



SYMPOSIUM ARTICLE

Multimodal Integration Across Spatiotemporal Scales to Guide Invertebrate Locomotion

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Synopsis Locomotion is a hallmark of organisms which has enabled adaptive radiation to an extraordinarily diverse class of ecological niches, and allows animals to move across vast distances. Sampling from multiple sensory modalities enables animals to acquire rich information to guide locomotion. Locomotion without sensory feedback is haphazard; therefore, sensory and motor systems have evolved complex interactions to generate adaptive behavior. Notably, sensory-guided locomotion acts over broad spatial and temporal scales to permit goal-seeking behavior, whether to localize food by tracking an attractive odor plume or to search for a potential mate. How does the brain integrate multimodal stimuli over different temporal and spatial scales to effectively control behavior? In this review, we classify locomotion into three ordinally ranked hierarchical layers that act over distinct spatiotemporal scales: stabilization, motor primitives, and higher-order tasks, respectively. We discuss how these layers present unique challenges and opportunities for sensorimotor integration. We focus on recent advances in invertebrate locomotion due to their accessible neural and mechanical signals from the whole brain, limbs, and sensors. Throughout, we emphasize neural-level description of computations for multimodal integration in genetic model systems, including the fruit fly, *Drosophila melanogaster*, and the yellow fever mosquito, *Aedes aegypti*. We identify that summation (e.g., gating) and weighting—which are inherent computations of spiking neurons—underlie multimodal integration across spatial and temporal scales, therefore suggesting collective strategies to guide locomotion.

Introduction

Behavior is the manifestation of information flow across different spatial and temporal scales, spanning from molecules to the whole brain and from milliseconds to years. This information is received via multiple sensory modalities and flows to multiple motor outputs and back by feedback loops. How does the brain integrate multimodal signals over different temporal and spatial scales to control behavior? In this review, we focus on how multimodal sensory information is combined at different

spatiotemporal scales to guide locomotion. We propose that locomotion, which serves to guide an animal in space over time, can be ordinally ranked along the space-time axis into three layers from low- to high-level: stabilization, motor primitives, and higher-order tasks, respectively (Fig. 1A). This classification of movement is a hypothesized hierarchy for how the brain might organize locomotory behavior in space and time. Furthermore, this classification shares similar structure to emergent, machine-learning-based lexical description of

