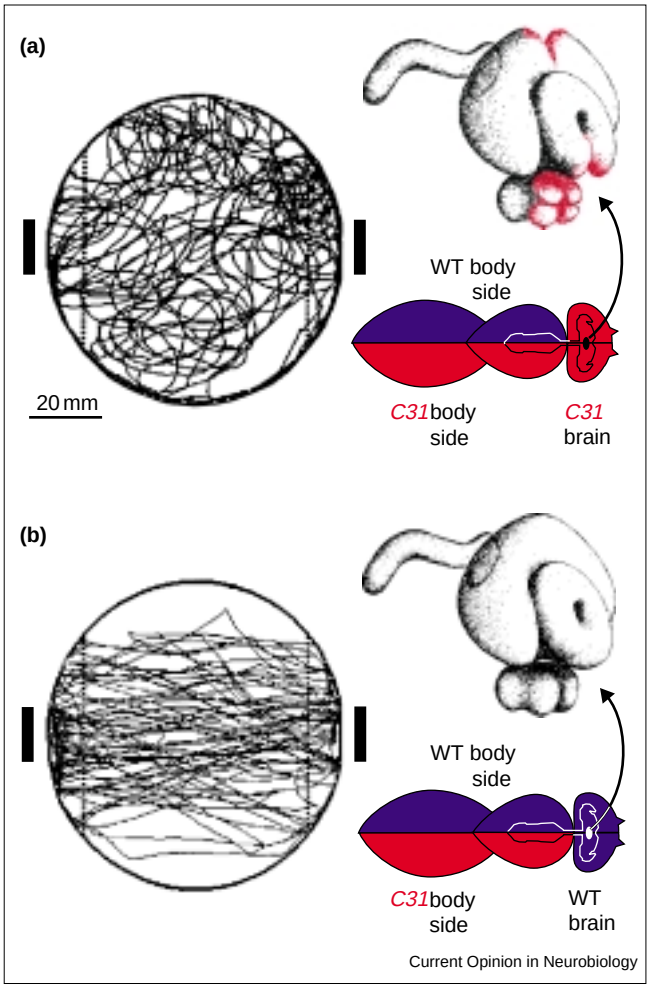
Identified in the screen for walking mutants, the *C31* line was later found to have its fan-shaped body and ellipsoid body partially interrupted along the midline of the brain. Flies completely defective in *C31* walked less and at only about half the speed of wild-type flies. Genetic mosaic techniques allowed extended patches of *C31*-defective tissue to be created in otherwise phenotypically normal flies [7]. Head-against-trunk comparisons showed that both brain and trunk require intact *C31* function to establish a normal walking speed [19]. When a *C31*-defective head and brain controlled a body with one intact and one *C31*-defective side, the flies were unable to walk straight ahead steadily; instead, they continually turned towards the *C31*-defective side, where the strides were shorter than on the intact side (Figure 2). Consequently, attractive landmarks were approached in spirals. When a wild-type brain controlled a unilaterally defective body the animals could walk straight ahead at a bilaterally reduced speed.

Collectively, these experiments show that an intact brain can apparently compensate for existing side asymmetries in the generation of steps, whereas a *C31*-defective brain is incapable of either recognising or correcting such asymmetries. Because full correlation between circling behaviour and the partial split in the CX was found, it is assumed that the CX accomplishes the respective balancing functions [19].

Circling behaviour in conjunction with sagittal CX defects has also been found in a new temperature-sensitive allele of *single-minded* (*sim*), which has allowed for the first time an assessment of post-embryonic functions of this gene [22••]. A reduction of *sim* function below a threshold of 50% results in flies with marked behavioural deficits, including walking at only a quarter of the normal speed, a decay in locomotor activity and severe circling behaviour. Further analyses indicated that the two last phenotypes are probably caused by defects in the protocerebral bridge and the fan-shaped body of the CX. This brain region expresses high levels of nuclear Sim protein in three clusters of neurons in each central brain hemisphere.

Earlier support for a role of the CX in right–left bargaining came from studies of the structural CX mutant *no bridge* (*nob*), which has a medially lesioned protocerebral bridge. Mutant *nob* flies fail to approach an attractive object in a straight line; their paths are more twisted than those of wild-type flies [9]. Moreover, they may spontaneously run into short episodes of uncoordination, which seem to be associated with changes in the walking direction [9].

