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Brain-wide representations of ongoing behavior: a universal principle?

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Recent neuronal activity recordings of unprecedented breadth and depth in worms, flies, and mice have uncovered a surprising common feature: brain-wide behavior-related signals. These signals pervade, and even dominate, neuronal populations thought to function primarily in sensory processing. Such convergent findings across organisms suggest that brain-wide representations of behavior might be a universal neuroscientific principle. What purpose(s) do these representations serve? Here we review these findings along with suggested functions, including sensory prediction, context-dependent sensory processing, and, perhaps most speculatively, distributed motor command generation. It appears that a large proportion of the brain's energy and coding capacity is used to represent ongoing behavior; understanding the function of these representations should therefore be a major goal in neuroscience research.

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Introduction

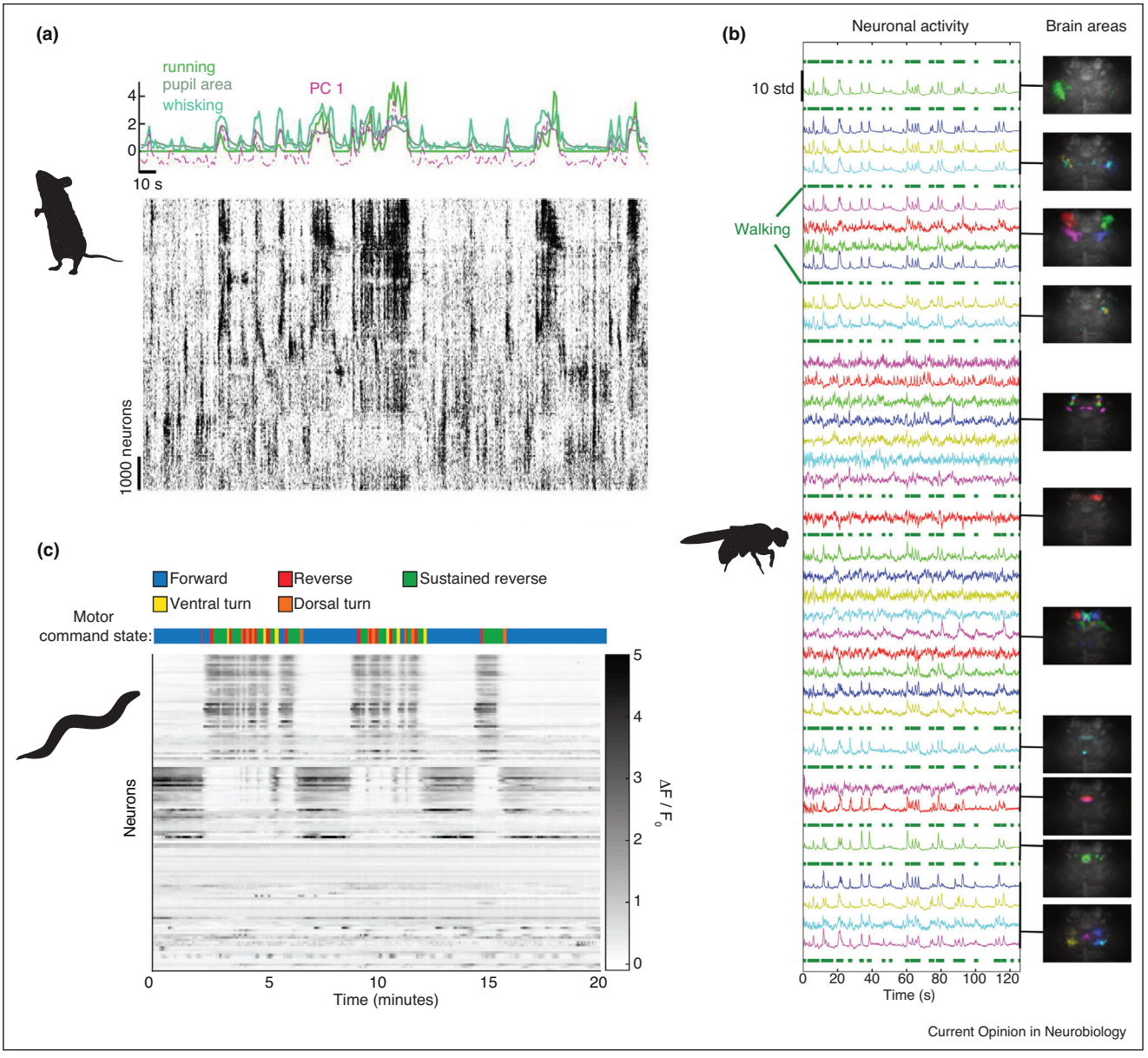
Recent advances in calcium imaging and electrophysiological techniques have enabled increasingly widespread high-resolution neuronal activity recordings, spanning much of a single brain area [1], several brain areas simultaneously [2–4], or even entire brains of smaller organisms [5–10]. One powerful approach is to use these techniques for a discovery-driven or data-driven, rather than hypothesis-driven, analysis of brain dynamics: we can ask, under a given set of conditions, what are the brain's major activities and computations? Thus far, the answer has been resoundingly clear, and surprising: signals primarily relate to the animal's own ongoing behavior [1–3,8,11]. This internal representation of behavior goes beyond simple behavioral state modulation. Instead, brain-wide behavior representations are both quantitative (co-varying with behavior in a graded continuous manner) and multi-dimensional (uniquely representing several aspects of behavior simultaneously). Here we summarize these cross-species findings and discuss potential functions. We are motivated by a few recent studies that examine brain-wide signals in mice [1–3], flies [8], and worms [11]. However, these studies are complemented by a larger body of work that examined the function of a few behavior-related signals in specific sensory brain regions (see Refs. [12,13] for more systematic reviews). Below, we synthesize this literature to discuss crucial questions regarding the source and function of brain-wide behavior-related signals. We expect the answers to be at least partly species-specific or modality-specific. Still, common principles may emerge from such a cross-species comparison.

