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Neuroanatomy: Connectome Connects Fly and Mammalian Brain Networks

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A recent study shows that brain connectivity in *Drosophila melanogaster* follows a small-world, modular and rich-club organisation that facilitates information processing. This organisation shows a striking similarity with the mammalian brain.

Within the last three decades, we have started to develop pictures of the global connectivity, at varying resolution, of the nervous systems of a number of phylogenetically disparate species. The archetypal 'connectome' to be elucidated was that of the hermaphrodite form of the round worm *Caenorhabditis elegans* [1], which has a relatively small, non-centralised nervous system, allowing for elucidation of a complete wiring diagram. Since then, we have started to discover meso-scale connectomes of the much more complex brains of the pigeon [2], rat [3], mouse [4], cat [5], and rhesus monkey [6]. These species live in different habitats, on water, on land, or airborne, but is this also reflected in a specialised organisation of brain connectivity? Even if the functional requirements were similar, did evolution come up with different solutions such as for the anatomy of the eye in cephalopods (such as the octopus) and vertebrates? A study reported in this issue of *Current Biology* by Shih *et al.* [7] has revealed connectivity between processing units in the brain of the fruit-fly *Drosophila melanogaster*, finding that major network features show striking similarities to the organization of the mammalian brain.

The Evolution of Neural Networks

As with other aspects of biology, it is useful to look at brain networks in terms of their evolution [8]. There are controversies over which metazoans are the most basal — particularly relating to the position of Ctenophores — but according to the conventional view of animal phylogeny, the earliest-evolving metazoans that show neural networks are Cnidaria (such as jellyfish). These animals show a diffuse two-dimensional nerve net in the polyp stage. To produce functionally specialised circuits, however, such a homogeneous organisation is unsuitable.

Starting with the formation of sensory organs and motor units, neurons aggregate in ganglia. Such ganglia are often not only formed by spatially clustered neurons, but are also topologically clustered: topological clusters, or modules, are sets of nodes with many connections within a module but few connections between modules. In this way, ganglia can process one modality without interference from neurons processing different kinds of information.

At a certain level of sophistication, having one module for one function is insufficient. An example is visual processing in the rhesus monkey (macaque), where the visual module consists of two sub-modules, one that processes object movement (the dorsal pathway), and one that processes object features such as colour and form (the ventral pathway) [9]. These more complex cases where sub-modules are nested within modules are examples of hierarchical networks.

The Mind of a Fly

*Drosophila melanogaster*s central brain has around 135,000 neurons, many more than the ~300 neurons of the *C. elegans* nervous system, but far fewer than the mouse's 100 million or the macaque's more than 1.3 billion. Shih *et al.* [7] established the *FlyCircuit* database with data from 12,995 projection neurons based on confocal microscopy (for details see [10]). These projection neurons link 43 local processing units, defined as subsets that contain local interneurons that only connect within a unit, and that exhibit bundled neural tracts between units. The 43 units form five modules: olfactory, mechano-auditory, left visual, right visual, and pre-motor. Such a functional specialisation is also seen in mammalian brains; for example, the cat brain is composed of visual, auditory, somatosensory-motor, and fronto-limbic modules [5].

The *Drosophila* brain also shows a 'small-world' network organisation [7]: a small-world network shows a high connectivity between regions that are connected to some other region (that is, between neighbours). At the same time, 'short-cuts', which often connect spatially distant regions [11], ensure that different parts of the network can be reached within few steps [12]. Despite their crucial role in speeding up processing in the fly, these connections that often run between modules are usually weaker (contain fewer axons) than many connections at the local level. The importance of these 'weak ties' [13] was also observed for human functional [14] and macaque structural integration [15]. Overall, the *Drosophila* connectome is comparable not only to neuronal networks that have been described in *C. elegans* [12] but also to fibre tract networks in the macaque [16], all showing a small-world organisation despite different brain size and architecture.

While modules ensure segregated processing of information, the integration of different kinds of information is also needed. Shih *et al.* [7] show that, within modules, some nodes have much higher strength than others, potentially functioning as information integrators or broadcasters. These nodes coordinate information flow locally within modules or help to link information of different modules at a more global scale. This local and global integration is comparable to the roles of provincial and connector highly-connected nodes (hubs) that have been extensively discussed in other species such as cat, rhesus monkey, and human.

Highly connected nodes, which Shih *et al.* [7] measured by the total strength of connections rather than the number of connected nods (node degree), tend to have stronger connections between each other than would be expected. Such a 'rich-club' organisation [17], with strong links between well-connected nodes, facilitates synchronisation and information integration at the global level. Consequently, removal of these nodes has a relatively severe effect on behavioural performance, consistent with many brain diseases in humans, including Alzheimer's disease and schizophrenia, that have been linked to changes involving rich-club nodes. It remains to be seen what functional consequences rich-club nodes have for *Drosophila*.

As for other networks, in species ranging from *C. elegans* to the macaque, the fly dataset contains information about the direction of connections, here described as polarity of neurons. When direction information is available we often find that for two connected regions, the connection in one direction might be a lot weaker compared to the opposite direction. In some cases, connections in one direction are absent leading to one-way streets of information flow. Such asymmetry allows for a larger repertoire of functional circuits with distinct feedforward and feedback loops and might be due to differences in the developmental time windows for synapse formation [18].