Figure 2



Walking traces recorded from two genetic mosaic flies from line *C31*, which was identified in a behavioural screen for locomotor mutants. For each 15-min analysis, a water-filled moat around an elevated platform and clipped wings prevented escape and made the two landmarks inaccessible. (a) Unilaterally *C31*-defective flies with a *C31*-defective brain and CX are unable to walk straight ahead. They continually turn towards the mutated body side, where the steps are smaller than on the intact side. Structural defects caused by *C31* comprise a dorsal cleft in the fan-shaped body, a ventral cleft in the ellipsoid body and mis-shapen noduli (highlighted in red). (b) Unilaterally *C31*-defective flies with an intact brain and CX are able to walk straight ahead, although their speed is reduced. It is most likely that the intact CX can sense and compensate for the existing asymmetries in the trunk of the mosaic fly.

In addition, subtle abnormalities have been found in the 'object response' of *nob* flies during stationary flight at a torque metre. This term signifies the tendency of wild-type flies to turn with the sense of rotation of an object on the side where the object moves front to back (following response), and to produce torque spikes against the sense of rotation on the side where the object moves from back to front (suitable to meet it). In wild-type flies the following response is triggered while the object is still moving

from back to front and entering the binocular overlap region. In mutant *nob* flies the onset of the following response is delayed with respect to wild type, and it could be the necessary binocular interaction [23] that is impaired in the *nob* brain.

Other examples that support the idea of insufficient right–left bargaining in CX structural mutants were identified in flight experiments using flies with medially split ellipsoid and fan-shaped bodies (*ellipsoid body open* [10]; reviewed in [11]).

The central complex optimises walking speed by controlling step length

The slower than normal walking speed of *nob* flies is caused by their inability to increase step length concomitantly with stepping frequency [9]. Their step lengths are normal only at the low end of the frequency range. By contrast, *nob* swing phases show the normal duration and dependence on frequency throughout the whole frequency range, because timing is most probably a function of the ventral ganglion. Thus, the influence of an intact protocerebral bridge and CX is seen in the increase of the leg swing 'speed' with frequency, which enhances the strides within given time frames [9]. Mosaic studies have shown that there is full correlation between step-length deficits and lesion of the protocerebral bridge, although a hypothetical inconspicuous brain defect located near but outside the bridge could not be ruled out as a possible source of the correlation by this method alone.

The *nob* results are now paralleled by those of two newly described alleles of *eyeless*, which cause defects in the CX and other brain regions but leave the eyes of the mutant flies largely intact [24••]. Because the protocerebral bridges of these flies are disintegrated into several chunks of neuropil, one would predict *nob*-like or worse walking deficits — that is, decaying locomotor activity, slow walking through insufficient increase of step length with frequency, and largely intact swing phases. These deficits were indeed found [24••]. Moreover, they were also demonstrated in each of the three other known protocerebral bridge mutants *C141*, *ocelliless* and *central complex* (*cex*) ([25–27]; and R Strauss, unpublished data).

C141, which has a medial incision of the protocerebral bridge, was isolated in the walking screen [20]. An allele of *orthodenticle*, long known as *ocelliless* because it causes a loss of the three dorsal eyes, has been reported to lack most of its protocerebral bridge [28]. Lastly, *cex* flies possess a protocerebral bridge with only loosely connected glomeruli; this mutant was isolated in a morphological screen [8].

The corresponding behavioural and morphological deficits in mutants of five different genes virtually exclude a mere coincidence. The specific regulation of the step length predominantly through the swing speed of legs does require the intact protocerebral bridge.

Regulation of locomotor activity

Most of the structural CX lines suffer from locomotor activity that decays rapidly within a 15-minute test of landmark orientation behaviour [8], and some of the strains are reluctant to initiate flight or walking (reviewed in [11]). A study has examined the role of the CX in the temporal structure of spontaneous locomotor activity over the range of a few hours [29]. A local network connecting the four neuropilar regions of the CX was disturbed either by structural mutations of the protocerebral bridge, or by the inactivation of small subsets of CX neurons through P[Gal4]-directed expression of tetanus toxin. Whenever this network was disturbed, flies showed a marked decrease in locomotor activity. More specifically, the locomotor activity was clustered in bouts, as it is in wild-type flies [30], and these bouts were initiated at a normal rate; however, their duration was greatly reduced. Note that this network is also involved in establishing functional alcohol tolerance ([31]; and see Rothenfluh and Heberlein, this issue). In contrast, when synapses of the ellipsoid body were blocked, the time structure of the locomotor activity deviated from the power law distribution found in intact flies, that is, the fractal properties got lost [32•].

Can hyperactive flies also be created? Indeed, ablation or blocking of the mushroom bodies instead of the CX increases the walking activity to above normal levels through a slower and less complete decay of the bout lengths over time [33].