Brain-wide representations of behavior across species

Three recent studies in mice [1–3] reported some of the largest-scale neuronal activity recordings to date. Using various techniques and experimental settings, the authors consistently found that a large proportion of brain activity correlates with the animal's ongoing behavior. This was the case in cortical (including primary sensory) as well as subcortical areas. Stringer *et al.* [1] reported strong neuronal activity relationships with spontaneous behavior either in the dark or during passive viewing of visual stimuli, using two techniques: single-cell resolution two-photon calcium imaging of excitatory V1 neurons, and neuropixel probes [4] in cortical and extra-cortical areas (Figure 1a). Musall *et al.* [2] and Salkoff *et al.* [3] reported widespread neuronal activity correlations to instructed and especially uninstructed movements during decision-making tasks; both studies used widefield calcium imaging in either excitatory only [2] or both excitatory and inhibitory neurons [3]. While the widefield imaging used in both studies [2,3] lacks single-cell resolution, Musall *et al.* [2] complemented these data with two-photon recordings of several areas as well as neuropixel probe recordings, both of which largely confirmed the findings from widefield imaging.

Earlier studies had reported behavior-related signals in primary sensory cortex (e.g. locomotion signals in visual cortex [14], discussed below), but these three studies [1–3] may portend a sea change in our understanding of the mouse brain, for at least two reasons. First, they show that

Figure 1



(a) In head-fixed mice running on an air-floating ball in the dark, visual cortex area 1 (V1) excitatory neurons show multi-dimensional activity patterns (bottom, GCaMP recording) that are coupled to multiple aspects of the animal's ongoing behavior (top, green traces). Purple trace shows neuronal activity projected onto principal component 1 (PC1). Adapted from Stringer *et al.* [1]. **(b)** Head-fixed flies alternated between running and resting periods on an air-floating ball. Left shows GCaMP activity traces extracted from brain regions with corresponding colors shown on the right. Repeated interspersed rows with green dashes indicate running periods, which correlated with activity increases in many brain areas. Adapted from Aimon *et al.* [8]. **(c)** Nervous-system-wide GCaMP recording in an immobilized *C. elegans* (bottom), with inferred motor command states (top) according to experiments analyzing several of the same neurons' activities in moving worms. A large fraction of neurons show tight relationships with the motor command state; inactive neurons consist primarily of sensory neurons. Figure adapted from Kaplan *et al.* [22]; motor command state inference described in Kato *et al.* [11].

many brain areas, including primary sensory areas, show signals related to several ongoing behaviors beyond locomotion. Different co-recorded behavioral measures (e.g. leg or orofacial movements) explained significant amounts of unique variance in neuronal activity, indicating that behavior-related signals did not reflect a few shared variables like arousal or locomotion. Second, these studies systematically characterized the surprising dominance of these signals: between 20 and 50 percent (depending on the metric used) of the explained variance in neuronal activity reflects ongoing behavior. This was the case across stimulus, task, and recording (imaging or electrophysiological) conditions.

