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Prominent inhibitory projections guide sensorimotor computation: An invertebrate perspective

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Abstract

From single-cell organisms to complex neural networks, all evolved to provide control solutions to generate context and goal-specific actions. Neural circuits performing sensorimotor computation to drive navigation employ inhibitory control as a gating mechanism, as they hierarchically transform (multi)sensory information into motor actions. Here, we focus on this literature to critically discuss the proposition that prominent inhibitory projections form sensorimotor circuits. After reviewing the neural circuits of navigation across various invertebrate species, we argue that with increased neural circuit complexity and the emergence of parallel computations inhibitory circuits acquire new functions. The contribution of inhibitory neurotransmission for navigation goes beyond shaping the communication that drives motor neurons, instead, include encoding of emergent sensorimotor representations. A mechanistic understanding of the neural circuits performing sensorimotor computations in invertebrates will unravel the minimum circuit requirements driving adaptive navigation.

Keywords: Active sensing; navigation; neural circuits; inhibition; *C. elegans;* invertebrate

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1. Introduction

"Life's aim is an act, not a thought. The brain seems a thoroughfare for nerve-action passing its way to the motor animal." **Sir Charles Scott Sherrington, The Brain and its Mechanisms (1933)**

If generating an action is the primary goal of the nervous system, studying neural computations that lead to motor behaviours across the evolutionary tree will ultimately unravel the (un)common solutions seemingly distinct neural network formations provide to perform behaviourally relevant adaptive computations. As navigation itself has evolved within species' habitats and the transformed body schemes, the composition of neural networks has become compliant to their new constraints. This sometimes leads them to acquire novel sensory inputs and often changes how effectors (e.g. muscles) interact with the environment. With increasingly complex circuit formations throughout the evolution, a preserved circuit motif might have allowed increasingly complex circuit formations and adaptive behaviours to evolve.

Navigation is a whole-brain computation. In animals with a central nervous system, it involves both egocentric (i.e. self-centred) and allocentric (i.e. world-centred) encoding of sensory information. The end point of this computation is an egocentric action sequence, that allows the interaction with the surrounding world. World-centred encoding of sensory information necessarily requires mapping sensory information in respect to navigational goals and contextual information. Thus, self-centred representation must be transformed and integrated with previously acquired sensory and perceptual experiences in the form of cognitive maps. Therefore, complex navigation is a whole-brain computation that consolidates information processing across a sensation-perception-action triangle while engaging memories and recruiting executive control.

Navigation can also be a task for a single cell; Mobility can be generated as a response to local sensory information by individual specialised "sensorimotor cells" that contain both sensory receptors and an organ for generating motion. Eukaryotes with cilia and ciliated sponge larvae, for example, employ ciliary motion to navigate their environment in response to a change in illumination, chemical gradients and gravity[1, 2]. It has been speculated that the first neurons evolved to provide fast electrical signal propagation to control navigation[3], which ultimately gave rise to organisms that employ muscle based locomotion as cilia evolved into a sensory organ[4].

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Independent from whether the mobility is provided by a ciliary organ or a muscle-based effector system [5, 6], coordinating navigation in a context where motor action is generated as a response to current (or recent history of the) sensory information, constitutes the basis of sensorimotor integration[7-9].

Although sensorimotor computation commonly leads to navigation (as well as other forms of motor control including vocalisation and vocal communication[10-14]), we refrain from discussing the circuits of navigation, which are reviewed elsewhere[15-20]. Here, we focus on the networks that have evolved to provide such sensorimotor control to address general principles of sensorimotor computation from a neural circuit perspective, with the focus being on *Caenorhabditis elegans*. By focusing our arguments in 3 key highlights, we show that *C. elegans*, like all animals, require sensorimotor integration to generate action and explore the computational roles of inhibitory neurons that allow adaptive sensorimotor computations. Ultimately, by understanding the mechanistic basis of the neural circuits that perform sensorimotor computations in a simple model organism such as *C. elegans*, this will help to unravel the minimum circuit requirements that drive adaptive navigation.

2. All animals use sensorimotor integration to generate context specific actions

From nematodes to primates, all animals have specialised neural circuits that enable them to integrate the variety of (often multimodal) sensory information to plan an appropriate motor action. Although the complexity of the behaviour, dimensionality of the sensory stimulus, and motor repertoire vary greatly, the basic principles of sensorimotor integration are preserved across species.

