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Publication Date
2018-11-01

DOI
10.1016/j.neulet.2018.10.023

Peer reviewed

HHS Public Access

Author manuscript

Neurosci Lett. Author manuscript; available in PMC 2019 November 20.

Published in final edited form as:

Neurosci Lett. 2018 November 20; 687: 290–303. doi:10.1016/j.neulet.2018.10.023.

Temperature-dependent behaviors of parasitic helminths

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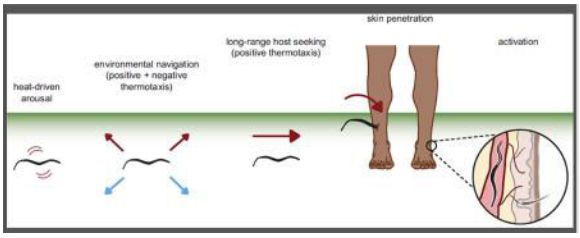
Abstract

Parasitic helminth infections are the most common source of neglected tropical disease among impoverished global communities. Many helminths infect their hosts via an active, sensory-driven process in which environmentally motile infective larvae position themselves near potential hosts. For these helminths, host seeking and host invasion can be divided into several discrete behaviors that are regulated by both host-emitted and environmental sensory cues, including heat. Thermosensation is a critical sensory modality for helminths that infect warm-blooded hosts, driving multiple behaviors necessary for host seeking and host invasion. Furthermore, thermosensory cues influence the host-seeking behaviors of both helminths that parasitize endothermic hosts and helminths that parasitize insect hosts. Here, we discuss the role of thermosensation in guiding the host-seeking and host-infection behaviors of a diverse group of helminths, including mammalian-parasitic nematodes, entomopathogenic nematodes, and schistosomes. We also discuss the neural circuitry and molecular pathways that underlie thermosensory responses in these species.

Graphical Abstract



Keywords

parasitic helminth; parasitic nematode; schistosomes; thermosensation; host seeking; sensory behavior

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12. Declarations of interest: none.

1. Introduction

Approximately 1 billion people are infected with harmful parasitic helminths, primarily within resource-limited communities located in tropical and subtropical climates [1–8]. Harmful parasitic helminths are classified into two phyla: Nematoda, which includes gastrointestinal nematodes; and Platyhelminthes, which includes schistosomes, other trematodes, and cestodes [9]. Chronic helminth infections in humans can lead to clinical symptoms such as gastrointestinal distress, cognitive impairment and stunted growth in children, anemia in the case of hookworms, cancer in the case of some trematode species, increased HIV infection rates in the case of some schistosome species, and even death in the case of the gastrointestinal nematode *Strongyloides stercoralis* and schistosomes [1–6,8–14]. Furthermore, helminth infections of livestock are common in both resource-rich and resource-limited countries, and are a major source of economic disruption due to reductions in livestock productivity [15–18]. In contrast to the harmful parasitic helminths, entomopathogenic nematodes (EPNs) in the genera *Heterorhabditis* and *Steinernema* are considered beneficial parasitic nematodes. EPNs infect and kill a wide variety of insect larvae, and are commonly used as biological control agents for insect pests [19–23].

Current treatment strategies for helminth infections in both humans and livestock are based on reducing the worm burden of ongoing infections via anthelminthic drugs. This strategy fails to prevent reinfection, and repeated drug treatments have driven the emergence of drug-resistant strains of livestock parasites; a similar phenomenon is expected to develop among human-parasitic helminths in the near future [15–17,24–26]. New treatment options or preventative strategies capable of eliminating or reducing the incidence of helminth infection in humans and livestock are needed. For many parasitic helminth species, one promising yet largely unexplored target for intervention is the infective larval stage, which lives outside of the host animal in soil or water. Species with an environmental infective stage include the soil-transmitted hookworm and *Strongyloides* species, and the water-transmitted schistosomes [27]. For many of these species, larvae located in the environment respond to host-emitted and environmental sensory cues, including heat and odors [19,28]. How these sensory signals maximize the chances that harmful infective larvae will find hosts is poorly understood. A better understanding of this process may enable the development of new prevention strategies that target infective larvae, such as traps or repellents. Furthermore, by understanding the effect of environmental temperatures on the behaviors of parasitic helminths, we may better predict the impact of global climate change on the transmission of soil-transmitted helminths [29,30]. In the case of EPNs, which also have an environmental infective larval stage, an improved understanding of the environmental conditions that regulate host seeking and infectivity could be useful in expanding their efficacy for pest management [23].

Many soil-transmitted mammalian-parasitic nematodes are infective as developmentally arrested third-stage larvae (iL3s). Some iL3s actively invade hosts via skin penetration, whereas others infect passively when they are swallowed (Fig. 1A-C). Skin-penetrating species include *Strongyloides stercoralis* and other species in the genus *Strongyloides*, as well as hookworms in the genera *Ancylostoma* and *Necator*. Passively ingested species include human-infective nodular worms in the genus *Oesophagostomum*, the rodent-

parasitic nematode *Heligmosomoides polygyrus*, and the ruminant-parasitic nematode *Haemonchus contortus* [31–35]. In addition, some skin-penetrating *Ancylostoma* species are known to be capable of infecting via passive ingestion [36–39]. Following host invasion, iL3s resume development, a process called "activation" [40–46]. The nematodes then migrate through the body, continuing to develop until they ultimately take up residence in the small intestine as reproductive adults [2]. The eggs and larvae of parasitic adults re-enter the environment with feces. For most soil-transmitted parasitic nematodes, the progeny of parasitic adults develop directly into iL3s. However, some *Strongyloides* species can develop through a limited number of free-living generations before developmentally arresting as iL3s [27].

The insect-parasitic EPNs also infect hosts as environmentally motile third-stage infective larvae, called infective juveniles (IJs). The IJ stage of EPNs is developmentally similar to the iL3 stage of soil-transmitted nematodes that parasitize vertebrate hosts (Fig. 1D) [23]. Like iL3s, IJs located in the soil or on plants activity seek out hosts in response to environmental and host-emitted sensory cues [19,47–49]. IJs invade and then rapidly kill their insect hosts; the cadaver can then serve as a food source for multiple parasitic generations [50,51]. Eventually, resource depletion within the insect cadaver triggers the formation of IJs that disperse into the environment [50].

Unlike soil-transmitted nematodes, the water-transmitted trematode life cycle requires both an intermediate and a definitive host (Fig. 1E) [27]. For *Schistosoma* species, free-swimming infective larvae called miracidia hatch from eggs and seek out and infect aquatic snails [52,53]. Inside the intermediate snail host, asexual reproduction produces new infective larvae called cercariae [27]. Once cercariae emerge from the snail into the aquatic environment, they find and penetrate the skin of their definitive host. Some schistosome species use host-emitted sensory cues to increase the likelihood of encountering both intermediate and definitive hosts; others appear to rely on spontaneous encounters with hosts [28]. Upon skin penetration, cercariae lose their tails and transform into schistosomula, which develop and migrate through the host circulatory system [27]. The final destination of parasitic adults varies between species but is generally in the veins draining blood from the intestines, bladder, or liver. Similarly, the pathway by which eggs exit the body varies between species. For species such as *Schistosoma mansoni* and *Schistosoma japonicum*, eggs laid by the adult females are transported to the gut and then excreted in feces; for species such as *Schistosoma haematobium*, eggs are instead deposited in the urinary tract and then excreted in urine [27]. Not all eggs are excreted, however; those that remain within the host elicit an immunopathological response responsible for most of the disease pathology [54–56].

