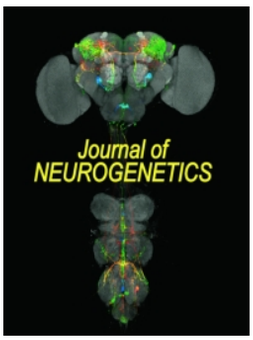

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Plasticity of pheromone-mediated avoidance behavior in *C. elegans*

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ABSTRACT

Caenorhabditis elegans secretes a complex cocktail of small chemicals collectively called ascaroside pheromones which serves as a chemical language for intra-species communication. Subsets of ascarosides have been shown to mediate a broad spectrum of *C. elegans* behavior and development, such as gender-specific attraction, repulsion, aggregation, olfactory plasticity, and dauer formation. Recent studies show that specific components of ascarosides elicit a rapid avoidance response that allows animals to avoid predators and escape from unfavorable conditions. Moreover, this avoidance behavior is modulated by external conditions, internal states, and previous experience, indicating that pheromone avoidance behavior is highly plastic. In this review, we describe molecular and circuit mechanisms underlying plasticity in pheromone avoidance behavior which pave a way to better understanding circuit mechanisms underlying behavioral plasticity in higher animals, including humans.

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Pheromone; avoidance behavior; plasticity; *C. elegans*

Introduction

Animals consistently modulate their behavior in response to the ever-changing environmental conditions and internal states. Thus, a major goal in neuroscience is to understand how animals sense environmental signals and internal metabolic status and how neuronal circuits process and translate this information into the appropriate behavioral programs. The correct sensation, integration, and processing of the external and internal cues is critical for the maintenance of physiology and behavior, and dysregulation of these pathways leads to multiple psychiatric and/or other neurological disorders. However, it is tremendously challenging to identify the underlying neuronal circuits and molecular and cellular mechanisms in higher animals. The nervous system of these animals is complex, and it is difficult to correlate specific behavioral changes with disruption of function of particular neurons and molecules.

The nematode *C. elegans* provides an excellent model system in which to explore the neural and molecular basis of environmentally influenced behavior. *C. elegans* has a relatively simple nervous system with only 302 neurons and over 7,000 synapses in hermaphrodites and 385 neurons and over 8,000 synapses in males, and their wiring diagrams have been completely reconstructed (Bhattacharya, Aghayeva, Berghoff, & Hobert, 2019; Cook *et al.*, 2019; Hall & Russell, 1991; Jarrell *et al.*, 2012; White, Southgate, Thomson, & Brenner, 1986). However, *C. elegans* displays a broad spectrum of behaviors, such as locomotion, chemosensation, nociception, foraging, and feeding. In addition, *C. elegans* exhibits more complex behaviors, including social and sleep-like behaviors as well as learning and memory [See review (Ardiel & Rankin, 2010; Byrne *et al.*, 2019; Rengarajan & Hallem, 2016)]. Moreover, most, if not all, of these behaviors are plastic and can be modulated by external and/or internal conditions [See review (Ardiel & Rankin, 2008; Garcia & Portman, 2016; Hobert, 2003; Sasakura & Mori, 2013; Sengupta, 2013)]. Here, we review recent findings regarding particular chemosensory behaviors, avoidance or attraction elicited by pheromone cues, as well as discuss their modulation by circuit state, sex, previous experience and the feeding state in *C. elegans*.

Ascaroside pheromones

Pheromones are blends of released chemicals that play major roles in intraspecies chemical communication (Karlson & Luscher, 1959). *C. elegans* secretes a complex cocktail of small chemicals that are collectively called ascaroside pheromones; these affect many aspects of *C. elegans* biology [See review (Butcher, 2019; Edison, 2009; Ludewig & Schroeder, 2013; McGrath & Ruvinsky, 2019; J. Park, Choi, Dar, Butcher, & Kim, 2019; Schroeder, 2015)]. Since *C. elegans* ascaroside pheromones were discovered as a dauer-inducing metabolite in 1982 (Golden & Riddle, 1982), the chemical components of ascaroside pheromones have been identified as hundreds of structurally related compounds (Artyukhin *et al.*, 2013; Butcher, Fujita, Schroeder, & Clardy, 2007;

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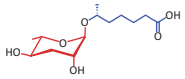
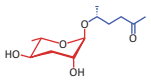
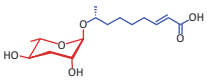
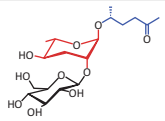
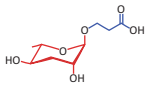
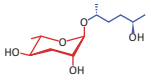
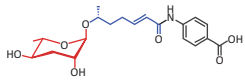
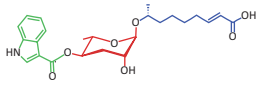
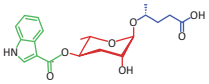
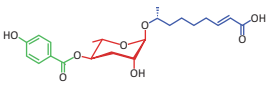
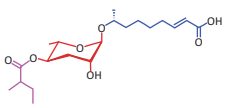
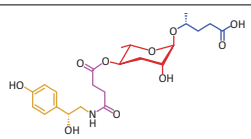
Butcher, Ragains, Kim, & Clardy, 2008; Butcher *et al.*, 2009; Jeong *et al.*, 2005; Pungaliya *et al.*, 2009; Srinivasan *et al.*, 2008; Srinivasan *et al.*, 2012).

