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Neuronal microcircuits for decision making in *C. elegans*

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Abstract

The simplicity and genetic tractability of the nervous system of the nematode *Caenorhabditis elegans* make it an attractive system in which to seek biological mechanisms of decision making. Although work in this area remains at an early stage, four basic types paradigms of behavioral choice, a simple form of decision making, have now been demonstrated in *C. elegans*. A recent series of pioneering studies, combining genetics and molecular biology with new techniques such as microfluidics and calcium imaging in freely moving animals, has begun to elucidate the neuronal mechanisms underlying behavioral choice. The new research has focussed on choice behaviors in the context of habitat and resource localization, for which the neuronal circuit has been identified. Three main circuit motifs for behavioral choice have been identified. One motif is based mainly on changes in the strength of synaptic connections whereas the other two motifs are based on changes in the basal activity of an interneuron and the sensory neuron to which it is electrically coupled. Peptide signaling seems to play a prominent role in all three motifs, and it may be a general rule that concentrations of various peptides encode the internal states that influence behavioral decisions in *C. elegans*.

Introduction

One of the primary functions of the nervous system is to make decisions that maximize evolutionary fitness in an unpredictable world. Neurobiologists investigate the neuronal mechanisms of decision making at two main levels of complexity. The simpler level, which may be called *behavioral choice* [1], mainly concerns the proximal causes of selecting between alternative sensory cues or behaviors. A typical experiment at this level seeks to identify the states of the nervous system that predict which of two or more mutually exclusive behaviors will be activated on each trial in a series of identical stimuli. The more complex level, which has been termed *value-based decision making* [2], examines not only proximal causes, but ultimate causes as well. Here, experimental conditions are arranged so that the subject's prior assessment of the relative benefits of distinct choices can be manipulated experimentally. At the neuronal level, researchers seek to understand how benefits are represented by the nervous system, and how these representations are integrated with the proximal causes of the selection between alternatives. In one simple scenario, the proximal causes of behavioral choice are the neuronal building blocks of value-based decision making. To the extent that this is so, the former serves as an important experimental model for the latter.

Historically, the neuronal analysis of decision making has emphasized humans and nonhuman primates. However, because of the difficulty of accurately manipulating the activity of functionally specific neuronal subpopulations in awake, behaving subjects, it has so far been easier to establish the neuronal correlates of decision making than its neuronal

causes. Clearly, progress toward a biological theory of decision making would be accelerated by a complementary approach that studies decision making in organisms that can be genetically engineered (nematode, fruit fly, zebrafish, mouse). Such organisms are unusually amenable to optogenetic methods for activating and inactivating subpopulations of neurons, which is one of the most efficient ways to demonstrate that a particular neuronal event is necessary and sufficient for decision making. For this reason, engineerable organisms are now being used at an increasing rate in studies of decision making [3,4].

The nematode *Caenorhabditis elegans* is an attractive system in which to seek biological mechanisms of decision making. Like other members of its genus, it is a so-called fruit nematode, which forages for capricious blooms of bacteria in rotting fruits, flowers, and stems [5]. Its tiny nervous system, with only 302 neurons, has been anatomically reconstructed almost completely at the ultrastructural level, yielding the celebrated ‘wiring diagram of the worm’ [6,7]. The well-known genetic tractability of *C. elegans*, together with technical advances in basic nematode neurophysiology — including patch clamp electrophysiology [8], calcium imaging [9], and optical control of neuronal and muscular activity [10–12] — is accelerating the pace of research into the neuronal basis of behavior in this organism. More recently, opto-mechanical systems have been developed that enable recordings from *C. elegans* neurons in freely moving animals engaged in natural behaviors [13•,14,15,16•]. Additionally, *C. elegans* uses many of the same neurotransmitters and neuromodulators as higher organisms, including dopamine and serotonin, which are involved in signaling positive and negative rewards in primate decision making [17,18]. Thus, *C. elegans* is well suited for the identification of genetic, synaptic, and network-level causes of action selection that may underlie decision making in more complex organisms.