For both soil-transmitted nematodes and water-transmitted trematodes, infective larvae must survive in the environment and locate suitable hosts for infection. Their ability to do so is likely dependent on their detection of an array of environmental and host-emitted sensory cues, including species-specific chemicals and temperature [19,28]. Our understanding of how different sensory modalities contribute to the behaviors of parasitic helminths remains incomplete. However, for many parasitic helminth species, it is becoming increasingly clear that thermosensation is a key regulator of behavior. Depending on the species,

thermosensation can drive infective larvae to navigate to favorable environments, migrate rapidly toward warm-blooded hosts, invade a host body, and transition into parasitic adulthood.

2. Thermosensory behaviors of skin-penetrating nematodes

2.1 Mammalian body heat stimulates host seeking and host invasion in skin-penetrating iL3s

For skin-penetrating mammalian-parasitic iL3s, thermal stimuli can elicit multiple robust behaviors related to finding and infecting host animals. Exposure to host body temperature stimulates iL3 movement and increases crawling speed in several *Ancylostoma* and *Strongyloides* species [36,57–59]. Host body temperature also promotes behaviors associated with host invasion, such as nictation – a behavior where the worm stands on its tail and waves its head to facilitate host attachment – and skin penetration [36,59,60]. Furthermore, thermal gradients drive multiple skin-penetrating species to engage in long-range positive thermotaxis, such that they migrate up thermal gradients toward temperatures above mammalian skin temperature (31–34°C) (Fig. 2A-B) [36,57,59,61–69]. For several species, thermal preferences are set above host body temperature [64,69]. Thus, even temperatures near host body temperature can generate strong thermal drive, likely ensuring that the ability of iL3s to navigate toward host-emitted heat will not attenuate as a function of increasing host proximity [69]. Taken together, these findings suggest that temperature is a major driver of both host-seeking and host-invasion behaviors in skin-penetrating nematodes.

Would thermal stimuli generated by host animals be sufficient to trigger the temperature-driven behaviors of skin-penetrating iL3s? The thermal microclimate that radiates from the lower half of the human body is approximately 8 cm thick [70,71]; thus, when skin-penetrating iL3s experience host-emitted heat they will be at most ~8 cm away from the host animal. However, in some experiments *S. stercoralis* iL3s displayed the ability to migrate toward mammalian skin temperature when located over 15 cm away in an artificial linear thermal gradient [69]. This ability suggests that skin-penetrating iL3s are likely to be capable of responding when they encounter thermal cues produced by the human body.

2.2 Below-ambient temperatures drive negative thermotaxis

Many skin-penetrating iL3s also display robust negative thermotaxis, migrating down thermal gradients to temperatures below ambient (Fig. 2B) [68,69]. The switch point between positive and negative thermotaxis is regulated by recently experienced environmental temperature (see Subsection 2.3), such that in general, iL3s exposed to temperatures above the switch point migrate toward host body temperature and iL3s exposed to temperatures below the switch point engage in negative thermotaxis toward cooler temperatures [68,69]. For *S. stercoralis* iL3s, environmental temperature differences of as little as 1°C are sufficient to dramatically alter the percentage of the population engaging in positive versus negative thermotaxis [69].

Why do iL3s engage in negative thermotaxis? Temperatures at or below the recently experienced environmental temperature are presumably more likely to be environmental than host-generated, and may therefore trigger environmental navigation rather than host seeking. Navigation toward cooler temperatures may enable iL3s to avoid environmental heat sources such as sun-heated soil. Temperatures of up to 40°C are permissive for the hatching and development of some skin-penetrating nematode eggs and larvae [72–75]. However, even when land surface temperatures exceed permissive temperatures for the survival of eggs and larvae, hookworm infections can still remain highly prevalent; this discrepancy has been attributed to the ability of hookworm larvae to migrate toward cooler soil microenvironments [76]. In addition, dispersal toward cooler soil microenvironments likely promotes better subsequent detection of host-related heat sources.

2.3 Environmental temperature regulates the temperature-driven behaviors of iL3s

The thermal environment experienced by iL3s modulates several aspects of sensory-driven navigation toward hosts, as well as subsequent host invasion. Most strikingly, a change in the environmental temperature regulates the likelihood that iL3s will engage in temperature-driven host seeking by controlling the thermal switch point between positive and negative thermotaxis [68,69]. The change in the thermal switch point can occur rapidly, over the course of hours. For example, *S. stercoralis* iL3s that are cultivated at 15°C for 2 hours will engage in positive thermotaxis at cooler temperatures than iL3s cultivated at 23°C (Fig. 2B) [69]. Similar shifts are observed in other soil-transmitted iL3s, although the time course of these shifts has not been investigated in detail [68,69]. The thermal environment can also influence host-invasion behaviors; prolonged cultivation at cool temperatures (7°C) was found to reduce the temperature that triggers skin penetration by the dog hookworm *Ancylostoma caninum* [59]. The ability of cooler ambient temperatures to enhance heat-seeking and host-invasion behaviors suggests that iL3s may be more likely to engage in temperature-driven host seeking and host infection in the early morning or late evening, when soil temperatures are low [77,78] but hosts are active. However, iL3s cultivated near mammalian body temperature (37°C) still engage in both positive thermotaxis and skin penetration [59,69], suggesting that thermal plasticity is reduced when environmental conditions closely mimic host body temperatures. Thus, iL3s are able to seek out mammalian hosts even when environmental temperatures are high.

2.4 Thermosensory stimuli regulate responses to chemosensory stimuli

In addition to responding to thermal stimuli, skin-penetrating iL3s respond to a wide range of host-emitted chemical cues [36,58–60,64,79–84]. Skin-penetrating nematodes and many other mammalian-parasitic nematodes have relatively narrow host ranges [85–89], and chemosensory preferences are likely to be critical for distinguishing potential hosts from other non-host mammals. How do the robust thermosensory responses of parasitic iL3s interact with their chemosensory responses? First, the environmental temperatures experienced by iL3s can influence their odor-driven behaviors. For example, prolonged cultivation of *Strongyloides ratti* iL3s at different temperatures alters their olfactory preferences (Fig. 2C-D) [80]. Together with the observation that environmental temperatures regulate the thermal preferences of iL3s, these results suggest that skin-penetrating iL3s use a host-seeking strategy that flexibly adjusts in response to changing environmental

conditions in order to ensure successful detection of host-emitted chemosensory and thermosensory cues.

In addition, experiments that paired thermal cues with host-emitted chemosensory cues observed a profound influence of heat on the responses of iL3s to chemosensory stimuli. For *Ancylostoma duodenale* and *Necator americanus* iL3s, CO_2 stimuli only elicit movement when combined with warmth or moisture, an effect that may result in responses to exhaled breath [36]. Thermosensory signals can also overcome iL3 attraction to host odorants during directed navigation [69]. For example, in thermal gradients below host body temperature, *S. stercoralis* iL3s will bypass a highly attractive host odorant in favor of engaging in positive thermotaxis [69]. However, in gradients near host body temperature, iL3s are less likely to bypass the odorant and instead accumulate in the thermal gradient near the odorant's temperature [69]. The ability of thermal drive to suppress the olfactory responses of iL3s suggests a sensory hierarchy wherein heat acts as a primary driver of long-range navigation toward hosts, and odorants act at closer range to enable host identification.