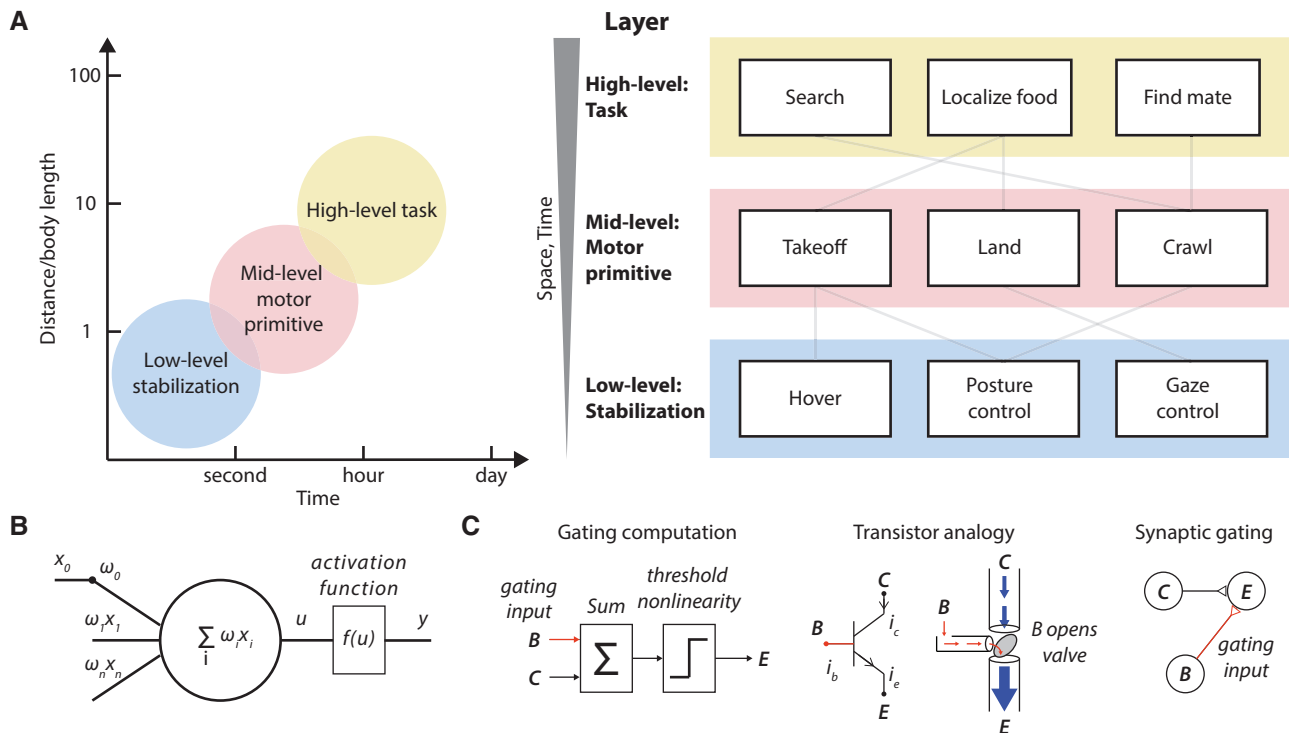


Fig. 1 Conceptual framework. **(A)** Framework for classifying multimodal, sensory-guided locomotion along the space-time axis. We propose that locomotion can be ordinarily ranked along the space-time axis into three layers from low- to high-level: stabilization, motor primitives, and higher-order tasks, respectively. Gray lines indicate possible scenarios to support high-level tasks by recruitment of motor primitives assisted by low-level stabilization. **(B)** Artificial neuron with inputs x and weights ω . The neuron sums synaptic inputs (u) which then passes through an activation function $f(u)$. **(C)** Left: Basic gating computation that combines summation and non-linear thresholding. Middle: (left) Bipolar junction transistor where i represents current in individual branches (C: Collector, B: Base, and E: Emitter). (Right) Transistor hydraulic analogy which can function as a switch or amplifier depending on the base flow (or current). Right: Basic organization of synaptic gating. Red lines indicate gating inputs.

behavior (Anderson and Perona 2014), and is analogous to subsumption architecture, a layered method proposed for designing adaptable mobile robots (Brooks 1986).

We divide this review into three sections spanning the space-time axis of locomotion, ordered from low- to high-level layers. First, we detail the role of multimodal integration for low-level stabilization that permits rapid postural control. Second, we discuss how multimodal information is integrated for mid-level motor primitives. Motor primitives are defined as a fundamental unit of motor behavior that includes, for instance, rhythmic locomotor patterns formed via a central pattern generator (CPG; Giszter et al. 1993). Finally, we review multimodal integration for higher-order tasks, such as localizing and navigating toward food. To function over large spatial and temporal scales, we posit that higher-order tasks “select” motor primitives (action selection) that are themselves stabilized by low-level behavior. We focus on invertebrate locomotion and, where available, highlight core findings in genetic model

systems, including the fruit fly *Drosophila melanogaster* (larva and adult) and the yellow fever mosquito, *Aedes aegypti* (Fig. 2). For each section, we discuss how multimodal information is integrated in neural circuits as animals traverse different spatiotemporal scales to guide locomotion.

Multimodal integration for low-level stabilization

Stabilization—rapid motor responses to perturbations to maintain a desired state—is essential for locomotion. For instance, reflexes of vestibular origin enable us to maintain posture during our daily activities. In vertebrates, maintaining balance involves the integration of visual, vestibular, and proprioceptive inputs, and thus, stabilization is fundamentally multimodal (Goldberg et al. 2012). Along the space-time axis of locomotion, stabilization behavior is fast (order of milliseconds) and spans a short distance (approximately one body length; Fig. 1A).

