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What if worms were sentient? Insights into subjective experience from the *Caenorhabditis elegans* connectome

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Abstract

Deciphering the neural basis of subjective experience remains one of the great challenges in the natural sciences. The structural complexity and the limitations around invasive experimental manipulations of the human brain have impeded progress towards this goal. While animals cannot directly report first-person subjective experiences, their ability to exhibit flexible behaviours such as motivational trade-offs are generally considered evidence of sentience. The worm *Caenorhabditis elegans* affords the unique opportunity to describe the circuitry underlying subjective experience at a single cell level as its whole neural connectome is known and moreover, these animals exhibit motivational trade-offs. We started with the premise that these worms were sentient and then sought to understand the neurons that were both necessary and sufficient for a motivational trade-off involving the rewarding experience of food and the negative experience of an aversive odour. A simple hierarchical network consisting of two chemosensory neurons and three interneurons was found to produce an output to motoneurons that enabled worms to respond in a contextually appropriate manner to an aversive odour according to the worm's hunger state. Given that this circuitry is like that found in the human spinal cord, retina, and primary visual cortex, three regions which are neither necessary nor sufficient for subjective experience, we conclude that motivational trade-offs are not a criterion for subjective experience in worms. Furthermore, once the neural substrate for a behaviour is described, we question the explanatory role of subjective experience in behaviour.

Keywords Phenomenal consciousness · *C. elegans* · Flexible behaviour · Nematode · Awareness · Neural circuitry · Neural network

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Introduction

Judging which non-human animals subjectively experience sensory stimuli as inner qualities such as pain or pleasure—i.e., are sentient/consciously aware—is a major challenge in comparative biology. Given that the subjective nature of such experiences is not directly assessable, animal sentience is typically inferred by examining gross motor responses to sensory stimuli. Characteristics of these responses are considered to reflect an animal's inner feeling of the stimulus. For example, Darwin (1881, pp. 23–36) contended that earthworms were conscious because they displayed non-reflexive behaviours. The underlying assumption here is that reflex movements are simple and unvarying, and executed without any need for conscious control. *Ipso facto*, "complex" behaviours must be under conscious control and hence they are considered sufficient evidence for sentience. Such behaviours have been cited in support of claims that some insects, crustaceans, molluscs, and fish are sentient—i.e., feel pain, enjoy playing, display optimism, have negative emotions, and feel anxious (Chittka 2022; Crump et al. 2022a, b; Sneddon and Roques 2023).

Defining a complex behaviour is not easy. Simply arguing that a complex behaviour is non-reflexive does not help as Sherrington (1910, 1913) showed that a mammalian reflex can be complex and consist of multiple, coordinated joint movements that may be flexibly executed (i.e., performed in a context-specific and appropriate manner). For Sherrington, a mammalian reflex was a behavioural response that was elicited in a spinal animal and hence defined a priori by the lack of conscious control from the cerebrum. But the presence of reflexes alone does not necessarily mean there is no conscious experience (Fischer and Truog 2015; Hopkin 2006; Owen et al. 2006). By what criteria does one then judge whether the behaviour of an invertebrate animal model such as *Caenorhabditis* (*C.*) *elegans,* a one-millimetre-long worm of the nematode family, reflects subjective experience? A common—although not particularly rigorous—approach is to search for similarities between cause and effect in behaviours in nematodes and humans (e.g., avoidance of noxious stimuli) (Abboud et al. 2021; Cirrincione and Rieger 2020; Koy and Plotnick 2008; Laurent et al. 2015; Madhivanan et al. 2018; Mills et al. 2012a, b; Puccetti et al. 2021), or to identify homologous genes associated with such behaviours (Komuniecki et al. 2012), or to demonstrate similar modulation of behaviours by drugs (Wittenburg and Baumeister 1999). Using these criteria, *C. elegans*—or 'worms' as we shall refer to them in this article—would be clearly capable of subjective experience.

More stringent definitions of subjective consciousness have been adopted. Ginsburg and Jablonka (2007) contend that "if an animal has integrated overall sensations, and these direct and guide its actions so that it has the potential to learn flexibly by association, it can be said to be conscious even when this (very basic) consciousness is very limited indeed". Given that *C. elegans* can integrate multiple sensory stimuli and learn flexibly to drive behaviours (Dal Bello et al. 2021; Flavell and Gordus 2022; Ghosh et al. 2017; Hobert 2003; Khan et al. 2022; Luo et al. 2014; Takeishi et al. 2020), then—by Ginsburg and Jablonka's definition—these animals can subjectively experience. Barron and Klein (2016) instead suggest a different set of criteria. They begin with the premise that subjective

experience occurs when an animal has an "integrated sense of space that includes the position, state and movement of the body", i.e., it has a unified internal model of its body in its 3-dimensional environment. This model allows an animal to navigate in the world in a controlled manner rather than via random trial and error. Barron and Klein (2016) argue that because insects exhibit behaviours consistent with the possession of neural models of space then they can subjectively experience. However, they deny that *C. elegans* have the capacity for subjective experience because they lack integrated models of space. While acknowledging that *C. elegans* can integrate multi-sensory stimuli and exhibit flexible behaviour, they claim that these worms can only respond to local environmental cues via random search and are unable to navigate directly to locations where food sources were in the past (i.e., that do not possess a sensory map/representation of their environment). Chittka (2022) refers to such behaviour as indicative of an animal that "lives entirely in the present, responding only with hard-wired responses to currently incoming stimuli". However, *C. elegans* do learn to perform targeted navigation within T-mazes in search of food rewards by using a combination of proprioceptive and mechanical sensory stimuli and they can execute that behaviour after food cues are removed (Gourgou et al. 2021). This means that their search behaviour is guided by learning and memory of sensory cues within the wider environment i.e., they use sensory maps. Given that Barron and Klein claim that this behaviour is both necessary and sufficient for subjective experience, it should follow for them that *C. elegans*—like insects—subjectively experience.

