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Review

Building and integrating brain-wide maps of nervous system function in invertebrates

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Abstract

The selection and execution of context-appropriate behaviors is controlled by the integrated action of neural circuits throughout the brain. However, how activity is coordinated across brain regions, and how nervous system structure enables these functional interactions, remain open questions. Recent technical advances have made it feasible to build brain-wide maps of nervous system structure and function, such as brain activity maps, connectomes, and cell atlases. Here, we review recent progress in this area, focusing on *C. elegans* and *D. melanogaster*, as recent work has produced global maps of these nervous systems. We also describe neural circuit motifs elucidated in studies of specific networks, which highlight the complexities that must be captured to build accurate models of whole-brain function.

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Introduction

Even in small animals, ethologically relevant behaviors can be remarkably complex. Nervous systems with a limited number of neurons can direct behaviors like foraging, courtship, and navigation, and allow animals to respond to threats, injuries, and infection. Understanding how neurons act together to direct context-appropriate behaviors is an essential question in modern neuroscience. To date, most research has focused on individual circuits or neurons controlling specific behaviors. However, recent technical advances have dramatically expanded the scope of what is possible, allowing researchers unprecedented access into the brains of animals.

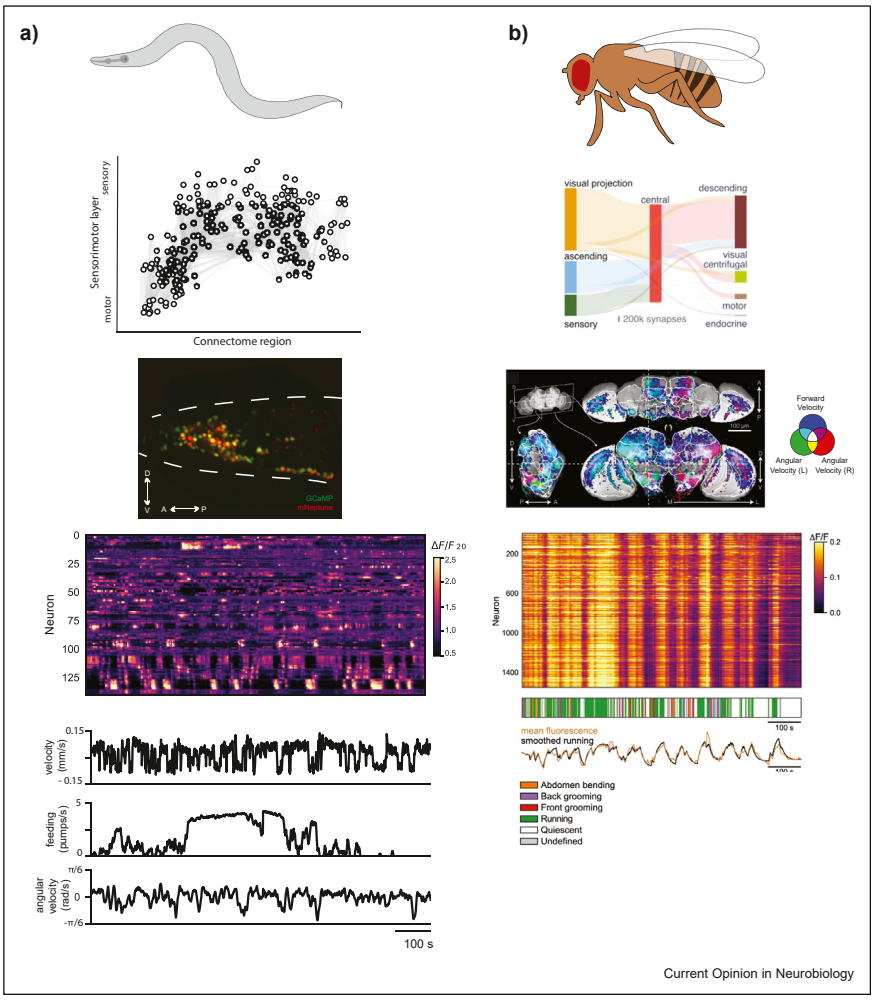
In this review, we discuss recent advances in building, connecting, and interpreting brain-wide maps of nervous system function in *C. elegans* and *Drosophila*. We first discuss whole-brain neural recordings from freely-behaving animals — studies that are mapping the relationship between neural activity and behavior. We then cover new, comprehensive maps of neuronal connectivity, genetic identity, and neuromodulation that have provided insights into nervous system structure. Finally, we discuss examples of individual circuit motifs with established links between structure and function that may aid our ability to interpret these new brain-wide maps. As this is a fast-moving field, we have largely limited our focus to developments over the past few years.

