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Sources of behavioral variability in *C. elegans*: Sex differences, individuality, and internal states

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Animal behavior varies across different timescales. This includes rapid shifts in behavior as animals transition between states and long-term changes that develop throughout an organism's life. This review presents the contributions of sex differences, individuality, and internal states to behavioral variability in the roundworm *Caenorhabditis elegans*. Sex is determined by chromosome composition, which directs neuronal development through gene regulation and experience to shape dimorphic behaviors. Genetically identical individuals within the same sex and reared in the same conditions still display distinctive, long-lasting behavioral traits that are controlled by neuromodulatory systems. At all life stages, internal states within the individual, shaped by external factors like food and stress, modulate behavior over minutes to hours. The interplay between these factors gives rise to rich behavioral diversity in *C. elegans*. These factors impact behavior in a sequential manner, as genetic sex, individuality, and internal states influence behavior over progressively finer timescales.

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Introduction

Individual animals of a single species can exhibit a vast range of different behavioral outputs that vary based on their sex, life history, individuality, and sensory environment. This variability is essential for animals to adapt their behavior to an endless set of environmental conditions. While studying aggressive behaviors, the evolutionary biologist John Maynard Smith noted that variability is also a necessary condition for selection [1]. In behavior, as in genetics, variation provides the raw material of evolution.

The nematode *Caenorhabditis elegans* (*C. elegans*) has long been a pivotal model organism in the study of biology due to its simple nervous system, well-characterized development, and ease of genetic manipulation. Its compact, well-defined nervous system has also made it a premier model organism for systems neuroscience since it is feasible to relate the functions of specific neurons and circuits to behavior in this simple system [2]. This review explores the mechanistic sources of behavioral variability in *C. elegans*, focusing on three critical effectors: sex differences, individuality, and internal states.

Sex differences

In sexually reproducing organisms, sex determination mechanisms set the stage for sex-biased phenotypes, some appearing early, even before gonadal maturation, and others only after sexual maturation. In *C. elegans*, there is only one sex chromosome, X, and the mechanism of sex determination is based on the ratio of sex-chromosomes (X) to autosomes [3]. Animals carrying two X chromosomes are hermaphrodites (so-called for their ability to produce sperm and self-fertilize), whereas males carry one X chromosome (X0). The difference in the genetic composition of each cell of males and hermaphrodites generates a sex-dependent variation of individuals, beginning at the one-cell zygote. X chromosome dosage is translated into sexual fate via many genes that interact in a complex regulatory cascade. One crucial readout of this cascade is the expression of TRA-1, the master regulator of sexual differentiation in *C. elegans* [4]. In XX somatic cells, TRA-1 is ubiquitously expressed and specifies female development, whereas its absence allows male development. TRA-1 acts cell-autonomously to drive female fate, allowing the sexual differentiation of each somatic cell to occur independently of hormonal signals. This autonomy in TRA-1's action allows researchers to build direct links between individual neurons and behavior, controlling for sex as a biological variable. In the nervous

system, TRA-1 expression in neurons is initially restricted to a small set of neurons, but as development progresses, it increases variability among individuals [5]. It will be interesting to investigate how this striking variability in the pattern of TRA-1 accumulation in the nervous system translates into animal-to-animal variability in the extent of sexual differentiation in the nervous system.

The differences between the sexes extend beyond reproductive roles, influencing behaviors such as mating, foraging, and response to environmental cues, which have been linked to differences in neural circuitry and gene expression, as described below.

Individuality

Even when they are genetically identical and reared in the same environment, different individuals exhibit behavioral differences that are stable over long periods, spanning hours and days [6–9]. These consistent inter-individual behavioral differences define the property of individuality within populations. Understanding how individuality patterns develop across an organism's lifespan requires behavioral monitoring of single individuals throughout their developmental trajectory, under tightly controlled environmental conditions. The nematode *C. elegans*, with its short development time of just 2.5 days from egg hatching to adulthood, provides an ideal model for studying the genes, circuits, and environmental influences that shape inter-individual behavioral variation across developmental timescales [10–12]. Such variable behaviors among individuals include differences in exploratory behavior, instantaneous speed, and fast-timescale postural changes identified using unsupervised methods. Similarly, at the neuronal activity level, variable neuronal responses were also observed among isogenic individuals when exposed to the same stimulus [13]. As described below, studies have started to reveal specific neuromodulators and environmental effects that control behavioral variation within populations.

Internal states

Over the timescale of minutes to hours, the *C. elegans* nervous system switches between a wide range of internal states that influence how animals respond to external stimuli and behave. The generation of these states is influenced by the sensory environment, like the presence of food or harmful chemicals, so that animals alter their long-term behavioral patterns in a manner that matches their needs. Animals deprived of food alter their food-seeking behaviors based on their internal state of hunger [14,15]. Prolonged exposure to stressful stimuli can elicit short-term arousal, followed by stress-induced sleep [16–18]. In the context of foraging, animals switch between many distinct behavioral states that depend on their immediate sensory surroundings, feeding state, and other factors [14,19–21]. The internal state can also modulate how animal prioritize their needs; for example, starvation in males leads to the temporary prioritization of feeding over mate-searching [22]. As is described below, a common theme in the mechanistic underpinnings of these states is the involvement of neuromodulation, which can alter neural circuit function over these long timescales.

Behavior in a Waddington landscape

The behavioral outputs that adult animals exhibit are influenced by their genetic sex, individuality, and current internal state. These factors are naturally organized in a sequential fashion: genetic sex is specified early in development and sexual maturation occurs throughout development; individuality arises over development and persists for an entire lifespan; and internal states shift over minutes to hours at all life stages. These relationships can be captured as a Waddington landscape, which was originally used to describe the gradual progression of developmental trajectories (Fig. 1) [23]. In this framework, the behavioral patterns that an individual can express across development are constrained by the early influence of genetic sex, followed by changes due to life history and individuality, and finally, state-dependent changes. In the remainder of this review, we describe the neural mechanisms that underlie these sources of behavioral variability and highlight how they interact to shape behavior.