It is widely acknowledged that animals use emotions to motivate conscious behaviours (Adolphs and Anderson 2018; Duncan 2006; Sneddon et al. 2014). Mate searching (Lipton et al. 2004), hunger (Rengarajan et al. 2019) and aversive responses to electric shocks (Tee et al. 2021) in *C. elegans* are therefore all considered indicative of basic or raw subjective experience. A favoured example of feelings-based behaviours is value-based decision making, or motivational trade-off paradigms. Here, a trade-off exists between the cost of an action and an expected reward or positive experience. It is presumed that if an animal is willing to endure a noxious stimulus to receive a benefit (e.g., food or water) then it must be capable of subjective experience. Birch et al. (2020) contend that only conscious animals can evaluate and decide in such circumstances because only they feel pain and pleasure. Unlike a typical autonomic and invariant response to a noxious stimulus, behavioural responses to opposing stimuli are flexible and considered indicative of a mind that can take into consideration competing motivations (DeGrazia 2020). Given that nematodes will endure an aversive stimulus or perceived threat to reach a positive stimulus (Ghosh et al. 2016; Ishihara et al. 2002; Shinkai et al. 2011), then they must join the likes of insects (Gibbons et al. 2022a, b) and crabs (Appel and Elwood 2009; Elwood and Appel 2009) as animals supposedly capable of subjectively experiencing emotions. This idea is part of a broader thesis that flexible behaviours are indicative of conscious awareness (Baars 1988; Bayne et al. 2019; Birch et al. 2020; Dehaene 2014; Droege 2017; Droege and Braithwaite 2015; Droege et al. 2021; Edelman and Seth 2009; Griffin 2013; Grinde 2013; Kabadayi and Osvath 2017; Kanai et al. 2019; Mather 2008; Mikhalevich et al. 2017; Perry and Chittka 2019; Rosslenbroich 2014; Schnell et al. 2021; Seth 2009).

Recently, Crump et al. (2022a; b) proposed eight criteria as a framework for evaluating evidence of animal sentience. In their view, some decapod crustaceans (crabs and lobsters) are highly likely to be sentient because they satisfy at least three of these eight criteria, namely: (criterion 1) the animal possesses receptors sensitive to noxious stimuli (nociceptors); (criterion 2) the animal possesses brain regions capable of integrating information from different sensory sources; and (criterion 4) the animal's behavioural response to a noxious stimulus is modulated by chemical compounds affecting the nervous system. While crabs in general (Brachyura and Anomura) satisfied their criterion 5 (motivational trade-offs) and criterion 6 (flexible self-protection) only Brachyura crabs satisfied criterion 7 (associative learning). There has been strong support for the approach by Crump et al. (2022a; b) as seen in the numerous commentaries to this target article in the journal Animal Sentience and by their application to other species (Crump et al. 2023; Gibbons et al. 2022a, b). Moreover, these criteria have led to the amendment of the United Kingdom Animal Welfare Sentience Bill to include decapod crustaceans as sentient beings (Browning and Veit 2022). Given that *C. elegans* satisfy five of the eight criteria (1, 2, 4, 5 and 7) they too must be considered highly likely to be sentient under this framework.

If *C. elegans* are considered sentient, we asked what can be learned from the worm connectome about the neural architecture generating subjective experience? The small, well-defined nervous system of the nematode make this animal an excellent model organism for studying subjective experience. Indeed, it is the only animal for which the complete wiring diagram is available (Varshney et al. 2011; White et al. 1986; Witvliet et al. 2021). Here, we analysed the worm connectome[1] through the lens of flexible behaviour in search of insights into the neural basis of subjective experience. We are not ourselves advocating that these worms are conscious, but rather we are hoping to identify the minimal neural circuitry needed to generate subjective experience if they are indeed accepted as sentient. We begin with an overview of the general organisational principles of the *C. elegans* nervous system ("General organisational principles in the C. elegans nervous system" section) and then build on that background to identify the neural circuitry underlying flexible behaviours associated with olfaction ("Neural circuitry generating flexible olfactory behaviours in C. elegans" section). In "Neural basis of subjective experience" section we discuss the implications of what we have revealed from *C. elegans* for understanding the neural basis of subjective experience.

General organisational principles in the *C. elegans* nervous system

The closest structure that *C. elegans* has to a brain[2] is a large cluster of neurons comprised of the nerve ring and ventral ganglia (containing 180 neurons in the adult) that encase the pharynx in the head (Witvliet et al. 2021) (Fig. 1A). The brain

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[1] We consider the connectome of the hermaphrodite animal rather than males.