For example, Stringer *et al.* [1] showed that in V1, motor information is represented at least as much as visual information during the display of natural images, and that these representations are often mixed in individual neurons. Another study by the same group found that during a visual discrimination task, action encoding is significantly more widespread than either stimulus or choice encoding, across cortical and subcortical brain areas recorded using neuropixel arrays [15]. In summary, whether the mouse is in the dark, passively viewing natural scenes, or engaged in a decision-making task, much of its brain activity is dynamically tracking various aspects of the state of its body (Figure 2a).

Surprisingly, recent work in invertebrates has come to similar conclusions: Aimon *et al.* [8] used light-field microscopy to record brain-wide calcium dynamics at high temporal resolution in head-fixed flies free to walk on a trackball (Figure 1b). The difference in brain activity between walking versus resting states was much more dramatic than activity changes induced by light or odor stimuli. Importantly, this held true in vision-impaired mutant animals, suggesting that these signals are not responses to visual feedback from the environment (e.g. trackball movement during running). Other studies in flies have shown multiple simultaneous representations of subjective heading direction [16–18]; this is also the case in mice [19], and in both species, this representation has been shown to depend partly on self-motion cues [16,19,20]. In *Caenorhabditis elegans*, recent studies [11,21,22] examined brain-wide dynamics at single-cell resolution, and found widespread brain activity representing various aspects of behavior beyond mere arousal states, including locomotion direction (forward or reverse), turning state, and locomotion speed (Figure 1c). As for flies and mammals, these studies accompanied a larger body of work showing locomotion signals in primary sensory circuits [23–26] (see Ref. [27] for a detailed discussion). Thus, as in mammals, brain-wide behavioral signals in worms pervade neuronal populations that, before these studies, were thought to be involved primarily in sensory processing. Further, brain-wide behavior-related dynamics persisted during sensory stimulation with only subtle modulations [11]. In all systems under study, these observations are only recently reported, and whether these results hold across more complex multisensory and unrestrained conditions remains to be shown. Importantly, brain-wide studies in zebrafish larvae do not report such brain-wide behavior-related signals; behavior signals rather appear more localized to the hindbrain [9,28,29] or in clusters in other regions [9], though most work has been limited to larval and largely immobilized animals. We therefore tentatively conclude that brain-wide encoding of ongoing behavioral variables may be a general principle of nervous systems across both invertebrates and vertebrates.