The simplest form of sensorimotor integration can be observed in *taxis,* where the motion of the organism is controlled as a direct consequence of a specific sensory stimulus, e.g. temperature for thermotaxis[21], light for phototaxis[22], chemical gradients for chemotaxis[23], and wind for anemotaxis[24]. As organisms use distinct cues to explore their environments, where and when the sensory stimuli are encountered is crucial in determining animals' motor responses. Although unimodal sensory stimulus could effectively control taxis, locomotor networks can also be driven by multimodal inputs, thanks in part to the multimodal integration in sensory neurons. Multimodal

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integration is experience dependent, at least in mammals[25]. However, experience dependent adaptive navigation strategies dominate navigation even if unimodal sensory information drives sensorimotor integration. Whether a bat hunts for a mouse using echolocation at night[26, 27] or a mouse contextually controls the position of its whiskers in space while foraging its environment in darkness[7, 28], neural circuits reconstruct, and otherwise memorise, the recent history of the sensory input. This time derivative of the incoming sensory input, often in relation to the motor state of the animal, is an important control signal that shapes the motor output of the organism[29].

A major difference between the simple and complex nervous systems is that the former perform navigation without a map. Thus, their motor control strategy is tightly coupled to the sensory information available in their immediate environment, rather than being based on planned (often goal-directed) actions, which require motor planning in the context of landmarks and world-centric coordinates[30-33]. Accordingly, as *C. elegans* moves through a chemical gradient, it navigates its environment using a biased random walk[34, 35], just like bacteria navigate a chemical gradient[36], using multi-protein receptor complexes for temporally integrating information[37]. Integrated sensory information can change animals' navigation strategies[38-40]. In *C. elegans*, the behaviour of the nematode in the absence of food will change the navigational state from "searching" to "dispersal", each of which requires a distinct set of sensory neurons[41, 42]. The rate of turns are regulated by the sensory experience across time scales as the worm adapts to its environment, e.g. a high number of turns are observed following the initial disappearance of food and if food sparsity continues, the number of turns will eventually decrease to a base level[41]. Consequently, even animals with simple nervous systems are capable of a rapid response to the ongoing changes in the environment, and over time they adapt to the new sensory state of their surroundings[41].

Consequently, the integration of sensorimotor information generates highly context specific actions[43], whether in terms of a quick escape from a predator, or navigation in response to food availability. Planned, goal-directed navigation provides a distinct advantage over navigation based on local cues, as it allows integration of sensory information across larger spatial domains while introducing (rapid) error correction for execution of sensorimotor behaviours. With increased mnemonic load, complex neural circuits progressively integrate long-term information storage capability to the circuits that perform sensorimotor integration that constitute the neural basis of

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perceptual and motor learning[41, 44-49]. Neural circuits have thus evolved to execute sensorimotor integration with ever increasing involvement from mnemonic contributions and executive control, for example in the mammalian brain, the circuits that plan, control, execute and monitor action generation[50-53].

3. Rudimentary neural circuits that mediate sensorimotor computation employ hierarchical information processing

One of the basic forms of sensorimotor computation is the activation of the body wall, or skeletal, muscles as sensory input from the environment is used to create a *reactive* control scheme for navigation. In simplified neural circuits, this control scheme involves hierarchical processing of (multi)sensory information by interneurons as action sequences are translated into motor commands by motor neurons e.g. the fast escape response in fish[54], the powerful escape action in flies[55], the reactive escape in lamprey[56] and the threat response in *C. elegans*[57].

Motor activity results from the interplay between excitatory and inhibitory interneurons that synapse onto motor neurons in both vertebrates and invertebrates. The small and compact nervous system of *C. elegans* means that only 2 layers separate sensory neurons from motor neurons (Fig. 1a). Here, the pre-motor interneurons (AVB and PVC) synapse onto excitatory B-type motor neurons to drive forward movement, while alternative interneurons (AVA, AVD and AVE) connect to the excitatory A-type motor neurons to stimulate reverse movement[41, 44]. The role of the inhibitory (GABA) D-type motor neurons is to innervate muscles of the opposing side, enabling modulation of the contralateral inhibition in the nematode worm[44]. The role of inhibitory neurons is not limited to gating and co-ordinating motion. Multimodal sensory input is collected and transmitted to the AIY interneuron, where the inhibitory signals and excitatory signals are integrated[41, 58] (Fig. 1b). The motor output is head turning and navigation across a variety of contexts, including chemotaxis, thermotaxis and swimming[41, 59-61]. Such feed-forward loops allow head movement to be mediated by a single inhibitory neuron, the RIA.