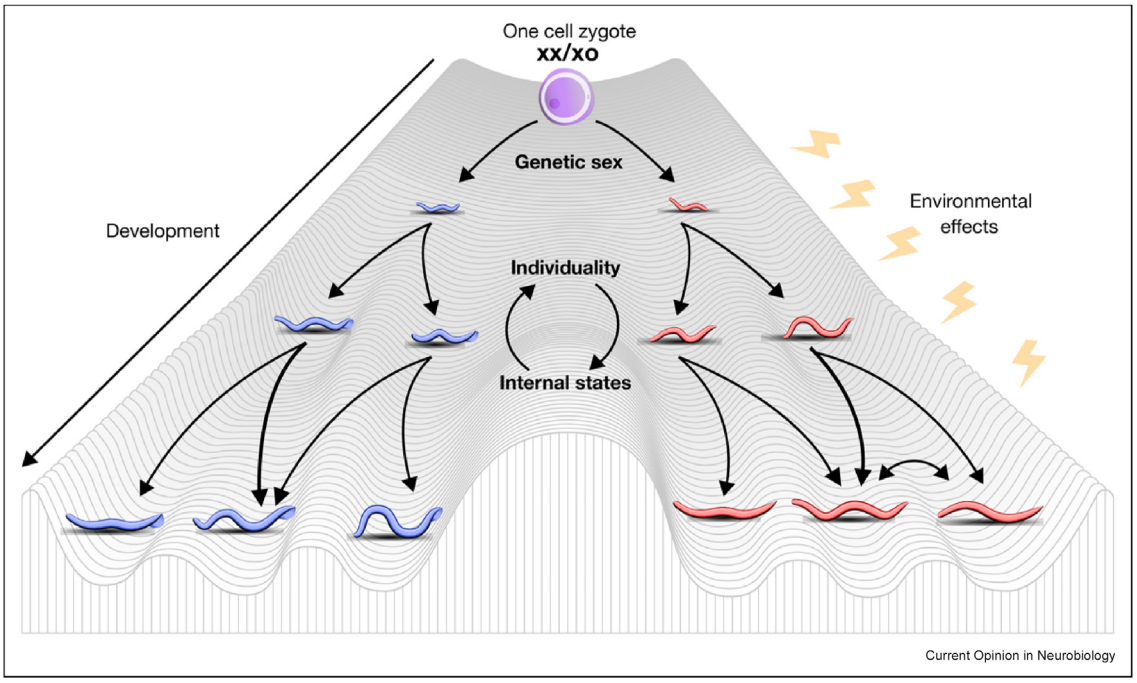
Themes

1. Genetic sex determines internal state responses

Like other organisms, in *C. elegans* genetic sex plays a pivotal role in determining the organism's responses to various internal states, such as stress, hunger, and reproductive readiness. Initially determined by the number of sex chromosomes, a genetic program distinguishes hermaphrodites and males, culminating at sexual maturation, where overt sex differences appear [24]. The presence of sex-specific neurons (2 in hermaphrodites, 93 in males) further diversify the neuronal network and its behavioral outputs. This sexual dimorphism in gene expression and neural circuitry ensures that each sex adopts behavior and physiological responses that are optimized for its unique reproductive and survival strategies.

Well-fed males usually prioritize mate searching and exploration over feeding [22,25]. This state-dependent food-leaving behavior is regulated by several mechanisms, including the activity of male-specific neurons [26] and PDF-1 neuropeptide signaling through PDFR-1 in sex-shared neurons [27]. The lower attraction of males to food is mediated by low expression levels of the

Figure 1



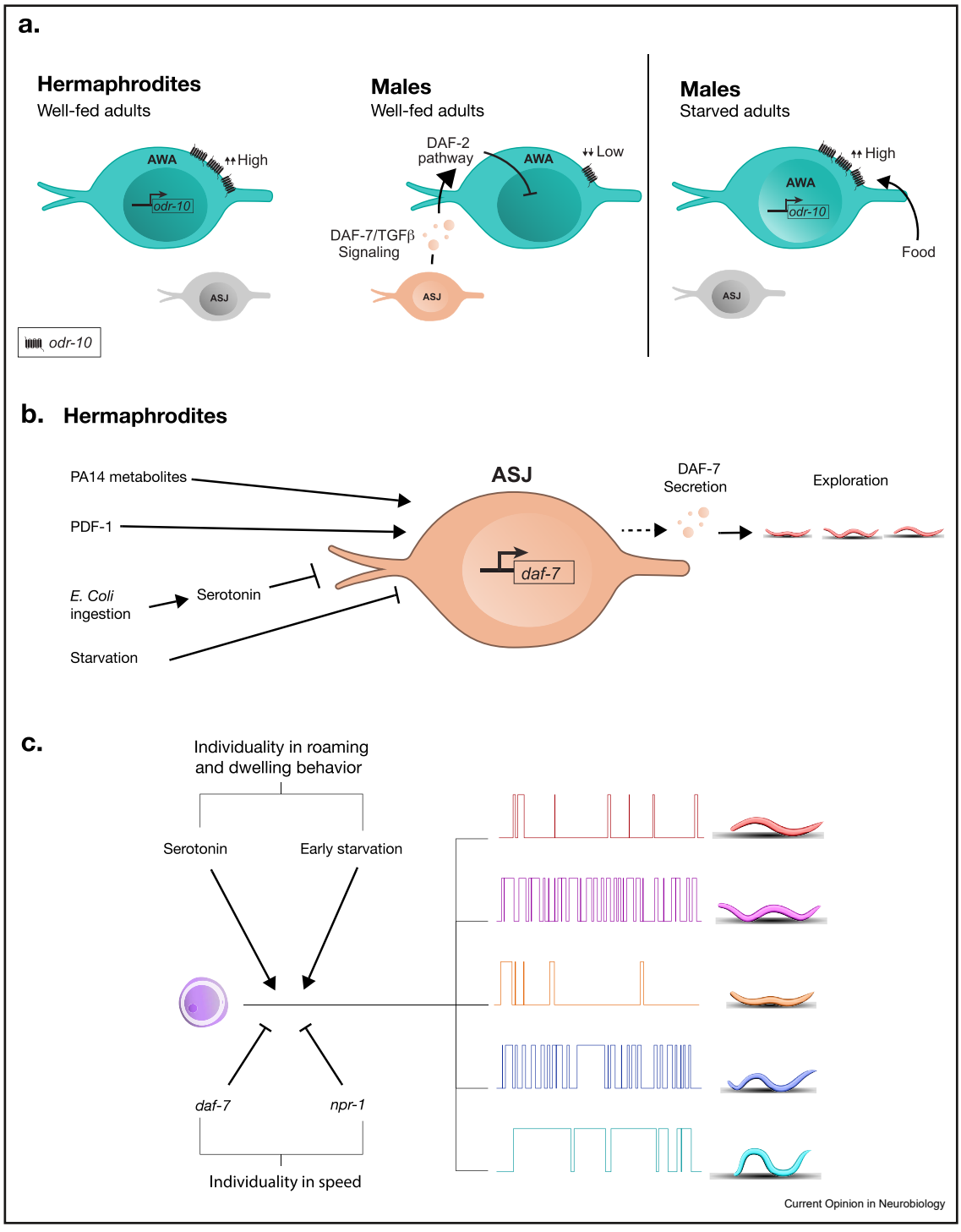
A Waddington landscape captures the effects of genetic sex, individuality, and internal state on behavioral variability in *C. elegans*. (a) The Waddington landscape [23] is a conceptual model used to illustrate how genetic and environmental factors interact to shape developmental pathways in a stable yet adaptable manner. Here, in the context of behavior, it represents developmental patterns of behavior and transitions between states as a ball rolling down a landscape, where each valley corresponds to a semi-stable state, influenced by both the organism's genetic makeup (e.g sexual identity), long-term individual biases, its internal states, and environmental interactions. Within the valleys of the landscape, individuals can transition between states.