Behavioral repertoire

The numerical simplicity of the *C. elegans* nervous system belies a sophisticated behavioral repertoire that continues to expand as researchers probe deeper into the behavioral abilities of this species. Currently, *C. elegans* behavior can be organized according to three broad functional categories (Table 1). The first is *housekeeping behavior*, which is concerned primarily with feeding and reproduction. The second category is *escape behavior*, which comprises short latency (< 1 s) withdrawal responses triggered by stimuli such as touch, vibration, noxious compounds, or extremes of osmolarity, heat, and light. The third category we shall refer to as *habitat and resource localization*. This category comprises a variety of spatial orientation behaviors that enable *C. elegans* to migrate into, or away from, hospitable or inhospitable environments, respectively, and to obtain consumable goods such as food and mating partners (males only). Habitat localization is accomplished mainly by approaching preferred temperatures and concentrations of oxygen, and by avoiding inhospitable levels of them; avoidance of carbon dioxide also plays a role [19]. Resource localization is accomplished mainly by approaching the sources of tastes, odors, and temperatures previously associated with food. Localization behavior is the most diverse category, consistent with the fact that *C. elegans* is a foraging species occupying a niche in which both habitat, and resources are believed to be patchy, transient, and unpredictable.

Several forms of learning have been demonstrated across the spectrum of *C. elegans* behaviors [20], and these play an important role in several types of choice behavior. Whereas housekeeping behaviors appear to be hardwired for the most part, escape reflexes exhibit nonassociative learning, which in some cases can be associated with the broader sensory context. Localization behaviors exhibit clear and robust forms of associative learning. These range from associations between food (or its absence) and environmental conditions such as temperature, odors, and salt concentration, to the ability to associate the

odors of different foods with food quality, ease of ingestion and, in the case of pathogenic bacteria, toxicity [21,22•].

Experimental paradigms of behavioral choice

Behavioral paradigms for investigating the proximal causes of behavioral choice vary widely in complexity. However, the simplest among them can be arranged in a two-by-two matrix (Figure 1a–d) according to the number of sensory stimuli manipulated in the experiment (S_1 , S_2) and the number of mutually exclusive behaviors (B_1 , B_2) that are monitored. All four types of choice behavior have been demonstrated in *C. elegans*.

One stimulus, one behavior (Figure 1a). This type of experiment is exemplified by what we shall refer to as *go, no-go* behaviors in which the choice is between action versus inaction. Escape reflexes comprise one broad class of behavior that fit this structure. In the example shown, the worm withdraws from an annulus on the substrate containing a toxic ion such as Cu^{2+} [23••]. Other examples include withdrawal from regions of high osmolarity [24] or from mechanical stimulation of the head or tail [25].

One stimulus, two behaviors (Figure 1b). This type of experiment is exemplified by what we shall refer to as a *behavioral competition*, in which a worm is presented with a stimulus that can be approached or avoided. In the example shown, the relative likelihoods of approach and avoidance are modified by associative conditioning in which an initially attractive taste is paired with the absence of food [26]; pairing an attractive odor with the absence of food can have a similar effect [27,28]. Another example of behavioral competition is the tendency to leave a patch of food before it is exhausted, which may have theoretical connections with so-called exploration–exploitation decisions [29,30].

Two stimuli, one behavior (Figure 1c). This type of experiment is exemplified by what we shall refer to as *stimulus competition*, in which the worm is presented with a choice between two attractive stimuli. The example shown is dietary choice [21,31], in which juvenile worms are cultivated in the presence of two types of edible bacteria. Over time, they learn to prefer the type that is easier to eat and better supports growth. Other examples include the choice between benign and pathogenic food [22•] (also known as bait shyness or the Garcia effect), contrasts between attractive odorants [32], and opposing chemical and thermal gradients [33].

Two stimuli, two behaviors (Figure 1d). This type of experiment is exemplified by what we shall refer to as *stimulus and behavioral competition*, in which worms are simultaneously presented with aversive and attractive stimuli, which elicit competing behaviors. In the example shown [23••], worms were placed on the low concentration side of an attractive chemical gradient and had to cross a stripe of a toxic compound to reach the source of the odor. Standardized conditions were found in which wild type worms chose to cross the stripe to reach the source of the attractant. However, a genetic screen for decision making mutants revealed a simple control mechanism that induces worms to resist the allure of the odor and to avoid the stripe. As discussed below, the molecular mechanism of this decision suggests that it could be operating under normal conditions in individual wild type worms.