Brain-wide activity maps: how the brain encodes behavior

Recent advances have made it possible to perform whole-brain calcium imaging in behaving animals, yielding new insights into how brain-wide activity generates motor outputs. In *C. elegans*, pioneering studies examined whole-brain activity in immobilized [1–3] and freely moving animals [4–6]. These studies showed that information about behavior is distributed across the brain, with neurons representing different aspects of locomotion such as velocity and turning.

Recent work combined brain-wide imaging in moving animals with reliable, brain-wide cell identification. This development allows comparisons of neuron activity to ongoing behavior (sample data shown in Figure 1a); importantly, these relationships can then be compared across animals. Imaging the sex-specific neurons of the *C. elegans* male tail during mating behavior showed that stereotyped sets of neurons are active during different phases of mating, like sliding, turning, and copulation [7*]. While some neurons have specialized functions, others are engaged in several aspects of mating. Functional correlations between neurons changed as animals switched behavioral outputs. Another recent study used

Figure 1



Brain wide recordings in *C. elegans* and *Drosophila* reveal how neurons and brain regions encode behavior features
a) Whole brain calcium imaging data collection in *C. elegans*. From top to bottom: Cartoon of *C. elegans*. The worm connectome, showing synaptic connections between neuronal cells (data from Refs. [19,21]). Sample image of whole brain calcium imaging in a freely moving worm, showing pan-neuronal GCaMP and mNeptune in the head of a worm [8]. Heatmap of brain-wide activity during spontaneous behavior, with behavior quantification for velocity, feeding rate, and angular velocity in the same animal[8].
b) Whole brain calcium imaging data collection in *Drosophila*. From top to bottom: Cartoon of a *Drosophila*. The flow of information via chemical synapses between different brain regions as found in the *Drosophila* connectome [26]. Sample image of a fly brain, depicting representations of behavior in different regions [12]. Three views show orthogonal slices through the brain of a fly. Color values show correlations for each brain region with forward velocity and left or right angular velocity. Heat map of brain-wide activity during spontaneous fly behavior, with behavioral annotations and speed shown for the same animal [13].

encoder models to describe how each neuron class in the head of the hermaphrodite worm encodes specific behavioral features [8**]. Many neurons encode single behavioral features, like velocity or feeding, but a surprising number of neurons conjunctively encode multiple behaviors, revealing widespread multiplexing. While many neuron classes represent behavior reliably, a stereotyped subset changed encoding upon changes in the animal's internal state, suggestive of flexible remapping. Neuronal identification allowed comparison to the *C. elegans* connectome: neurons that are connected, especially by gap junctions, are more likely to show similar activity [7–9]. However, anatomical predictions of activity are not perfect, suggesting additional information is needed.

Whole-brain recordings in freely-behaving *Drosophila* similarly found a vast distribution of locomotor information. Behaviors such as walking elicit changes in activity across most brain regions, while less intensive grooming behavior only recruits specific brain regions (for example, compare heatmap of brain-wide activity to simultaneous behavior in Figure 1b) [10], [11**], [12**], [13**]. Careful analysis of different locomotor

features showed that specific brain regions are active during distinct behavioral components such as movement initiation, forward velocity, and turning [10–13]. Brain-wide activity is similar during freely-initiated and forced walking behavior, suggesting that many of these signals may be proprioceptive rather than motor commands [11]. These behavioral signals are accompanied by widespread sensory signals, which are also starting to be mapped at brain-wide scale [14].