[2] We define a brain as an integrated set of centralised neurons with executive control functions.
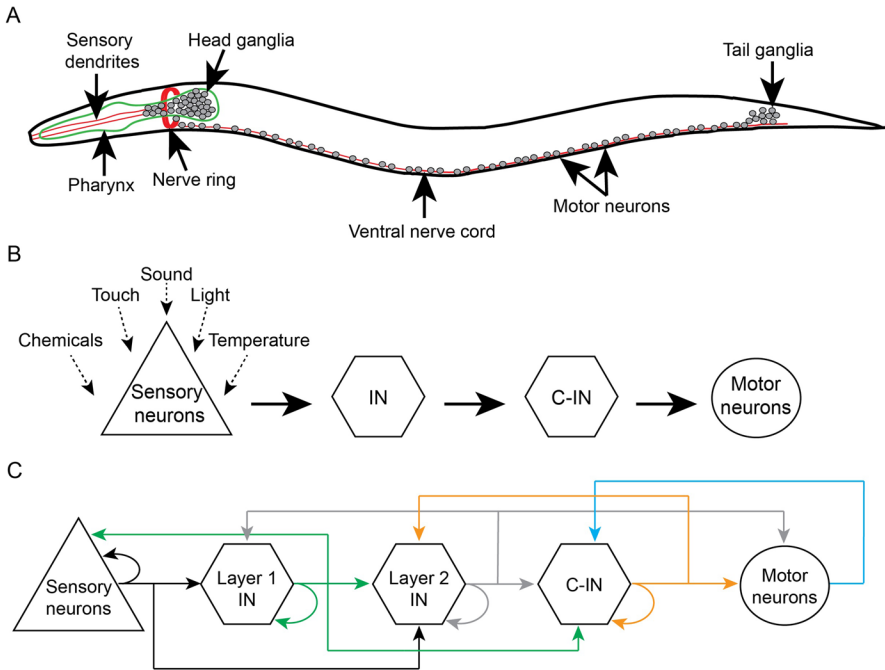
Fig. 1 The structure of the *C. elegans* nervous system. **A** Schematic of an adult *C. elegans*, showing major features of the nervous system. The head of the animal is facing the left of the image, the tail of the animal is towards the right of the image. Most chemosensory neurons reside in the head ganglia, which together with the nerve ring, is considered the brain of the worm. The dendrites of sensory neurons project anteriorly (to the left of the image). Motor neurons are in the head and throughout the ventral nerve cord. Sensory neurons are also located in the tail ganglia. Axons or processes are shown in red. Not all commissures are shown. **B** Basic wiring diagram of the worm nervous system. Sensory neurons detect volatile and soluble chemicals, touch, sound, light and temperature. Sensory neurons project to interneurons (IN), command interneurons (C-IN) and finally to motor neurons. In this and subsequent figures, we adopt the convention of displaying sensory neurons as triangles, interneurons as hexagons and motor neurons as circles. **C** Schematic representing the distributed information flow within the *C. elegans* nervous system. Sensory neurons project (black arrows) to layer 1 interneurons and layer 2 interneurons. Layer 1 interneurons project (green arrows) to sensory neurons, layer 2 interneurons and command interneurons (C-IN). Layer 2 interneurons project (grey arrows) to layer 1 interneurons, command interneurons (C-IN) and motor neurons. C-IN project (orange arrows) to layer 2 interneurons and motor neurons. Recurrent connections, as defined by connections within neurons of the same layer, are represented by curved arrows

consists of three principal classes of neurons: sensory neurons, interneurons, and motor neurons. Neurons in *C. elegans* are typically bilaterally symmetrical, and individually designated by a unique name of either three or four letters e.g., amphid wing A, AWA (Bargmann 2006).

There are 85 sensory neurons in *C. elegans* that detect chemical, mechanical, temperature, light and sound stimuli (Hobert et al. 2016; Iliff et al. 2021; Perkins et al. 1986; Ward 1973; White et al. 1986). Unlike in vertebrates, where sensory neurons are located peripherally, the cell bodies of the sensory neurons in *C. elegans* reside in the brain. The sensory neurons typically project to interneurons, a

specialised class of neurons that bridge the gap between sensory input and motor output (Fig. 1B). There are 81 interneurons in the worm (Hobert et al. 2016). These interneurons exhibit several key features underpinning their central role in information processing: they are directly innervated by sensory neurons, they provide feedback to these sensory neurons, they typically receive converging inputs from different sensory modalities, and they divergently innervate other interneurons as well as motor neurons. Some of these interneurons are dubbed 'command interneurons', or premotor interneurons, because of their dominant role in orchestrating specific movements (Chalfie et al. 1985; Hart et al. 1995; Jorgensen and Nonet 1995). For example, AVB command interneurons drive coordinated forward movement while AVA command interneurons drive coordinated backward or reversal movement (Chalfie et al. 1985; Kawano et al. 2011). Analysis of the local connectivity of the interneurons shows they form a so-called 'rich club' (Towlson et al. 2013; Uzel et al. 2022) and have an 'hourglass' organisation (Sabrin et al. 2020). What this means is that the interneurons are highly interconnected, not only with other neuron classes but with each other, and form an information processing bottleneck that integrates information from different modalities (Kaplan and Zimmer 2018; Sabrin et al. 2020).

The third class of neurons, the motor neurons, comprise approximately one third of the nematode nervous system (Altun and Hall 2011; Hobert et al. 2016) and are directly responsible for executing motor behaviours. There are distinct pools of motor neurons that contribute to forward and reversal movements (Zhen and Samuel 2015). Motor neurons receive input from both command interneurons and other interneurons, with forward command interneurons specifically activating forward motor neurons, and reverse command interneurons specifically activating reverse motor neurons (Faumont et al. 2012). The motor neurons are distributed throughout the brain and ventral nerve cord. Motor neurons can also feedback to command interneurons and interneurons so that there is information flowing upstream and downstream at all levels in sensorimotor pathways in *C. elegans* (Fig. 1C).