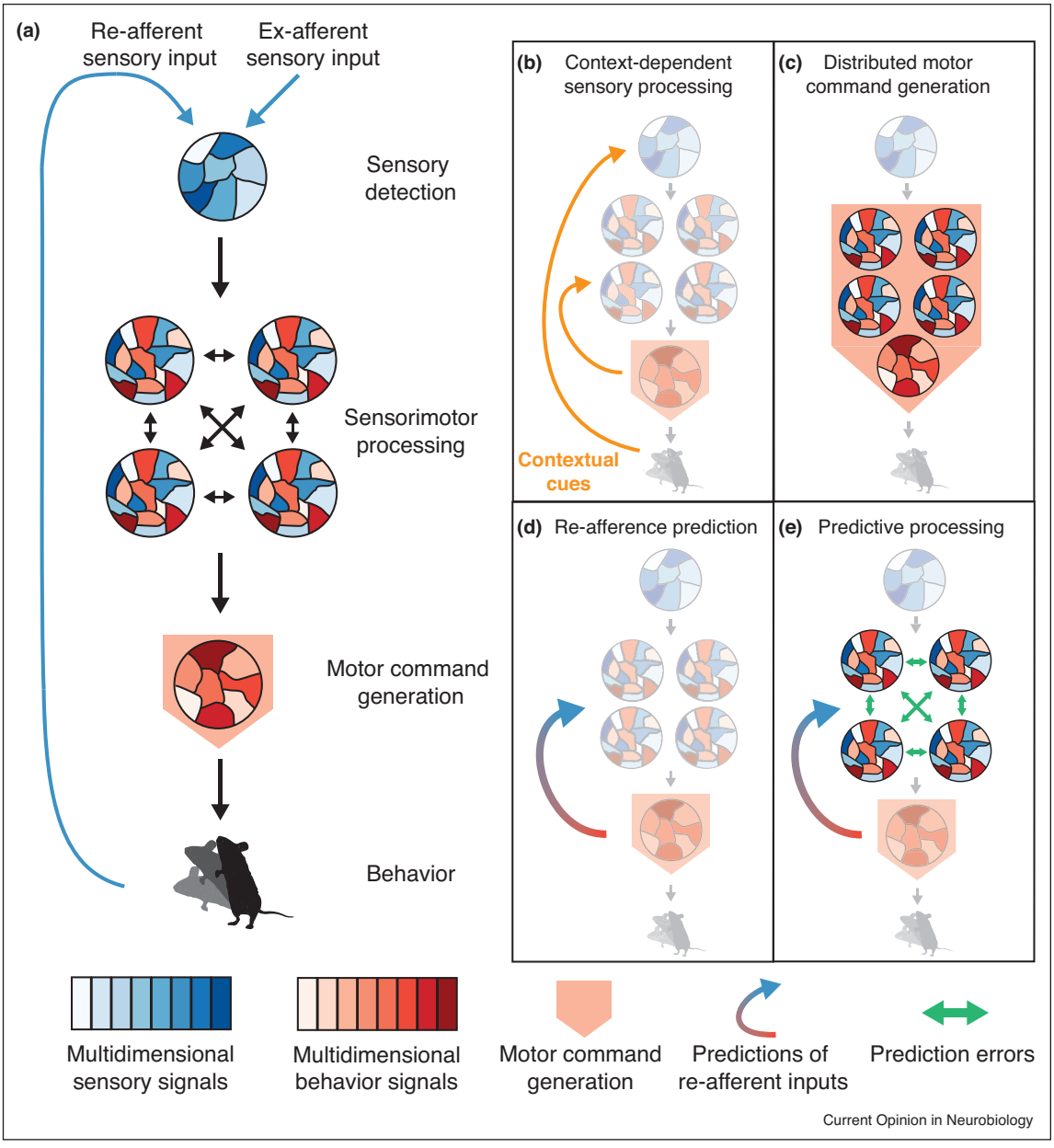
A natural next question is what functions brain-wide behavior-related signals might serve. A related question concerns the origin of these signals: do they correspond to re-afferent (i.e. self-generated) sensory inputs, efference copies of motor commands, or network states underlying distributed motor commands (see Box 1 'Looking ahead')? The brain-wide studies discussed above only provided speculation. In parallel work, however, several groups have been exploring these questions, and several hypotheses have emerged. Below, we discuss how these proposed functions might explain the multitude of recently discovered brain-wide behavior representations. Note that these hypotheses are not mutually exclusive, and that multiple functions may occur simultaneously.

Potential functions (i): context-dependent sensory processing

The processing of sensory input is well known to depend on behavioral state. For example, thresholds for response to sensory input are much higher during sleep versus wake states [30]. Within wake states, arousal level and attention strongly affect brain sensory responses, and perception [31,32]. These different signals can affect sensory processing as early as the sensory organ itself [33], so it is perhaps not surprising to find such modulation in early sensory areas. However, Stringer *et al.* [1] and Musall *et al.* [2] both showed that behavioral signals in primary visual cortex (and other areas) are multidimensional, that is, encoding multiple behavioral variables ranging from locomotion parameters to orofacial behaviors, indicating that much more than a simple arousal signal is encoded. Indeed, differential effects of arousal and locomotion on V1 activity have been dissociated [34,35]; note, however, that movement and arousal signals are interrelated and could affect sensory processing via the same neuromodulators, such as acetylcholine [36–38]. The multidimensional nature of behavior-related signals in mice [1–3] as well as worms [11] suggests a more complex role for behavioral context. Natural behavior involves a tight coupling of sensory and motor signals — consider a mouse whisking or sniffing, or a worm's sensory organs in the nose oscillating in space during its sinusoidal gait. The animal's own behavior strongly affects the spatiotemporal statistics of its sensory input (for example, see Wachowiak *et al.* [39], and Liu *et al.* [40]). A ubiquitous quantitative mixing of sensory and motor information might therefore be expected (Figure 2b).