Comparing studies from these two species reveals some consistent principles. In both animals, locomotor information is distributed across a surprisingly large area of the brain. This organization may enable coordinated behavioral outputs, allowing circuits throughout the brain to receive information about current behavior. Sleep or quiescence states consistently evoke broad downregulation in brain-wide activity [15,16]. In addition, anatomy may dictate activity: neurons that are connected tend to have similar activity patterns in *C. elegans*; in *Drosophila*, individual brain regions often contain small functional units of neurons with related dynamics [8,11–13]. Finally, activity in bilaterally symmetric neurons or brain regions is mostly similar [8,9,12,17], with a notable exception seen in turning neurons that activate on a specific side for directed turns [12,18].

An interesting feature of brain-wide dynamics in both organisms is the timescale of behavior representation. Neuronal activity can represent current behavior or behavior in the recent past [8,12,13]. Neurons with related behavioral information can show varied timescales in their tuning to that behavior, allowing for an ordered recruitment of different neurons as behavior progresses [8,12,13]. In flies, neural activity could even predict upcoming turning behavior, revealing signals related to motor planning [18]. These studies reveal consistent principles in the organization of global brain dynamics that are conserved across evolutionarily distant species.

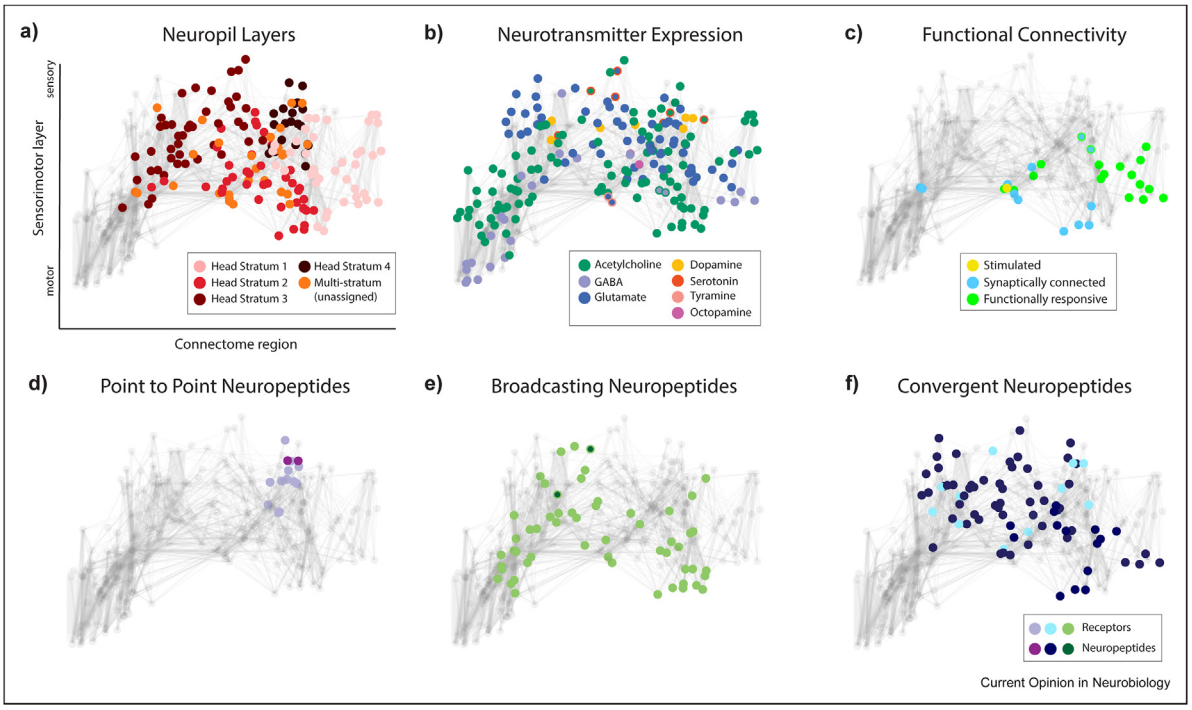
Maps of neuronal architecture and genetic identity