Generation of adaptive, yet robust, behavioural output with limited circuit components would benefit from experience-dependent plasticity of neuronal communication and compartmentalisation of computation[39, 62]. Indeed, *C. elegans* displays many aspects of plasticity,

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including learning and memory[63-65], in the absence of which navigational trajectories become more random, less ordered and less directional[66]. For example, during isothermal tracking, where worms migrate towards their cultivation temperature[67], expression of the calcium sensor *ncs-1* in the interneuron AIY has a crucial function in influencing experience-dependent learning. Studies in mice have shown that NCS-1 may facilitate learning and memory together with motivational and reward circuits, where over-expression of *ncs-1* promotes exploration and acquisition of spatial memory while *ncs-1* knockout impairs exploration and long-term memory[68]. As NCS-1 regulates synaptic communication of the presynaptic inhibitory AIY neuron projections in *C. elegans*[67, 69], targeted regulation of inhibitory neuron communication might enable the emergence of adaptive sensorimotor transformation.

Strikingly, the AIY interneuron has the ability to regulate two different outputs via multiple downstream circuits[70]. The inhibitory connections between the AIY interneuron and AIZ provide a means to control direction of movement, while the excitatory connection between AIY and AIB allow speed of movement to be modified[70]. In addition, depending on the intensity of a stimulus, the AIB is able to modulate behavioural output accordingly[71].

In postsynaptic neurons, compartmentalisation is an important computational feature and is likely to be a conserved mechanism for signal processing[72, 73]. In *C. elegans*, the axon of the RIA interneurons has several distinct domains (the loop, nrD and nrV) in which dynamic calcium levels result in head movement: SMDV innervates the nrV and displaying ventral head bends while SMDD synapses onto nrD enabling dorsal head bending[72] (Fig. 1b). These calcium dynamics were also observed in the presence of levamisole, a nicotinic acetylcholine receptor agonist, suggesting that RIA axonal activity is independent of movement[72], further arguing that inhibitory RIA neurons represent proprioceptive feedback and/or corollary discharge, also known as efference copy[72, 74].

Synapses are dynamically controlled to modulate behaviour, and compartmentalisation is a level of organisation by which different pathways can be activated, suppressed or otherwise modulated for generation of behaviour. By spatially restricting signalling, as in the *C. elegans* RIA neuron, different sub-circuits can be selected from a larger pool of possible circuits, enabling the fine-

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tuning of a response[65, 74-76]. Compartmentalised activity has been shown in complex networks including the optic lobe of the fruit fly[77, 78] and the starfish[79, 80]. Compartmental computations are also preserved in more complex circuits, including in the mammalian brain[81]. Thus, mapping the origins (e.g. presynaptic soma location, neuron type and synapse class) of synapses made onto the postsynaptic neuron will complement these functional studies while enabling circuit level description of spatiotemporal integration for sensorimotor transformation.

By spatiotemporally confining neuronal activity to a specific subcellular region, the computational power of neurons can be expanded dramatically. Furthermore, this form of circuit organisation allows convergence of synaptic inputs originating from non-overlapping presynaptic pools of neurons while preserving stimulus selectivity before the neuronal representations can be passed along the neuronal circuits. By forming routine operations of the nervous system, e.g. gain modulation, stimulus selectivity, around feed-forward computations, neuronal representations can be maintained across a broad range of stimuli.

4. Independent of the evolutionary age of the organism, inhibitory neurons powerfully shape the motor control during sensorimotor computation

It has been known since 1863 that inhibitory neurons regulate motor control[82], although it was not for another 50 years that the significance of inhibition truly took hold[83, 84]. Now, it is clear that inhibition is an important building block of sensorimotor circuits, and is required to establish the correct patterns of motor activity and shape its plasticity[85] and inhibitory circuits are present throughout sensorimotor circuits.