The nervous system of the worm is often described as precise and invariant. While this may be generally true of the anatomical positioning of cell bodies and their cell lineage (Sulston et al. 1983; White et al. 1986), it is now apparent that the worm connectome is not completely and innately hard-wired (Brittin et al. 2021; Witvliet et al. 2021). The connectome represents the reconstruction of individual connections between neurons, being either chemical or electrical synapses, and the strength of those connections, as defined by the number of synapses. On average, each pair of connected neurons has ~ 7 synapses. While some connections (~ 800) are found in all adult animals (i.e., stable) there are just as many that are highly variable between animals (Witvliet et al. 2021). In most cases, the variable connections are weak since they have fewer synaptic connections compared to stable connections. Stable connections are predominately found between interneurons, suggesting that these represent an innately wired circuit essential for worm survival (*i.e.*, critical "decision-making") (Witvliet et al. 2021). Interestingly, of the stable connections, ~ 45% are feedforward (i.e., from sensory to interneurons), versus ~ 35% that are recurrent (i.e., between neurons of the same class, such as interneurons to interneurons) and ~ 20% that are feedback (i.e., from interneurons to sensory

neurons) (Witvliet et al. 2021). Overall, there is a feedforward connectivity bias, with the proportion of synapses in feedforward connections increasing across maturation of the worm, favouring the rapid generation of behaviour from sensory stimuli (Witvliet et al. 2021).

Perhaps the most important organisational principle for function in the *C. elegans* nervous system is the hierarchical nature of the interneuron network. Sensory information is typically processed through three layers of interneurons. Layer 1 and 2 interneurons integrate information from sensory neurons, and this is then integrated and read out by layer 3 command interneurons. This layered, hierarchical structure of the neurons is reflected in their anatomical layered arrangement around the nerve ring (Brittin et al. 2021; Cook et al. 2019; Kaplan et al. 2020; Moyle et al. 2021; Tsalik and Hobert 2003). While information flow is often depicted as simply feeding forward through each of these layers (Fig. 1B), there is variable routing of neural signals. For example, some sensory neurons project directly to layer 2 interneurons, and some layer 1 interneurons communicate directly with command neurons in layer 3 (Fig. 1C).

Neural circuitry generating flexible olfactory behaviours in *C. elegans*

Subjective experience of sensory stimuli is considered to motivate flexible behaviours such as motivational trade-offs. That is, worms will overcome an unpleasurable aversive sensory stimulus to obtain a more rewarding and pleasing stimulus. According to this argument, the neural circuitry considered necessary and sufficient for behaviours in motivational trade-offs must be responsible for subjective experience. 'Necessity' refers to the circuitry that is essential for a particular behaviour and is assessed by loss-of-function approaches. For instance, if electrically silencing or ablating a neuron in worms inhibits a specific behaviour then that neuron is considered necessary for that behaviour. While a neuron may be necessary for a behaviour, it need not be sufficient (i.e., other neurons may also be required for function). Sufficiency is typically determined by gain-of-function whereby the activation of a neuron generates the behaviour. However, artificially stimulating a neuron fails to identify which upstream and recurrently connected neurons are necessary for its normal activation. Only by combining both loss- and gain-of-function techniques is it possible to construct a circuit containing all the necessary and sufficient neurons to generate subjective experience and drive motivational trade-offs.

We concentrate here on olfactory-mediated behaviours since the neural circuitry underpinning these behaviours is well described. *C. elegans* detect odours using four pairs of olfactory chemosensory neurons: AWC, AWA, AWB and ASH (Fig. 2). By using laser ablation and analysis of chemotaxis behaviour,[3] the odour response profiles of these chemosensory neurons have been characterised. The

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[3] Chemotaxis assays are typically conducted by placing worms on an agar plate, with the test odorant at one end and a control odorant at the opposite end. After a set time point (usually 1 h), the number of worms at either odorant are counted. Results are displayed as a ratio of worms at the test odorant.
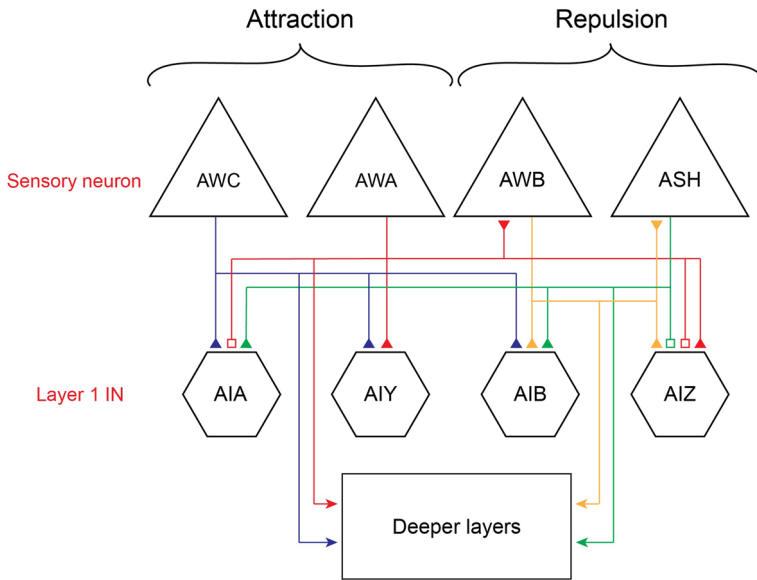
Fig. 2 Neural circuitry involved in odour processing in *C. elegans*. Simplified overview of the circuitry involved in odour processing. Four chemosensory neurons (AWC, AWA, AWB and ASH) that detect odorants and their connections to the four major layer 1 interneurons (AIA, AIY, AIB and AIZ) and to deeper layers within the nervous system (rectangle) are shown. The different colours represent the connections made by the different neurons: AWC (blue), AWA (red), AWB (yellow) and ASH (green). Two neurons, AWA and AWC, mediate attraction—movement towards an odorant. The other two neurons, AWB and ASH mediate repulsion—movement away from an odorant. Synaptic connections are represented by triangles for chemical synapses while squares denote electrical synapses. The number of synapses and type of the synapse (excitatory or inhibitory) is not shown. Wiring diagram based on Bhatla (2009)