As a dauer-inducing cue, ascaroside pheromones act as a population density indicator to regulate growth in the early larval developmental stage: high pheromone concentrations cause animals to enter into an alternative non-aging, stress-resistant, and developmentally arrested dauer larval stage (Butcher *et al.*, 2007; Butcher *et al.*, 2009; Golden & Riddle, 1982, 1984; Jeong *et al.*, 2005; Pungaliya *et al.*, 2009; Srinivasan *et al.*, 2008) (Table 1). Subsequently, over a dozen research groups have shown that ascaroside pheromones play additional roles in several behaviors, including gender-specific attraction and repulsion, aggregation, and foraging (Artyukhin *et al.*, 2013; Chute *et al.*, 2019; Fagan *et al.*, 2018; Greene, Dobosiewicz, Butcher, McGrath, & Bargmann,

Table 1 Structure and function of ascaroside pheromones in *C. elegans*.

Name	Chemical structure	Function						Reference
		Avoidance	Dauer formation	Male attraction	Hermaphrodite attraction	Foraging	Aggregation	
ascr#1 (daumone-1, C7)		O	O					1, 12, 17
ascr#2 (daumone-2, asc-C6-MK, C6)		O	O	O		O		3, 7, 10, 11, 12, 14, 17, 21
ascr#3 (daumone-3, asc-ΔC9, C9)		O	O	O		O		3, 7, 10, 11, 12, 15, 16, 17, 18, 19, 21
ascr#4			O	O				7
ascr#5 (asc ωC3, C3)		O	O					4, 11, 13, 21
ascr#6.1			O					6
ascr#8			O	O		O		6, 10, 15
icas#3			O	O		O		8
icas#9 (C5)				O			O	5, 8, 10, 22
hbas#3			O	O		O	O	2
mbas#3					O			2, 20
osas#9		O						9

1. Jeong *et al.*, 2005; 2. von Reuss *et al.*, 2012; 3. Butcher *et al.*, 2007; 4. Butcher *et al.*, 2008; 5. Butcher *et al.*, 2009; 6. Pungaliya *et al.*, 2009; 7. Srinivasan *et al.*, 2008; 8. Srinivasan *et al.*, 2012; 9. Artyukhin *et al.*, 2013; 10. Greene *et al.*, 2016; 11. Macosko *et al.*, 2009; 12. Kim K *et al.*, 2009; 13. McGrath *et al.*, 2011; 14. Park *et al.*, 2012; 15. Narayan *et al.*, 2016; 16. Fagan *et al.*, 2018; 17. Park *et al.*, 2017; 18. Hong *et al.*, 2017; 19. Ryu *et al.*, 2018; 20. Zhang *et al.*,2017; 21. Fenk *et al.*, 2017; 22. Greene *et al.*, 2016.

2016; Jang *et al.*, 2012; Macosko *et al.*, 2009; Narayan *et al.*, 2016; D. Park *et al.*, 2017; Pungaliya *et al.*, 2009; Srinivasan *et al.*, 2008; Srinivasan *et al.*, 2012; von Reuss *et al.*, 2012; Zhang, Sanchez-Ayala, Sternberg, Srinivasan, & Schroeder, 2017) (Table 1). Moreover, complexity of ascaroside signaling further modulates these biological processes. Thus, *C. elegans* ascaroside pheromones elicit long-term changes in development and physiology as well as short-term behavioral changes, making it an outstanding model organism to explore the mechanisms by which biologically relevant cues are sensed and integrated to direct critically important developmental and behavioral programs.

Ascr#3 avoidance behavior and its plasticity

A few pheromones that elicit chemosensory responses have been well-characterized in *C. elegans*. Srinivasan *et al.* showed that adult wild-type males were attractive to a blend of femto- or pico-molar concentrations of three ascarosides, namely ascr#2 (asc-C6-MK, C6), ascr#3(asc-ΔC9, C9), and ascr#4, whereas adult wild-type hermaphrodites avoided higher concentrations of ascr#2 or ascr#3 (Srinivasan *et al.*, 2008). This group also showed that in males, ascr#3 appeared to be sensed by two chemosensory neuron-types, the ASK amphid neurons and the male-specific CEM neurons (Srinivasan *et al.*, 2008). Macosko *et al.* further showed that hermaphrodites from social feeding strains with low *npr-1* neuropeptide receptor gene acitivity (215-valine) or *npr-1* loss-of-function mutant (*ad609lf*) strains exhibited attraction behavior to a 10 nM mixture of ascr#2, ascr#3, and ascr#5 (asc ωC3, C3) but not to any one of these pheromone components individually (Macosko *et al.*, 2009). However, wild-type solitary feeding hermaphrodites with high *npr-1* activity (215-phenylalanine) avoided the ascaroside mixture (Macosko *et al.*, 2009). The ASK pheromone-sensing neurons elicited acute Ca^{2+} transient upon exposure to this pheromone mixture: pheromone-evoked Ca^{2+} response was much stronger in *npr-1(lf)* mutant animals than in wild-type animals (Macosko *et al.*, 2009). This enhanced Ca^{2+} response in the ASK neurons upon pheromone exposure may contribute to attraction behavior toward the pheromone in *npr-1(lf)* mutant animals. These two studies indicate that pheromone responses in *C. elegans* vary depending on sex and a neuropeptide circuit that controls solitary or social feeding behavior.