Inhibition circuitry is an important feature of sensorimotor circuits which are required to establish the correct patterns of motor activity to enable locomotion. Sensorimotor inhibition is required to regulate the processing of sensory information via presynaptic pathways and via postsynaptic inputs to neurons that are involved in receptive sensory transmission and control the excitability of motor neurons by directly or indirectly reducing excitation [86]. Stopping or lowering the sensory feedback before it reaches a spinal target is efficient way to control afferent inputs in different motor tasks. Purkinje cells (PCs) are the sole output from the cerebellar cortex and it is generally accepted that the PCs are important in the fine control of movements. The ability of PCs to

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contribute to motor control is that firstly, they are inhibitory neurons and secondly that they have a relatively high spontaneous firing frequency which can be modulated[87, 88]. Modulation of the firing frequency is possible via the excitation from parallel fibres and inhibition from inhibitory interneuron inputs[89, 90]. Indeed, this type of modulation of inhibitory neurons is not limited to mammals, it has recently been shown that *the C. elegans* AWA neuron is capable of firing an all-or-none calcium based action potentials[91].

Sensorimotor circuits are crucial to guide goal-oriented locomotion across evolution. Irrespective of organism, the flow of information is preserved as the sensory input from the environment is processed by way of inhibitory interneuron gating (for detailed reviews see [92, 93]). Before the motor output is generated, the information is further processed along excitatory feed-forward circuits whose activity is shaped by feed-forward and feed-back inhibitory projections. Such circuitry is likely to have appeared early during multicellular organisms' evolution and as organisms are exposed to new environments, the sensorimotor computation must also increase in complexity to allow existing networks to adapt and gain new functionality[94]. The sensorimotor circuit organisation across the evolutionary tree might serve as an example for the adaptive changes in circuit organisation. Over time, the basic circuit elements evolve into more complex, parallel circuit loops that enable advanced multimodal computation, integration of mnemonic information and executive control for top-down regulation of the sensorimotor control (see Fig. 2 for a phylogenetic view on the circuits from the sea slug to fruit fly).

The sea slug, *Hermissenda crassicornis,* has one of the simplest invertebrate sensorimotor networks (Fig. 2). Here, sensory information (light and vestibular) converges on the interneurons, but there is also reciprocal inhibition between the hair cells and photoreceptors[1, 4, 6, 95]. Such reciprocal inhibition is crucial for bilateral activity in invertebrates and vertebrates, including in *C. elegans*, where locomotion is accomplished by either inhibitory commissural neurons (CN) acting directly on motor neurons (or interneurons) or indirectly via excitatory CNs acting on pre-motor inhibitory neurons[96]. The axons of CN cross the midline and thus provides a direct line of communication enabling changes in left-right coordination[96]. Aquatic vertebrates, such as tadpoles and lampreys also display the same bilateral action of CNs as observed in mammals[96-99].

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While interneurons allow computation of multimodal sensory integration in simple animals, such as the nematode, the presence of layers of network structures demonstrate more organisation. Sensorimotor control loops are observed in the fly, where navigation is achieved via a combination of path integration (tracking position relative to a reference point) and known visual landmarks[100]. Figure 2 shows a concise representation of the fly sensorimotor loops, for more details, see[18, 101, 102]. The central complex (CX) is a point of convergence, having many inputs from sensorimotor circuits with only a few outputs to guide flight pathways[100, 103]. The CX is composed of a number of structures, including the protocerebral bridge (PB), the fan shaped body (FB) and the ellipsoid body (EB) as well as various substructures (Fig. 2). Within this circuit excitatory and inhibitory pathways create bidirectional circuits and contribute to sensorimotor control loops[103]. Indeed, the PB is likely to be the location in which most sensorimotor computations occur, and is analogous to the mammalian basal ganglia[103]. Within the CX are a series of neurons arranged in a ring (ring neurons) which have both excitatory and inhibitory receptive fields (similar to cells in the mammalian primary sensory cortices)[100, 104].

Ultimately, reciprocal inhibition is a computation common to all organisms throughout evolution, and inhibitory neurons remain central to the performance of such networks. As sensorimotor networks evolve, interneurons allow computation of multimodal sensory integration, as evidenced in the nematode[65, 75, 105, 106]. While in the fly[77, 78, 100, 103, 107], rodent[108] and mammalian brain[50-53, 109-112]. the presence of layers of network structures demonstrate a hierarchical organisation. Within this circuit, excitatory and inhibitory pathways create bidirectional circuits and contribute to sensorimotor control loops[81] as convergent projections targeting the circuit enable integration of multimodal bottom-up and top-down information while divergent projections enable modulation of a broad range of sensorimotor circuits throughout the brain.