chemoreceptor ODR-10 in the sensory neuron AWA, which senses diacetyl, a food-associated odor [28,29]. In hermaphrodites ODR-10 levels are high, determined by the genetic sex of AWA. ODR-10 expression levels in males are sensitive to food deprivation: in the absence of food, its levels increase, causing increased male attraction to food. Interestingly. TRA-1 seems to control, at least partially, the starvation-induced activation of ODR-10 [30]. These results highlights how sex-specific gene regulatory mechanisms can underlie the balance between behavioral states (Fig. 2a).

Two recent studies demonstrate the intricate mechanisms by which learning is also modulated by sex-specific internal states. One study showed that while hermaphrodites are able to learn to avoid pathogenic bacteria (PA14) [31,32] after a short training period, males do not learn to avoid the same bacteria over the same time scale [33]. This sex-specific learning discrepancy is attributed to differential activity in AWB and AIY neurons and the differential expression of the neuropeptide receptor *npr-5*, an ortholog of the mammalian NPY receptor, which modulates neuronal activity and thus learning in males. Investigation of the neuronal representation of the pathogen exposure experience reveals distinct sex-specific activation levels and responses to PA14 stimuli in the sensory neurons and interneurons. Interestingly, NPR-5 regulates male learning by modulating sensory neuronal activity. These results suggest that genetic sex can influence how sensory information is encoded or processed. Moreover, the ability of males to learn depends on their sexual status, placing the sexual state as an important determinant of the internal state, which in turn influences the specific behavioral output of the individual.

A second study focuses on the differential impact of rewarding and punishing experiences based on sex [34]. It demonstrates that males and hermaphrodites react differently to the same stimuli, after a bout of conditioning where animals were exposed to the stimuli in the absence or presence of mates. Sexual conditioning to salt is regulated by the PDF-1 neuropeptide [35], which modulates odor preference after sexual conditioning. Interestingly, PDF-1 can encode positive or negative valence, depending on the neuron it is secreted from and its target cells. These results underscore genetic sex as a determinant in the neural circuitry underlying how neuromodulators direct learning. Together, these studies reveal that genetic sex determines not just

Figure 2



Mechanisms that link genetic sex, internal states and individuality to behavior. (a) Receptor expression is modulated by genetic sex and internal states. In hermaphrodites, high levels of ODR-10 in AWA control attraction to Diacetyl (food source). ODR-10 expression in well-fed males is low due to the inhibitory action of DAF-7 secreted from ASJ, that activates DAF-2 signaling in AWA, leading to downregulation of *odr-10* expression. In starved males, ODR-10 levels increase, prioritizing feeding over mate searching. (b) The ASJ interneuron integrates a wide range of developmental, sensory, and state-related stimuli to control its expression of the *daf-7* gene, which influences the exploratory behavior of the organism. (c) Individuality in behavior is established across development, reflected by consistent behavioral activity patterns across stages that are variable among individuals (shown as a schematic ON-OFF trace for each individual). Different colors and shapes of the worms are meant to highlight their individuality. Serotonin and early-life starvation promote individuality in roaming and dwelling behavior and the neuronal genes *daf-7,* and *npr-1* restrict individuality in roaming speed.

features of baseline behavior but also how organisms interact with and learn from their environment. These studies also highlight a key role for neuropeptide signaling in sexually dimorphic behaviors. Recent advances in mapping the full neuropeptidergic connectome of *C. elegans* [36,37] will facilitate the identification of additional critical peptidergic systems.

2. Behavioral individuality is shaped by neuromodulatory systems

Neuromodulatory pathways are known to establish internal behavioral states that can be further modified by the past and current environmental experiences of an individual [38,39]. Specifically, central neuromodulators such as biogenic amines can affect the levels of inter-individual variation. For example, in the fruit fly *D. melanogaster*, a decrease in serotonin activity was shown to generate higher individual consistency levels in phototactic preference within isogenic populations [8], but decreased individual consistency in olfactory preference [40]. In *C. elegans*, the effects of neuromodulation on long-term patterns of individuality were studied across the complete developmental trajectory [10–12]. Long-term imaging of single worms at high spatiotemporal resolution and under tightly controlled environmental conditions revealed that a fraction of individuals within the wild-type populations had consistent biases in their roaming and dwelling behavior throughout all developmental windows (Fig. 2c). The neuromodulator serotonin, released by the NSM and HSN neurons, exerts strong control over roaming and dwelling states [21,41–43]. High serotonin levels increase dwelling behavior while low serotonin levels increase roaming. Animals lacking the *tph-1* gene, necessary for serotonin production, exhibited lower long-term consistency levels in the roaming activity of individuals across all developmental stages [10]. The decrease in individuality in roaming activity was recaptured in animals mutant for the serotonin receptor *ser-4*, suggesting that serotonin may act via specific receptors and potentially through specific neuronal circuits to shape individuality. In contrast, mutations in other neuronal genes such as *npr-1* (neuropeptide receptor), *daf*-7 (TGF-β), and *tdc-1* (necessary for tyramine/octopamine production) increased the levels of individuality in roaming speed within the population without affecting individuality levels in the fraction of time spent roaming. Overall, this study implicates specific neuromodulatory pathways in controlling long-term behavioral diversity among individuals.