Jang *et al.* further dissected molecular and circuit mechanisms by which worms modulate pheromone-mediated chemosensory behaviors depending on circuit state and sex (Jang *et al.*, 2012). Using the pheromone drop test that detects acute avoidance responses upon pheromone exposure (Hilliard, Bargmann, & Bazzicalupo, 2002; Jang & Bargmann, 2013), the group showed that adult wild-type hermaphrodites specifically avoided nano-molar concentrations of ascr#3 but not of ascr#2 or ascr#5 (Jang *et al.*, 2012). Calcium imaging, genetic analysis, behavioral analysis, and tools to manipulate neuronal activity supported that the ADL amphid chemosensory neurons sense ascr#3 and mediate ascr#3 avoidance in adult wild-type hermaphrodites (Jang *et al.*, 2012). Subsequently, the ADL ascr#3 Ca^{2+} activities were significantly decreased in *npr-1(lf)* hermaphrodites and wild-type males, indicating that reduced ADL ascr#3 responses are required for ascr#3 attraction behavior in *npr-1(lf)* hermaphrodites and wild-type males (Jang *et al.*, 2012). Strikingly, the ADL neurons drove ascr#3 avoidance in wild-type hermaphrodites via ADL chemical synapses likely onto the AVA and AVD command interneurons for backward locomotion and drove attraction through gap junctions via the RMG neurons in *npr-1(lf)* hermaphrodites (Jang *et al.*, 2012). In males, the ADL neurons exhibited decreased ascr#3 responses which were independent of *npr-1* activities and were possibly due to differences in their own sexual state and/or inputs from other sexually dimorphic neurons (Cook *et al.*, 2019; Jang *et al.*, 2012). These results suggest that the ADL neurons are capable of contributing to either attraction to or avoidance from ascr#3 and that their sensitivity to ascr#3 is modified in worms based on the function of the *npr-1* gene and animal's sex (Figure 1(A,B)). Furthermore, since the *npr-1* genotype seems to reflect a stress-related behavioral state (de Bono, Tobin, Davis, Avery, & Bargmann, 2002; Rogers, Persson, Cheung, & de Bono, 2006), ascr#3 avoidance behavior could be modulated by stressful conditions. More recently, Fagan et al showed that the ADF neurons of males sensed and promoted attraction to ascr#3, while ADF-ablated hermaphrodites were repelled to ascr#3. In this sexual dimorphic process, the sexual regulator *tra-1* and its direct target *mab-3* cell-autonomously regulated the male state of ADF to promote ascr#3 attraction and the hermaphrodite state of ADF to permit ascr#3 repulsion (Fagan *et al.*, 2018).

The ascr#3 avoidance behavior is further modulated by the feeding state. Ryu *et al.* found that starved animals showed increased ascr#3 avoidance behavior compared to well-fed animals and that this effect was dependent on the *daf-2* insulin-like receptor gene (Ryu *et al.*, 2018). Although *daf-2* mutant animals exhibited normal ADL Ca^{2+} activities upon ascr#3 exposure, they exhibited reduced synaptic transmission from the ADL ascr#3 sensing neurons to first-order AVA command interneurons (Ryu *et al.*, 2018). The group further showed that *daf-2* acted through the canonical IGF pathway in the ADL neurons to downregulate the *snb-1* presynaptic protein (Ryu *et al.*, 2018). Remarkably, an intestinal insulin-like peptide, INS-18, acted upstream of DAF-2 in an inhibitory manner and modulated ascr#3 avoidance, and the INS-18 release was reduced in starved worms (Ryu *et al.*, 2018). This study significantly advances our understanding of how the feeding state can fundamentally change the behavioral output via hormonal signaling (Figure 1(C)).

Hong *et al.* investigated whether ascr#3 avoidance behavior is modulated by previous experience. The group demonstrated that in hermaphrodites, exposure to the ascr#3 pheromone during the critical period of the L1 larval stage led to enhanced ascr#3-specific avoidance behavior as an adult (Hong *et al.*, 2017). Interestingly, this increased ascr#3 avoidance was not attributed to increase in the synaptic transmission via ADL–AVA synapses but to the recruitment of the SMB motor neurons into the circuit activated by the