In what ways could multidimensional behavior-related signals contextualize sensory processing? This has been most carefully investigated in mouse V1. Niell *et al.* and Fu *et al.* [14,36] provided evidence that locomotion controls the gain of sensory responses. This occurs via a disinhibitory circuit mechanism in which one interneuron class is activated by locomotion and then inhibits another interneuron class, ultimately disinhibiting principal excitatory neurons [36]. Further, another study showed that the effect of locomotion depends not only on cell type but

Figure 2



(a) A schematic summary of the findings reported by brain-wide studies [1–3,8,11]. Circles represent neuronal populations, which contain both sensory signals of different types (e.g. modalities), represented by different blue shadings, and behavior-related signals of different types, represented by different red shadings. In the intermediate step 'Sensorimotor processing,' sensory and behavior-related signals are mixed. The studies reviewed here showed that behavior-related signals are widespread and dominate brain activity in worms, flies, and mice, even in primary sensory areas. 'Sensory detection' may therefore refer only to sensory organs themselves, as downstream neuronal populations are dominated by signals related to behavior. Similarly, it is not clear precisely where in the nervous system the line should be drawn between 'sensorimotor processing' and 'motor command generation'. Note that a significant portion of brain activity may consist of signals that cannot be explained by either behavior or sensory input [86], which are not represented here. This schematic serves as the foundation for different models in panels **(b)–(e)**, which illustrate different potential functions for brain-wide behavior-related signals. (b) Model illustrating hypothesized function (i), which suggests that brain-wide behavior-related signals are important for contextualizing sensory processing. These contextual behavior signals (orange arrows) could originate from re-afferent sensory input (and therefore reach the nervous system via 'sensory detection') or from motor command copies sent back from regions that generate motor commands. (c) Model illustrating hypothesized function (ii), which suggests that brain-wide behavior-related signals reflect a distributed motor command network. In this model, motor commands are generated not by a small core neuronal circuit, but rather by many neurons spread throughout most brain regions, potentially including 'primary sensory' regions. (d) Model illustrating hypothesized function (iii), which suggests that brain-wide behavior-related signals are used to predict re-afferent sensory inputs resulting from behavior. Such predictions arise from motor command copies and must therefore be transformed from motor to sensory coordinates (arrow with red-blue gradient, indicating the transformation; see text). (e) Model illustrating hypothesized function (iv), in which

also on the type of visual input (e.g. stimulus size) [41]. Combining wide-field calcium imaging with electrophysiology, [35] showed that V1 neurons are more strongly coupled to local (i.e. intra-areal) versus distal circuits during running versus rest periods. Higher-level navigational variables can also have a surprisingly major impact on sensory processing: V1 neurons' visual responses were extremely sensitive to the animal's subjective encoding of its position [42]. This was also true in higher visual areas, and was enhanced during active navigation [43]. In auditory cortex, a variety of movements produced similar subthreshold membrane potential changes [44]. In flies, dopamine neurons' activities depend upon both sensory input and behavioral state (flailing or still), suggesting that the latter might provide a reinforcement signal [45,46]. In worms, behavioral responses to mechanosensory stimuli were transiently inhibited during turn events [47]; moreover, thermosensory responses of the AIY interneuron, unlike those of the upstream sensory neuron AFD, were restricted to episodes when animals crawled forward [48]. Both behaviors correspond to distinct brain-wide neuronal activity states [11]. Behavioral state could therefore affect sensory processing, and thus behavioral responses, in many different cell-type-specific, circuit-specific and stimulus-specific ways.

Potential functions (ii): distributed motor command generation

Could brain-wide behavior-related signals actually be involved in directly generating motor commands (Figure 2c)? This hypothesis is currently less developed and more speculative. We propose that brain-wide behavior-related signals might be driven neither by re-afference (i.e. self-generated sensory input) nor motor command copies generated in specific motor areas, but might rather be causal components of distributed motor command generation networks. In this framework, behavior is generated by brain-wide networks that include neurons in primary sensory areas; sensory input is then able to impinge upon and influence behavior generation at multiple points within this network. This is consistent with observations in *C. elegans* [11]. Remarkably, many *C. elegans* neurons that showed activity tightly correlated with specific behaviors in moving worms continued showing vigorous, coordinated dynamics in fully immobilized worms. Moreover, these dynamics showed strong between-neuron correlations, such that neurons active during the same behavior in moving worms were co-active in immobilized worm brain-wide recordings [11]. These coordinated dynamics were therefore interpreted as reflecting motor command signals: the worm was attempting to move forward, backward, or turn, even though it could not execute those behaviors [11,27]. These findings ruled out a role for re-afferent sensory input in the generation of the worm's brain-wide behavior-related dynamics.