The logic of behavioral choice

Each behavioral choice paradigm constitutes a distinct switching logic, as indicated by the circuit diagrams in Figure 1. The simplest case is that of the *go, no-go* behaviors (Figure 1a), in which the presence or absence of the behavior under investigation (B) is dictated by the presence or absence of the stimulus (S) and the internal state of the animal. Internal state regulates the disposition of a simple single-pole/single-throw switch that puts the animal in a

permissive or nonpermissive state for escape behavior. Behavioral competition and stimulus competition require a single-pole/double-throw switch (Figure 1b,c), whereas stimulus and behavioral competition, when studied together, require a double-pole/double-throw switch. The circuit diagrams are intended as a compact representation of phenomenology of each paradigm, rather than as models of the underlying neuronal mechanisms.

Behavioral strategies for habitat and resource localization

Each of the three more complex behavioral choice paradigms investigated to date in *C. elegans* is an instance of habitat and resource localization (Table 1). *C. elegans* localizes resources utilizing three main behavioral strategies that are common across the animal kingdom [34]: orthokinesis, klinokinesis, and klinotaxis. In orthokinesis, locomotion slows when the animal encounters the habitat or resource, which results in accumulation at the population level, by analogy to a traffic jam. Klinokinesis involves a biased random walk up (or down) a stimulus gradient [35–37]. In klinotaxis, the animal's course is continuously corrected toward the line of steepest ascent (or descent) within the gradient [38,39]. Klinokinesis and klinotaxis were first demonstrated in *C. elegans* by tracking worms crawling in continuous stimulus gradients [37,38]. However, further research has shown that both strategies are also effective in the case of discontinuous or step-like gradients, such as the sharp odor gradients that might be encountered at the margin of a food patch, or the oxygen gradients encountered at the edge of a cluster of worms [40–42]. Klinokinesis and klinotaxis are equally valid starting points for analysis of behavioral choice. However, a prerequisite for investigating the neuronal basis of behavior choice is a detailed understanding of the underlying circuitry. As the neuronal circuitry has been described more completely for klinokinesis than for the other two strategies, we shall focus primarily on this behavior.

Klinokinesis

In the laboratory, *C. elegans* localization behaviors are mainly studied on the surface of an agar-filled plate where locomotory thrust is generated by snake-like undulations. These undulations occur in the dorso-ventral plane because worms crawl on their sides. Locomotion in *C. elegans* is dominated by periods of relatively straight forward movement, called *runs* [37,43], which are punctuated about twice a minute by turning events capable of significantly reorienting the worm. Each event involves a stereotypical sequence of actions: cessation of forward movement, a brief period of reverse locomotion (~2 s in duration), and resumption of forward locomotion that usually coincides with a deep body bend that alters the animal's course. Bouts of turns in close temporal succession are called *pirouettes* or instances of *dwelling*, depending on experimental context [37,43].

The behavioral algorithm underlying *C. elegans* klinokinesis has been identified [36,37]. Dwell times in forward and reverse locomotory states are exponentially distributed [44,45], indicating that *C. elegans* locomotion is fundamentally stochastic, and this stochasticity is the foundation for all large-scale search behaviors in *C. elegans*. In an isotropic environment, the probability of switching between forward and reverse locomotion (or conversely), and thus the likelihood of initiating a run or a reorienting turn, is fixed at a baseline level. When a worm is moving through a stimulus gradient, however, it experiences a changing stimulus environment and switching probabilities are modulated by the apparent rate of change of the stimulus, $dS(t)/dt$. When the animal happens to be going up a gradient of an attractant ($dS(t)/dt > 0$), turns become less probable whereas runs become more probable [37], thereby extending movement in that direction. In contrast, when the animal happens to be going down a gradient of attractant ($dS(t)/dt < 0$), turns become more probable whereas runs become less probable [37], thereby limiting movement in that

direction. Together, these two modulations form the basis of the approach behaviors illustrated in Figure 1. A converse pair of modulations of turn and run probabilities occurs when worms are moving in a gradient of repellent, and these modulations are the basis for avoidance behaviors (Figure 1). Turns are also suppressed and facilitated, respectively, as the worm enters or leaves a patch of food or high-quality habitat [42]. A behavior similar to klinokinesis, called area-restricted search [46], can be induced experimentally by removing a worm from a food patch and placing it on a foodless plate. Thus, klinokinesis is an all-purpose strategy for localizing resources in *C. elegans*.