2.5 Strong thermal drive transforms iL3 migration patterns

As iL3s near host body temperature, they transition from relatively straight long-distance navigation to highly curved local search [28,58,69]. Unstimulated iL3 movements are also highly curved [57,69], suggesting that strong thermal drive suppresses local-search behavior in favor of directed navigation toward thermal cues. Once iL3s reach host body temperatures, they re-engage local-search behavior and other temperature-driven host-invasion behaviors [36,58–60,69]. Interestingly, iL3s engaged in migration toward attractive odorants also display highly curved tracks [69]; olfactory responses may therefore be generated by biased movement within the local-search paradigm. This behavior contrasts with the relatively straight movements elicited by strong thermal drive [69]. Thus, temperature-driven responses and odorant-driven responses are likely produced using different sensorimotor strategies.

2.6 Exposure to host body temperature triggers the transition to parasitic adulthood

Following host invasion iL3s activate, resuming feeding and development in a process that is mechanistically similar to exit from the *Caenorhabditis elegans* dauer state [46,90–93]. Activation is triggered by both endogenous signals such as dafachronic acid [93] and host-related sensory cues, including host body temperature [40–46]. For example, *A. caninum* iL3s are most likely to activate *in vitro* following prolonged incubation in sensory conditions that mimic host entry: temperatures above 32°C with 5% CO_2 in tissue culture medium supplemented with dog serum and reduced glutathione [40,43]. Similar conditions can also induce activation in the human-parasitic nematodes *S. stercoralis*, *A. duodenale* and *Ancylostoma ceylanicum* [40,44– 46]. Thus, elevated temperatures are necessary but not sufficient to trigger activation in these species.

3. Thermosensory behaviors of passively ingested parasitic nematodes

For passively ingested nematodes, some species display temperature-driven behaviors similar to those of the skin-penetrating nematodes. For example, iL3s of the passively

ingested murine parasite *H. polygyrus* exhibit positive thermotaxis toward host body temperature and negative thermotaxis toward temperatures below ambient [69]. Moreover, the thermal switch point between positive and negative thermotaxis is regulated by the recently experienced cultivation temperature, as in skin-penetrating nematodes [69]. Heat-seeking behaviors may enable *H. polygyrus* iL3s to position themselves close to a host, thus maximizing the likelihood of subsequent ingestion. Consistent with this strategy, *H. polygyrus* iL3s are attracted to several host-emitted odorants [81,94]. However, not all passively ingested nematodes use heat to position themselves near hosts; iL3s of the passively ingested ruminant parasite *H. contortus* do not migrate toward host body temperatures but instead display an experience-dependent preference for their previous cultivation temperature [95]. Whether temperature-driven host seeking is exhibited by other passively ingested nematodes has not been tested.

4. Thermosensory behaviors of free-living nematodes

The free-living nematode *C. elegans* also engages in positive and negative thermotaxis, and provides a useful comparative model for the parasitic nematodes. Within a physiological range (15–25°C), *C. elegans* adults migrate in relation to a “remembered” cultivation temperature (T_C), performing negative thermotaxis at temperatures above T_C and positive thermotaxis at temperatures below T_C [96–104]. In a narrow temperature range near T_C, *C. elegans* adults transition from directed navigation to movement aligned isothermally to T_C [96,97,103]. This behavior, called isothermal tracking, is characterized by relatively straight runs aligned perpendicular to the thermal gradient [96,97,103]. In contrast, skin-penetrating parasitic iL3s do not appear to engage in isothermal tracking [69]. *C. elegans* adults that are exposed to temperatures in a noxious temperature range (>26°C) display avoidance and escape behaviors [103,105–110]. *C. elegans* dauer larvae, which are developmentally similar to parasitic iL3s, are less well-studied. However, *C. elegans* dauers appear relatively indifferent to thermal stimuli that are in the noxious temperature range for *C. elegans* adults [69,105]. Thus, the behaviors of both *C. elegans* adults and dauers in response to warm temperatures contrast strikingly with the heat-seeking behaviors of most mammalian-parasitic iL3s.

Similar to the thermal preferences of mammalian-parasitic nematodes, the thermal preferences of *C. elegans* are regulated by recently experienced cultivation temperatures [97]. Cultivation at a new temperature for several hours resets T_C, altering thermotaxis navigation [96–98,111–113]. In some assays, the threshold for triggering noxious heat responses can also be modulated by changes to the cultivation temperature [110]. Ethologically, thermotaxis and noxious heat avoidance are thought to enable *C. elegans* to maintain exposure to favorable thermal environments [96,99,114].

5. Thermosensory behaviors of entomopathogenic nematodes

Entomopathogenic nematodes (EPNs) are found in a wide range of climates, and in some cases, the thermal niche of an individual species is very broad [115]. EPN IJs are long-lived, in some cases surviving in the soil for a year or more [116–119]. Prolonged cultivation at different temperatures can alter the lifespan and infectivity of some EPN species [120–126].

Nevertheless, the IJs of many EPN species are capable of surviving large differences in ambient temperatures associated with both differential geography and seasonal cycles [115,126,127].

5.1 EPNs engage in thermotaxis behavior

EPNs infect insects, which are primarily poikilotherms: their body temperature varies with that of the environment. Thus, EPN host seeking is not thought to rely on thermosensory cues. Instead, the thermosensory responses of EPNs likely drive environmental navigation toward favorable temperatures. For example, like *C. elegans* adults and *H. contortus* iL3s, *S. carpocapsae* IJs migrate toward their cultivation temperature [128]. Moreover, the thermal preferences of *S. carpocapsae* IJs are modulated by the recently experienced environmental temperature [128]. *S. carpocapsae* IJs also actively avoid noxious temperatures [69]. However, at least one set of experiments observed that *S. carpocapsae* IJs were attracted to temperatures slightly above ambient (< +1°C), a temperature differential associated with insect metabolism [129]. The host-seeking strategy of *S. carpocapsae* IJs is also regulated by cultivation temperature: IJs cultivated at 25°C are more likely to remain stationary and ambush passing hosts, while IJs cultivated at 15°C are more likely to actively cruise toward hosts [80].

5.2 Temperature regulates the chemosensory behaviors of EPNs

Host-emitted chemosensory cues play a dominant role in driving EPN host-seeking behaviors [19,48,49,130]. IJs are attracted to a diverse array of insect-emitted odorants and carbon dioxide [49,131–137]. IJs are also attracted to plant odorants, including some that are released in response to insect predation [138–144]. In combination, these olfactory preferences suggest that IJs both seek out insect hosts directly, and use environmental cues to migrate to locations where they are likely to encounter insect hosts.

The responses of some EPN species to host-derived odorants are strongly modulated by cultivation temperature [80]. For example, when *S. carpocapsae* IJs are cultivated at 15°C, their olfactory preferences are dramatically altered in comparison to IJs cultivated at 25°C. In some cases, odorants that are repulsive to IJs previously cultivated at 25°C are attractive to IJs previously cultivated at 15°C, and vice versa (Fig. 2E). Moreover, these temperature-induced changes in olfactory preferences are reversible over the course of weeks. Temperature-dependent modulation of olfactory behavior was observed across multiple phylogenetically distant EPN species, although some EPN species showed greater behavioral plasticity than others [80]. Furthermore, temperature-dependent modulation of olfactory behavior appears to be more extreme for EPNs than for mammalian-parasitic nematodes [80]. The temperature-dependent olfactory plasticity of EPNs may reflect the need for EPNs to adjust their host preferences in response to seasonal variation in the availability of different host species [145–147].