AWA and AWC neurons typically mediate attractive chemotaxis (i.e., movement towards an odour) while the AWB and ASH typically mediate repulsive chemotaxis (i.e., movement away from an odour) (Bargmann et al. 1993; Bargmann et al. 1990; Kaplan and Horvitz 1993; Troemel et al. 1995; Troemel et al. 1997). During chemotaxis, worms display locomotor behaviours called 'runs' and 'pirouettes'. A run is a period of straight-forward, sinusoidal crawling movement while a pirouette is a reorientation strategy that includes a reversal (backward sliding) and a sharp body turn known as an omega turn (as the worm's body resembles the Greek letter Ω) (Luo et al. 2014; Pierce-Shimomura et al. 1999). The reversal movement and the turning behaviour changes the direction of movement of the worm before the animal resumes a new forward run (Gray et al. 2005; Pierce-Shimomura et al. 1999). The pirouette strategy enables the animal to reorient within an odour gradient (Pierce-Shimomura et al. 1999). Worms can alter the frequency of pirouettes according to local environmental conditions such as food availability (Chalasani et al. 2007; Tsalik and Hobert 2003). A worm will also use a 'weathervane' strategy during chemotaxis to orient its head up an odour or salt gradient, like a weathervane pointing into the wind (Iino and Yoshida 2009; Ward 1973).

Weathervanes are not considered to be random searches but rather a technique to fine-tune the forward direction of locomotion (Iino and Yoshida 2009).

Worms exhibit flexible responses to aversive odours depending on food (i.e., bacteria) availability. When worms are food deprived (i.e., in a hunger state) they will delay their aversive response to a point source of dilute octanol. A hungry worm takes longer to stop moving forward i.e., it trades-off negative experience of octanol in the hope of finding food. However, the animal soon loses motivation to continue without food reward and reverses and turns to begin a food search in a new direction away from the aversive stimulus. In contrast, in a food-rich environment, worms quickly respond to octanol, perform only short reversals, and then again move forward to continue feeding (Chao et al. 2004; Harris et al. 2011; Summers et al. 2015). This is a classic example of a motivational trade-off where worms weigh up whether the positive reward of food experience is greater than the negative experience of octanol.

We now examine how gain- and loss-of-function approaches have helped reveal the neural substrate that motivates a worm to overcome an aversive olfactory sensory stimulus. The overall behaviour of the worm in response to octanol is critically dependent on the neural circuit that controls the decision to stop forward locomotion and begin a reversal since it is during this phase that the worm must weigh the costs and benefits of continuing to move along its chosen path. By focussing on this behaviour, our task of understanding the neural underpinnings of a worm's subjective experience of sensory stimuli is simplified. The ASH chemosensory neurons lie at the top of the circuitry necessary for eliciting the stopping behaviour because ablation of these neurons causes worms to become oblivious to dilute octanol either when feeding or hungry (Chao et al. 2004). When ASH is instead artificially stimulated by optogenetic activation, it causes worms to execute an avoidance response (Ezcurra et al. 2011). However, this response is the same whether these worms were feeding or hungry. These results indicate that other neurons must be modulating the behaviour and that while ASH was necessary, it was not sufficient for the flexible responses.

The AWC chemosensory neurons play a modulatory role in the octanol response. AWC neurons are tonically active, and although this activity does not initiate reversals it does prolong them and reduces the likelihood that worms will move forward again after a reversal (Summers et al. 2015). Food odorants dampen the tonic activity of AWC chemosensory neurons which hastens the initiation of reversals, shortens their length, and promotes subsequent forward locomotion (Summers et al. 2015). In addition, the bacteria used as a food source stimulate two neurons in the pharynx, NSM, that secrete the monoamine serotonin (Harris et al. 2011; Horvitz et al. 1982). When worms are off food, the addition of exogenous serotonin causes worms to behave like animals on food in response to dilute octanol i.e., they decrease time to respond to octanol and move forward towards octanol after reversal (Chao et al. 2004; Harris et al. 2011). When worms are on food, the selective loss of serotonin from NSM neurons, and not any other serotonin expressing neurons, causes worms to behave as though they are off food (Harris et al. 2011). Serotonin receptors present on ASH neurons are essential for this flexible response (Harris et al. 2009). Octopamine is a neuroactive substance
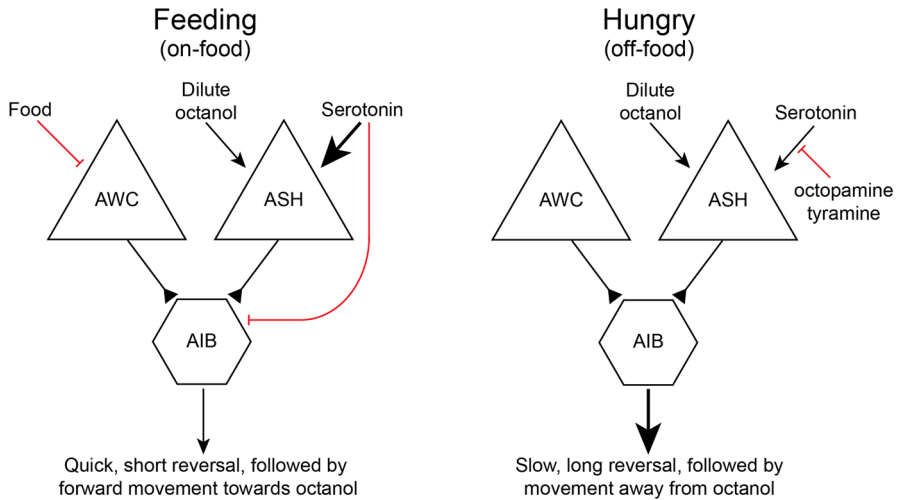
Fig. 3 Example neural architecture that supports flexible behaviour in *C. elegans*. AIB integrates the input from AWC and ASH neurons to regulate motivational behaviour involving satiety and the aversive stimulus octanol (Harris et al. 2009; Summers et al. 2015). The contrasting scenarios of when worms are feeding or on-food (left) versus when they have been off-food (right) i.e. are hungry, is shown. Dilute octanol and serotonin activate ASH neurons. When worms are feeding (left), food decreases activity in AWC neurons, and serotonin inhibits AIB. AIB regulates the behavioural response by integrating the input from AWC and ASH. When on-food (left), AIB signalling is inhibited, and worms will quickly reverse, but continue forward locomotion towards octanol. When worms have been off-food and are hungry, AIB is stimulated and worms perform a long, slow reversal and then continue to move away from the octanol. Octopamine and tyramine inhibit serotonin's effect on ASH neurons. Black arrows indicate activation, with thicker lines representing enhanced activity, and red bars indicate inhibition