In conclusion, an intact ellipsoid body is required to establish the fractal structure in the temporal pattern of the walking bouts. An intact protocerebral bridge and fan-shaped body along with connecting circuitry are required to up-regulate the walking motivation to a normal level, whereas the intact mushroom bodies are required to down-regulate it to the wild-type level. Regulation is achieved by either extending or limiting the bout length, respectively.

Orientation behaviour and the central complex

Flies from a few of the lines with structural defects in the ellipsoid body and/or the fan-shaped body display altered orientation behaviour when walking or flying toward permanently visible attractive landmarks (reviewed in [11]; and R Strauss, unpublished data). But flies from almost all of these lines quickly loose their bearings as soon as the chosen target landmark becomes invisible [34]. By contrast, wild-type flies are able to keep their course towards the former position for considerably longer times and path lengths [35]. P[Gal4] lines directing expression of tetanus toxin to the ellipsoid-body behave like ellipsoid-body mutants (R Strauss, unpublished data).

After-fixation might involve an internal representation of the direction towards the concealed landmark (or a more general representation of the visual surroundings) and idiothetical course control to maintain this direction. It has been suggested that at least part of these functions are

located in the ellipsoid body [34]. In line with this notion are electrophysiological studies of neurons of the central body of the locust *Schistocerca gregaria*. These studies identified interneurons that are sensitive to polarised light and have spike rates dependent on the e-vector orientation of linearly polarised light. The authors suggest that these interneurons function in sky compass-mediated spatial navigation [36•]. Notably, most of the neurons were found in the lower division of the central body, which corresponds to the ellipsoid body of Diptera.

The central complex precursor and control functions in larval locomotion

The precursor of the CX in larvae of holometabolous insects — except for that of legged maggots — is poorly developed compared with the CX of nymph stages of hemimetabolous insects [12]. In addition, the bar-bell shaped CX of late third instar *Drosophila* larvae has only about 1970 fibres within the interhemispheric commissure and hardly any synapses [37]. To determine possible functions of the CX, the main differences in the insect lifestyles have been considered. Nymphs tend to have a higher speed of action (which is also due to their legs), a better resolution of the sensory space and a richer behavioural repertoire [12]. But would the less demanding tasks of a *Drosophila* larva really already require the larval CX precursor?

This seems to be the case because locomotor defects were found in early third instar larvae of six strains that were originally isolated for their adult CX abnormalities [38]. Differences from the control strain were found in all of them in at least one of three assays, namely, locomotion on a non-nutritive agar surface, locomotion on a nutritive yeast surface and a roll-over assay of muscle tone. Larvae of all six strains produced significantly shorter paths on yeast, although two strains moved normally when agar was used as substrate (*nob* and *ellipsoid body open*). The specificity of the defect might well indicate a disturbance in a higher control function, because the motor programme is properly carried out under some but not all of the conditions under which a wild-type larva would show the respective behaviour. The outcome of the roll-over assay further strengthened the notion that basic motor functions are normal [38]. A broader genetic dissection of larval locomotor and foraging behaviour is underway and has identified nine novel gene loci [39].

Conclusions and future prospects

Genetic dissection of locomotion in *Drosophila* has identified the CX as a principal site of locomotor control in larvae and adults. One of its functions is to regulate locomotor activity in interplay with the mushroom bodies. It establishes the across-body symmetry of locomotion through right–left bargaining, facilitates landmark orientation and enhances walking speed through an adaptive increase of the swing speed of legs. Thus, comparatively easy-to-conceive technical functions such as the balancing of step length on both sides of the body, along with seemingly complex decision functions such as whether to initiate walking voluntarily, are located in the CX.

Although it is tempting to attach a label like 'motor cortex of the fly' or 'visual integration centre' to the CX, it seems to me that we still do not have a unifying concept at hand. A tractable hypothesis is that much of the model-dependent inactivity or low speed of action found in CX mutant strains is caused by a failure to resolve conflicting inputs. If, for example, two attractive landmarks are seen, one with the left eye and one with the right eye, a normal brain (and CX) will readily pick one for further exploration. In technical terms, the stimulus of one side will defeat the other in a comparison stage and takeover completely. But if the comparison stage is defective, then each body side might follow up its own goal and the observable net behaviour could be inactivity. Taking this model to the extreme, the autonomous behaviour of the fly might be explainable in terms of a collection of parallel and nested comparators, which of course also involve comparisons among inputs of different sensory modalities and internal states after extensive pre-processing, along with 'winner-takes-all' mechanisms and plasticity of the weights for the different inputs. If so, we might then coin the term 'comparison centre' for the CX.

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