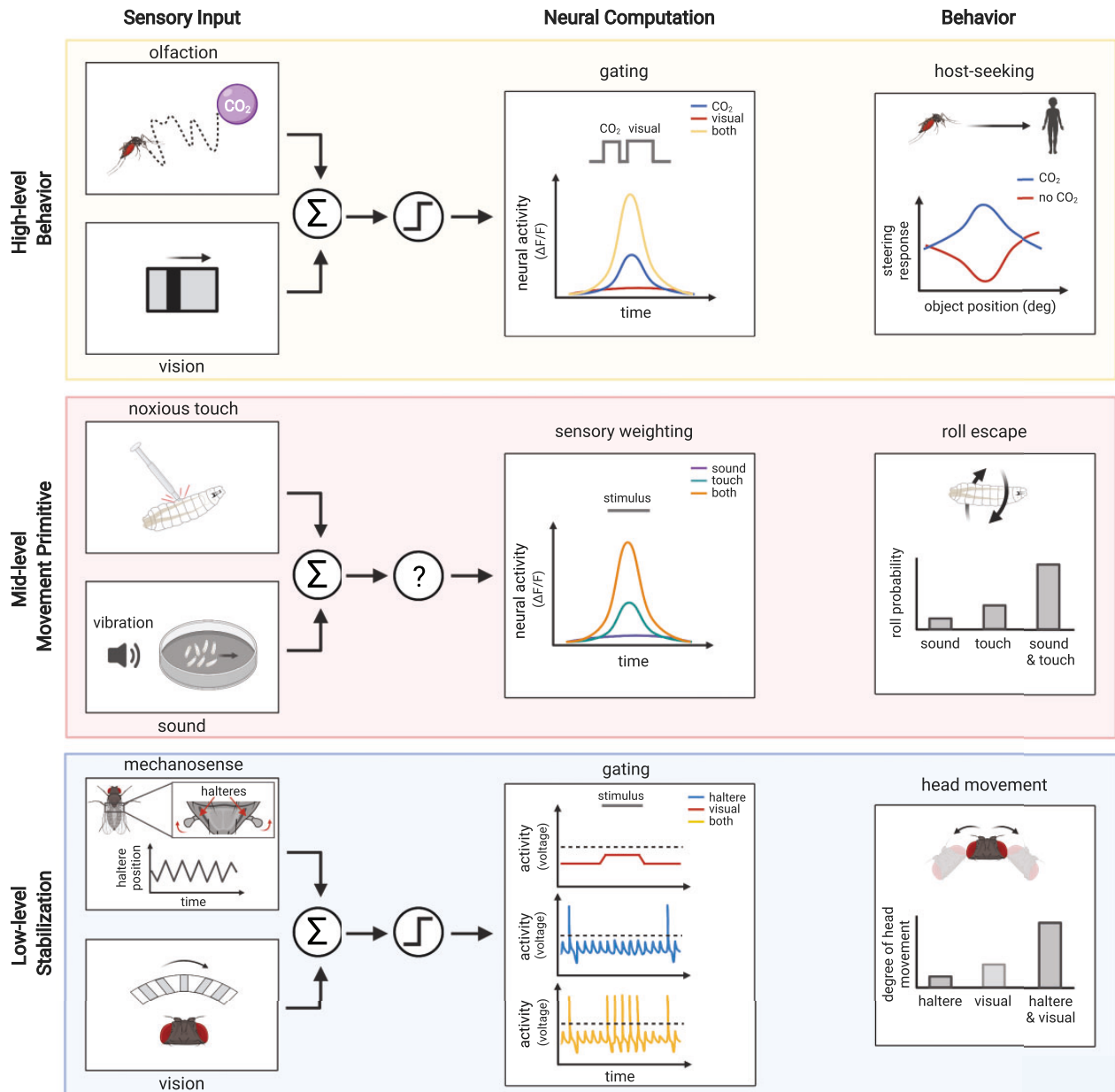


Fig. 2 Summary of common invertebrate neural computations that enable multimodal integration acting over different spatial and temporal scales (low-, mid-, and high-level). We highlight computations in flies (blowflies and fruit flies) and the yellow fever mosquito (*A. aegypti*). Bottom: Gaze stabilization via head movements in flies (Diptera) combines rapid mechanosensory feedback from gyroscopic organs (halteres) with slower visual feedback via non-linear summation (gating; adapted from [Huston and Krapp 2009](#)). Such nonlinear summation is reflected in head movement responses at the behavioral level. For the behavior column, the light grey bar indicates *Drosophila* head movement data relative to the haltere & vision bar ([Mureli et al. 2017](#)). Middle: Roll escape in *Drosophila* larva is triggered by sensory weighting and summation of sound vibration and noxious touch inputs, which permit rapid escape from a predator (e.g., parasitoid wasps) via stereotyped recruitment of muscles (adapted from [Ohyama et al. 2015](#)). Top: The yellow fever mosquito combines visual and olfactory information to search for a potential host. At long distances from the host, asymmetrical gating of visual stimuli by olfactory (e.g., CO₂ concentration) stimuli guides host-seeking behavior (adapted from [Vinauger et al. 2019](#)).

Integrating multimodal signals with different delays and information content

Animals integrate sensory information from multiple modalities, but integration is challenging because signals from different modalities propagate and are

transduced at different speeds and may contain distinct information. Because stabilization behavior underlies basic tasks such as maintaining posture, low-delay transmission of information is critical, as delays can make locomotion unstable ([Cowan et al.](#)

2014). Transmission speed constraints in neural systems can lead to compensatory strategies, such as mechanical “preflexes” that exploit stabilizing properties of passive body mechanics (Jindrich and Full 2002) and feedforward control that predicts the consequence of motor actions (Wolpert and Ghahramani 2000). Transmission speed, which is constrained by nerve conduction delays, is only one of many constraints on the total sensorimotor delay: sensory transduction, synaptic, motor nerve, neuromuscular junction, electromechanical, and force generation delays must also be considered (More and Donelan 2018). Furthermore, inertial delays arise because the body cannot easily oppose a corrective action whether at rest or in motion, a consequence of Newton’s first law (Mohamed Thangal and Donelan 2020). Taken together, sensorimotor and inertial delays make up the total effective delay during locomotion.

Sensory transduction delays can have important consequences for the integration of information from multiples senses for stabilization. For instance, vision and proprioception have different transduction delays, as phototransduction is a relatively slower process than mechanotransduction (Goldberg et al. 2012). Phototransduction involves a biochemical cascade to convert light into electrical energy, whereas mechanotransduction relies on the activation of ion channels via direct mechanical linkages. These cross-modal delays impact critical postural reflexes that maintain visual equilibrium. For instance, in humans, the vestibulo-ocular reflex, which stabilizes the eyes when the head rotates, relies on mechanosensory information from vestibular organs and operates with a delay of only approximately 5–7 ms (Goldberg et al. 2012). In contrast, the optokinetic reflex, which stabilizes visual motion by moving the eyes, is driven by visual inputs and has a longer delay of ~50–100 ms. How is information with different temporal dynamics integrated at the neural level to generate an appropriate motor response? As this question is relevant across multiple scales of locomotion, throughout we will discuss recent research that provides new insights into this question.