If brain-wide behavior-related dynamics in *C. elegans* are not re-afferent responses, do they correspond to brain-wide motor command networks? Or do they instead reflect copies of motor commands generated by a small network, then broadcast ('copied') to the rest of the brain? While there is evidence for motor command copies in worms [48,49], Kato *et al.* [11] ruled out that brain-wide behavior-related signals result from one particular 'command neuron,' AVA. AVA had previously been considered the most crucial neuron for reversal command generation: consistently, AVA-killed or AVA-inhibited animals showed near-complete loss of reversal behaviors [11,50–54], and AVA stimulation reliably triggered reversals [26,55,56]. However, many neurons (along with AVA) showed activity tightly correlated with reversals in moving worms [11,25,26,57], suggesting that reversal motor commands could be generated by distributed neuronal population activity. Indeed, in AVA-inhibited animals, brain-wide dynamics including reversal motor commands persisted in the absence of reversal behaviors [11]: in immobilized animals, motor command signals resembled those in AVA-intact animals, with distinct, coordinated neuronal population activity patterns; in moving animals, reversal-active neurons continued showing activity, coincident with the worm stopping rather than reversing. These results confirmed that while AVA is required for reversal behavior execution (likely due to its major output to reversal-active motor neurons), it is not required for reversal motor command generation [11]. Therefore, if brain-wide reversal-related signals are motor command copies, they are not emanating from AVA.

Thus far, behavior-related signals in *C. elegans* appear tightly correlated with behavioral execution or the corresponding motor command [11,23], and many of these neurons have reliable behavioral effects when manipulated [55,56,58]. Analogous to the observations in mice, behavioral representations in worms extended to interneurons previously implicated in primary sensory processing [11]. In such a recurrent network, the distinction between motor command generation versus copy may be diffused and thus difficult or impossible to disentangle. This is because both the neurons that generate motor commands as well as those that receive motor command copies should both causally influence behavior [40,48,49,58]. For example, one recent study indicates that a motor command copy sent to AIY feeds

brain-wide behavior-related signals represent internal models and their predictions, used for comparison with sensory input to update the internal model. Unlike function (iii), predictive processing proposes that neuronal processing consists primarily of internal model generation and updating, such that projections between brain regions carry mostly prediction and prediction error signals. Note that the models in (b)–(e) are not mutually exclusive.

Box 1 Looking ahead: which experiments will be informative?

Going forward, what types of experiments might prove useful to dissociate potential functions for brain-wide behavior-related signals? We are inspired by two particular approaches in previous work. First, experiments can be designed to dissociate different types of behavioral signals (such as locomotion and arousal [34]) and their effects. For this, careful recording and quantification of behavior is required [74,75]; the conclusions made by Stringer *et al.*, Musall *et al.* and Salkoff *et al.* [1–3] depended on detailed co-recording and quantification of several behaviors. Second, certain experiments can determine whether behavior-related signals come from feedback from behavior itself (re-afference such as proprioception) or from motor command signals (such as motor command generation or copies). This is a crucial question that can help disentangle the potential functions (Figure 2); for example, behavior-related signals may in fact result from sensory signals such as proprioception, which would only be consistent with function (i) (Figure 2b). To distinguish potential sources of behavior-related signals, experiments can be designed to uncouple motor commands from the corresponding (and typically tightly coupled) behavioral execution. One study achieved this in mice by carefully tuning the optogenetic stimulation of a midbrain locomotory region to subthreshold levels, such that behavior was not induced, but locomotion-associated changes in visual responses in V1 did occur [76]. These changes therefore result from a motor command copy signal rather than from re-afferent sensory input. That experiment was inspired by work on visual attention in monkeys, where subthreshold micro-stimulation dissociated attentional effects on receptive fields from eye movements [77]. In cases where subthreshold stimulation isn't feasible, motor-to-sensory pathways that send motor command copies could be identified using a combination of projection tracing, optogenetic, and neuronal recording techniques [36,44,78]. Careful experimental design and behavior monitoring could also provide important insight: for example, widespread behavior-related neuronal activity may occur before movement onset, indicating that these signals do not come from sensory re-afference [15]. In invertebrates, motor commands and behavior might be more easily be dissociated. For example, Kato *et al.* [11] demonstrated that in *C. elegans*, several neurons showing activity tightly coupled to particular behaviors in moving animals also show dynamic activity in immobilized (but not anesthetized) animals. Importantly, these dynamics were coordinated across neurons as expected by their behavioral correlations — that is, neuron classes that were active (or suppressed) during reversal behaviors were all co-active (or co-suppressed) in immobilized worm recordings. Dynamic changes in these neurons' coordinated patterns suggested that the immobilized worm dynamically generates the corresponding motor commands, indicating that they can be decoupled from movement. Because the worm has several sources of proprioceptive information [79,80], dissociating re-afference from motor commands was crucial. Finally, prediction error signals (functions iii and iv) can be probed using virtual reality environments allowing quantitative manipulation of sensory-motor coupling [70,81].