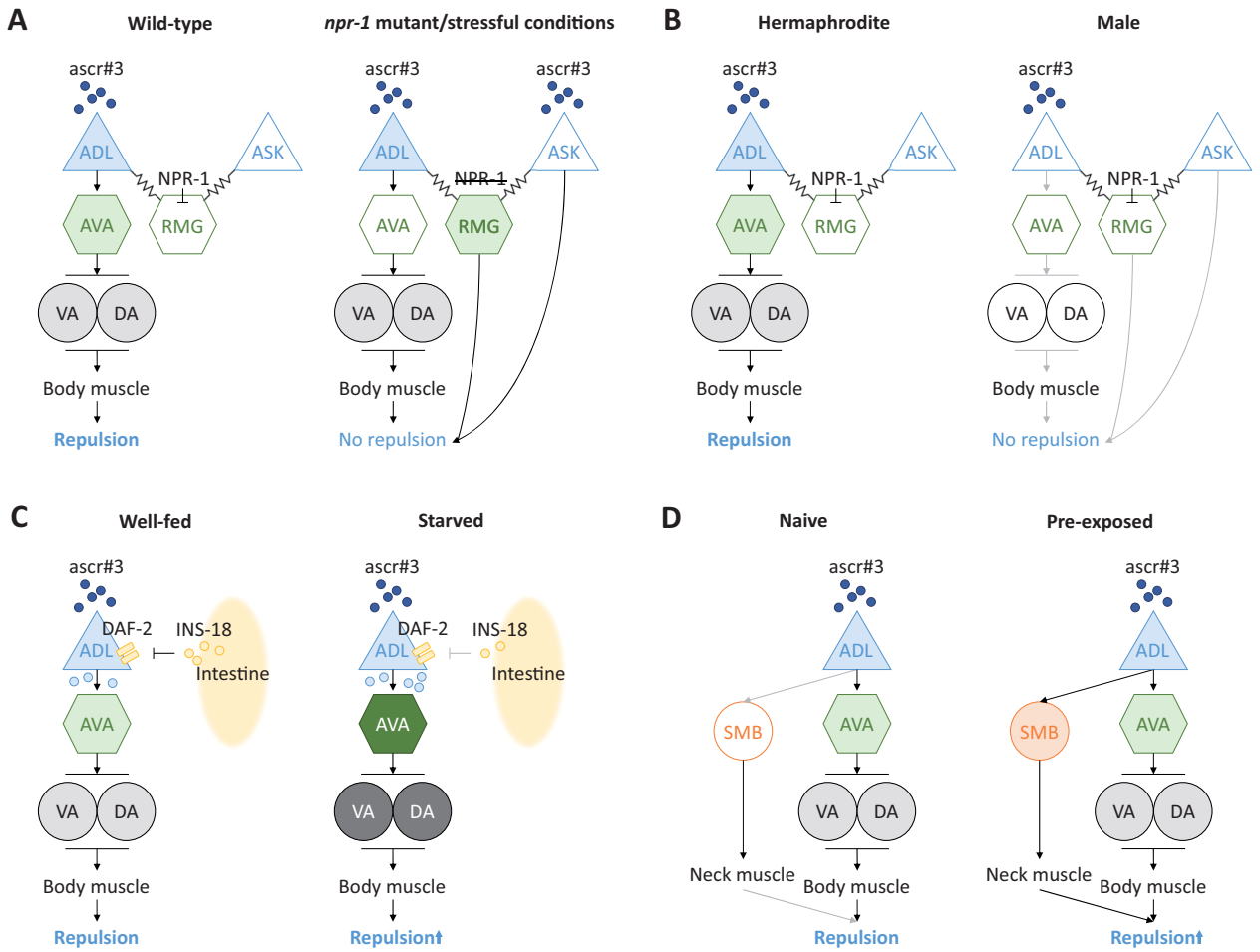


Figure 1. Models for behavioral plasticity of ascr#3 avoidance. (A) In *npr-1(lf)* hermaphrodite, ASK and RMG antagonize ADL chemical synapses and decrease ascr#3 avoidance. (B) In wild-type male, ADL ascr#3 response is decreased due to sexual dimorphism. ASK and RMG circuit antagonizes ADL output to further reduce ascr#3 avoidance. (C) In starved conditions, secretion of INS-18 from the intestine is decreased, which activates the DAF-2 signaling of ADL, resulting in increase in synaptic release from ADL to downstream neurons, and promotes enhanced ascr#3 avoidance. (D) In pre-exposed condition, ADL-SMB synaptic activities that are inactive in naïve animals is altered to promote enhanced ascr#3 avoidance.

ascr#3-sensing ADL neurons (Hong *et al.*, 2017). The SMB motor neurons, which are one of over twenty post-synaptic neurons (Cook *et al.*, 2019; White *et al.*, 1986), exhibited Ca^{2+} activities upon ascr#3 exposure only in ascr#3 pre-exposed animals (Hong *et al.*, 2017). These results indicated that ascr#3-experienced animals form a long-lasting memory or imprint for ascr#3 experience (Figure 1(D)). Thus, this work provides fundamental circuit mechanisms underlying how individual synapses are functionally or anatomically altered upon sensory imprinting.

Avoidance behavior to other ascarosides

In addition to ascr#3, osas#9 ascaroside was characterized as a single pheromone component which causes avoidance behavior in wild-type hermaphrodites (Artyukhin *et al.*, 2013; Chute *et al.*, 2019). osas#9 is an interesting ascaroside since its side chain is derived from the neurotransmitter octopamine and it is produced mainly by starved young L1 larvae (Artyukhin *et al.*, 2013). Chute *et al.* found that starved but not well-fed, young adult hermaphrodites avoided micro-molar concentrations of osas#9 (Chute *et al.*, 2019). This osas#9 avoidance was mediated by not the ADL neurons but the nociceptive ASH neurons via the osas#9-sensing *tyra-2* tyramine/octopamine G protein-coupled receptor (GPCR) (Chute *et al.*, 2019). Interestingly, the group found that *trya-2* expression was increased in starved worms, suggesting that changes in the expression level of the osas#9-chemoreceptor gene depending on the feeding state are responsible for starvation-dependent osas#9 avoidance. The ways in which the feeding state regulates the expression of the *trya-2* gene remain to be explored. Moreover, since the osas#9-sensing ASH neurons also participate in the RMG gap junction circuit (Cook *et al.*, 2019; White *et al.*, 1986), synergistic avoidance with ascr#3 and osas#9 needs to be examined in starved animals, which will provide further molecular and circuit mechanisms underlying starvation-dependent ascaroside avoidance behavior.

Park *et al.* found that micromolar concentrations of ascr#1 (daumone, C7) elicited avoidance behavior in young adult hermaphrodites (D. Park *et al.*, 2017). The group also suggested that the ascr#1 avoidance behavior is mediated by the *daf-16*/*FoxO* gene and glutamatergic transmission via the

AWB chemosensory neurons but not either by ADL or ASH neurons (D. Park *et al.*, 2017). However, roles of the AWB neurons in ascr#1 avoidance need to be further characterized for better understanding the ascr#1 avoidance behavior.