In addition, signals from different modalities contain different information which must somehow be combined to generate a coherent behavioral response. For instance, vision provides information about image slip speed on the retina whereas vestibular organs provide information about how an animal is oriented in space (e.g., linear and/or rotational acceleration). How are the different information contents weighted given different arrival times to

the brain? To address these questions within the context of multimodal integration along the space-time axis, we will focus on advances in understanding of the fly’s sense of balance, which integrates visual and mechanosensory information. In particular, we discuss recent advances in the fly genera *Drosophila* and *Calliphora* (Fig. 2, bottom panel).

A computational framework for multimodal integration

To contextualize multimodal integration, it is useful to consider basic neural computations for spatiotemporal integration. For a neuron that weights different synaptic inputs x_i

$$u = \sum_{i=1}^n \omega_i x_i$$

(1) where u is the weighted sum, ω is a vector of synaptic weights, and x is a vector of inputs, the output y is subject to the following activation (step) function

$$y = \begin{cases} 1 & \text{if } u \geq \theta \\ 0 & \text{if } u < \theta \end{cases}$$

(2) where θ is the activation threshold (Fig. 1B). Thus, weighting and summation combined with thresholding of sensory inputs provide collective strategies to integrate information across spatiotemporal scales. Nonspiking neurons could add more nuance to multimodal integration, but here we focus on a spiking neuron as an exemplar. Changes in resting membrane potential u of the soma can influence or “gate” synaptic input, thus modulating post-synaptic potentials y in a way analogous to a transistor (Fig. 1C; Katz 2003). For example, for a neuron with two synaptic inputs, a gating input can change the membrane potential (B in Fig. 1C), which releases the response of another input (C in Fig. 1C) to generate an output that is amplified nonlinearly or suppressed (E in Fig. 1C). Gating has also been defined phenomenologically (Huston and Krapp 2009), but unifying the mechanistic and phenomenological definitions is the dependence on a threshold nonlinearity. Thus, gating is a form of nonlinear summation.

Visual and mechanosensory integration for flight stabilization in flies

Flight is an intrinsically unstable mode of locomotion and therefore requires constant sensory feedback for postural control (e.g., during hovering). In particular, flight is unstable about the pitch axis, as manifested by an unstable oscillatory mode during

hovering (Taylor and Thomas 2003). Sensory feedback, presumably at every wing beat (Chang and Wang 2014), complements passive stabilization mechanisms, such as flapping counter-torque during rapid aerial maneuvers (Hedrick et al. 2009). Visual and mechanosensory feedbacks act synergistically to stabilize insect flight (Sherman and Dickinson 2003; Dahake et al. 2018). Vision is slower and tuned to low angular velocities but provides spatially broad exteroceptive information. The compound eyes sense optic flow, which provides information to correct deviations from an intended course and to infer depth cues from motion parallax (Land 1999). For instance, the visual system could correct small drift via temporal integration (Schnell et al. 2014). Conversely, mechanosensory feedback from halteres—vestibular organs that act as the fly's gyroscope/metronome—travels much faster and is tuned to higher angular velocities but provides spatially restricted interoceptive information about self-orientation. There is a direct connection between haltere and wing motor neurons via an electrical synapse, thereby enabling sensory feedback during every stroke cycle (Fayyazuddin and Dickinson 1996). Due to their complementary velocity tuning, visual and mechanosensory inputs extend the sensory bandwidth available to flies. Taken together, even though the dynamics of visual and vestibular modalities differ, both modalities act together to maintain visual equilibrium and compensate for perturbations. How is visual and mechanosensory information combined to enable rapid flight stabilization? While the answer to this question is not fully resolved, several studies point to a weighted summation for wing steering responses and a gating neural computation for the control of stabilizing head movements (Fig. 2, bottom panel). Gating, as described above, refers to a computation wherein the presence of one stimulus releases or switches a response to another.

Neural computation for visuo-mechanosensory integration for flight stabilization in flies

Flies constantly adjust wing movements, whether to adjust their body position via ballistic saccades or body velocity to minimize retinal slip (Cellini and Mongeau 2020a). At the behavioral level, previous work suggested that haltere and visual inputs are summed to control flight motor responses in *Drosophila* (Sherman and Dickinson 2004). Specifically, visual and mechanosensory information are combined into a weighted sum, in which mechanosensory information is weighted more heavily. Rotation of a fly along the yaw, pitch, and roll

axes decreases the gain of visual responses, acting like a switch. Although this work identified a model of sensory integration, it remained unclear how integration might be implemented physiologically to stabilize flight. In addition, within a control theoretic interpretation of flight, low-delay mechanosensory information from antennae and halteres might actively damp the high-gain visual system for flight stabilization (Elzinga et al. 2012; Fuller et al. 2014). These results point to a stronger weighting of mechanosensory than visual information to stabilize flight. To maintain stability, we would indeed expect the nervous system to prioritize or weigh more heavily information that is transmitted on a shorter timescale.