back to maintain the motor command and thereby the corresponding action in spite of fluctuating sensory inputs transmitted to AIY [48]. It is thus crucial to carefully define 'motor command'; we propose that a motor command signal should directly instruct specific actions and an immediate attempt of their execution by motor neurons and muscles. In a different example, a visual processing area in zebrafish, the tectum, showed spontaneous neuronal assembly activity in the dark or even in the absence of eyes [59,60]. This activity was correlated with (and precedes) tail movements, but not for all tail movements. This suggests that these neurons represent one of several potential drivers of behavior; whether these signals do indeed reflect motor commands generated within a sensory processing area, rather than one of many sources contributing to a downstream motor command network, remains to be shown. In mice, there is evidence that somatosensory cortex can directly drive whisker movements [61] and locomotion [62], independent of motor cortex. While it seems unlikely that behavior-related signals in V1 directly drive locomotion or whisking, visual input is expected to affect behavior at some point in the cortical hierarchy. Whether this indeed happens as early as V1 for at least some behaviors (e.g. eye movements) could be tested; for example, tools for activity-guided holographic stimulation [63] could be used to drive activity in subsets of neurons that are active during particular behaviors.

Potential functions (iii): re-afference prediction

It has long been appreciated that a substantial portion of sensory inputs result directly from the animal's own behavior [64]. Importantly, such re-afferent inputs can be predicted quantitatively, based on the motor command signal (i.e. a left turn of your head will generate right-ward motion of your visual field). There is accumulating evidence from several species that the brain indeed makes such predictions, and uses them in various ways (Figure 2d; see Ref. [65] for a thorough review of older literature). Walking signals in flies [66] and mice [67] as well as flight saccades in flies [68] provide quantitatively precise information to sensory processing areas in order to cancel self-generated input, thus extracting the contributions of ex-afferent, that is, external, inputs for perception. In crickets, motor command copies of singing behavior retune the sensitivity and prevent saturation of central auditory pathways [69]. Specific neurons in zebrafish report mismatches between expected and produced visual feedback, in order to detect when the fish's motor command is unsuccessful, and thus induce an energy-saving passive behavioral state [70]. Could brain-wide behavior-related signals represent predictions of sensory input, which might be used in any of these ways? It is noteworthy that behavior-related signals in V1 persist even in prolonged darkness, when there is no visual feedback to be predicted [1]. Still, the mouse may keep track of the predicted effects of its own movement, for example, for navigational purposes [42], even without immediate visual re-afference. Quantitative, multidimensional, and widespread behavior-related signals could indeed make for sophisticated predictions of re-afferent input. If this is the case, the cross-modal nature of brain-wide behavior-related signals is particularly puzzling: why are visual areas like V1 modulated by behaviors like whisking or leg movements, which may produce tactile but not visual re-afferent signals?

Potential functions (iv): predictive processing

The brain may not only predict re-afferent input, but also ex-afferent (i.e. non-self-generated) input [71,72]. In a growing body of theoretical and experimental work (recently summarized by Keller and Mrsic-Flogel [73]), the mammalian cortex is proposed to make such large-scale predictions, in the form of generative internal models of the world, including body and environment. Sensory input is then processed in the context of these internal models — that is, sensory signals are used to update the internal model when its predictions do not agree with sensory inputs. The role of sensory cortex is therefore to compare expected and actual sensory input, according to the theory.