Avoidance behavior to other pheromones

Worms appear to avoid other putative pheromone components. Zhou *et al.* found that the internal fluid from injured worms elicited repulsive behavior in adult hermaphrodites via the ASI and ASK chemosensory neurons (Zhou *et al.*, 2017). The group also found that this internal fluid did not affect the lifespan of worms, suggesting that this fluid acts as not a harmful repellent chemical but as an alarm pheromone (Zhou *et al.*, 2017). This potential pheromone was none of the known ascarosides but comprised at least three nonvolatile components (Zhou *et al.*, 2017). Notably, this avoidance was decreased in starved animals, indicating that this behavior is also dependent on the feeding state (Zhou *et al.*, 2017). The chemical identity of these pheromones needs to be examined to further unravel the molecular and circuit mechanisms underlying this distinct pheromone avoidance behavior.

Pristionchus pacificus is a necromantic insect-dwelling nematode and a facultative predator of *C. elegans* (Serobyan, Ragsdale, & Sommer, 2014). It was reported that *P. pacificus* secreted a few ascarosides, indicating that *C. elegans* avoids this predator nematode (Choe *et al.*, 2012). Interestingly, Liu *et al.*, found that starved, but not well-fed, *P. pacificus* secreted additional non-volatile chemicals which elicited a strong avoidance behavior in *C. elegans* (Liu *et al.*, 2018). They identified these chemical signals as a mixture of sulfolipids and found them to be similar to a known *C. elegans* repellent, sodium dodecyl sulfate (SDS) (Liu *et al.*, 2018). These sulfolipids appeared to be detected redundantly by multiple chemosensory neurons, including the ADL, ASH, ASI, and ASJ neurons (Liu *et al.*, 2018). Taken together, these results suggest that *C. elegans* ensures rapid and life-saving avoidance behavior against the predator by detecting predator-secreted ascaroside as a pheromone as well as sulfolipid as a kairomone (Brown, Eisner, & Whittaker, 1970; Stowe, Turlings, Loughrin, Lewis, & Tumlinson, 1995).

Conclusions and future outlook

Connectomics, the description of comprehensive maps of anatomical connections between every neuron in an organism, is a rapidly evolving field in neuroscience. These large-scale wiring diagrams are expected to offer a unique opportunity to understand not only the structural details of neural connectivity but also neural functions. However, previous studies demonstrated that the wiring diagrams are insufficient to decipher circuit and neural mechanisms of behavior. Studies on the plasticity of *C. elegans* pheromone avoidance further support that behavior cannot be predicted by anatomy alone and eventually requires delicate physiological and behavioral analysis at high resolutions. Studies on *C. elegans*' ascr#3 pheromone avoidance behavior and its functional circuits have provided plentiful information on anatomical and functional logics of the circuit mechanisms including the ASK–RMG–ADL "hub and spoke" and "push and pull" circuit models which are conserved in higher organisms (Bargmann & Marder, 2013). It is intriguing to examine whether ascr#3 avoidance behavior is further modulated by temperature, mating experience, maternal age, and other internal or external conditions (Parida, Neogi, & Padmanabhan, 2014; Perez, Francesconi, Hidalgo-Carcedo, & Lehner, 2017; Shi & Murphy, 2014), that could lead to findings of unexpected but crucial circuit mechanisms. Moreover, it will help us more deeply understand how the nervous system is functionally organized to generate behavioral outcomes.

Understanding how individual synapses are functionally or anatomically altered in response to changes in environmental conditions and internal states is the essential first step toward being able to dissect out the molecular and neuronal mechanisms underlying many forms of behavioral plasticity. Given that the structures and functions of neural circuits are evolutionarily conserved, these works will lead to the development of a general framework for understanding how circuits are modulated in higher animals, including humans, and in disease states (Aitman *et al.*, 2011; Aryal & Lee, 2019; Wangler *et al.*, 2017). Moreover, these works will not only pave the way to identify molecular mechanisms underlying behavioral plasticity but also provide a useful platform to develop tools to modulate behaviors.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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References

Aitman, T.J., Boone, C., Churchill, G.A., Hengartner, M.O., Mackay, T.F., & Stemple, D.L. (2011). The future of model organisms in human disease research. *Nature Reviews. Genetics*, *12*(8), 575–582. doi:10.1038/nrg3047

Ardiel, E.L., & Rankin, C.H. (2008). Behavioral plasticity in the *C. elegans* mechanosensory circuit. *Journal of Neurogenetics*, *22*(3), 239–255. doi:10.1080/01677060802298509

Ardiel, E.L., & Rankin, C.H. (2010). An elegant mind: learning and memory in *Caenorhabditis elegans*. *Learning & Memory (Cold Spring Harbor, N.Y.).)*, *17*(4), 191–201. doi:10.1101/lm.960510

Artyukhin, A.B., Yim, J.J., Srinivasan, J., Izrayelit, Y., Bose, N., von Reuss, S.H., … Schroeder, F.C. (2013). Succinylated octopamine ascarosides and a new pathway of biogenic amine metabolism in

Caenorhabditis elegans. *The Journal of Biological Chemistry*, *288*(26), 18778–18783. doi:10.1074/jbc.C113.477000

Aryal, B., & Lee, Y. (2019). Disease model organism for Parkinson disease: Drosophila melanogaster. *BMB Reports*, *52*(4), 250–258. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/30545438. doi:10.5483/BMBRep.2019.52.4.204