Visual and mechanosensory information are also combined to control gaze via head movements (Hengstenberg 1993) and both inputs appear to sum nonlinearly to control gaze in *Drosophila* (Rauscher and Fox 2021). During the corrective yaw optomotor reflex, head movements play a critical role in shaping visual inputs and coordinating wing steering responses (Cellini and Mongeau 2020b). The haltere-to-neck motor neuron latency is only about 3–5 ms, suggesting rapid head postural feedback from organs mediating balance (Sandeman and Markl 1980), although the total delay is likely longer due to other sensorimotor and inertial delays. In blowflies *Calliphora*, the ventral cervical nerve motoneuron (VCNM)—which controls head movements—receives synaptic input of visual and mechanosensory origin (antennae and halteres; Haag et al. 2010). Visual motion alone generates subthreshold activity, but when combined with a wind stimulus sensed by the antennae or with haltere motion, the VCNM neuron generates action potentials, implicating gating as a mechanism to combine visual and mechanosensory information. Specifically, visual motion increases the membrane potential which permits post-synaptic action potentials in the presence of wind and/or haltere motion. Similarly, some neck motor neurons will not generate action potentials in response to visual motion alone, but will produce action potentials when the halteres are concurrently beating (Huston and Krapp 2009; Fig. 2, bottom panel). Correspondingly, at the behavior level, haltere motion in tethered blowflies generates some head movements (Haag et al. 2010). In *Drosophila*, halteres are not necessary for head movements. Specifically, head movements in haltereless flies are attenuated, particularly at higher speeds of visual motion (Mureli et al. 2017). Recent work suggests that behavioral nonlinear summation of visual and mechanosensory information underlies gaze control

via head movements (Rauscher and Fox 2021). These results suggest that sensory weighting and neural gating are candidate mechanisms for the nervous system of Dipterans to combine visual and mechanosensory information of different delays and information content. Further work is necessary to determine whether neural summation mechanisms acting in parallel closely predict behavioral output.

Multimodal integration for mid-level motor primitives

Motor primitives (a.k.a. movement primitives) are elementary building blocks of complex movement. Akin to how phonemes underlie speech, motor primitives (or “movemes”) (Del Vecchio et al. 2003) are fundamental units of locomotion which are modulated or arranged to form higher-order action (Giszter et al. 1993; Flash and Hochner 2005). Broadly defined, motor primitives are described across kinematic, kinetic, and/or neural levels of organization and stem from neural circuits and muscle synergies that underlie locomotion (Giszter 2015). Operating over mid-level spatiotemporal scales, motor primitives occur over several body lengths and seconds and are supported by rapid stabilization (Fig. 1A).

Neurosensory coordination of rhythmic motor primitives

Walking, crawling, swimming, pharyngeal pumping, and other rhythmic movements all constitute motor primitives, which are derived from the stereotyped, coordinated activation of muscles within the body. CPGs underlie rhythmic movement and can be derived from individual cells (e.g., cardiac pacemaker neurons); however, those underlying motor primitives often stem from repeating circuits of neural activation and the coordination of those circuits between body segments or limbs. Motor primitives depend on sensory detection and integration as different stimuli are known to initiate and help coordinate rhythmic movement (Dickinson et al. 2000). Specifically, the onset, timing, and spatial coordination of rhythmic movement can be guided by extrinsic sensory inputs, such as chemical, mechanical, and nociceptive cues (e.g., Ohyama et al. 2013; Sánchez-Alcañiz and Benton 2017) as well as by feedback derived from proprioception (Dickinson et al. 2000).

Proprioceptive feedback, in particular, is thought to play a critical role in executing motor primitives, as specialized proprioceptive neurons sense changes in force production created by movement and help

to coordinate rhythmic movement across the body (Dickinson et al. 2000; Borgmann et al. 2009; Tuthill and Wilson 2016). For example, in the walking stick *Carausius morosus*, proprioceptive signals generated from front-leg movement cause individual middle-leg and hind-leg CPG circuits to fire in phase. Further, disruption of phase symmetry by middle-leg manipulation suggests that interleg CPG coordination results from a combination of interleg and intraleg sensory feedback signals (Borgmann et al. 2009). Similarly, a role of proprioceptive feedback in motor primitives has been shown in the roundworm *Caenorhabditis elegans* and leech *Hirudo medicinalis*, indicating that rhythmic activation of proprioceptors helps to coordinate muscle contraction phase relationships that are critical for axial locomotion, such as crawling or swimming (Cang and Friesen 2000; Yeon et al. 2018).