Many advances in *C. elegans* neuroscience were enabled by early mapping of the connectome [19]. Recent studies expanded that understanding, identifying connections that vary across individuals, throughout development, and based on sex [20,21]. Notably, this work found that the greatest variability in connectivity was observed in modulatory neurons [21]. Careful analysis also revealed a previously unrecognized degree of organization in the neuropil of the *C. elegans* nerve ring, which could influence functional interactions between neurons (Figure 2a) [22,23]. In *Drosophila*, a sophisticated electron microscopy (EM) platform [24] was instrumental in the generation of the first complete map of synaptic connectivity [25**], [26], adding to an earlier connectivity map of the hemibrain [27]. This valuable atlas revealed key principles in brain organization; for example, densely connected groups of "rich club" neurons represent about 30% of neurons [28]. The *Drosophila* connectome is also defined for larvae [29] and the Ventral Nerve Cord [30–33], and more targeted work has mapped the mushroom body [34] and central complex [35], providing a wealth of maps to aid studies of neural circuits. For example, analysis of the mushroom body connectome found many more visual inputs than previously known, perhaps allowing for integration with other convergent sensory cues. The *Drosophila* connectomes are limited to chemical synapses thus far, owing to technical constraints. Future annotations of electrical synapses will provide additional insights into the synaptic organization of this nervous system.

Identifying connections is only part of the battle. To understand how these synapses function, we must determine the identities of the underlying neurotransmitters and receptors. The *Drosophila* connectome benefits from artificial neural network predictions of neurotransmitter identity based on EM data [36*]. In both species, transcriptomic atlases revealed the distribution of neurotransmitters and receptors [37–39**]. Fluorescent reporters have also been valuable in mapping the expression of neurotransmitters [40–42] and receptors [43], [44*]. This work has suggested that there may be widespread extrasynaptic signaling: many receptors are expressed in cells that do not receive synapses from a cell expressing that neurotransmitter. These genetic maps are essentially complete for the main *C. elegans* neurotransmitter systems at the level of cell types (for example, neurotransmitter identity is shown in Figure 2b). Completion of single synapse resolution maps in worms and flies – a major challenge for the future – will yield additional advances.

Another factor not accounted for in connectivity maps is neuropeptide signaling. Understanding of *C. elegans* neuropeptide systems expanded enormously with the identification of 461 novel ligand-receptor pairs out of over 55,000 possible pairs tested [45**]. These findings were combined with single-cell sequencing data to construct a brain-wide neuropeptide signaling map. Compared to synaptic signaling, neuropeptide signaling is more decentralized and far denser, with >10-fold more connections [46**]. Neuropeptide networks also link the synaptically disconnected pharyngeal network to the central brain. In addition, different peptidergic systems feature dramatically different organizations: point-to-point signaling, autocrine signaling, and broadcasting architectures, which may enable different features of emergent activity (Figure 2d–f). Mapping of the neuropeptide network in *Drosophila* showed neuropeptide expression limited to clusters of neurons but receptor expression throughout the brain [43].

Figure 2



Structural, genetic, and network maps of the *C. elegans* connectome

a-f) Six identical arrangements of neurons from the *C. elegans* connectome, where neurons are organized by sensorimotor layer (y-axis) and connectivity (x-axis). In each panel, neurons are colored according to different structural or functional features.

a) Neurons are colored based on their neuropil layer assignments as determined in Ref. [23]. "Unassigned" neurons span multiple strata.

b) Neurotransmitter expression in all *C. elegans* neurons (data summarized in Ref. [40]). Neurons with multiple colors release multiple neurotransmitters.

c) Sample result comparing functional and anatomical connectivity for a single neuron, SAADL (shown in yellow). Neurons in green had changes in activity upon SAADL stimulation [48]. Neurons in blue are synaptically connected to SAADL [19,21].

d-f) Examples of three different signaling motifs found in the neuropeptidergic connectome of *C. elegans* (data on neuropeptide and receptor expression patterns from Refs. [39,45,46]).