Bargmann, C.I., & Marder, E. (2013). From the connectome to brain function. *Nature Methods*, *10*(6), 483–490. doi:10.1038/nmeth.2451

Bhattacharya, A., Aghayeva, U., Berghoff, E.G., & Hobert, O. (2019). Plasticity of the electrical connectome of *C. elegans*. *Cell*, *176*(5), 1174–1189. e1116. doi:10.1016/j.cell.2018.12.024

Brown, W.L., Jr., Eisner, T., & Whittaker, R.H. (1970). Allomones and kairomones: Transspecific chemical messengers. *BioScience*, *20*(1), 21–21. doi:10.2307/1294753

Butcher, R.A. (2019). Natural products as chemical tools to dissect complex biology in *C. elegans*. *Current Opinion in Chemical Biology*, *50*, 138–144. doi:10.1016/j.cbpa.2019.03.005

Butcher, R.A., Fujita, M., Schroeder, F.C., & Clardy, J. (2007). Small-molecule pheromones that control dauer development in *Caenorhabditis elegans*. *Nature Chemical Biology*, *3*(7), 420–422. doi:10.1038/nchembio.2007.3

Butcher, R.A., Ragains, J.R., Kim, E., & Clardy, J. (2008). A potent dauer pheromone component in *Caenorhabditis elegans* that acts synergistically with other components. *Proceedings of the National Academy of Sciences of the United States of America*, *105*(38), 14288–14292. doi:10.1073/pnas.0806676105

Butcher, R.A., Ragains, J.R., Li, W., Ruvkun, G., Clardy, J., & Mak, H.Y. (2009). Biosynthesis of the *Caenorhabditis elegans* dauer pheromone. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(6), 1875–1879. doi:10.1073/pnas.0810338106

Byrne, J.J., Soh, M.S., Chandhok, G., Vijayaraghavan, T., Teoh, J.-S., Crawford, S., … Neumann, B. (2019). Disruption of mitochondrial dynamics affects behaviour and lifespan in *Caenorhabditis elegans*. *Cellular and Molecular Life Sciences : Cmls*, *76*(10), 1967–1985. doi:10.1007/s00018-019-03024-5

Choe, A., von Reuss, S.H., Kogan, D., Gasser, R.B., Platzer, E.G., Schroeder, F.C., & Sternberg, P.W. (2012). Ascaroside signaling is widely conserved among nematodes. *Current Biology : CB*, *22*(9), 772–780. doi:10.1016/j.cub.2012.03.024

Chute, C.D., DiLoreto, E.M., Zhang, Y.K., Reilly, D.K., Rayes, D., Coyle, V.L., … Srinivasan, J. (2019). Co-option of neurotransmitter signaling for inter-organismal communication in *C. elegans*. *Nature Communications*, *10*(1), 3186. doi:10.1038/s41467-019-11240-7

Cook, S.J., Jarrell, T.A., Brittin, C.A., Wang, Y., Bloniarz, A.E., Yakovlev, M.A., … Emmons, S.W. (2019). Whole-animal connectomes of both *Caenorhabditis elegans* sexes. *Nature*, *571*(7763), 63–71. doi:10.1038/s41586-019-1352-7

de Bono, M., Tobin, D.M., Davis, M.W., Avery, L., & Bargmann, C.I. (2002). Social feeding in *Caenorhabditis elegans* is induced by neurons that detect aversive stimuli. *Nature*, *419*(6910), 899–903. doi:10.1038/nature01169

Edison, A.S. (2009). *Caenorhabditis elegans* pheromones regulate multiple complex behaviors. *Current Opinion in Neurobiology*, *19*(4), 378–388. doi:10.1016/j.conb.2009.07.007

Fagan, K.A., Luo, J.T., Lagoy, R.C., Schroeder, F.C., Albrecht, D.R., & Portman, D.S. (2018). A single-neuron chemosensory switch determines the valence of a sexually dimorphic sensory behavior. *Current Biology: CB*, *28*(6), 902–914.e5. +. doi:10.1016/j.cub.2018.02.029

Fenk, L. A., & de Bono, M.. (2017). Memory of recent oxygen experience switches pheromone valence in Caenorhabditis elegans. *Proceedings of the National Academy of Sciences of the United States of America*, 114(16), 4195–4200. doi:10.1073/pnas.1618934114

Garcia, L.R., & Portman, D.S. (2016). Neural circuits for sexually dimorphic and sexually divergent behaviors in *Caenorhabditis elegans*. *Current Opinion in Neurobiology*, *38*, 46–52. doi:10.1016/j.conb.2016.02.002

Golden, J.W., & Riddle, D.L. (1982). A pheromone influences larval development in the nematode *Caenorhabditis elegans*. *Science (New York, N.Y.).)*, *218*(4572), 578–580. doi:10.1126/science.6896933

Golden, J.W., & Riddle, D.L. (1984). The *Caenorhabditis elegans* dauer larva: Developmental effects of pheromone, food, and temperature. *Developmental Biology*, *102*(2), 368–378. doi:10.1016/0012-1606(84)90201-X

Greene, J.S., Dobosiewicz, M., Butcher, R.A., McGrath, P.T., & Bargmann, C.I. (2016). Regulatory changes in two chemoreceptor genes contribute to a *Caenorhabditis elegans* QTL for foraging behavior. *eLife*, *5*, e21454. doi:10.7554/eLife.21454