Crawling in *Drosophila* larvae also requires the contraction and relaxation of adjacent body segments in a particular spatial and temporal order (Fushiki et al. 2016). As for other motor primitives, *Drosophila* achieve both forward and backward crawling through the timed activation of excitatory and inhibitory neurons within inter-segmental CPGs (Clark et al. 2018), signaling between those CPGs (Heckscher et al. 2012; Kohsaka et al. 2019), and coordination of those signals by proprioceptive feedback (Büschges 2005; Pehlevan et al. 2016; Vaadia et al. 2019). Although individual CPGs that underlie motor primitives can operate in the absence of sensory feedback, proprioceptive inputs are required for coordinated signaling between CPGs (Dickinson et al. 2000; Marder and Bucher 2001). The study of CPGs underlying rhythmic motor primitives has largely focused on how individual sensory modalities regulate behavior; however, CPGs are downstream of circuits that process sensory information from multiple different modalities. The role of multimodal integration combined with sensory feedback, on CPG coordination of motor primitives, remains far less understood.

Neural basis of multimodal integration in the *Drosophila* larval escape roll

One example of a rhythmic motor primitive that has been studied in the context of multimodal integration is the roll escape response in the *Drosophila* larva. Larval rolling behavior is one of multiple motor primitives (others include fast-crawling, backward crawling, and reversing) that a larva may perform as part of an escape response sequence (Ohyama et al. 2013; Eschbach and Zlatić 2020).

During rolling, larvae continuously rotate from side-to-side in a corkscrew-like pattern for 1–2 s at speeds of $3\text{--}5\text{ mm s}^{-1}$ (Tracey et al. 2003; Hwang et al. 2007; Ohyama et al. 2013). Strong nociceptive stimulation, such as harsh touch or noxious heat, typically leads to rolling followed by fast-crawling (Tracey et al. 2003; Hwang et al. 2007; Ohyama et al. 2013). Rolling is thought to be the most energetically costly motor primitive within the escape response sequence, and one that is reserved for situations of extreme danger, such as the threat of a parasitoid wasp attack. The wingbeat vibrations and sting of a wasp may stimulate nociceptive and mechanosensitive chordotonal neurons that tile the larva's body wall (Robertson et al. 2013; Zhang et al. 2013; Ohyama et al. 2015). Simultaneous low intensity nociceptive and mechanosensory stimulation leads to a nonlinear, superadditive enhancement in the probability of larval rolling behavior, in comparison to that evoked by either modality alone (Ohyama et al. 2015; Fig. 2, middle panel). Rolling in response to the synergistic presentation of multimodal cues mimicking the sensory experience associated with a life-threatening parasitoid attack may greatly benefit the chances of larval survival, making it harder for a wasp's ovipositor to penetrate the larva cuticle (Robertson et al. 2013; Zhang et al. 2013; Ohyama et al. 2015). How are nociceptive and mechanosensory neural pathways integrated to enable rapid detection of threatening stimuli and how do they, in turn, lead to rolling behavior?

In the *Drosophila* larva, the functional integration of mechanical and nociceptive cues in multimodal interneurons follows a similar synergistic relationship to that described at the behavioral level. Connectome reconstructions of the larval nervous system and calcium imaging experiments identified first-order interneurons in the ventral nerve cord that receive direct inputs from mechanical and nociceptive sensory neurons (Ohyama et al. 2015). A subset of these first-order interneurons responds to the combination of mechanical and nociceptive cues such that multimodal responses are significantly greater than the sum of unimodal responses, and nociceptive information is more highly weighted (Fig. 2, middle panel). Multimodal information represented in these interneurons, as well as second- and third-order interneurons that receive distinct combinations of mechanosensitive and nociceptive inputs, is eventually relayed to a command-like neuron called Goro (Ohyama et al. 2015; Jovanic et al. 2016; Eschbach and Zlatic 2020). Neural activation of Goro is

sufficient to trigger rolling behavior, suggesting that a CPG circuit that initiates rolling is likely downstream of this neuron (Ohyama et al. 2015). Overall, these results support a sensory weighting strategy of multimodal integration. Furthermore, forms of nonlinear summation, such as gating, cannot be ruled out as it remains to be tested whether activity above an activation threshold is required to elicit the multimodal response (Ohyama et al. 2015).

Larval rolling behavior is also mediated by multimodal noxious touch and light cues, which are integrated via a gating neural computation. At the sensory level, both of these cues activate overlapping sets of neurons that are a part of the neural pathway leading to rolling behavior. However, only strong noxious mechanosensitive cues evoke rolling, while noxious light stimulation leads to reorientation and photoavoidance behavior. The selection between these two behavioral response types is mediated by a neuromodulatory neuron that releases one neuropeptide (short Neuropeptide F) to gate noxious touch responses, and a different neuropeptide (Insulin-like peptide 7) to gate noxious light responses (Imambocus et al. 2020). Each neuropeptide activates distinct downstream circuitry to elicit either a rolling or photoavoidance escape response depending on the sensory input. Specifically, short Neuropeptide F released during noxious touch stimulation provides feedback onto the touch sensory neuron which in turn enables the roll response, while feedforward signaling to a downstream interneuron via Insulin-like peptide 7 elicits the photoavoidance response. Overall, studies of larval rolling behavior suggest that sensory weighting and synaptic gating computations are implemented in different multimodal sensory integration circuits underlying the selection and initiation of escape response motor primitives.