How does predictive processing differ from re-afferent prediction (discussed in the previous section)? Keller and Mrsic-Flogel [73] proposed that predictive processing is an alternative to the classical 'representational framework' of cortical function, in which the brain processes sensory signals into progressively more sophisticated and higher-level representations of the outside world. Re-afference prediction (Function (iii)), as well as contextualization of sensory input (Function (i)), could occur within such a representational framework: bottom-up sensory input could be modulated in many ways before being passed on for computations underlying higher-order representations. In contrast, in a predictive processing framework (function (iv), bottom-up input will only be passed on to other brain regions if it is found to disagree with the internal model [73]. In this case, communication between brain regions consists primarily of prediction or prediction error signals, and computations involve comparisons between those signals, or internal model updating, rather than feature extraction for increasingly specific representations [73].

If predictive processing is indeed a canonical computation, brain-wide behavior-related signals could represent internal model information (or predictions from those models) broadcast to sensory areas to enable the comparison of expected and actual sensory input. This requires a transformation of motor commands from motor coordinates (e.g. specifying head movement parameters) into sensory coordinates (e.g. wide-field motion signals expected from such head movements) [73]. The widespread signals recently reported in worms and mice showed clear quantitative relationships to behavioral variables; would such signals be so strongly correlated with behavior if they are meant to be predictions in sensory coordinates? Or are these the signals before transformation into sensory coordinates? Finally, Keller and Mrsic-Flogel [73] discussed predictive processing as the role of the cortex; however, motor command copies have been repeatedly demonstrated in invertebrates (see above section), which also show brain-wide behavior-related signals. Could re-afference prediction be an evolutionary precursor to generative models and predictive processing? While predictive processing could be a unifying framework for cortical function, these questions could aid our understanding of brain-wide behavior-related signals more generally.

Conclusions

The preponderance of behavior-related neuronal activity in both vertebrates and invertebrates suggests a fundamental role. Above, we described a few prominent hypotheses and discussed experiments that could distinguish them (see Box 1 'Looking ahead'). We conclude with three thoughts to encourage further discussion. First, examining these data in *C. elegans*, we have wondered why the brain would use so many neurons to seemingly redundantly encode the same information. Referring to the connectome, we observed that neurons showing similar behavior-related signals nevertheless often have very different connectivity, including both inputs and outputs. These neurons could therefore serve as alternative channels for differentially mixing sensory information with ongoing behavior signals, perhaps to ultimately affect motor command generation (function ii) [27]. Indeed, Stringer *et al.* [1] showed that such mixing of sensory and motor information in individual neurons is ubiquitous in V1. Second, the majority of neuronal activity recordings, especially those measuring brain-wide signals, are performed in at least somewhat restrained settings (e.g. head fixation in mice). It is important to consider how these and other experimental settings, such as non-naturalistic and open-loop stimuli, might affect the results [82]. Several studies have indicated the potential importance of motor error signals [70,73]; the failure of head movement motor commands in head-fixed animals could massively engage such error detectors. Further, eye and head movements are typically closely coupled in freely moving mice [83]; disruption of this coupling during head fixation could have a major effect on behavior and neuronal activity. This brings us to our third and final point: behavioral coordination, such as eye and head movement coupling, is far from atypical. Rather, behaviors exhibit complex multi-scale spatial and temporal organization [75], for example, in the form of probabilistic sequences [84] or hierarchies [85]. These interdependencies could have structure that eludes the aforementioned unique neuronal activity variance measures. Brain-wide behavior-related signals should reflect the organizations and interdependencies of behavior. Indeed, we found this to be the case in *C. elegans*: (1) brain-wide dynamics relating to various behaviors are tied together in specific sequences, reflecting the animal's action sequence [11], and (2) interactions between global and local neuronal dynamics implement a multi-scale behavioral hierarchy [22]. Crucially, our understanding of the worm's behavior focused our attention on important neuronal activity relationships that might otherwise have been overlooked. We therefore suggest that better descriptions of the rules governing animal behavior are likely to aid our understanding of the associated brain-wide neuronal activity

patterns. These organizational rules likely also have a major impact on the processing of sensory input, especially if they pervade neuronal activity patterns in sensory processing circuits.

Conflict of interest statement

Nothing declared.

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