The neuronal circuit for klinokinesis

The neuronal circuitry that implements *C. elegans* klinokinesis algorithm has been described in draft form [45,47–51]. It can be summarized as a cascade of four subcircuits composed of, respectively, sensory neurons and their electrically coupled interneurons, sensory interneurons, pre-motor interneurons, and motor neurons (Figure 2). Synaptic transmission is likely to be graded for the most part in *C. elegans* [52•,53] and thus interactions between subcircuits may have a substantial tonic component. However, in some *C. elegans* neurons, we have observed small-amplitude voltage fluctuations with a stereotyped, action potential-like waveform (Figure 3). The all-or-none character of these events, known in other contexts as spikelets [54,55], suggests that information might be transmitted between neurons in a more discrete form in some cases. Spikelets could also contribute to long-distance signaling which might be required in command neurons (see below) because their axons run the length of the animal (1 mm; [7]).

Sensory neurons

To a first approximation, sensory processing follows a labeled line scheme, with particular classes of sensory neurons being dedicated to stimulus modalities such as taste, olfaction, temperature, partial pressure of gases such as oxygen and carbon dioxide, and pheromones. Certain exceptions to this scheme have been identified [56–58]. Most *C. elegans* sensory neurons appear to function mainly as either ON cells or OFF cells, which are activated by increases or decreases in stimulus strength, respectively. Some sensory neurons are coupled by gap junctions to hub-like interneurons that receive gap junctions from other sensory neurons, including those that represent a variety of stimulus modalities [59••,60]; these interneurons may serve the purpose of reporting to downstream neurons an averaged, multimodal assessment of the local environment, and have been found to play a role in behavioral choice. Sensory neurons project mainly to sensory interneurons.

Sensory interneurons

Ablation of sensory interneurons indicates that they fall into two main classes, run interneurons that promote run behavior at the expense of reorienting turns, and turn interneurons that promote reorienting turns at the expense of runs. Anatomical reconstructions imply that labeled sensory information is likely to be lost at this stage of processing. Sensory interneurons project to other sensory interneurons and to command neurons.

Command neurons

There are two distinct pools of pre-motor interneurons, commonly referred to as ‘command neurons’ in the *C. elegans* literature. Using optical recordings in moving animals and neuronal ablations [13••,15,16•,25,51,61–63], researchers have shown that one pool of command neurons is mainly devoted to forward locomotion whereas the other pool is mainly devoted to reverse locomotion (the first phase of a reorienting turn). Anatomical reconstructions indicate that the two pools are heavily interconnected, and it has been

proposed that these connections are inhibitory such that the command neuron subcircuit functions as a bi-stable switch to regulate the direction of locomotion [51]. In support of this model, calcium imaging from restrained and freely moving animals indicates that forward command neurons are specifically activated during forward locomotion whereas reverse command neurons are specifically activated during reverse locomotion. Genetic manipulation of the membrane potential of command neurons, or of presumptive tonic synaptic input to them [51], indicates that the frequency of transitions between forward and reverse locomotion may be correlated with depolarization and anticorrelated with hyperpolarization of command neurons. It seems likely, therefore that sensory interneurons could promote turns and runs by regulating the membrane potential of the command neurons.

Motor neurons

The motor neurons required for generating locomotory thrust are distributed along the length of the animal and innervate local regions of dorsal and ventral longitudinal musculature of the body wall. The command neurons connect to motor neurons via long processes that project along anterior–posterior axis of the worm. Neuronal ablations and anatomical reconstructions indicate that there are distinct pools of excitatory motor neurons for forward and reverse locomotion. Calcium imaging from motor neurons in slowed or freely moving worms shows that dorsal and ventral motor neurons are rhythmically excited, respectively, during dorsal and ventral contraction, as would be expected of motor neurons that produce undulatory locomotion [13•,16•]. Surprisingly, however, this rhythm persists in reverse motor neurons during forward locomotion, and forward motor neurons during reverse locomotion, suggesting that the functional distinction between forward and reverse motor neurons may not be absolute. The excitatory motor neurons receive chemical and gap-junction inputs from the command neurons. Importantly, forward and reverse command neurons project overwhelmingly to forward and reverse motor neurons, respectively [7]. This pattern of connectivity is the basis of a model in which forward locomotion results when tonic activation of the forward command neurons specifically depolarizes the forward motor neurons, whereas reverse locomotion results when tonic activation of the reverse command neurons specifically depolarize the reverse motor neurons. This model recently received support from calcium imaging of motor neurons in restrained and slowly moving worms [16•,64], which showed that during forward locomotion, activation of the forward motor neurons was greater than activation of the reverse motor neurons, whereas during reverse locomotion the opposite pattern was established. During locomotory pauses, by contrast, activation of the two pools of command neurons was approximately equal. Together, these results suggest that the direction of locomotion is governed by a simple code that depends on the relative mean level of activation of the forward and reverse motor neuron pools.