closely related to norepinephrine (Roeder 1999) that is expressed and secreted humorally by RIC interneurons in the absence of food. Octopamine inhibits any residual serotonin-dependent enhancement of ASH neurons (Alkema et al. 2005; Mills et al. 2012a, b; Suo et al. 2009; Wragg et al. 2007). RIM interneurons secrete tyramine (the precursor to octopamine) that, like octopamine, also inhibits serotonin effects on ASH neurons (Alkema et al. 2005; Hapiak et al. 2013; Wragg et al. 2007). Bacteria also stimulate dopaminergic mechanosensory neurons to secrete dopamine (Sawin et al. 2000) and worms deficient in dopamine have a slowed response to dilute octanol (Baidya et al. 2014). Thus, as with serotonin, dopamine acts on ASH (Ezcurra et al. 2011) to quicken the response of feeding worms to octanol. In summary, AWC chemosensory neurons, serotonin, dopamine, octopamine, and tyramine act together with the ASH chemosensory neurons to modulate the aversive response to octanol to ensure that it is context appropriate. While these and many other neuromodulatory agents influence worm behaviour (Florman and Alkema 2022; Hapiak et al. 2013; Hardege et al. 2022; Mills et al. 2016), it is clear that ASH and AWC chemosensory neurons sit at the top of the neural circuitry controlling the motivational trade-off between the subjective experiences of food and octanol (Fig. 3).

Fig. 4 Candidate neural architecture for subjective experience in *C. elegans*. Two sensory input neurons (AWC and ASH) and an integrating network of three interneurons (AIB-RIM-AVA) form a 4-layered hierarchical neural circuit that is both necessary and sufficient for motivational trade-off behaviours. The synaptic interconnections, either as chemical synapses (triangles) or electrical synapses (squares) are shown. Wiring diagram based on Bhatla (2009)
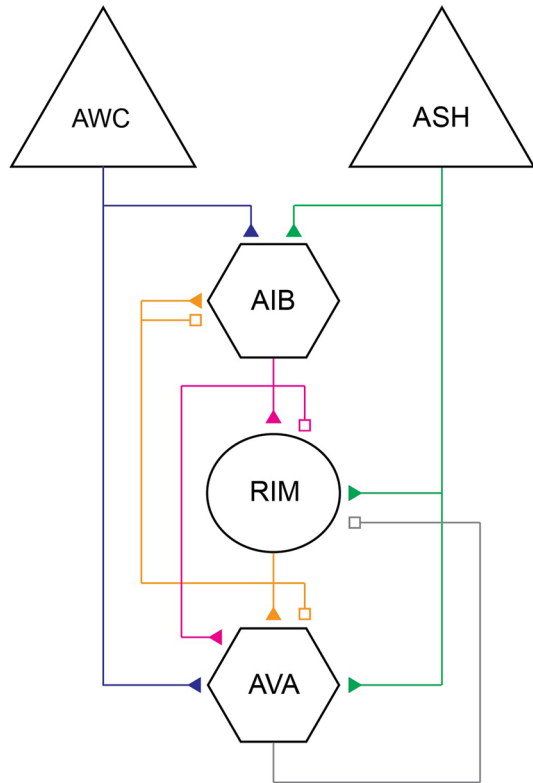
The layer 1 interneuron AIB lies downstream of both AWC and ASH where it integrates the outputs of these chemosensory neurons. Loss- and gain-of-function approaches have been instrumental in clarifying the role of AIB in motivational trade-offs. Ablation of AIB interneurons causes hungry worms to rapidly stop moving forward in response to octanol, which is a response normally demonstrated by worms feeding in a food-rich environment (Summers et al. 2015). If AIB neurons were genetically engineered to decrease their activity, feeding worms responded more slowly to octanol just like hungry worms (Summers et al. 2015). In contrast, selective optogenetic activation of AIB stimulated reversals (Zou et al. 2018). Thus, AIB is both necessary and sufficient for modulating the time it takes for worms to respond to octanol. Together, experimental manipulations suggest that ASH, AWC and AIB are driving a neural circuit that underpins subjective experience (Fig. 4).