More recent work extended the quantification of behavioral individuality using unsupervised detection of unique modes of body movements, which revealed changes in individuality levels across multiple populations subjected to neuromodulatory perturbations [12]. The variable effects of multiple neuromodulatory genes on individual variation, which may depend on the specific behavioral parameter, suggest that the effects of diverse neuromodulatory systems may be integrated to generate a 'profile' of individuality composed of different behaviors. The effects of the same neuromodulators on behavioral variation across different species implies a conserved evolutionary role for neuromodulatory signaling in shaping behavioral diversity within populations.

3. Early life experience impacts behavioral variation among individuals

The influence of environmental experiences on neuronal and behavioral states during distinct developmental stages has been explored in many species [44–48]. Sensory stimuli experienced during early life periods, known as critical periods, can generate life-long behavioral effects that are highly stable. Newly hatched *C. elegans* exposed to pathogenic PA14 bacteria show long-lasting aversive memory across development that is formed and executed using defined neural circuitry and neuromodulators [46]. Moreover, adult individuals that went through a starvation-induced dauer stage early in development show less behavioral exploration than animals that did not experience dauer. These behavioral changes were associated with changes in neurons that are known to be involved in navigation [49]. In addition, early life starvation during the L1 stage generates distinct behavioral responses across different developmental stages that are controlled via opposite functions of dopamine and serotonin [11].

While animals show stereotyped behavioral effects that are shared by many individuals within the population when exposed to the same environment, individuals can also show modes of behavioral responses that are unique. Previous studies in mice have demonstrated that environmental enrichment at an early stage can increase behavioral diversity [50]. In addition, environmental enrichment in flies led to changes in individual variation that depended on the behavior, genotype, and enrichment paradigm [51]. In *C. elegans*, analyzing behavioral variation among individuals across development, following starvation early in life (L1 arrest), revealed stress-induced changes in individuality [11]. In particular, by utilizing unsupervised methods for detecting temporal patterns of individual biases across development, it was demonstrated that multiple 'individuality types' exist within the isogenic population and that different stress regimes early in life can change the composition of these individuality types. In addition, the effects of early stress depend on the neuromodulatory state of the population [11]; for example, in serotonin-deficient individuals (*tph-1*) where consistency levels are relatively low, early-life starvation led to

increased consistency in roaming activity. Overall, these effects of early-life experiences on both the average behavioral response of the population, as well as on the diversity in behavioral responses within the population, suggest a close interaction between the environment and the nervous system in generating variation, even within isogenic populations that are exposed to the same early environment. An open question is whether generating or constraining behavioral variation by the environment may have a fitness effect on the isogenic population. A plausible hypothesis is that upon a stressful or unpredictable environment, it will be beneficial to increase variation in behavioral strategies, thus increasing the probability of the population to survive a wide diversity of scenarios [52,53].

4. Gene expression as a source of variability in behavior

In many instances, changes in gene expression have been identified as a causal source of behavioral variability. Gene expression can differ across individuals, over development, and dynamically in adulthood, providing a flexible means to alter neural function. As is described above, transcriptional changes due to genetic sex are widespread in *C. elegans*. Recently, these effects have been mapped across development. Comparison of the whole transcriptome of males and hermaphrodites from early larval stages to adulthood uncovered numerous differentially expressed genes, including neuronal gene families like transcription factors, neuropeptides, and GPCRs, highlighting the notion that molecular mechanisms might drive sex-specific traits at each developmental stage [54].

Across both sexes, the *daf*-7 gene provides an instructive example of how gene expression can be influenced by many factors to alter behavior. While *daf*-7 is expressed in ASI neurons in both males and hermaphrodites, it is also expressed in ASJ neurons in male *C. elegans*, which drives an exploratory mate-seeking behavior [55]. This ASJ-specific expression in males is driven by the PDF neuropeptide system [56], which promotes exploratory behaviors under many circumstances. In hermaphrodites, *daf*-7 becomes expressed in ASJ neurons only under specific circumstances related to the animal's internal state. ASJ plays a key role in exploratory food-leaving decisions in healthy hermaphrodites [57]. In addition, infection by a pathogen leads to *daf*-7 expression in ASJ, which induces exploratory food-leaving behavior to avoid the pathogenic food source [58]. Animals that can smell food that they are not currently ingesting upregulate *daf*-7 in ASJ, which contributes to their exploratory food search [59]. These studies suggest that the regulation of *daf*-7 expression in ASJ based on a multitude of factors controls exploratory behaviors under different circumstances (Fig. 2b).

Changes in feeding state have also been shown to cause changes in gene expression in many cases. Adult hermaphrodites deprived of food upregulate a large set of olfactory receptors, which contribute to hunger state-dependent behavioral changes [60—62]. Similar signatures of gene expression can be found in larval animals that have passed through dauer diapause arrest [63]. Metabolic changes can also impact expression of *daf*-7 expression in ASI neurons [64]. In addition, starvation of young larvae alters the expression of a biosynthetic enzyme required for octopamine production, which can have a long-lasting impact on circuit function by altering synaptic pruning [65]. Moreover, stochastic differences in gene-expression [66,67] may also be a potential source of variation in neuronal function. Through these diverse mechanisms, changes in gene expression can cause immediate or long-lasting changes in behavior.