The neuronal basis of klinokinesis

The characteristic functions of the four subcircuits involved in klinokinesis provide a model of how klinokinesis occurs at the neuronal level. In the case of localizing a resource, for example, sensory neurons that function as ON cells are activated when the animal is moving up the gradient, whereas sensory neurons that function as OFF cells are activated when the animal is moving down the gradient. Thus, the behaviorally effective conditions are not the presence or absence of stimulation but changes in stimulus strength. ON cells excite chemosensory interneurons in the run pool, which depolarize forward command neurons to increase the probability of runs at the expense of turns. Conversely, OFF cells excite chemosensory interneurons in the turn pool, which depolarize reverse command neurons to increase the probability of turns at the expense of runs.

Calcium imaging from chemosensory neurons and chemosensory interneurons in response to the addition or removal of a food-associated odor provides support for this model and supplies additional details [47,48•]. The *C. elegans* chemosensory neuron known as AWC^{ON}, which is important for chemotaxis to food odors is, despite its name, an OFF neuron. Calcium imaging shows that AWC^{ON} is activated by the removal of odor, and that this response activates the downstream chemosensory interneuron AIB, which is a member of the turn pool. Conversely, addition of the odor deactivates AWC^{ON}, and this response activates the chemosensory interneuron AIY, which is a member of the run pool. Similar results have been obtained for a second run neuron, known as AIA. Taken together, these results suggest that the first step in the cascade of subcircuits is likely to utilize a push–pull mechanism, in which OFF cells excite turn interneurons and inhibit run interneurons. It is likely that this motif extends to ON cells and other sensory modalities [65].

Neuronal microcircuits for behavioral choice

A recent series of pioneering studies — unique in using a combination of classical and molecular genetics, microfluidics, and *in vivo* calcium imaging to investigate decision making in *C. elegans* — has begun to elucidate the neuronal mechanisms of behavioral choice in this organism [23•,47,59•,66–68]. Focusing primarily on behavioral competition (Figure 1c), and stimulus and behavioral competition (Figure 1d), these studies provide a set of circuit motifs that may form the basis for models of behavioral choice in this and other modalities. To date, two distinct models have been proposed for behavioral competition and one model has been proposed for stimulus and behavioral competition.

The first model for behavioral competition (Figure 4a) is based on the push–pull circuitry believed to underlie klinokinesis [47]. In the simplest version of the model, treatments such as associative conditioning cause the circuit to reconfigure in such a way that the overall reciprocal effects of a given chemosensory neuron on its run interneurons and its turn interneurons are reversed. Figure 4a shows how the outputs of OFF cells might be reconfigured; analogous changes are proposed to occur in the case of ON cells (not shown). The reconfiguration model is supported by an imaging study showing that conditioning animals to avoid NaCl eliminates the positive-going calcium transient normally observed in a representative turn interneuron in response to a sudden decrease in NaCl concentration [66]. Elimination of this connection could contribute to the shift from net excitation to net inhibition from the OFF cell to its set of turn interneurons, as predicted by the model. The same study reported a reduction in the magnitude of a positive-going calcium transient in a representative run interneuron in response to a sudden increase in NaCl concentration. This reduction could contribute to the shift from net excitation to net inhibition in the connection from the ON cell to its set of run interneurons. Similar imaging results have been reported in a representative turn interneuron in response to sudden changes in odor concentration in connection with a likely neuronal correlate of odor avoidance conditioning [67]. This finding provides support for the reconfiguration model in a second sensory modality. In both modalities, identified peptides or peptide receptors play an essential role in the behavioral plasticity, suggesting that the level of peptide signaling may be the source of the bias imposed on the presumptive switching mechanism.