The layer 2 interneuron RIM and the layer 3 command interneuron AVA are downstream of AIB and are key mediators of aversive behaviours (Fig. 4). While there are no studies that selectively examine the behavioural response to octanol following RIM and AVA loss- and gain-of-function manipulations, we do know that direct optogenetic activation of either RIM or AVA generates reversals (Gordus et al. 2015; Guo et al. 2009; Katz et al. 2019). Furthermore, blocking RIM activity by hyperpolarisation causes simultaneous inhibition of AVA since these two neurons are interconnected by electrical synapses (i.e., gap junctions) (Sordillo

and Bargmann 2021). This RIM mediated inhibition of AVA suppresses reversals. Similarly, reversals are abolished when AVA is selectively inhibited using ectopic expression of chloride channels in these neurons (Kato et al. 2015). There is redundancy in this circuitry since worms can still perform long reversals after ablation of RIM (Gray et al. 2005). Presumably, in this case, AIB directly activates AVA. Nonetheless, RIM normally plays an important modulatory role in the behavioural response. The AIB-RIM-AVA neurons typically act as a coupled network that exists preferentially in either a high or low activity state (Gordus et al. 2015; Sato et al. 2021). Variability in how this network behaves over time, particularly with respect to the timing of transitions between active and inactive states for individual neurons and how long these neurons remain in correlated states provides a mechanism for regulating motivational trade-offs. Silencing RIM alone strengthens the correlated states between AIB and AVA and creates a highly deterministic or reflex-like response (Gordus et al. 2015). It seems that RIM normally weakens the correlated state of the network and in doing so exerts a strong modulatory role over the excitatory output of the network and hence the behavioural response. Thus, RIM plays a driving role in controlling the activity state of individual neurons (both by direct connections and secretion of tyramine) in this network and this facilitates context-specific behavioural responses. It should be noted that RIM plays a central modulatory role in different forms of motivational trade-offs involving hunger states, attractive odours (e.g., diacetyl), hyperosmotic repulsive barriers and other repellent odours (e.g., 2-nonanone) (Bauknecht and Jekely 2017; Florman and Alkema 2022; Ghosh et al. 2016; Gordus et al. 2015; Hardege et al. 2022; Harris et al. 2019). Finally, ablation or silencing of AVA prevents worms from performing reversals which confirms its necessity for this aversive behaviour (Gray et al. 2005; Kato et al. 2015). Together, these gain- and loss-of-function studies have demonstrated that the ASH/AWC-AIB-RIM-AVA network (Fig. 4) is both necessary and sufficient for the motivational trade-off involving hunger state and an aversive odorant.

Neural basis of subjective experience

We have described here a 4-layered hierarchical neural circuit (Fig. 4) consisting of two sensory input neurons (ASH and AWC) and an integrating network of three interneurons (AIB-RIM-AVA) that provides an output to motor neurons controlling gross motor responses. The ASH/AWC-AIB-RIM-AVA circuit is both necessary and sufficient for motivational trade-off behaviours that involve weighing the costs of overcoming the subjective experience of an aversive olfactory stimulus against the benefits of the rewarding experience of food. Interestingly, this circuit shares many of the same structural features of the mammalian spinal cord stretch reflex involving group II muscle spindle afferents (Jankowska and Edgley 2010) (Fig. 5). Group II afferents from muscle spindles are activated by skeletal muscle stretch (analogous to ASH chemosensory neurons responding to odours) and synapse directly on spinal interneurons (analogous to layer 1 AIB interneurons). The spinal interneurons are convergently innervated by sensory neurons from both group Ib tendon organ afferents and group II muscle spindle afferents (Jankowska and Edgley 2010) and, in
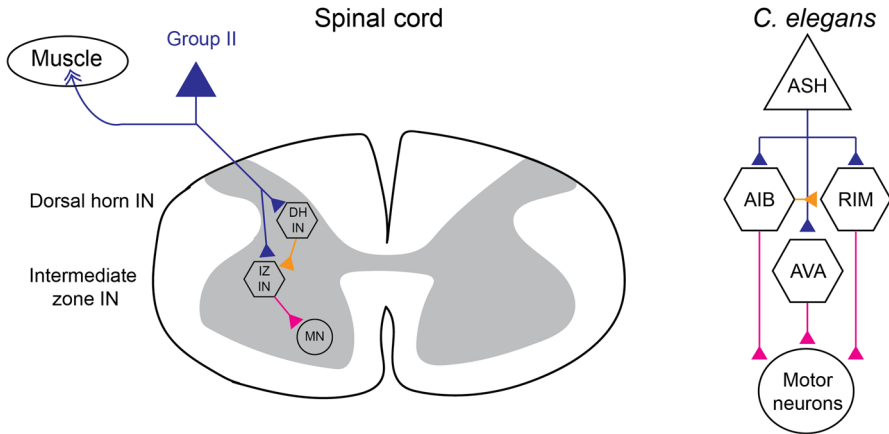
Fig. 5 Comparison of mammalian spinal cord circuitry and simplified hierarchical neural network for motivational behaviour in *C. elegans*. The mammalian spinal cord stretch reflex (left) is analogous to the output from ASH neurons in *C. elegans* (right). Group II afferents from muscle spindles are activated by skeletal muscle stretch and connect serially to two distinct pools of interneurons (IN): dorsal horn (DH) interneurons and intermediate zone (IZ) interneurons of the grey matter. Group II afferents can bypass dorsal horn interneurons and connect directly to intermediate zone interneurons. Intermediate zone interneurons can directly innervate motor neurons. Note the similarities with ASH chemosensory neurons in the worm (right), that innervate interneurons in all three layers in parallel and can connect directly to motor neurons (not shown). Spinal cord figure based on Jankowska et al. (2002) and Jankowska (2016). Wiring diagram based on Bhatla (2009)