d) Point to point signaling, with only a few neurons expressing either the neuropeptide *nlp-23* or its cognate receptor *gnrr-3* (data from Refs. [39,45,46]).

e) Broadcasting expression from a single neuron pair (HSN) releasing neuropeptide *flp-23* to many downstream partners expressing receptor *dmsr-7* (data from Refs. [39,45,46]). Interestingly, HSN expresses both the neuropeptide and receptor, representing a possible autocrine loop.

f) Convergent signals emanating from many neurons releasing *flp-5* are integrated by only a handful of neurons expressing its receptor *egl-6* (data from Refs. [39,45,46]).

A central goal of future research will be to connect brain-wide activity and connectivity maps. In *C. elegans*, a recent investigation focused on comprehensively mapping the serotonin system's structure and function [47*]. The serotonergic NSM neuron is activated by food ingestion, and its non-synaptic release of serotonin induces slow locomotion and increased feeding behavior. A combination of approaches was used to identify the contributions of each of the six serotonin receptors to these behavioral changes, determine the neurons across the connectome that express these receptors, and investigate how serotonin release impacts brain-wide activity. Different receptors mediated behavioral responses to different patterns of serotonin release. In addition, knowledge of each neuron's serotonin receptor expression could partially predict how their activity changed during serotonin release, providing links between structure and function.

Another study recently attempted to bridge the gap between architecture and activity by assembling a map of functional connectivity [48**]. This work combined cell-specific optogenetic activation, whole brain imaging, and neuronal identification to quantify how perturbing each neuron's activity affects all other neurons' activities. Many relationships were identified between neurons that are not directly connected through synapses (example shown in Figure 2c). Additionally, many of these fast, functional connections were dependent on dense core vesicle release, providing evidence for functionally important extrasynaptic signaling that may be critical to understand brain-wide dynamics.

Efforts to build increasingly precise and accurate network models of fly and worm nervous systems are ongoing. In *Drosophila*, modeling constrained by connectome and neurotransmitter data generated novel

hypotheses about sensory and motor pathways [49]. Many of these predictions held true in subsequent testing; for example, novel neurons predicted to be important for water responses indeed caused a change in water intake upon optogenetic perturbation. Accurate predictions of known visual system neurons were also generated by a neural network model of a smaller region, the optic lobe, which was built using constraints from the connectome and deep learning methods [50]. Still other work used behavioral data to train a deep neural network model, cleverly using behavior recordings from flies with silenced neurons to probe the visual courtship circuitry [51]. Current modeling efforts are limited by a lack of data about electrical signaling, receptor dynamics, neuromodulation, and individual neuron characteristics such as co-neurotransmitter release.

Although the work described here has produced a wealth of information about circuit organization and function, many challenges still need to be solved in order to interrogate circuit function at brain-wide scale. In the meantime, studies of specific circuits provide valuable intuition about how nervous system structure relates to function in the context of behavior.

Neural circuit motifs in invertebrate nervous systems

Our understanding of how neural circuits generate behavior has been greatly aided by case studies of individual circuits. Here, we discuss examples of studies that uncovered network motifs that contribute to defined features of animal behavior.

At first glance, the most straightforward pathways are point to point signals, where one neuron communicates directly to another. Hundreds, if not thousands, of such connections have been identified, often underlying specific sensorimotor responses. Recent studies have shown that even neuropeptides can act in this direct manner to impact behavior. For example, in worms, the neuropeptide *flp-1* promotes avoidance of pathogenic bacteria [52*]. Upon infection, this neuropeptide is released from one neuron class, called AVK, to promote avoidance behavior through a single receptor, *dmsr*-7, which functions in RIM/RIC neurons. *flp-1* is produced in other neurons and has other receptors; *dmsr*-7 is similarly broadly expressed and has many ligands, yet a single connection within this complex network has a specific behavioral function. In *Drosophila* larvae, a similar motif was found when examining nociceptive responses to heat: the neuropeptide DSK acts via one receptor on a single cell type to inhibit heat avoidance [53].