Hall, D.H., & Russell, R.L. (1991). The posterior nervous system of the nematode *Caenorhabditis elegans*: Serial reconstruction of identified neurons and complete pattern of synaptic interactions. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, *11*(1), 1–22. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/1986064. doi:10.1523/JNEUROSCI.11-01-00001.1991

Hilliard, M.A., Bargmann, C.I., & Bazzicalupo, P. (2002). *C. elegans* responds to chemical repellents by integrating sensory inputs from the head and the tail. *Current Biology: CB*, *12*(9), 730–734. doi:10.1016/S0960-9822(02)00813-8

Hobert, O. (2003). Behavioral plasticity in *C. elegans*: paradigms, circuits, genes. *Journal of Neurobiology*, *54*(1), 203–223. doi:10.1002/neu.10168

Hong, M., Ryu, L., Ow, M.C., Kim, J., Je, A.R., Chinta, S., … Kim, K. (2017). Early pheromone experience modifies a synaptic activity to influence adult pheromone responses of *C. elegans*. *Current Biology: CB*, *27*(20), 3168.e3–3177.e3. doi:10.1016/j.cub.2017.08.068

Jang, H., & Bargmann, C.I. (2013). Acute behavioral responses to pheromones in *C. elegans* (adult behaviors: attraction, repulsion). *Methods in Molecular Biology (Clifton, N.J.).)*, *1068*, 285–292. doi:10.1007/978-1-62703-619-1_21

Jang, H., Kim, K., Neal, S.J., Macosko, E., Kim, D., Butcher, R.A., … Sengupta, P. (2012). Neuromodulatory state and sex specify alternative behaviors through antagonistic synaptic pathways in *C. elegans*. *Neuron*, *75*(4), 585–592. doi:10.1016/j.neuron.2012.06.034

Jarrell, T.A., Wang, Y., Bloniarz, A.E., Brittin, C.A., Xu, M., Thomson, J.N., … Emmons, S.W. (2012). The connectome of a decision-making neural network. *Science (New York, N.Y.).)*, *337*(6093), 437–444. doi:10.1126/science.1221762

Jeong, P.-Y., Jung, M., Yim, Y.-H., Kim, H., Park, M., Hong, E., … Paik, Y.-K. (2005). Chemical structure and biological activity of the *Caenorhabditis elegans* dauer-inducing pheromone. *Nature*, *433*(7025), 541–545. doi:10.1038/nature03201

Karlson, P., & Luscher, M. (1959). Pheromones': a new term for a class of biologically active substances. *Nature*, *183*(4653), 55–56. doi:10.1038/183055a0

Liu, Z., Kariya, M.J., Chute, C.D., Pribadi, A.K., Leinwand, S.G., Tong, A., … Chalasani, S.H. (2018). Predator-secreted sulfolipids induce defensive responses in *C. elegans*. *Nature Communications*, *9*(1), 1128. doi:10.1038/s41467-018-03333-6

Ludewig, A.H., & Schroeder, F.C. (2013). Ascaroside signaling in *C. elegans*. *WormBook*, 1–22. doi:10.1895/wormbook.1.155.1

Macosko, E.Z., Pokala, N., Feinberg, E.H., Chalasani, S.H., Butcher, R.A., Clardy, J., & Bargmann, C.I. (2009). A hub-and-spoke circuit drives pheromone attraction and social behaviour in *C. elegans*. *Nature*, *458*(7242), 1171–1175. doi:10.1038/nature07886

McGrath, P.T., & Ruvinsky, I. (2019). A primer on pheromone signaling in *Caenorhabditis elegans* for systems biologists. *Current Opinion in Systems Biology*, *13*, 23–30. doi:10.1016/j.coisb.2018.08.012

McGrath, P. T., Xu, Y., Ailion, M., Garrison, J. L., Butcher, R. A., & Bargmann, C. I. (2011). Parallel evolution of domesticated Caenorhabditis species targets pheromone receptor genes. Nature, 477(7364), 321–325. doi:10.1038/nature10378

Narayan, A., Venkatachalam, V., Durak, O., Reilly, D.K., Bose, N., Schroeder, F.C., … Sternberg, P.W. (2016). Contrasting responses within a single neuron class enable sex-specific attraction in *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(10), E1392–1401. doi:10.1073/pnas.1600786113

Parida, L., Neogi, S., & Padmanabhan, V. (2014). Effect of temperature pre-exposure on the locomotion and chemotaxis of *C. elegans*. *PLoS One*, *9*(10), e111342. doi:10.1371/journal.pone.0111342

Park, J., Choi, W., Dar, A.R., Butcher, R.A., & Kim, K. (2019). Neuropeptide signaling regulates pheromone-mediated gene expression of a chemoreceptor gene in *C. elegans*. *Molecules and Cells*, *42*(1), 28–35. doi:10.14348/molcells.2018.0380

Park, D., O'Doherty, I., Somvanshi, R. K., Bethke, A., Schroeder, F. C., Kumar, U., & Riddle, D. L. (2012). Interaction of structure-specific and promiscuous G-protein-coupled receptors mediates small-molecule signaling in Caenorhabditis elegans. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(25), 9917–9922. doi:10.1073/pnas.1202216109

Park, D., Hahm, J.-H., Park, S., Ha, G., Chang, G.-E., Jeong, H., … Paik, Y.-K. (2017). A conserved neuronal DAF-16/FoxO plays an important role in conveying pheromone signals to elicit repulsion behavior in *Caenorhabditis elegans*. *Scientific Reports*, *7*(1), 7260. doi:10.1038/s41598-017-07313-6