There are still many open questions about how multiple sensory circuits modulate the rhythmic oscillations of CPGs, such as those controlling larval rolling behavior. For example, is CPG onset dependent on a graded increase in multimodal inputs or is it an all-or-none event dependent on an activation threshold? How do the temporal sequence and varying intensities of multimodal inputs influence CPG activation? In what contexts do other forms of multimodal integration, such as suppression or association (Currier and Nagel 2018), underly the selection of motor primitives? These questions present an exciting avenue for future research on multimodal integration mediating action selection via motor primitives.

Multimodal integration for higher-order tasks

At the top of the hierarchy of locomotion control are higher-order processes that recruit from a library of motor primitives for actions such as finding a host, locating food, courtship, or migrating long distances. All these tasks take place in complex and dynamic environments with a wide range of information sources, creating unique challenges for multimodal information processing. Higher-order processes involve large temporal and spatial scales, spanning hours, days, and years, and hundreds to millions of body lengths (Fig. 1A).

Multimodal processing over long distances and timespans

Successful execution of long-distance locomotory behaviors requires individuals to continually integrate new sensory information because the very nature of locomotion in heterogeneous environments implies that sensory cues will change over time. Neural computations for higher order tasks must therefore enable versatility in the processing of and response to multimodal information over space and time. At this level, sensory weighting is likely to be dominated by the reliability of cues in space and time, as cues that persist in time and propagate further in space will be most salient. Furthermore, some cues may only be relevant at certain distances. For instance, in long-range mate attraction in insects, broadcast chemical cues may serve for initial detection and localization of mates, while courtship involves other, shorter-range modalities (Nakano et al. 2015). In addition, top-down processes, along with learned experiences, likely play a role in mediating higher-order tasks, requiring integrating multimodal information with memory, and cognitive reasoning centers. Because of the changing relevance of stimuli across different modalities as the animal nears its target, sensory gating is likely to be an important neural computation in higher-order tasks.

In insects, visual and olfactory modalities are highly salient for higher-order locomotory tasks as together they provide complementary long-range information. Depending on outdoor conditions, odor plumes can disperse over kilometers, providing rich spatial information about odor concentration (Murlis et al. 1992). Likewise, visual features and the horizon can be discerned over long distances by specialized compound eyes and ocelli, respectively, aiding in visually guided approach (Land and Nilsson 2012). Several lines of evidence point to gating of visual and olfactory information for

higher-order behaviors, and that these two modalities can influence each other. In fly flight, the mere presence of an odor source is not sufficient for successful odor source localization: for instance, flying *Drosophila* require visual feedback (Frye et al. 2003). Similarly, in *Drosophila*, the presence of vinegar odor increases the strength of the fly optomotor reflex by up to 40% via odor-activated octopaminergic neurons that innervate the visual system, leading to an increased calcium response in a neuron sensitive to yaw optic flow (Hx) (Wasserman et al. 2015). These findings are consistent with gating of vision by olfactory stimuli in *Drosophila*, although other modes of integration involving nonlinear summations cannot yet be ruled out. At the behavioral level, assays in butterflies (Yoshida et al. 2015) and bees (Kunze 2001) are suggestive of olfactory gating of visual stimuli. In female *Papilio xuthus* butterflies, the presence of orange and lily oils cause individuals to switch their naive color preference from blue flowers to red ones (Yoshida et al. 2015). In bumble bees (*Bombus terrestris*), the presence of an olfactory cue on artificial flowers improves discrimination between rewarding and nonrewarding artificial flowers on the basis of color (Kunze 2001). The improvement in color discrimination—stimulated only by the presence of a scent that gives no information about which stimuli are rewarding/unrewarding—suggests that olfactory cues at a minimum enhance attention to color differences, and may gate responses to visual stimuli. In these insects, visuo-olfactory integration appears to take place in the mushroom body (Strube-Bloss and Rössler 2018). Taken together, gating of visual and olfactory information likely plays a critical role in insect localization behavior, although further investigation of the neural mechanisms of these behaviors is needed to confirm the role of gating. In the next section, we highlight recent behavioral and neural evidence of multimodal integration for host-seeking in mosquitoes, an exemplar for how animals may integrate information across vast scales in space and time.

Visual, olfactory, and thermal integration for host-seeking behavior in mosquitoes

An example of higher-order locomotion that is but all too familiar is mosquito host-seeking behavior, which requires the integration of multimodal information at multiple spatiotemporal scales (Fig. 2, top panel). Host localization has been studied particularly intensively in *A. aegypti*, the vector for yellow fever in humans. Initial detection and orientation toward a human host can occur up to dozens of

meters away, whereas decisions about whether and where to land and initiate feeding take place within centimeters of the host (Bidlingmayer and Hem 1980; Zollner et al. 2004). Mosquitoes are sensitive to many host cues in several modalities (Bowen 1991; Gibson and Torr 1999), and the integration of these cues during host localization is largely a product of the distances at which they are detectable and provide useful information, which itself depends on propagation characteristics of each modality and the sensitivity of sensory receptors for each type of cue (Cardé and Gibson 2010). In general, olfactory cues from host exhaled CO₂ are detected at the greatest distances (dozens of meters) (Dekker and Cardé 2011), visual cues are used for host localization at intermediate ranges (5–15 m; Allan et al. 1987), and thermal, moisture, and other odor cues are used to select the final landing area (within centimeters; Burgess 1959; Dekker et al. 2001; Lacey et al. 2014).