6. Thermosensory behaviors of mammalian-parasitic schistosomes

The life cycle of mammalian-parasitic schistosomes features two free-living infective larval stages: the miracidia, which infect marine snails; and the cercariae, which infect mammalian

hosts [27,28]. Environmental conditions can affect the behavior of both miracidia and cercariae. Higher environmental temperatures stimulate increased emergence of cercariae from snails, as well as increased swimming rates in both miracidia and cercariae [148– 151]. Temperature also has life-stage-specific effects on cercariae and miracidia. The miracidia of many species are thought to rely on snail-specific chemosensory cues rather than thermal cues for host seeking, a preference consistent with their need to infect ectothermic hosts [28]. In contrast, some cercariae rely on both thermal and chemosensory cues for infecting mammalian hosts [28].

The process by which cercariae recognize and invade mammalian hosts consists of multiple behaviors, including attachment to host skin, maintenance of contact with host skin, creeping along the skin, and skin penetration [28]. The cercariae of some species may also actively navigate toward or orient to host skin at close-range [152]. Thermal cues can influence each of these behaviors, although responses to thermal cues vary across species [28]. For example, directed migration of cercariae in response to thermal gradients has been observed in a number of mammalian-parasitic schistosome species, including the human-parasitic species *S. mansoni* and *S. haematobium* [153–157]. However, the relative importance of thermal versus chemical cues varies across the two species, with *S. mansoni* showing greater sensitivity to chemical cues and *S. haematobium* showing greater sensitivity to thermal cues [155]. Similarly, higher environmental temperatures stimulate host attachment, enduring contact, and skin penetration by the cercariae of some species but not others [153–156]. Thus, temperature appears to be an important regulator of host seeking and host invasion for some but not all schistosome species.

7. Possible effects of climate change on parasitic helminth infectivity

The influence of environmental temperature on host-seeking behavior raises the question of whether parasitic helminth infection rates will be altered by global climate change. The effects of climate change on parasitic helminth survival and infectivity are predicted to vary greatly across species. For example, increased environmental temperatures may restrict schistosome transmission in some regions by negatively impacting freshwater snail populations [29]. In the case of parasitic nematodes with an environmentally motile iL3 stage, the iL3s are capable of engaging in positive thermotaxis after experiencing a wide range of environmental temperatures [59,68,69], suggesting that the nematodes will be able to host seek despite changing climate conditions. However, differences in optimal growth conditions across species may alter the geographical ranges of some parasitic nematodes [29,30]. The relative prevalence of different species may also change in certain regions as some species gain growth advantages over others [29]. In addition, global climate change may affect the utility of some EPNs as biocontrol agents [158].

8. The neural basis of thermosensation in parasitic helminths

8.1 The neural basis of thermosensation in free-living and parasitic nematodes

The neural basis of thermosensation in parasitic nematodes has not been extensively studied. In contrast, the neural mechanisms underlying *C. elegans* thermosensation are relatively well understood. Nematode sensory neuroanatomy is broadly similar across many species,

including free-living and parasitic species [95,159–166]. Thus, knowledge of the *C. elegans* thermosensory circuit may provide insight into the circuitry underlying temperature-driven behaviors in parasitic nematodes.

In *C. elegans*, the bilateral amphid sensilla are the primary sensory organs; each amphid consists of 12 ciliated sensory neurons located in the head [167,168]. The amphid neuron pair AFD is the primary thermosensory neuron pair (Fig. 3A) [96,100,167,169–174]. *C. elegans* AFD neurons are characterized by a highly complex "finger-like" dendritic structure (Fig. 3B) [174,175]. AFD is required for thermotaxis navigation and isothermal tracking within *C. elegans*' physiological temperature range [100,169,171,173]. AFD also plays a role in noxious heat detection [176,177]. A different amphidial neuron pair, AWC (Fig. 3A), has elaborate "wing-like" dendritic endings (Fig. 3B) and also responds to thermal stimuli, including noxious heat [96,176,178,179]. Several nonamphidial sensory neurons are also associated with thermal nociception, including the FLP neuron pair [108,177,180].

Morphological studies have found that parasitic nematode amphids are similar to those of *C. elegans*, although in some species the amphids are innervated by 13 neurons rather than 12 neurons [161–165]. The morphology of amphidial sensory endings can vary dramatically between species and life stages, and the precise arrangement of neuron cell bodies within the amphid also varies slightly [161–165]. These differences can complicate comparisons between parasitic amphid neurons and *C. elegans* amphid neurons. For example, *S. stercoralis* lacks amphidial neurons with "finger-like" and "wing-like" dendritic processes; instead a "lamellar" cell called ALD is thought to be the homolog of either AFD or AWC (Fig. 3C-D) [161–163]. Many other parasitic nematode species lack neurons with "wing-like" dendritic structures, but have amphid neurons with cell body positions similar to those of the *C. elegans* AWC neurons (Fig. 3E-F) [95,163–166]. The paths taken by the dendrites of these neurons through the amphidial channel are also similar to those taken by the *C. elegans* AWC neuron dendrites [163–165]. However, unlike *S. stercoralis*, these species all have amphid neurons with elaborate "finger-like" sensory endings that are clear homologs of *C. elegans* AFD (Fig. 3E-F) [95,163–166].

Until recently, techniques for genetic manipulation were severely limited in parasitic nematodes. Thus, functional assessments of the contributions of different sensory neurons to parasite thermosensation have been restricted to laser ablation combined with behavioral assays. Using this approach, AFD was shown to be required for positive thermotaxis in both *A. caninum* and the passively ingested ruminant-parasitic nematode *H. contortus* [95,181]. In *H. contortus*, the AWC homolog is not required for positive thermotaxis [95], although it is possible that these neurons nevertheless contribute to thermosensation in a manner similar to *C. elegans* AWC. In *S. stercoralis*, the ALD neurons are required for positive thermotaxis by iL3s [65,163]. In addition, the ALD neurons contribute to chemosensory behaviors [163]. Thus, whether the *S. stercoralis* ALD neuron is functionally more similar to the *C. elegans* AFD neuron or the *C. elegans* AWC neuron remains unclear. Resolving this issue will likely require using genetic markers to identify putative homologs of AFD and AWC in *S. stercoralis* [44], in combination with both morphological analysis and functional analyses of thermosensory and chemosensory behaviors. Interestingly, ALD does not appear to contribute to the temperature-dependent activation of *S. stercoralis* iL3s, suggesting that the

diverse temperature-driven behaviors of iL3s could rely on distinct thermosensory mechanisms [46].

Parasite-specific behavioral responses to temperature cues may reflect adaptations of conserved neural circuits, as well as thermosensory mechanisms unique to parasitic nematodes. In *C. elegans*, the elaborate sensory endings of amphidial neurons are often critical for proper neuronal function [167,168,182–186], and the complexity of the "finger-like" processes of AFD is thought to enhance neuronal sensitivity to thermal stimuli by increasing the dendritic surface-to-volume ratio [174]. Thus, variations in the sensory endings of parasitic neurons, such as the unique dendritic structure of *S. stercoralis* ALD, may reflect functional specializations necessary for host-seeking behaviors. In addition, neural imaging studies have revealed that *C. elegans* thermosensory coding is regulated by mechanisms such as sensory adaptation in AFD and synaptic plasticity between AFD and the downstream interneuron AIY [170,187–190]. Experimental manipulation of these neurons or their connectivity can elicit dramatic changes in thermotaxis behaviors. For example, modulating the strength of the AFD-AIY synapse can alter the valence of thermosensory drive in *C. elegans* [170]. Future experiments are needed to determine whether parasite-specific thermotaxis behaviors are generated by unique thermosensory properties of the parasite thermosensory neurons, differences in their synaptic connections, or a combination of both. Similarly, whether conserved mechanisms generate experience-dependent thermal plasticity in parasitic and free-living nematodes has not yet been investigated. Decoding the functional properties of the parasitic nematode thermosensory circuit will undoubtedly require monitoring the neural activity of thermosensory neurons and interneurons using genetically encoded calcium indicators, and these experiments are currently most feasible in *S. stercoralis* and other closely related species that are readily amenable to genetic transformation [191–199].