Another common network motif is broadcasting or "one to many" signaling, where a single neuron signals to several downstream partners. This network logic is effective for behavioral outputs that require synchronization, such as changes in behavioral state. In *C. elegans*, stress induced sleep is regulated by the ALA neuron, which releases multiple neuropeptides to downregulate distinct behavioral features such as feeding, head movement, and locomotion [54,55]. Broadcasting signals are also useful as teaching signals during learning. In *Drosophila* spatial learning, dopaminergic ExR2 neurons broadly innervate the head direction network and facilitate learning during rotational movements so that animals can update their internal representations of space [56].

There are several circuit architectures that can support coincidence detection. In *C. elegans*, "hub neurons" receiving convergent signals can weigh multiple sensory inputs and generate integrated behavioral responses. For example, in response to gentle touch, several mechanosensory neurons send concurrent signals via gap junctions to a single downstream neuron, RIH, which acts as a coincidence detector to direct avoidance behavior [57,58]. Coincidence detection circuits are also central to learning. In *Drosophila*, dopaminergic DAN neurons that contain information about motor state, internal state, and even reward and punishment converge onto defined compartments of the mushroom body; coincident activation of specific DANs with olfactory-responsive Kenyon cells changes how Kenyon cells couple to mushroom body outputs and behavior [59–68].

Studies of defined neural circuits have also demonstrated that behavioral outputs are not always governed by a single, linear circuit. Degenerate signaling pathways can often exist, where different neural sources can lead to the same outcome. In *C. elegans*, feeding behavior can be initiated by several independent neurons [69]. This work is reminiscent of degeneracy in the stomatogastric ganglion (STG) of crustaceans, where many underlying circuit configurations can generate the same circuit outputs [70–72]. Work on the STG has also demonstrated that neurons can co-release several neuropeptides that have additive or antagonistic effects (reviewed in Ref. [73]). In flies and worms, release of different neurotransmitters from the same neuron can impact distinct behavioral outputs [74,75], effectively allowing them to participate in multiple networks. In order to accurately capture brain-wide activity, we will need to consider that the underlying signaling can be flexible, degenerate, and multiplexed and may contain many interlinked network motifs that contribute to overall circuit function.

Conclusion

The recent developments reviewed here have opened an exciting new chapter in neuroscience research. Advances in hardware and software (reviewed in Refs. [76,77]) have yielded bountiful data on neuronal

activity in freely behaving animals under a variety of conditions. While similarities between worms and flies suggest that principles of brain-wide organization may span species, examining brain-wide activity in mammals is challenging. Recent advances have allowed for recording of over a million neurons in the mouse neocortex [78], but brain-wide imaging will require additional innovations. *C. elegans* now have an atlas of how most neurons encode spontaneous behavior [8], and activity maps for the larger *Drosophila* brain provide a global view of its dynamics. In addition, both species now have genetic maps of neurotransmitter and receptor expression, as well as maps of synaptic connections. Despite this wealth of data, we are still missing information crucial to our understanding of how these nervous systems function.

Going forward, future experiments will need to address the flexibility of how neural activity encodes behavior. Examining brain-wide responses across animals in different behavioral states, in defined sensory surroundings, or during motivated behaviors will show how neuronal encoding can change based on context (see [65*]). Our current understanding of flexibility and degeneracy derived from smaller circuits suggests that brain activity maps will not be fixed.

To fully integrate the activity and molecular maps, we need a more complete understanding of neurotransmitter system dynamics. Further studies about the timescales of neurotransmitter release, the spatial organization of heterogeneous receptors on a single neuron, the extent of extrasynaptic signaling, and the kinetics of different receptors will provide valuable information. Currently, these questions are typically addressed on a case-by-case basis, but large-scale approaches [48] may be well positioned to tackle some questions at scale. In addition, sensors for neuropeptides [79] and neurotransmitters [80,81] may be useful to further address these problems. As future work expands our view of brain-wide dynamics and organization, it will be increasingly possible to create accurate models of brain activity to generate novel, testable predictions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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