The second model for behavioral competition is derived from a molecular analysis of the genetic predisposition of *C. elegans* to be attracted or repelled by the pheromones it releases [59•]. This predisposition is believed to be the cellular basis of differences in sociality among worms [69]. The model is based on the effects of an electrical synapse between a chemosensory OFF neuron and a hub neuron (Figure 4b). It is believed that wild type worms are nonsocial because of a sustained hyperpolarization of a hub neuron which, being transmitted to its associated sensory neuron, clamps it at a low membrane potential and

prevents it from responding strongly to increases in pheromone concentration. In the model, the hyperpolarized state is established by a sustained increase in the concentration of one or more neuropeptides, which act on the hub neuron. Calcium imaging from a representative run interneuron confirms that it responds only weakly to pheromone in wild type animals, thereby reducing, or possibly eliminating, the tendency to approach pheromone sources. It should be noted, however that parallel changes in other run and turn interneurons, which could take place by the same mechanism, would be required to fully reverse the valence of the pheromone. Although the mechanism underlying the model was inferred from differences between genetic strains, the fact that the hyperpolarization of the hub neuron can be triggered by peptide release suggests that this mechanism could operate within individual worms to alter their behavioral choices. Evidence of environmental factors that can switch worms from a solitary to a social disposition supports this view [70].

The model for stimulus and behavioral competition was derived from genetic analysis of the predisposition to cross, or not to cross, a toxic stripe in order to reach the source of an attractive odorant [23••]. In this model, the decision locus is a run neuron that receives an electrical connection from the ON cell that detects the attractant, and an inhibitory chemical connection from the ON cell that detects the toxin (Figure 4c). Wild type worms cross the toxic stripe because the combined effect of the attractant ON cell and the run interneuron overpowers the opposing behavioral effects of the toxin ON cell. This state of affairs is maintained by the presence of a peptide that depolarizes the run interneuron. However, mutants have been isolated in which the run interneuron is rendered insensitive to the peptide, a condition that induces chronic hyperpolarization. This hyperpolarization blocks the synaptic output of the run interneuron and spreading to the attractant ON cells makes them less responsive to the attractant. As a result, the tendency to approach the attractant is weakened or eliminated and the worm avoids the toxins. This model is supported by the observation that laser ablation or genetically induced hyperpolarization of the run interneuron in wild type animals phenocopies the mutation. Although the mechanism underlying the competition model was inferred from differences between genetic strains, the fact that the state of the run neuron is regulated by a neuropeptide implies that this mechanism could operate within individual wild type worms to bias behavioral choices.

Generalities and prospects

The investigation of the neuronal basis of decision making in *C. elegans* is just beginning. Focusing primarily on behavioral choice, researchers have identified three circuit motifs that appear to be sufficient to explain the outcomes of two choice paradigms. One motif (Figure 4a) is based mainly on changes in the strength of functional synaptic connections whereas, the other two motifs (Figure 4b,c) are based on changes in the basal activity of an interneuron and the sensory neuron to which it is electrically coupled. Nevertheless, peptide signaling seems to play a prominent role in all three motifs, and it may be a general rule that concentrations of various peptides encode the internal states that influence behavioral decisions. Such a role has been proposed for another class of neuromodulators, the catecholamines [1], and there is evidence that these also play a role in behavioral choice in *C. elegans* [22•,29]. It will be interesting to determine whether most forms of behavioral choice in *C. elegans* utilize peptide signaling, or neuromodulation in general. It is conceivable that internal state could also be encoded via mechanisms operating on time scales shorter than those amenable to genetic analysis, such as short-term dynamics of neurons and networks [71,72]. The new synthesis that is emerging between optical recording and optical control of neuronal activity [73,74] is likely to accelerate discoveries of dynamical choice mechanisms in *C. elegans*.

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Figure 1.