8.2 The schistosome sensory nervous system

The ultrastructure of the schistosome nervous system is distinct from that of nematodes. Relatively little is known about schistosome sensory neuroanatomy, both because trematodes have much larger and more complex nervous systems than nematodes [200] and because the field lacks a well-studied, genetically tractable model system with similar neuroanatomy that can serve as a basis for comparison, like *C. elegans* for parasitic nematodes. In *S. mansoni* cercariae, the ciliated endings of sensory neurons are organized in sensory papillae [201,202]. Approximately 38 pairs of bilaterally symmetrical sensory papillae, with 6 structural types, are located bilaterally and symmetrically at the anterior organ and along the length of the cercarial body [201–203]. The functional properties of these sensory organs are unknown, although one structural group has been identified as putative photoreceptors based on morphology [204]. Thermosensory neurons have not been identified in schistosomes.

9. Molecular mechanisms of thermosensation in parasitic helminths

9.1 Molecular mechanisms of thermosensation in parasitic nematodes

Until recently, a lack of tools for genetic manipulation in parasitic nematodes has hindered efforts to elucidate the molecular mechanisms underlying their thermosensory behaviors.

However, high-quality reference genomes for many parasitic nematode species are now available [205], as is life-stage-specific RNA-Seq data [91,205,206]. In addition, an ever-expanding molecular toolkit for parasitic nematodes now includes CRISPR/Cas9-mediated targeted mutagenesis, heritable transgenesis, chemical mutagenesis, and RNA interference in some species [191–193,195–199,207]. These methods are now enabling the identification of molecular mechanisms that underlie the diverse array of temperature-driven behaviors in parasitic nematodes.

Critically, genetic similarity between nematode species is enabling a comparative genomics approach that provides an invaluable starting point for investigations of the molecular and genetic basis of parasitic behaviors [206,208]. The genetic similarities between different nematode species belie the evolutionary timeline over which these lineages have evolved. Although assessing the phylogenetic relationships within Nematoda is a complex problem [209–211], some analyses estimate that Chromadorea, a class of Nematoda that includes *C. elegans*, hookworms, and *Strongyloides* species, split from other nematode lineages over 400 million years ago [212,213]. Current estimates suggest that Chromadorea subsequently diversified into distinct clades within the last 200300 million years [212,213]. The time at which Clade IV (*Strongyloides* species) diverged from Clade V (*C. elegans* and hookworms) is not clear [209–211], although some estimates suggest the split occurred approximately 190–217 million years ago [212,213]. Nevertheless, species such as *C. elegans* and *S. stercoralis* retain sufficient genetic similarity that homologs of genes required for thermosensation in *C. elegans* can be identified and then tested for a role in mediating thermosensation in parasitic nematodes [69]. Specifically, targeted mutagenesis is now feasible in *S. stercoralis* and *S. ratti* due to the recent adaptation of the CRISPR/Cas9 system for use in these species, thus enabling the first loss-of-function studies of candidate thermosensory genes [191,207].

Using this approach, the role of the *S. stercoralis tax-4* gene in mediating heat seeking by *S. stercoralis* iL3s was recently investigated [69]. In *C. elegans*, the *tax-4* gene encodes a cyclic nucleotide-gated channel subunit that is expressed in several head sensory neurons and is required for multiple sensory modalities, including thermosensation [100–102,167,179,214–217]. *Ce-tax-4* is required for temperature-driven activation of AFD and plays a role in isothermal tracking, thermotaxis navigation, and noxious heat detection [100–102,172,173,177,179,214]. In *S. stercoralis*, CRISPR/Cas9-mediated homozygous disruption of *Ss-tax-4* [69,207] was found to severely disrupt several temperature-driven behaviors in *S. stercoralis* iL3s, including positive thermotaxis toward host body temperatures [69]. These results demonstrate that despite notable differences in their temperature-driven behaviors, the molecular mechanisms underlying thermosensation are at least partially conserved across free-living and parasitic nematode species.

Our understanding of the molecular pathways involved in various aspects of *C. elegans* thermosensation provides several additional gene targets that may contribute to the temperature-driven behaviors of parasitic nematodes. For example, the sensitivity of *C. elegans* AFD to thermal stimuli is dependent on three receptortype guanylate cyclases − GCY-8, GCY-18, and GCY-23 − which act upstream of TAX-4/TAX-2 (collectively referred to here as the AFD-rGCs) [172–174,177,179,218–220]. The AFD-rGCs act to set the

operating range of the AFD thermosensory neurons, and altering the sequences of the AFD-rGCs can shift the AFD thermosensory response threshold [218]. The AFD-rGCs regulate multiple thermosensory behaviors, including positive and negative thermotaxis, isothermal tracking, and thermal avoidance [172–174,177,179,218–220]. Species-specific specializations in the functional properties of the parasite homologs of the *C. elegans* AFDrGCs could contribute to the thermal preferences of parasitic nematodes.

Other potential targets include genes that encode members of the transient receptor potential (TRP) superfamily. For example, the *C. elegans ocr-2* and *osm-9* genes encode TRPV channels and contribute to multiple sensory responses, including noxious heat avoidance [106,108,177]. These channels are notable given the involvement of TRPV channels with thermosensation in many species, including vertebrates [221]. In addition, TRPA1 channels are involved in thermosensory responses in a wide range of species, from planarians to *C. elegans* to mammals [103,221,222]. The molecular mechanisms by which TRPA1 mediates temperature-driven behaviors likely vary among evolutionarily distant species. In some cases, TRPA1 is thought to respond to temperature changes directly; in other cases, TRPA1 is thought to indirectly mediate temperature responses by sensing the reactive oxygen species generated by heat-damaged tissue [221,223,224]. Species-specific adaptations in the functional properties of TRP channels can alter heat tolerance and cold sensitivity in mammals [225,226]. In parasitic nematodes, it is possible that similar TRP channel adaptations could contribute to the dramatic preference of mammalian-parasitic nematodes for host body temperature.

9.2 Molecular mechanisms of thermosensation in schistosomes

The molecular mechanisms underlying sensory transmission in *Schistosoma* species have not been studied extensively. One recent study tested the effect of changes in ambient temperature on kinase signaling in *S. mansoni* cercariae. Switching the cultivation temperature from 24°C to 37°C resulted in increased activation of protein kinase C (PKC), extracellular signal-regulated kinase (ERK), and p38 mitogen-activated protein kinase (p38 MAPK) [227]. Activated kinases were localized to several neural structures [227]. The functional role of these kinases in temperature-driven host seeking, if any, is not known. However, protein kinase signaling triggered by host-emitted heat is thought to regulate transcriptional changes required for cercarial development within the host [227]. In addition, the heat-shock protein Hsp70 was found to regulate host invasion by schistosome cercariae, providing insight into the mechanism by which elevated temperatures trigger host-invasion behaviors [228].

The genomes of *Schistosoma* species contain several TRP channel genes [229]. Interestingly, the *S. mansoni* genome appears to lack genes coding for TRPV channels [229]; however, the genome does encode a TRPA1like channel that may have pharmacological sensitivities similar to those of both mammalian TRPA1 and TRPV channels [230]. The functional role of these channels in schistosome thermosensation has not been assessed. However, RNAi has been established in *Schistosoma* at some life stages [231,232], and the first instance of CRISPR/Cas9-mediated genome editing was recently

reported [233]. Future studies could therefore assess the functional contributions of TRP channels to the temperature responses of these life stages.