5. Variability in nervous system structure contributes to behavioral variation

Neuronal connections, or connectomes, are critical determinants of an animal's behavioral repertoire, linking the structural intricacies of neural circuits directly to the execution of complex behaviors. The *C. elegans* wiring diagram has been crucial for mapping circuits and linking them to behavior, and the completion of the male connectome almost three decades after that of the hermaphrodite has added considerable depth to our ability to deconstruct sex-specific behaviors [68—70]. In addition, a connectome from an animal in dauer diapause has also been reconstructed recently, which will aid our understanding of early-life stress on connectivity [71]. However, given the nervous system's ability to adapt its connections based on experience and inter-animal variability, it was unclear whether these static maps of connectivity were representative of all animals. A recent study added valuable data by reconstructing the nerve ring connectomes of eight additional animals across development [72]. This study found that isogenic animals exhibited both stereotyped and variable connections. The layout of the interneuron circuit, the "decision-making" portion of the nervous system, remains largely stable across development and between individuals. However, maturation changes how sensory information is integrated and relayed to downstream neurons. Thus, variation in nervous system structure occurs across development and between individuals. In addition, it was estimated that more than 30 % of the connections vary between hermaphrodites and males [70]. Since only one male connectome currently exists, it is hard to evaluate, solely based on those electron-micrograph reconstructions, the extent of sex-dependent wiring variability in *C. elegans*. Sexually dimorphic behavioral responses to aversive stimuli have been previously reported in *C. elegans* [73]. Imaging of interneurons in response to aversive stimuli revealed

variability in their activity across male individuals, where some males exhibited hermaphrodite-like neuronal activity levels [73]. It is possible that such functional differences may arise from variability in connectivity between individual males. Future work will be necessary to evaluate the relationship between sex, connectivity, and behavior at the individual animal level.

Concluding remarks

The individual's genetics, developmental trajectory, and environmental influences converge to shape its behavioral repertoire. This review has highlighted the sequential organization of these factors, from genetic sex determination to the modulation by internal states, each layer adding complexity and adaptability to behavioral outcomes. As research progresses, further exploration into this behavioral landscape will enhance our understanding of the robust yet flexible nature of behavior.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

References

Papers of particular interest, published within the period of review, have been highlighted as:

** of outstanding interest

1. Maynard Smith J, Harper DG: **The evolution of aggression: can selection generate variability?** *Philos Trans R Soc Lond B Biol Sci* 1988, **319**:557–570, https://doi.org/10.1098/rstb.1988.0065.

2. Sengupta P, Samuel ADT: **Caenorhabditis elegans: a model system for systems neuroscience**. *Curr Opin Neurobiol* 2009, **19**:637–643, https://doi.org/10.1016/j.conb.2009.09.009.

3. Zarkower D: **Somatic sex determination**. *WormBook Online Rev C Elegans Biol* 2006:1–12, https://doi.org/10.1895/wormbook.1.84.1.

4. Hunter CP, Wood WB: **The tra-1 gene determines sexual phenotype cell-autonomously in C. elegans**. *Cell* 1990, **63**: 1193–1204, https://doi.org/10.1016/0092-8674(90)90415-b.

5. Bayer EA, Sun H, Rafi I, Hobert O: **Temporal, spatial, sexual and environmental regulation of the master regulator of sexual differentiation in C. elegans**. *Curr Biol CB* 2020, **30**: 3604–3616.e3, https://doi.org/10.1016/j.cub.2020.06.060.

6. Bierbach D, Laskowski KL, Wolf M: **Behavioural individuality in clonal fish arises despite near-identical rearing conditions**. *Nat Commun* 2017, **8**, 15361, https://doi.org/10.1038/ncomms15361.

7. Freund J, Brandmaier AM, Lewejohann L, Kirste I, Kritzler M, Krüger A, Sachser N, Lindenberger U, Kempermann G: **Emergence of individuality in genetically identical mice**. *Science* 2013, **340**:756–759, https://doi.org/10.1126/science.1235294.

8. Kain JS, Stokes C, de Bivort BL: **Phototactic personality in fruit flies and its suppression by serotonin and white**. *Proc Natl Acad Sci USA* 2012, **109**:19834–19839, https://doi.org/10.1073/pnas.1211988109.

9. Schuett W, Dall SRX, Baeumer J, Kloesener MH, Nakagawa S, Beinlich F, Eggers T: **Personality variation in a clonal insect: the pea aphid, Acyrthosiphon pisum**. *Dev Psychobiol* 2011, **53**: 631–640, https://doi.org/10.1002/dev.20538.

10. Stern S, Kirst C, Bargmann CI: **Neuromodulatory control of long-term behavioral patterns and individuality across development**. *Cell* 2017, **171**:1649–1662.e10, https://doi.org/10.1016/j.cell.2017.10.041.

11. ** Ali Nasser R, Harel Y, Stern S: **Early-life experience reorganizes neuromodulatory regulation of stage-specific behavioral responses and individuality dimensions during development**. *Elife* 2023, **12**, e84312, https://doi.org/10.7554/eLife.84312.
This study highlights the combined contribution of both the early-life environment and the neuromoduatory state of the population for establishing a spectrum of individuality types within isogenic populations.

12. Harel Y, Nasser RA, Stern S: **Mapping the developmental structure of stereotyped and individual-unique behavioral spaces in C. elegans**. *Cell Rep* 2024, **43**, 114683, https://doi.org/10.1016/j.celrep.2024.114683.

13. Couto A, Oda S, Nikolaev VO, Soltesz Z, de Bono M: ***In vivo* genetic dissection of O2-evoked cGMP dynamics in a Caenorhabditis elegans gas sensor**. *Proc Natl Acad Sci USA* 2013, **110**:E3301–E3310, https://doi.org/10.1073/pnas.1217428110.

14. Ben Arous J, Laffont S, Chatenay D: **Molecular and sensory basis of a food related two-state behavior in C. elegans**. *PLoS One* 2009, **4**, e7584, https://doi.org/10.1371/journal.pone.0007584.