Perez, M.F., Francesconi, M., Hidalgo-Carcedo, C., & Lehner, B. (2017). Maternal age generates phenotypic variation in *Caenorhabditis elegans*. *Nature*, *552*(7683), 106–109. doi:10.1038/nature25012

Pungaliya, C., Srinivasan, J., Fox, B.W., Malik, R.U., Ludewig, A.H., Sternberg, P.W., & Schroeder, F.C. (2009). A shortcut to identifying small molecule signals that regulate behavior and development in *Caenorhabditis elegans*. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(19), 7708–7713. doi:10.1073/pnas.0811918106

Rengarajan, S., & Hallem, E.A. (2016). Olfactory circuits and behaviors of nematodes. *Current Opinion in Neurobiology*, *41*, 136–148. doi:10.1016/j.conb.2016.09.002

Rogers, C., Persson, A., Cheung, B., & de Bono, M. (2006). Behavioral motifs and neural pathways coordinating O_2 responses and aggregation in *C. elegans*. *Current Biology: CB*, *16*(7), 649–659. doi:10.1016/j.cub.2006.03.023

Ryu, L., Cheon, Y., Huh, Y.H., Pyo, S., Chinta, S., Choi, H., … Kim, K. (2018). Feeding state regulates pheromone-mediated avoidance behavior via the insulin signaling pathway in *Caenorhabditis elegans*. *The EMBO Journal*, *37*(15), e98402. doi:10.15252/embj.201798402

Sasakura, H., & Mori, I. (2013). Behavioral plasticity, learning, and memory in *C. elegans*. *Current Opinion in Neurobiology*, *23*(1), 92–99. doi:10.1016/j.conb.2012.09.005

Schroeder, F.C. (2015). Modular assembly of primary metabolic building blocks: a chemical language in *C. elegans*. *Chemistry & Biology*, *22*(1), 7–16. doi:10.1016/j.chembiol.2014.10.012

Sengupta, P. (2013). The belly rules the nose: feeding state-dependent modulation of peripheral chemosensory responses. *Current Opinion in Neurobiology*, *23*(1), 68–75. doi:10.1016/j.conb.2012.08.001

Serobyan, V., Ragsdale, E.J., & Sommer, R.J. (2014). Adaptive value of a predatory mouth-form in a dimorphic nematode. *Proceedings of the Royal Society B: Biological Sciences*, *281*(1791), 20141334. doi:10.1098/rspb.2014.1334

Shi, C., & Murphy, C.T. (2014). Mating induces shrinking and death in Caenorhabditis mothers. *Science (New York, N.Y.).)*, *343*(6170), 536–540. doi:10.1126/science.1242958

Srinivasan, J., Kaplan, F., Ajredini, R., Zachariah, C., Alborn, H.T., Teal, P.E.A., … Schroeder, F.C. (2008). A blend of small molecules regulates both mating and development in *Caenorhabditis elegans*. *Nature*, *454*(7208), 1115–1118. doi:10.1038/nature07168

Srinivasan, J., von Reuss, S.H., Bose, N., Zaslaver, A., Mahanti, P., Ho, M.C., … Schroeder, F.C. (2012). A modular library of small molecule signals regulates social behaviors in *Caenorhabditis elegans*. *PLoS Biology*, *10*(1), e1001237. doi:10.1371/journal.pbio.1001237

Stowe, M.K., Turlings, T.C., Loughrin, J.H., Lewis, W.J., & Tumlinson, J.H. (1995). The chemistry of eavesdropping, alarm, and deceit. *Proceedings of the National Academy of Sciences of the United States of America*, *92*(1), 23–28. doi:10.1073/pnas.92.1.23

von Reuss, S.H., Bose, N., Srinivasan, J., Yim, J.J., Judkins, J.C., Sternberg, P.W., & Schroeder, F.C. (2012). Comparative metabolomics reveals biogenesis of ascarosides, a modular library of small-molecule signals in *C. elegans*. *Journal of the American Chemical Society*, *134*(3), 1817–1824. doi:10.1021/ja210202y

Wangler, M.F., Yamamoto, S., Chao, H.-T., Posey, J.E., Westerfield, M., Postlethwait, J., … Bellen, H.J, Members of the Undiagnosed Diseases Network (UDN). (2017). Model organisms facilitate rare disease diagnosis and therapeutic research. *Genetics*, *207*(1), 9–27. doi:10.1534/genetics.117.203067

White, J.G., Southgate, E., Thomson, J.N., & Brenner, S. (1986). The structure of the nervous system of the nematode *Caenorhabditis elegans*. *Philosophical Transactions of the Royal Society of London. B, Biological Sciences* , *314*(1165), 1–340. doi:10.1098/rstb.1986.0056

Zhang, Y.K., Sanchez-Ayala, M.A., Sternberg, P.W., Srinivasan, J., & Schroeder, F.C. (2017). Improved synthesis for modular ascarosides uncovers biological activity. *Organic Letters*, *19*(11), 2837–2840. doi:10.1021/acs.orglett.7b01009

Zhou, Y., Loeza-Cabrera, M., Liu, Z., Aleman-Meza, B., Nguyen, J.K., Jung, S.-K., … Zhong, W. (2017). Potential nematode alarm pheromone induces acute avoidance in *Caenorhabditis elegans*. *Genetics*, *206*(3), 1469–1478. doi:10.1534/genetics.116.197293