10. Conclusions

Thermal stimuli drive a diverse array of behaviors in both free-living and parasitic animals. There is growing evidence that the specialized thermosensory responses of many parasitic helminths play critical roles in driving the diverse range of behaviors that enables the environmentally motile infective larvae to find and infect their hosts. In mammalian-parasitic nematodes, thermosensation contributes to multiple aspects of host seeking and infectivity, including generalized arousal, long- and short-range navigation toward hosts, skin penetration, and activation (Fig. 4). In both parasitic and free-living nematodes, thermosensation also contributes to environmental navigation (Fig. 4). In addition, temperature regulates host seeking and environmental navigation indirectly by modulating behavioral responses to olfactory cues. In schistosome cercariae, thermosensation also contributes to multiple behaviors, including orientation toward host skin and subsequent skin invasion. Recent additions to the molecular toolkit for parasitic helminths are supporting efforts to elucidate the cellular, molecular, and circuit adaptations that mediate parasite-specific thermosensory responses. These efforts have so far demonstrated that the different temperature-driven behaviors of free-living and parasitic nematodes are likely generated by genetic and neural mechanisms that are at least partially conserved across species. Future studies will be necessary to identify the parasite-specific thermosensory adaptations that underlie host-seeking and hostinvasion behaviors. By gaining insight into how parasitic helminths use thermosensation to guide host seeking, future research may enable the development of new strategies for helminth control. Furthermore, a better understanding of how temperature regulates sensory behaviors in EPNs could increase their utility as biocontrol agents.

11. Acknowledgements

We thank Navonil Banerjee, Taylor M. Brown, Michelle L. Castelletto, and Spencer S. Gang for thoughtful comments on the manuscript. This work was supported by grants from the National Institutes of Health [T32NS058280 to A.S.B. and 1DP2DC014596 to E.A.H]. A.S.B. is supported by an A.P. Giannini Postdoctoral Fellowship. E.A.H is supported by a Burroughs Wellcome Fund Investigators in the Pathogenesis of Disease Award, and a Howard Hughes Medical Institute Faculty Scholar Award.

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Highlights

- Thermosensation is a critical sensory modality for many parasitic helminth species.
- Thermal cues drive multiple behaviors necessary for host seeking and host invasion.
- The neural and molecular basis of parasite thermosensation is understudied.
- Parasite thermosensation requires sensory cascades found in free-living nematodes.

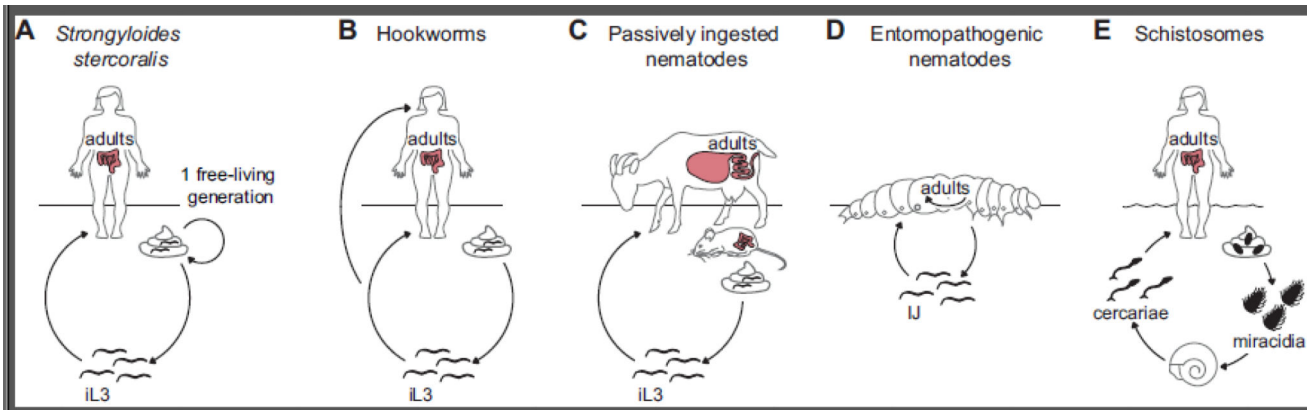

Fig. 1. The life cycles of parasitic helminths.

A-C. Life cycles of mammalian-parasitic nematodes. Soil-dwelling developmentally arrested infective larvae (iL3s) seek out hosts using host-emitted sensory cues, including heat [19]. Across species, infection routes include skin penetration (A) and oral ingestion (C), or both in the case of certain hookworm species (B) [2,27,36–39,89]. Following host infection, the nematodes resume development and migrate to the small intestine, where they take up residence as reproductively capable parasitic adults [2]. Larvae or eggs then exit hosts in feces. For *Strongyloides stercoralis,* larvae may develop into iL3s or free-living adults; the progeny of free-living adults exclusively become iL3s (A). For hookworms and passively ingested nematodes, the progeny of parasitic adults develop into iL3s (B-C).

D. The life cycle of entomopathogenic nematodes (EPNs). Soil-dwelling infective juveniles (IJs), which are developmentally similar to the iL3s of mammalian-parasitic nematodes, invade and then rapidly kill insect hosts [50,51]. EPNs can develop and reproduce inside the host cadaver for multiple generations, until depleted resources within the cadaver trigger the formation of IJs that are released into the environment [50].

E. The life cycle of schistosomes. Unlike parasitic nematodes, the schistosome life cycle involves an intermediate and a definitive host animal [27,28]. Some schistosome species seek out both intermediate and/or definitive hosts using host-emitted sensory cues. Free-swimming miracidia infect aquatic snails (intermediate hosts). Following snail penetration the schistosomes develop into mother sporocysts and produce daughter sporocysts whose larval progeny become cercariae [27]. Water-transmitted cercariae emerge from snails and infect the definitive hosts. Inside the definitive host, cercariae transform into schistosomula, which develop and migrate through the host circulatory system. Depending on the schistosome species, parasitic adults will ultimately reside in the veins draining blood from the intestines, liver, or bladder. The eggs of parasitic adults are excreted in feces or urine, and subsequently develop into miracidia [27].

Diagrams are not drawn to scale.