15. Sawin ER, Ranganathan R, Horvitz HR: **C. elegans locomotory rate is modulated by the environment through a dopaminergic pathway and by experience through a serotonergic pathway**. *Neuron* 2000, **26**:619–631, https://doi.org/10.1016/s0896-6273(00)81199-x.

16. Ardiel EL, Yu AJ, Giles AC, Rankin CH: **Habituation as an adaptive shift in response strategy mediated by neuropeptides**. *NPJ Sci Learn* 2017, **2**:9, https://doi.org/10.1038/s41539-017-0011-8.

17. Chew YL, Tanizawa Y, Cho Y, Zhao B, Yu AJ, Ardiel EL, Rabinowitch I, Bai J, Rankin CH, Lu H, *et al.*: **An afferent neuropeptide system transmits mechanosensory signals**

triggering sensitization and arousal in C. elegans. *Neuron* 2018, **99**:1233–1246.e6, https://doi.org/10.1016/j.neuron.2018.08.003.

18. Hill AJ, Mansfield R, Lopez JMNG, Raizen DM, Van Buskirk C: **Cellular stress induces a protective sleep-like state in C. elegans**. *Curr Biol CB* 2014, **24**:2399–2405, https://doi.org/10.1016/j.cub.2014.08.040.

19. Gray JM, Hill JJ, Bargmann CI: **A circuit for navigation in Caenorhabditis elegans**. *Proc Natl Acad Sci USA* 2005, **102**:3184–3191, https://doi.org/10.1073/pnas.0409009101.

20. Fujiwara M, Sengupta P, McIntire SL: **Regulation of body size and behavioral state of C. elegans by sensory perception and the EGL-4 cGMP-dependent protein kinase**. *Neuron* 2002, **36**:1091–1102.

21. Flavell SW, Pokala N, Macosko EZ, Albrecht DR, Larsch J, Bargmann CI: **Serotonin and the neuropeptide PDF initiate and extend opposing behavioral states in C. elegans**. *Cell* 2013, **154**:1023–1035, https://doi.org/10.1016/j.cell.2013.08.001.

22. Lipton J, Kleemann G, Ghosh R, Lints R, Emmons SW: **Mate searching in Caenorhabditis elegans: a genetic model for sex drive in a simple invertebrate**. *J Neurosci Off J Soc Neurosci* 2004, **24**:7427–7434, https://doi.org/10.1523/JNEUROSCI.1746-04.2004.

23. Waddington CH: *The strategy of the genes: a discussion of some aspects of theoretical biology*. Allen & Unwin; 1957.

24. Salzberg Y, Gat A, Oren-Suissa M: **One template, two outcomes: how does the sex-shared nervous system generate sex-specific behaviors?** *Curr Top Dev Biol* 2021, **144**:245–268, https://doi.org/10.1016/bs.ctdb.2020.08.003.

25. Barrios A: **Exploratory decisions of the Caenorhabditis elegans male: a conflict of two drives**. *Semin Cell Dev Biol* 2014, **33**:10–17, https://doi.org/10.1016/j.semcdb.2014.06.003.

26. Barrios A, Nurrish S, Emmons SW: **Sensory regulation of C. elegans male mate-searching behavior**. *Curr Biol CB* 2008, **18**:1865–1871, https://doi.org/10.1016/j.cub.2008.10.050.

27. Barrios A, Ghosh R, Fang C, Emmons SW, Barr MM: **PDF-1 neuropeptide signaling modulates a neural circuit for mate-searching behavior in C. elegans**. *Nat Neurosci* 2012, **15**:1675–1682, https://doi.org/10.1038/nn.3253.

28. Ryan DA, Miller RM, Lee K, Neal SJ, Fagan KA, Sengupta P, Portman DS: **Sex, age, and hunger regulate behavioral prioritization through dynamic modulation of chemoreceptor expression**. *Curr Biol CB* 2014, **24**:2509–2517, https://doi.org/10.1016/j.cub.2014.09.032.

29. ** Wexler LR, Miller RM, Portman DS: **C. elegans males integrate food signals and biological sex to modulate state-dependent chemosensation and behavioral prioritization**. *Curr Biol CB* 2020, **30**:2695–2706.e4, https://doi.org/10.1016/j.cub.2020.05.006.
This study underscores the complex interplay between genetic and environmental factors, revealing how biological sex and feeding state dynamically regulate the expression of the chemoreceptor ODR-10 to mediate behavioral plasticity in response to changing conditions.

30. Lawson HN, Wexler LR, Wnuk HK, Portman DS: **Dynamic, non-binary specification of sexual state in the C. elegans nervous system**. *Curr Biol CB* 2020, **30**:3617–3623.e3, https://doi.org/10.1016/j.cub.2020.07.007.

31. Tan MW, Mahajan-Miklos S, Ausubel FM: **Killing of Caenorhabditis elegans by Pseudomonas aeruginosa used to model mammalian bacterial pathogenesis**. *Proc Natl Acad Sci USA* 1999, **96**:715–720, https://doi.org/10.1073/pnas.96.2.715.

32. Zhang Y, Lu H, Bargmann CI: **Pathogenic bacteria induce aversive olfactory learning in Caenorhabditis elegans**. *Nature* 2005, **438**:179–184, https://doi.org/10.1038/nature04216.

33. ** Peedikayil-Kurien S, Haque R, Gat A, Oren-Suissa M: **: Modulation by NPY/NPF-like receptor underlies experience-dependent, sexually dimorphic learning**. *Nat Commun* 2025, **16**:662.
This study reveals sex-specific adaptations in *C. elegans* learning, showing that males and hermaphrodites process the same environmental threats differently due to the action of the neuropeptide receptor NPR-5, which regulates neuronal activity and learning in males. By highlighting the role of NPR-5 as a 'sensory gatekeeper,' the research underscores the evolutionary importance of tailored behavioral responses to optimize survival and reproduction.

34. Molina-García L, Colinas-Fischer S, Benavides-Laconcha S, Lin L, Clark E, Treloar NJ, García-Minaur-Ortíz B, Butts M, Barnes CP, Barrios A: **Conflict during learning reconfigures the neural representation of positive valence and approach behavior**. *Curr Biol CB* 2024, **34**:5470–5483.e7, https://doi.org/10.1016/j.cub.2024.10.024.