Together, these observations suggest that independent from their position in the evolutionary tree, all animals are capable of using sensorimotor integration to generate context-specific actions, and this integration requires closed-loop computations. Inhibitory neurons are capable of shaping the control of movement and they function in parallel to, and as a part of, the seeded sensorimotor loops. Now, the challenge is to understand how the sensorimotor computation emerges from

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simple circuit elements as an emergent computation of the distributed networks in the brain. The ability to have independent control over each synaptic input to a cell/circuit component while monitoring the motor output, will enable the computation of specific neuronal projections and provide causal links between neural activity and behaviour.

bioprocess

5. Conclusions and future perspectives

Over the past century, scientists working on invertebrate animal models have unravelled the cellular atlas, especially in *C. elegans*[113, 114], how cells interact across a network of brain regions and which cell types encode the various sensory inputs[115]. Now, we also have models of the mechanisms by which environmental cues are combined with goal-driven information to generate a spatial representation[100, 103, 104]. However, questions remain concerning the contribution of higher-order processes, e.g. memory, to drive navigation in invertebrates. To answer them, we must leap from systems biology to systems neuroscience - with its quantitative framework - to causally link elementary neural circuit computations to behaviour in freely behaving animals. The ultimate goal is to understand how complex behaviour emerges from seemingly rudimentary neural processes, and identify generalisable circuit computations that enable adaptive sensorimotor transformations in the context of navigation. The ability to have independent control over each synaptic input, including those of neuromodulatory transmitters, to a cell/circuit component whilst monitoring an output will address the computational roles of specific synaptic connections. This provides causal links between neural activity and behaviour, and the availability of genetic tools will be crucial in working towards this goal[76, 91, 115-119].

In understanding circuitry and by showing that the same processes apply to both simple model organisms (e.g. the fly and worm) as well as more complex mammalian species (mice and human), the scope for the inspection of how circuits function, signals are integrated and loops function alone or in combination is significantly more achievable. Indeed, knowledge gleaned from this type of research will have profound implications in understanding the basis of sensorimotor deficits in neurological disorders and neurodegenerative disease[120-122]; It might even provide a route to enabling development of bionic limbs as efficient control sensorimotor control algorithms will facilitate rapid closed-loop control of artificial actuators.

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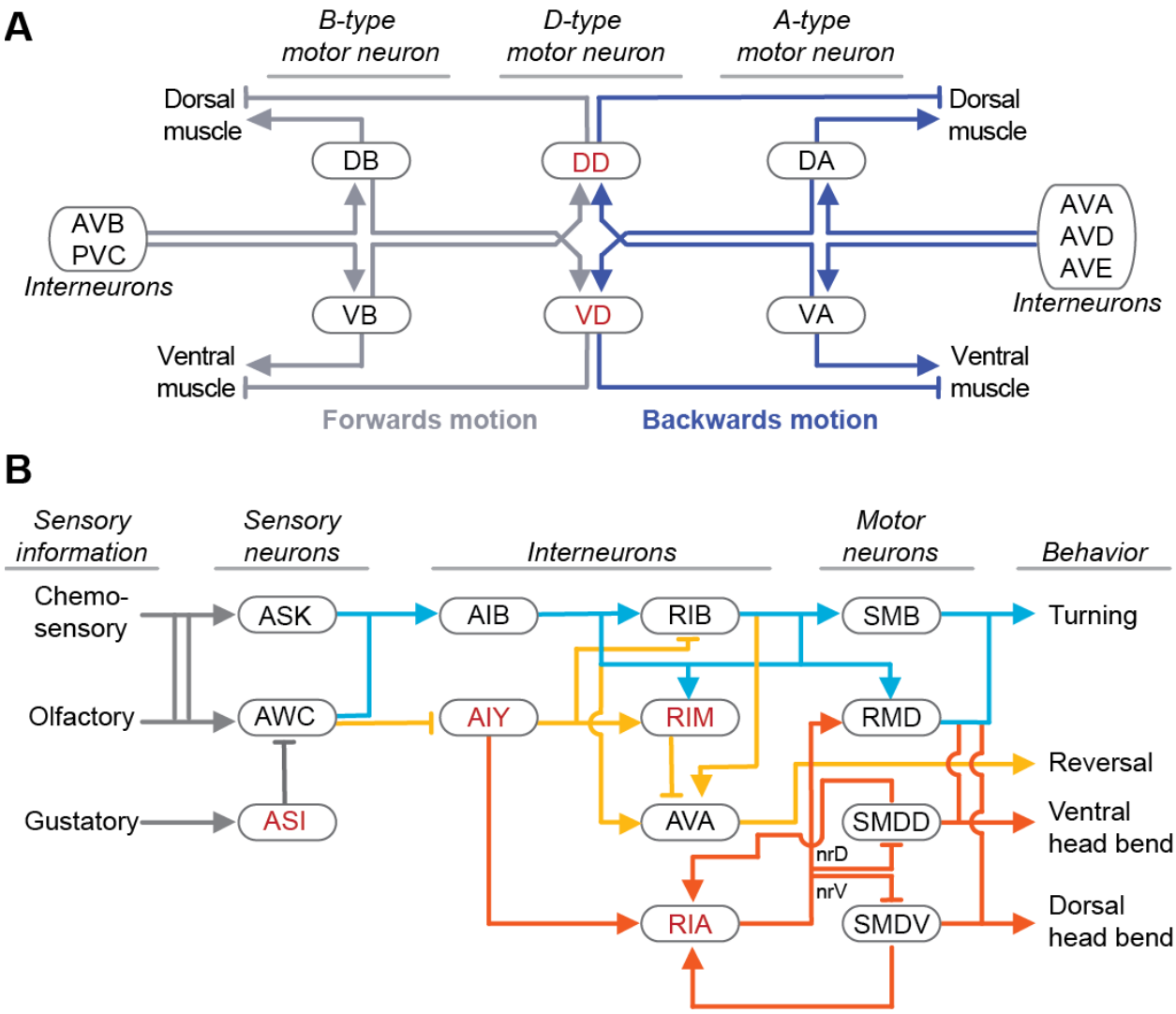