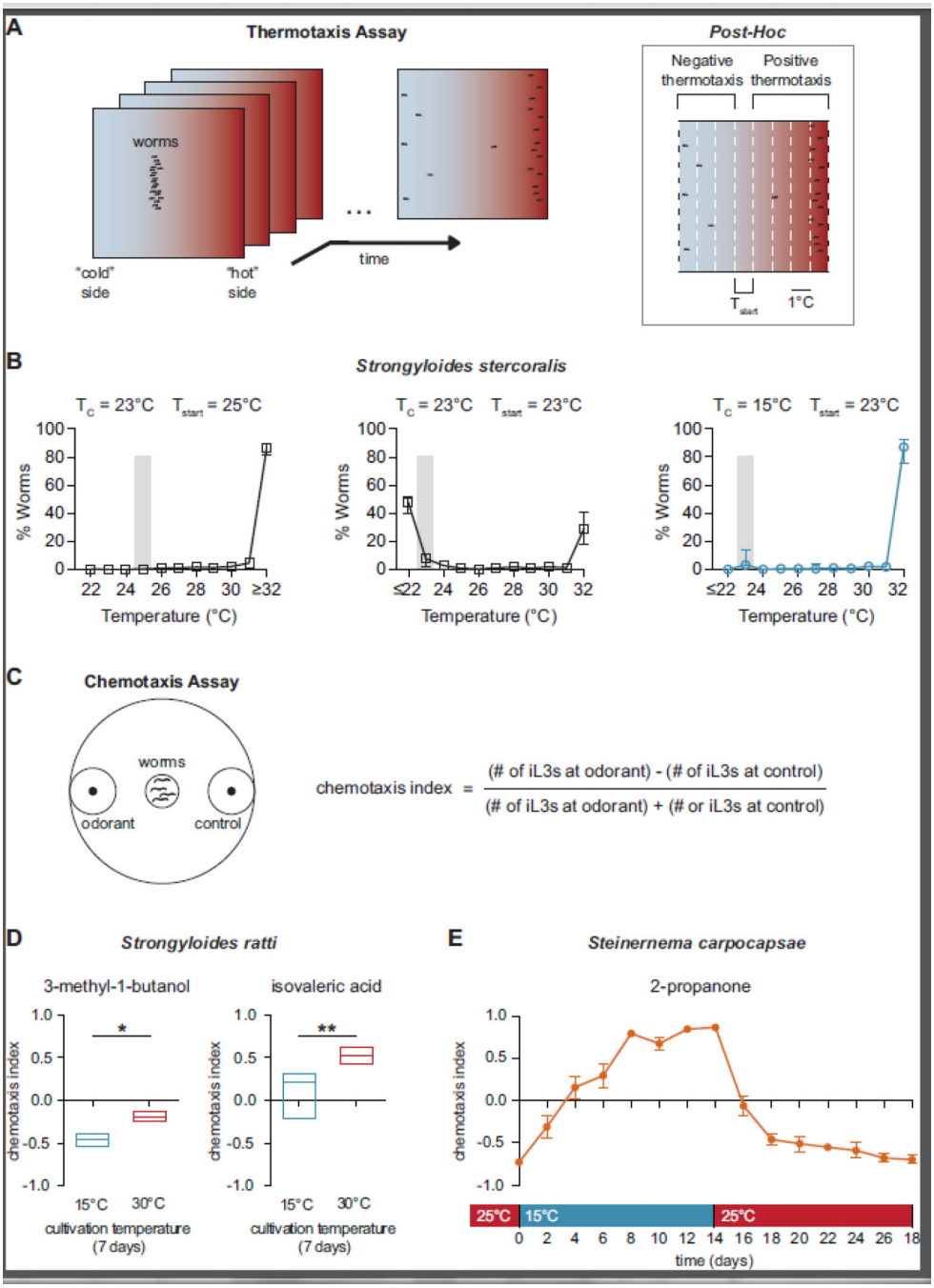

Fig. 2. Temperature-dependent navigation behaviors of parasitic nematodes

A. Schematic of a thermotaxis assay. A linear thermal gradient is established across a 22 × 22 cm agar surface, using a custom thermal stage [69]. iL3s are placed at a selected starting temperature (T_{start}) and allowed to disperse. Two cameras record worm movements, each camera monitoring approximately half of the thermal gradient. The final position of worms in the thermal gradient is calculated *post hoc*: images corresponding to the desired experimental time point are divided into 1°C temperature bins, and the number of worms in each bin is tallied [69]. Positive thermotaxis is defined as movement into a temperature bin

warmer than T_{start}; negative thermotaxis is defined as movement into a temperature bin cooler than T_{start}. Worms are not drawn to scale.

B. *S. stercoralis* iL3s engage in long-range positive and negative thermotaxis, and the switch point between these behaviors is set by the recently experienced cultivation temperature (T_C). Left: *S. stercoralis* iL3s cultivated at 23°C and then placed at 25°C in a ~22°C-34°C gradient engage in long-range positive thermotaxis toward mammalian body temperatures. Center: *S. stercoralis* iL3s cultivated at 23°C and then placed at 23°C in ~22°C33°C gradient display both positive and negative thermotaxis. Right: *S. stercoralis* iL3s that have been cultivated at 15°C for 7 days exhibit only positive thermotaxis when placed at 23°C in a ~22°C-33°C gradient. Assay duration: 15 minutes, n = 15 trials with >50 iL3s per trial. Gray shading indicates the starting temperature of the iL3s (T_{start}). All graphs show medians and interquartile ranges; in some cases, error bars are too small to be visible. Data are reproduced with permission from Bryant *et al.,* 2018 [69].

C. Schematic of a chemotaxis assay. iL3s are placed in the center of a 10 cm agar plate containing a point source of an odorant on one side and a point source of a control (often paraffin oil) on the other side. The distribution of iL3s in the odorant gradient is then quantified after 3 hours by calculating a chemotaxis index using the formula shown. The chemotaxis index ranges from −1 to +1, with −1 indicating maximum repulsion and +1 indicating maximum attraction. Worms are not drawn to scale. Figure is adapted from Lee *et al.,* 2016 [80].

D. Temperature-dependent changes in the chemosensory responses of the skin-penetrating nematode *Strongyloides ratti.* Left: *S. ratti* iL3s cultivated at 15°C for 7 days are repelled by the host-emitted odorant 3meythl-1-butanol, whereas *S. ratti* iL3s cultivated at 30°C for 7 days show significantly reduced repulsion. Right: *S. ratti* iL3s cultivate at 15°C for 7 days are neutral to isovaleric acid, whereas *S. ratti* iL3s cultivated at 30°C for 7 days are attracted to isovaleric acid. *, $p<0.05$; **, $p<0.01$; two-way ANOVA with Tukey's post-test. n = 6–8 trials with >100 iL3s per trial. Lines and boxes show medians and interquartile ranges. Figure is adapted from Lee *et al.*, 2016 [80].

E. Time course of temperature-dependent changes in chemosensory responses of the EPN *Steinernema carpocapsae.* Temperature-swapping IJs from 25°C to 15°C altered chemosensory responses over the course of days. Prior to the temperature swap, IJs cultivated at 25°C were strongly repelled by the insect-emitted odorant 2-propanone; over time at 15°C, the response gradually shifted to strong attraction. When IJs were swapped back to 25°C, their response to 2-propanone reverted to repulsion over the course of days. n = 6–22 trials for each time point. Graph depicts means and standard errors of the mean. Data are from Lee *et al.,* 2016 [80].