Loops are circuits where information can originate in one node, pass through other nodes, and arrive back at the origin. Using a simulation of information propagation, Shih *et al.* [7] show that signals that start within strongly connected loops can persist longer than those that involve weaker loops. Such persistent signals, in this study lasting ten times as long for strong compared to weak loops, could be crucial for generating stable oscillations or forming memories.

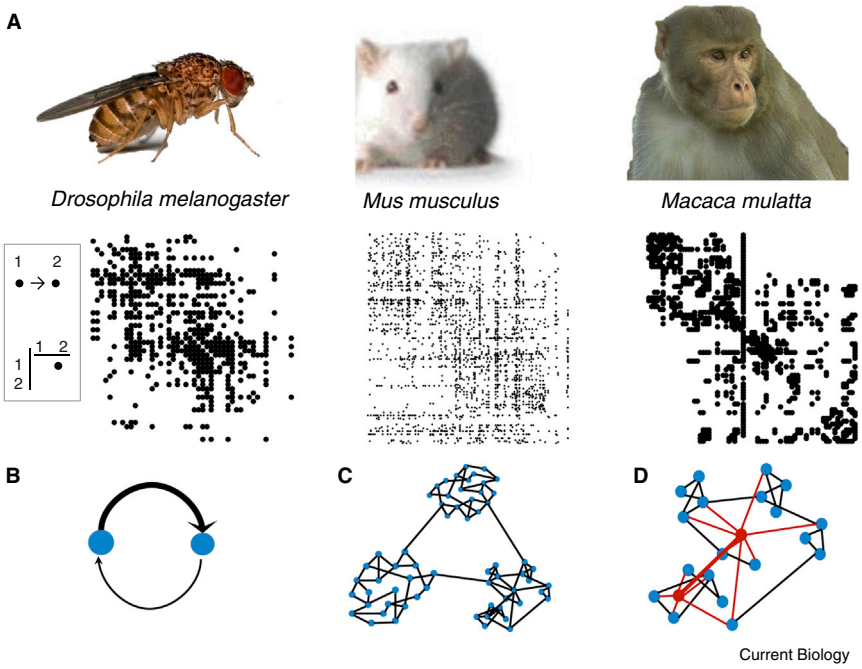

Figure 1. Brain connectivity across phyla.
(A) Connectivity between brain regions for fruit fly (photo: Bbski, Wikimedia Commons) [7], mouse (photo: FloNight, Wikimedia Commons) [4], and rhesus monkey (photo: Yann, Wikimedia Commons) [6] (top). A black dot in the connectivity matrix (bottom) indicates an existing connection between brain regions (inset, left). All networks share common characteristics such as (B) asymmetric connectivity where a connection in one direction could be either weaker or absent, (C) modules with many connections within but few between modules, (D) highly-connected nodes or hubs (red) with stronger connections between them (rich-club).

Future Directions

The connectivity of the fruit-fly brain reported by Shih *et al.* [7] is based on a reconstruction of a large number of neurons from all brain regions, thereby giving a more complete picture of brain connectivity. Moreover, for many neurons, the secreted neurotransmitter is known, allowing a first estimate of the balance of excitation and inhibition. This balance is not uniform, indicating that local negative feedback is much more crucial for some processing units than for others.

Despite the similarities with the organisation of the mammalian brain (Figure 1), it is important to also keep in mind some differences beyond the size of these brains: for the arthropod *Drosophila*, somata of interneurons and motor neurons are commonly uni-polar, motor fibre bundles are not myelinated, and they have sensory organs, such as compound eyes, ocelli, and antennae, which lack obvious counterparts in mammals.

The paper by Shih *et al.* [7] is an important step towards uncovering the structural connectivity in the fruit fly, but there are several open avenues for future discoveries. For *C. elegans*, cell ablation studies were used to observe the role of individual neurons [19] and simulated and real lesions in mammalian brains were used to assess the role of brain regions. Similar studies in *Drosophila* might help to elucidate the links between network structure and function. Secondly, the currently used method is unable to resolve individual synapses. With higher-resolution methods, information about synapses could be gained to estimate

synaptic weight, the location of synapses with excitatory *versus* inhibitory effects in the post-synaptic neuron, and the ability for computation within the dendritic tree of a neuron. Finally, simultaneous intracellular or extra cellular recordings from neurons in different modules could help to evaluate the link between network structure and function.

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Tumor Metabolism: MAGE-A Proteins Help TRIM Turn Over AMPK

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MAGE-A proteins are testis-specific E3 ubiquitin ligase components whose expression is upregulated in many cancers. MAGE-A3 and -A6 act as oncogenes and recent work now shows that they degrade the central metabolic regulator AMPK, providing a novel mechanism for rewiring cancer metabolism.

AMP-activated protein kinase (AMPK) is a serine/threonine kinase that is activated under conditions of low cellular energy, such as those that accompany loss of nutrients, particularly glucose and oxygen. AMPK plays a highly conserved role as an energy sensor and acts to restore metabolic homeostasis on a cellular and ultimately organismal level by downregulating anabolic biosynthetic ATP-consuming processes, like protein and lipid biosynthesis, and upregulating catabolic ATP-restoring processes, like autophagy and fatty acid oxidation. As such, AMPK is one of the central metabolic regulators that dominantly impacts overall metabolic state across most cell types and tissues studied to date in all eukaryotes [1].

AMPK has also been linked with cancer, being one of the best-studied substrates of the LKB1 tumor suppressor, which is inactivated in ~25% of lung adenocarcinomas and is the single gene responsible for the inherited cancer predisposition disorder Peutz-Jeghers