Figure 1. Hierarchical feed-forward information processing for sensorimotor navigation in *C. elegans*. a) The undulatory forward/backward movement of the animal is driven by contraction and relaxation of muscle on the dorsal (D) and ventral (V) side of the worm. Cholinergic motor neurons (A- and B-type) which are postsynaptic to interneurons and drive locomotion while the GABAergic neurons (D-type) inhibit muscle contraction. This is repeated along the length of the animal in a contralateral inhibitory mechanism, i.e. DB motor neurons excite a dorsal muscle at the same time as VD motor neurons inhibit the opposing ventral muscle[44]. Blue lines demonstrate forward movement and grey lines, backwards movement, with cell ID labels in red to denote inhibitory interneurons. **b)** The amphid sensory neurons, AWC, ASK and ASI, direct their synaptic output to the primary layer of interneurons (AIB and AIY) and then to the secondary layer

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interneurons (RIM, RIB and RIA). The AVA is a command interneuron and is able to act in parallel to, as well as in concert with, the interneurons. The AIY neuron has a key role in head bending in response to various taxis behaviours via the RIA. The RIA neuron makes reciprocal connections with SMDV and SMDD motor neurons, where the connections are spatially segregated so that the dorsal nrD region of the RIA innervates SMDD and results in ventral head bends via local calcium ion levels and *vice versa* for nrV innervation of SMDV[41, 58, 74, 123, 124]. Cell ID labels in red denote inhibitory interneurons. Blue lines demonstrate neuronal circuitry that promotes movement, green lines show both excitatory and inhibitory synapses from a sensory stimulus, while yellow lines are inhibitory circuitry. Orange lines indicate the circuitry associated with corollary discharge.