Experimental paradigms of behavioral choice in *C. elegans*. **(a–d)** The top and bottom rows show paradigms involving one or two stimuli (S_1 , S_2), respectively; the left and right columns show paradigms involving one or two behaviors (B_1 , B_2). Each panel contains a schematic illustration of a typical application of the paradigm, together with a simple electrical circuit that represents the switching logic entailed by the behavior. In the circuit diagrams, the ΔS switches close only when the stimulus is increasing; behaviors are symbolized by lamps which can be turned on by closing particular switches. The dashed line in c means that when one ΔS switch is closed the other is open, because the stimulus gradients rise in opposite directions. The ‘state’ switches in the yellow boxes are sensitive to the animal's internal state. In c and d, the circuits are more complex to allow for the correct behaviors when one or both stimuli are presented. Here the state switches serve the function of removing one of the resistors (R) from the circuit, thereby increasing the behavioral effect of one stimulus relative to the other (c) or causing one behavior to be more strongly activated than the other (d).

Figure 2.

The neuronal circuit for klinokinesis in *C. elegans*. The circuit is depicted in schematic form as a cascade for four subcircuits, as labeled on the left. The overall function of each subcircuit is shown on the right. Groups of neurons of similar function are indicated by rectangles in some cases. Symbols are given in the key. Feedback connections from command neurons to sensory interneurons, and from sensory interneurons to sensory neurons, have been omitted for clarity; inhibitory motor neurons have been omitted for the same reason. The main anatomically defined classes of neurons summarized in this diagram are as follows. ON cells (8 classes, 13 neurons): Salts (ASEL, ADF); temperature (AFD, AWC); oxygen (AQR, PQR, URX); CO₂ (BAG). OFF cells (5 classes, 8 neurons): Salts (ASER, ASH); odors (AWC); O₂ (BAG); CO₂ (AFD). *Hub neurons*: RMG, RIH. *Run interneurons* (6 classes, 24 neurons): RMD, SMD, AIY, RIM, SMB, AIA. *Turn interneurons* (6 classes, 14 neurons): RIA, RIV, RIB, SIB, AIZ, AIB. *Command neurons, forward locomotion* (2 classes, 4 neurons): AVB, PVC. *Command neurons, reverse locomotion* (3 classes, 6 neurons): AVA, AVD, AVE. *Excitatory motor neurons, forward locomotion* (2 classes, 19 neurons): DB, VB. *Excitatory motor neurons, reverse locomotion* (3 classes, 32 neurons): DA, VA, AS. The number of sensory interneurons was estimated from Refs. [45,49,50].

Figure 3.

Evidence for spikelets in *C. elegans* neurons. **(a)** Whole-cell recording of membrane potential in a neuron identified by expressing green fluorescent protein under the control of the promoter for the gene *sra-11*, which is known to be expressed specifically in three neuron classes (2 neurons per class): AIY, AVB and AIA; the recorded neuron is a member of one of these classes. Six current pulses (upper trace, 3 pA, 10 ms) were injected at 0.5 Hz. **(b)** A train of spikelets evoked in the same neuron by a longer current pulse (3 pA, 1.125 s). The recording pipette contained (mM): 125 KGlu, 18 KCl, 4 NaCl, 1 MgCl₂, 3 CaCl₂, 10 HEPES, and 20 BAPTA. The bath solution contained (mM): 5 KCl, 143 NaCl, 8 CaCl₂, 30 glucose, and 10 HEPES.

Figure 4. Neuronal microcircuits for behavioral choice. **(a and b)** Proposed neuronal circuits for behavioral competition. **(c)** A proposed neuronal circuit for stimulus and behavioral competition. Symbols are given in the key.

Table 1Functional categories of behaviors commonly studied in *C. elegans*.

Functional category	Examples	Stimulus modalities
House keeping	Ingestion	
	Defecation	
	Egg laying	
Escape	Head withdrawal ^a	Lateral nose touch [85–87]
	Reversal	Nose or head touch [25,85]
		Substrate vibration [81]
		Noxious heat [84]
		Noxious chemicals [83]
		High osmolarity [24]
		UV light [82]
Habitat and resource localization	Acceleration	Tail touch [25]
		Substrate vibration [81]
	Orthokinesis	Food patch [80]
		Oxygen [76]
		Carbon dioxide [19]
	Klinokinesis	Taste [36,37]
		Odor [46,79]
		Temperature [77,78]
		Oxygen [56,76]
	Klinotaxis	UV light
		Taste [38,39]
		Odor [41]
		Electric field [75]

^a Movement is in the dorso-ventral plane, orthogonal to the body axis.