Gating appears to be a key mechanism of multimodal integration in mosquitoes. While the specifics of the interactions between cues in different modalities are debated (Cardé 2015), in general gating follows the order in which stimuli are encountered. CO₂, in particular, has been shown to gate behavioral responses to visual, thermal (Kröber et al. 2010), and chemical (Dekker et al. 2005) cues that are typically encountered closer to the host (McMeniman et al. 2014; Van Breugel et al. 2015). However, evidence for CO₂ gating is not universal and some studies have reported no effects of CO₂ in response to visual (Liu and Vosshall 2019) or thermal stimuli (Van Breugel et al. 2015). Furthermore, even mosquitoes genetically engineered to be insensitive to CO₂ could still localize a host (McMeniman et al. 2014), suggesting that the effectiveness of CO₂ gating may be context-dependent (van Breugel et al. 2018) or determined by the experimental paradigm (Wynne et al. 2020). Many of the unimodal cues used by mosquitoes do not unambiguously identify an appropriate host, but combined cues are more reliable and receive a stronger response. Gating, therefore, appears to function in part to ensure correct host detection. Nevertheless, the sensory modalities have been argued to operate at least somewhat independently of each other, such that responses to unimodal stimuli still occur and may be sufficient for host finding when they can be reliably detected and localized (Van Breugel et al. 2015).

Most studies have examined multimodal integration at the behavioral level in mosquitoes, but a recent study demonstrated neural correlates of integration of olfactory and visual cues (Vinauger

et al. 2019). In mosquitoes genetically engineered to express the calcium indicator GCaMP6s in a broad class of neurons, the modulation of flight behavior by CO₂ exposure was mirrored in many cases by CO₂ modulation of the responses of neuropils in the lobula (a region of the optic lobe) toward the same visual stimuli. For those regions of the lobula that did experience a modulatory effect of CO₂, there was almost always increased neural activity, corresponding to the increased acceleration of flight seen at the behavioral level (Fig. 2, top panel). However, integration of these stimuli was asymmetric, meaning that there were no effects of exposure to visual stimuli on responses to CO₂ in the olfactory lobe. Thus, while much remains to be understood about the neural mechanisms of integration in mosquitoes, these findings accord with expectations based on the sequential nature in which stimuli are encountered by individuals as they navigate toward their host. One complication is that at very close range, mosquitoes no longer follow CO₂ plumes and instead are more attracted by other odors and cues from short-range signals (Lacey et al. 2014). Thus, it will be interesting to examine the mechanism by which these stimuli suppress both direct responses to CO₂ and potentially also the modulation of response to other stimulus modalities by CO₂. Mosquitoes are also likely to encounter stimuli with different temporal delays following initial host cue detection. In a behavioral assay, a brief exposure to CO₂ enhanced mosquito attraction to a visual stimulus for at least 20 s afterward (Van Breugel et al. 2015). Therefore, a promising future direction will be to examine the effects of timing of stimuli in different modalities on integration.

Conclusion

Here we presented a hypothesized hierarchy for how the brain may organize multimodal sensory information acting over different spatial and temporal scales to guide locomotion. While it is unclear if the brain truly operates in this manner (Fig. 1A), we can look to behavior as a readout to infer how the brain might be organized. Supporting this hierarchy, recent studies using unsupervised techniques to classify behavior in *Drosophila* have pointed to a hierarchical organization that acts over appreciable time scales (Berman et al. 2016). This organization may therefore provide important clues about how the brain controls movement.

In our review, we highlighted how summation and sensory weighting are used to integrate sensory information across multiple spatiotemporal scales to

guide invertebrate locomotion (Fig. 2). In flight, flies implement weighting and nonlinear summation to rapidly stabilize gaze via wing and head movements, respectively (Fig. 2, bottom). Similarly, roll escape behavior in *Drosophila* larva is mediated by sensory weighting reflected at both the neural and behavior level (Fig. 2, middle). Gating, in a way analogous to transistors, is one possible solution for combining sensory information that acts over different time and spatial scales. For instance, gating of visual cues by olfactory information plays a critical role in mosquito host-seeking behavior (Fig. 2, top). Indeed, nonlinear summation across space and time is an intrinsic property of a spiking neuron (Fig. 1B). However, in some invertebrates sensory information combines linearly to guide low- and high-level tasks (Roth et al. 2016; Rauscher and Fox 2021). Summation of sensory inputs at the behavioral level could manifest as linear—within a behaviorally relevant range—even though the underlying neural computations are not, although it remains unclear exactly how this process manifests in neural networks. An interesting avenue for future research will be to detail the trade-offs of different summation mechanisms for multimodal integration.

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