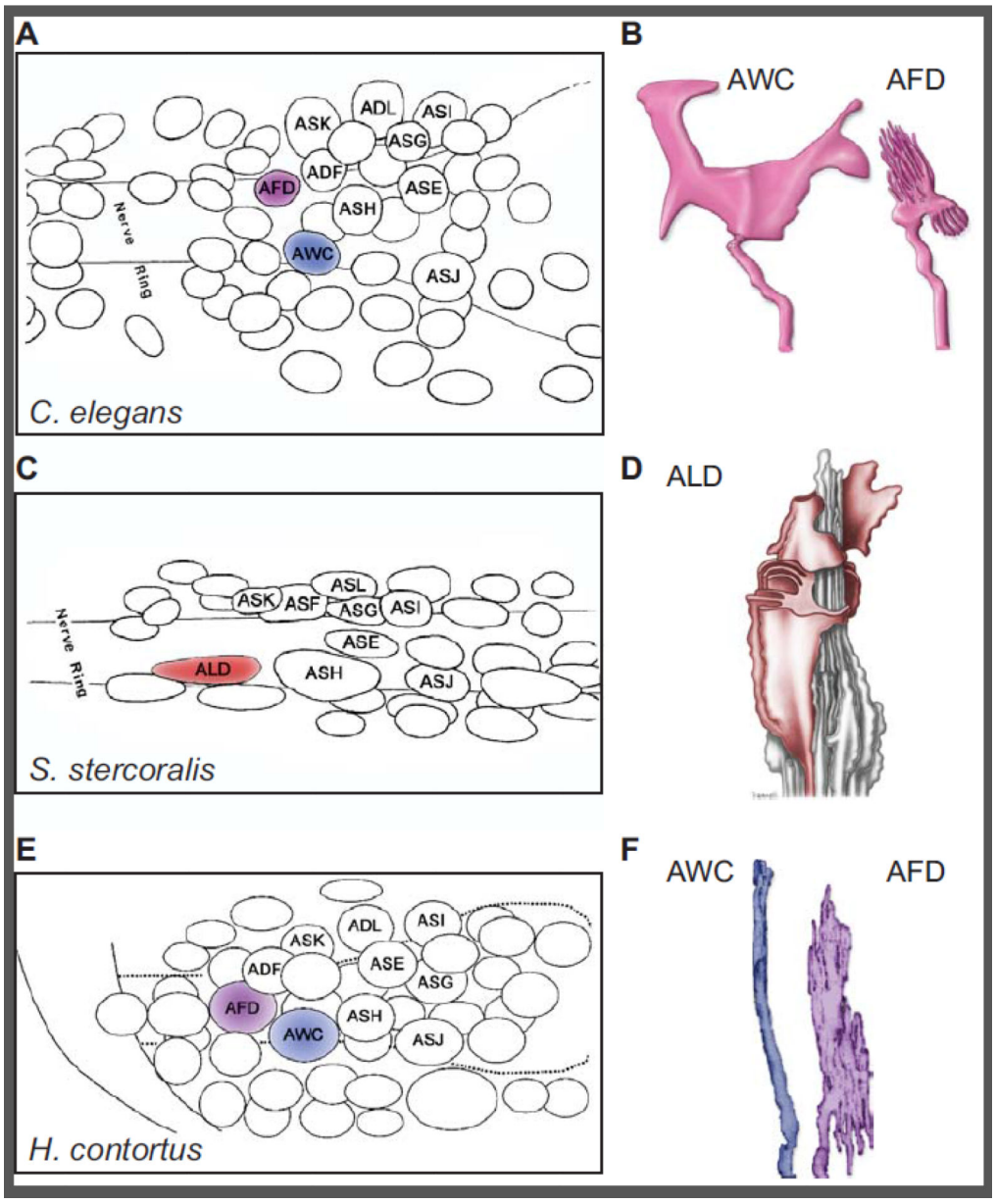

Fig. 3. Neuroanatomy of *C. elegans, S. stercoralis* and *H. contortus* thermosensory amphid neurons.

A-B. The cell body positions **(A)** and dendritic structures **(B)** of the thermosensory amphid neurons in a *C. elegans* L1 larva. The *C. elegans* AFD neurons are the primary thermosensory neurons in the amphids; they are characterized by highly elaborate "finger-like" endings [174]. The *C. elegans* AWC olfactory neurons also respond to thermosensory cues; their dendritic endings are characterized by large "wing-like" structures. A number of other amphid sensory neurons are also labeled. **A** is modified from Ashton *et al.,* 1995 with permission [161]; **B** is reproduced from Altun and Hall, 2010 [234].

C-D. The cell body position **(C)** and dendritic ending **(D)** of the ALD thermosensory neuron pair in an *S. stercoralis* iL3. *S. stercoralis* lacks cells with "finger-like" or "wing-like" dendritic endings; the ALD neuron has a "lamellar" structure, has thermosensory function,

and is the homolog of either *C. elegans* AFD or AWC [65,161–163]. A number of other amphid sensory neurons are also labeled. **C-D** are modified from Ashton *et al.,* 1995 and Lopez *et al.,* 2000 with permission [65,161].

E-F. The cell body positions **(E)** and dendritic ending **(F)** of the AFD and AWC neurons in an *H. contortus* L1 larva. The *H. contortus* AFD neurons are required for thermotaxis, whereas the *H. contortus* AWC neurons are not known to be required [95]. A number of other amphid sensory neurons are also labeled. **E-F** are adapted from Li *et al.,* 2000a and Li *at al.,* 2000b with permission [95,166].

For panels showing cell body positions (**A, C, E**), anterior is to the left. For panels showing dendritic endings (**B, D, F**), anterior is to the top.

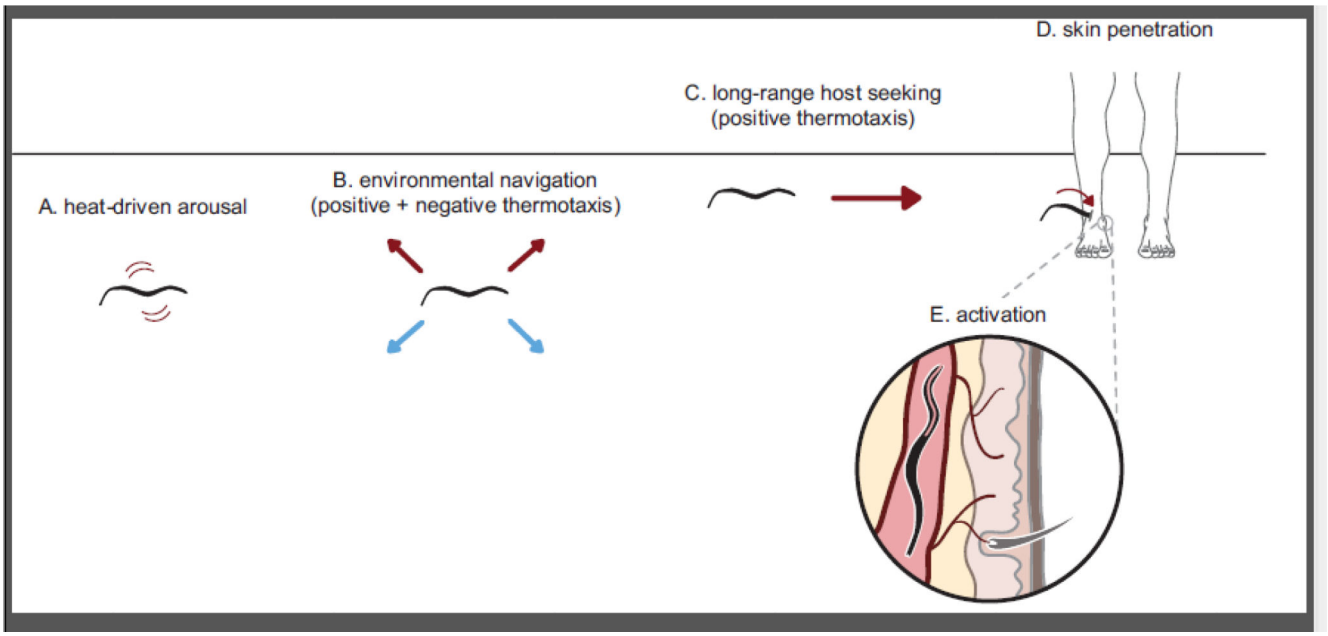

Fig. 4. Temperature-driven behaviors of skin-penetrating nematodes.

Thermal cues elicit a diverse set of behaviors in the soil-dwelling iL3s of skin-penetrating nematodes. These behaviors include: (A) arousal, characterized by non-directional movement in the presence of heat; (B) environmental navigation, characterized by positive and negative thermotaxis; (C) long-range host seeking, characterized by positive thermotaxis; (D) skin penetration; and (E) activation, in which the developmentally arrested iL3s resume development inside the host. Diagrams are not drawn to scale.