35. ** Sammut M, Cook SJ, Nguyen KCQ, Felton T, Hall DH, Emmons SW, Poole RJ, Barrios A: **Glia-derived neurons are required for sex-specific learning in C. elegans**. *Nature* 2015, **526**:385–390, https://doi.org/10.1038/nature15700.
This study investigates how male-specific interneurons, derived from glial progenitors during sexual maturation, integrate into existing neural circuits to align behavioral responses with reproductive priorities.

36. Beets I, Zels S, Vandewyer E, Demeulemeester J, Caers J, Baytemur E, Courtney A, Golinelli L, Hasakioğullarõ I, Schafer WR, *et al.*: **System-wide mapping of peptide-GPCR interactions in C. elegans**. *Cell Rep* 2023, **42**, 113058, https://doi.org/10.1016/j.celrep.2023.113058.

37. Ripoll-Sánchez L, Watteyne J, Sun H, Fernandez R, Taylor SR, Weinreb A, Bentley BL, Hammarlund M, Miller DM, Hobert O, *et al.*: **The neuropeptidergic connectome of C. elegans**. *Neuron* 2023, **111**:3570–3589.e5, https://doi.org/10.1016/j.neuron.2023.09.043.

38. Flavell SW, Gordus A: **Dynamic functional connectivity in the static connectome of Caenorhabditis elegans**. *Curr Opin Neurobiol* 2022, **73**, 102515, https://doi.org/10.1016/j.conb.2021.12.002.

39. Bargmann CI, Marder E: **From the connectome to brain function**. *Nat Methods* 2013, **10**:483–490, https://doi.org/10.1038/nmeth.2451.

40. Honegger KS, Smith MA-Y, Churgin MA, Turner GC, de Bivort BL: **Idiosyncratic neural coding and neuromodulation of olfactory individuality in Drosophila**. *Proc Natl Acad Sci USA* 2020, **117**:23292–23297, https://doi.org/10.1073/pnas.1901623116.

41. Rhoades JL, Nelson JC, Nwabudike I, Yu SK, McLachlan IG, Madan GK, Abebe E, Powers JR, Colón-Ramos DA, Flavell SW: **ASICs mediate food responses in an enteric serotonergic neuron that controls foraging behaviors**. *Cell* 2019, **176**:85–97.e14, https://doi.org/10.1016/j.cell.2018.11.023.

42. Huang Y-C, Luo J, Huang W, Baker CM, Gomes MA, Meng B, Byrne AB, Flavell SW: **A single neuron in C. elegans orchestrates multiple motor outputs through parallel modes of transmission**. *Curr Biol CB* 2023, **33**:4430–4445.e6, https://doi.org/10.1016/j.cub.2023.08.088.

43. ** Dag U, Nwabudike I, Kang D, Gomes MA, Kim J, Atanas AA, Bueno E, Estrem C, Pugliese S, Wang Z, *et al.*: **Dissecting the functional organization of the C. elegans serotonergic system at whole-brain scale**. *Cell* 2023, **186**:2574–2592.e20, https://doi.org/10.1016/j.cell.2023.04.023.
This study characterized the functional architecture of the serotonergic system in *C. elegans*, which promotes the dwelling state. A combination of behavioral genetics and brain-wide calcium imaging highlighted how serotonin action of different receptor types impacts brain-wide activity.

44. Lorenz KZ: **The companion in the bird's world**. *The Auk* 1937, **54**:245–273, https://doi.org/10.2307/4078077.

45. Korosi A, Naninck EFG, Oomen CA, Schouten M, Krugers H, Fitzsimons C, Lucassen PJ: **Early-life stress mediated modulation of adult neurogenesis and behavior**. *Behav Brain Res* 2012, **227**:400–409, https://doi.org/10.1016/j.bbr.2011.07.037.

46. Jin X, Pokala N, Bargmann CI: **Distinct circuits for the formation and retrieval of an imprinted olfactory memory**. *Cell* 2016, **164**:632–643, https://doi.org/10.1016/j.cell.2016.01.007.

47. Remy J-J, Hobert O: **An interneuronal chemoreceptor required for olfactory imprinting in C. elegans**. *Science* 2005, **309**:787–790, https://doi.org/10.1126/science.1114209.

48. Nevitt GA, Dittman AH, Quinn TP, Moody WJ: **Evidence for a peripheral olfactory memory in imprinted salmon**. *Proc Natl Acad Sci USA* 1994, **91**:4288–4292, https://doi.org/10.1073/pnas.91.10.4288.

49. ** Pradhan S, Quilez S, Homer K, Hendricks M: **Environmental programming of adult foraging behavior in C. elegans**. *Curr Biol CB* 2019, **29**:2867–2879.e4, https://doi.org/10.1016/j.cub.2019.07.045.
This study reveals how early-life experiences, such as starvation, can permanently influence foraging strategies in *C. elegans*, leading to a more cautious approach characterized by reduced exploration.

50. Zocher S, Schilling S, Grzyb AN, Adusumilli VS, Bogado Lopes J, Günther S, Overall RW, Winter Y, Kempermann G: **Early-life environmental enrichment generates persistent individualized behavior in mice**. *Sci Adv* 2020, **6**, eabb1478, https://doi.org/10.1126/sciadv.abb1478.

51. Akhund-Zade J, Ho S, O'Leary C, de Bivort B: **The effect of environmental enrichment on behavioral variability depends on genotype, behavior, and type of enrichment**. *J Exp Biol* 2019, **222**, jeb202234, https://doi.org/10.1242/jeb.202234.

52. Cooper WS, Kaplan RH: **Adaptive "coin-flipping": a decision-theoretic examination of natural selection for random individual variation**. *J Theor Biol* 1982, **94**:135–151, https://doi.org/10.1016/0022-5193(82)90336-8.

53. Honegger K, de Bivort B: **Stochasticity, individuality and behavior**. *Curr Biol CB* 2018, **28**:R8–R12, https://doi.org/10.1016/j.cub.2017.11.058.