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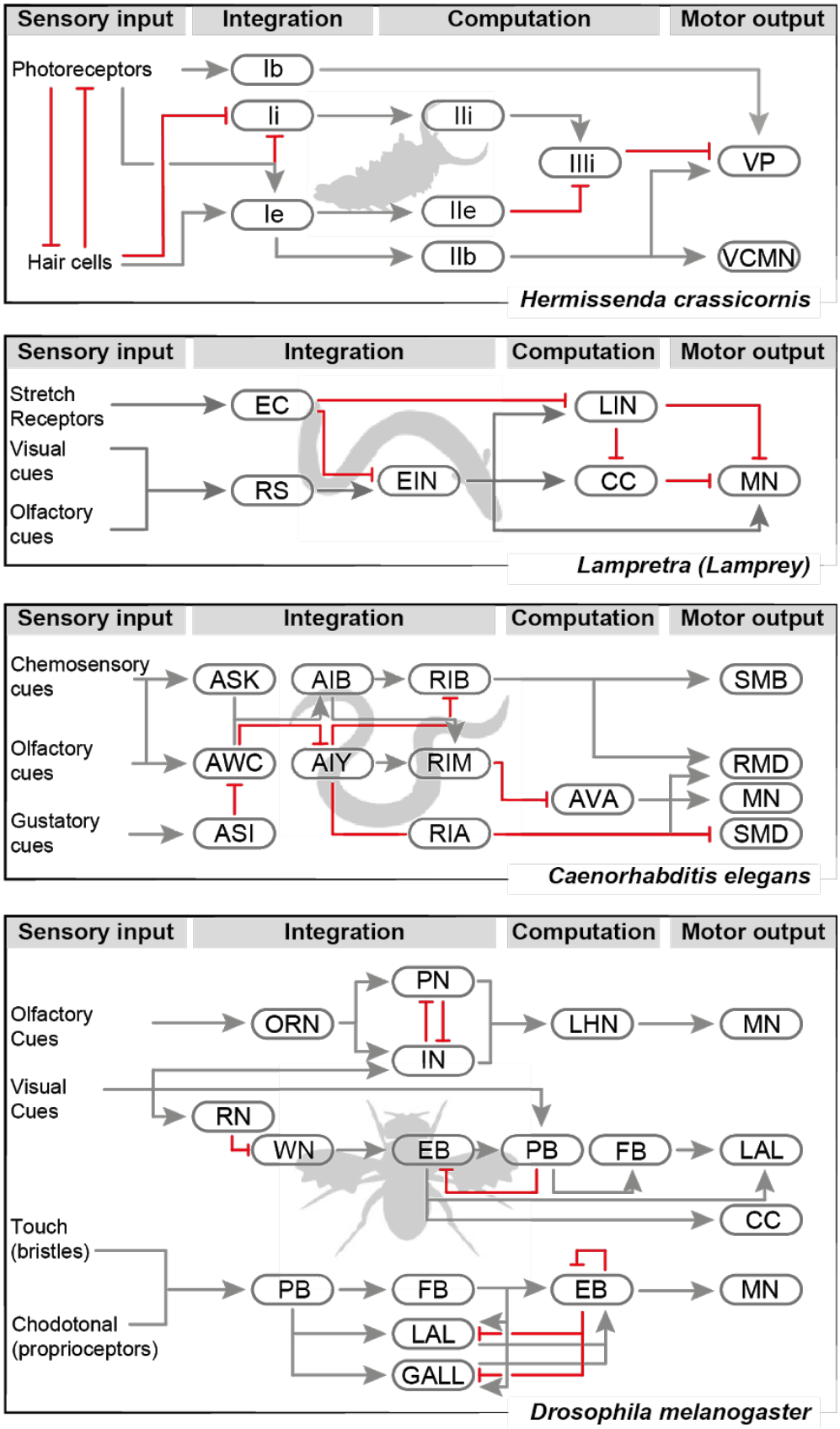

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Figure 2. Sensorimotor computations require inhibition at all levels of neural circuits. Simplified circuit maps for four non-mammalian model organisms where sensorimotor transformations are experimentally well studied. The sea slug, *Hermissenda crassicornis*, has a simple nervous system[1, 6, 95]. Inhibitory neurons are key in integrating information from the hair cells and photoreceptors to drive movement via cilia and tentacles. I,II,III, interneurons; VP, Ventral Pedal; VCMN, Ventral Contraction Motor Neuron. The lamprey requires inhibition to enable it to propagate forward movement via the contralateral activation and inhibition of body muscles[125, 126]. LIN, Lateral Interneuron; CC, Cross Caudal inhibitor interneuron; EIN, Excitatory Interneuron; IIN, Inhibitory Interneuron; ED, Edge Cell; RS, Reticulospinal Cells. Similarly, *Caenorhabditis elegans* requires contralateral inhibition for forward movement, See Figure 1 for more details. In contrast, *Drosophila melanogaster* is a much more complex system[100, 103, 104, 127-131]. Here, a combination of seeded sensorimotor loops and inhibition as well as compartmentalisation enable the fly to integrate multiple senses in the central complex and respond accordingly. PN, Projection Neuron; LHN, Lateral Horn Neuron; MN, Motor Neuron; IN, Interneuron; ORN, Olfactory Receptor Neuron; PB, Protocerebral Bridge; FB, Fan shaped Body; WN, Wedge Neuron; RN, Ring Neuron; LAL, Lateral Accessory Lobe. Note, the sensorimotor circuit shown for the fly is concise, and is not intended to represent the complete circuitry[18, 101, 102].