54. Haque R, Kurien SP, Setty H, Salzberg Y, Stelzer G, Litvak E, Gingold H, Rechavi O, Oren-Suissa M: **Sex-specific developmental gene expression atlas unveils dimorphic gene networks in C. elegans**. *Nat Commun* 2024, **15**:4273, https://doi.org/10.1038/s41467-024-48369-z.

55. Hilbert ZA, Kim DH: **Sexually dimorphic control of gene expression in sensory neurons regulates decision-making behavior in C. elegans**. *Elife* 2017, **6**, e21166, https://doi.org/10.7554/eLife.21166.

56. ** Hilbert ZA, Kim DH: **PDF-1 neuropeptide signaling regulates sexually dimorphic gene expression in shared sensory neurons of C. elegans**. *Elife* 2018, **7**, e36547, https://doi.org/10.7554/eLife.36547.
This paper highlights how neuromodulatory systems, like the PDF neuropeptide system, and genetic sex interact to shape neuronal gene expression, which impacts behavior.

57. Scheer E, Bargmann CI: **Sensory neurons couple arousal and foraging decisions in Caenorhabditis elegans**. *Elife* 2023, **12**, RP88657, https://doi.org/10.7554/eLife.88657.

58. Meisel JD, Panda O, Mahanti P, Schroeder FC, Kim DH: **Chemosensation of bacterial secondary metabolites modulates neuroendocrine signaling and behavior of C. elegans**. *Cell* 2014, **159**:267–280, https://doi.org/10.1016/j.cell.2014.09.011.

59. Boor SA, Meisel JD, Kim DH: **Neuroendocrine gene expression coupling of interoceptive bacterial food cues to foraging behavior of C. elegans**. *Elife* 2024, **12**, RP91120, https://doi.org/10.7554/eLife.91120.

60. McLachlan IG, Kramer TS, Dua M, DiLoreto EM, Gomes MA, Dag U, Srinivasan J, Flavell SW: **Diverse states and stimuli tune olfactory receptor expression levels to modulate food-seeking behavior**. *Elife* 2022, **11**, e79557, https://doi.org/10.7554/eLife.79557.

61. van der Linden AM, Nolan KM, Sengupta P: **KIN-29 SIK regulates chemoreceptor gene expression via an MEF2 transcription factor and a class II HDAC**. *EMBO J* 2007, **26**:358–370, https://doi.org/10.1038/sj.emboj.7601479.

62. Sengupta P: **The belly rules the nose: feeding state-dependent modulation of peripheral chemosensory responses**. *Curr Opin Neurobiol* 2013, **23**:68–75, https://doi.org/10.1016/j.conb.2012.08.001.

63. Kyani-Rogers T, Philbrook A, McLachlan IG, Flavell SW, O'Donnell MP, Sengupta P: **Developmental history modulates adult olfactory behavioral preferences via regulation of chemoreceptor expression in Caenorhabditiselegans**. *Genetics* 2022, **222**, iyac143, https://doi.org/10.1093/genetics/iyac143.

64. O'Donnell MP, Chao P-H, Kammenga JE, Sengupta P: **Rictor/TORC2 mediates gut-to-brain signaling in the regulation of phenotypic plasticity in C. elegans**. *PLoS Genet* 2018, **14**, e1007213, https://doi.org/10.1371/journal.pgen.1007213.

65. Bayer EA, Hobert O: **Past experience shapes sexually dimorphic neuronal wiring through monoaminergic signalling**. *Nature* 2018, **561**:117–121, https://doi.org/10.1038/s41586-018-0452-0.

66. Casanueva MO, Burga A, Lehner B: **Fitness trade-offs and environmentally induced mutation buffering in isogenic C. elegans**. *Science* 2012, **335**:82–85, https://doi.org/10.1126/science.1213491.

67. Raj A, Rifkin SA, Andersen E, van Oudenaarden A: **Variability in gene expression underlies incomplete penetrance**. *Nature* 2010, **463**:913–918, https://doi.org/10.1038/nature08781.

68. White JG, Southgate E, Thomson JN, Brenner S: **The structure of the nervous system of the nematode Caenorhabditis elegans**. *Philos Trans R Soc Lond B Biol Sci* 1986, **314**:1–340.

69. Jarrell TA, Wang Y, Bloniarz AE, Brittin CA, Xu M, Thomson JN, Albertson DG, Hall DH, Emmons SW: **The connectome of a decision-making neural network**. *Science* 2012, **337**:437–444, https://doi.org/10.1126/science.1221762.

70. Cook SJ, Jarrell TA, Brittin CA, Wang Y, Bloniarz AE, Yakovlev MA, Nguyen KCQ, Tang LT-H, Bayer EA, Duerr JS, *et al.*: **Whole-animal connectomes of both Caenorhabditis elegans sexes**. *Nature* 2019, **571**:63–71, https://doi.org/10.1038/s41586-019-1352-7.

71. Yim H, Choe DT, Bae JA, Choi M-K, Kang H-M, Nguyen KCQ, Ahn S, Bahn S-K, Yang H, Hall DH, *et al.*: **Comparative connectomics of dauer reveals developmental plasticity**. *Nat Commun* 2024, **15**:1546, https://doi.org/10.1038/s41467-024-45943-3.

72. ** Witvliet D, Mulcahy B, Mitchell JK, Meirovitch Y, Berger DR, Wu Y, Liu Y, Koh WX, Parvathala R, Holmyard D, *et al.*: **Connectomes across development reveal principles of brain maturation**. *Nature* 2021, **596**:257–261, https://doi.org/10.1038/s41586-021-03778-8.
This paper shows both stable and variable neuronal connections across development in the *C. elegans* nervous system. By comparing across single animals, the study reveals inter-individual variation in connectome structure that may potentially impact individual-specific behaviors.

73. Pechuk V, Goldman G, Salzberg Y, Chaubey AH, Bola RA, Hoffman JR, Endreson ML, Miller RM, Reger NJ, Portman DS, *et al.*: **Reprogramming the topology of the nociceptive circuit in C. elegans reshapes sexual behavior**. *Curr Biol CB* 2022, **32**:4372–4385.e7, https://doi.org/10.1016/j.cub.2022.08.038.