that sense, they have a similar multi-modal integrating function as AIB interneurons that are innervated by different types of upstream chemosensory neurons (Fig. 2). Group II afferents also connect serially to two distinct pools of interneurons that are spatially segregated in the dorsal horn and intermediate zones of the grey matter as described in the cat spinal cord (Jankowska et al. 2002). In addition, group II afferents can by-pass the dorsal horn interneurons and directly innervate intermediate zone interneurons (which, in turn, directly innervate motor neurons) (Jankowska et al. 2002). This is like the ASH chemosensory neurons in the worm that innervate interneurons in all three layers in parallel (Figs. 2, 4). While the fine intra-layer connectivity of interneurons within the dorsal horn and intermediate zones of the spinal cord remains unresolved, it seems that the layering of distinct pools of interneurons between sensory neurons and motor neurons is a general organisational principle that is conserved in both the worm brain and the mammalian spinal cord.

It is well accepted that the isolated vertebrate spinal cord is not subjectively aware. The brain is necessary for muscle sensory information to be subjectively experienced in humans (Goodwin et al. 1972). More specifically, the cerebral cortex is essential for subjective experience as revealed by feelings elicited with direct electrical stimulation of the cortex in epilepsy patients (Penfield and Rasmussen 1950). It is unlikely that isolated spinal cord generates experience while the brain merely reports on it since the sensation of body position is subjectively experienced independently of spinal cord function (i.e., in a tetraplegic patient) by intracortical electrical stimulation of the somatosensory cortex (Armenta Salas et al. 2018). Clearly,

Fig. 6 Visual pathway and neural circuit diagrams comparing the vertebrate visual system and *C. ele-* ▶
gans nervous system. **A** Schematic of the main pathways involved in visual processing. Visual signals
pass from the retina via the optic nerve to the lateral geniculate nucleus (LGN) of the thalamus (grey
dashed box). The LGN projects to primary visual cortex (V1, green box), and secondary visual cortex
(V2, connection not shown). Visual signals are further processed in visual association areas 3, 4 and 5
(V3, V4, V5/MT). The pulvinar nucleus of the thalamus receives input from the retina and sends projec-
tions to V1 and V2; the superior colliculus sends output to V3 via the pulvinar. The superior colliculus
also receives input from the retina and sends projections to the frontal eye field and basal ganglia. Note:
not all interconnections (such as feedback connections) or brain regions involved in visual processing are
shown. Diagram adapted from Choi et al. (2020) and (Urbanski et al. 2014). **B** The retina consists of
three neuronal layers: photoreceptor cells (triangle, representing rods or cones), interneurons (hexagons
in red box), including horizontal cells (H), amacrine cells (A) and bipolar cells (B). The interconnections
of the interneurons are shown with grey dashed arrows: horizontal cells form interconnections between
photoreceptor cells and bipolar cells and amacrine cells synapse with bipolar cells. Horizontal cells can
send feedback to the photoreceptor cells (curved arrow). Ganglion cells (circle) make up the final layer—
the axons from these cells form the optic nerve to carry visual signals to the brain. **C** Overview of V1
circuitry. V1 (green box) consists of six layers, which have been grouped based on their similar inputs
and projections. Most of the input to V1 from the LGN (triangle) comes to layer 4 (L4). L4 neurons
send output to other layers within V1 (grey arrows). V1 provides output to extrastriate visual areas (V2,
V3, V4, V5) and strong feedback to LGN (thick black arrow). Not shown are outputs of V1 to sub-
cortical areas, including the pulvinar, superior colliculus and pons. **D** Overview of the *C. elegans* nerv-
ous system. Sensory neurons (triangle) process sensory cues and synapse with interneurons (hexagons
in blue box). Interneurons can be further categorised as layer 1 (L1 IN), layer 2 (L2 IN) and command
interneurons (C-IN). Each interneuron category is interconnected (grey arrows) and sends feedback to
sensory neurons (black arrow). Motor neurons (circle) receive input from interneurons and send feedback
to interneurons (curved arrow). The predominate feedforward nature of the worm nervous system is rep-
resented by the thick black arrows

it is the isolated brain that both generates and reports on subjective experience. It
should be noted that the somatosensory cortex does not act alone in creating sub-
jective experience. The feeling of body position depends on multiple cortical areas
outside the somatosensory cortex, as observed in stroke patients with lesions in the
temporoparietal and insular cortices who have perturbed sensory experiences (Chil-
vers et al. 2021).

Our comparative discussion of the structure–function relationships between the
mammalian spinal cord and the worm ASH/AWC-AIB-RIM-AVA circuit suggests
that information processing in a sensory afferent-interneuron-motor neural circuit is
not itself sufficient for subjective experience. While reflex and flexible behaviours
rely on such circuits in both worms and humans, we know from humans, at least,
that outputs from this circuit must be further processed by higher-order centres,
which are functionally defined by their more complex receptive fields (Schellekens
et al. 2021), for subjective experience. However, is it possible that spinal cord-like
circuitry subserves subjective experience in other mammalian sensory systems, such
as vision? While visual processing begins in the retina, it is neither necessary nor
sufficient for subjective visual experience since downstream electrical stimulation of
the optic nerve produces visual sensations (Veraart et al. 1998). Retinal ganglionic
cells are the output neurons of the retina that project axons via the optic nerve to
both the lateral geniculate nucleus (LGN) of the thalamus and the superior colliculus
(Fig. 6A). Visually responsive neurons in these two brain regions principally target
the primary visual cortex (V1) and pulvinar of the thalamus, respectively. It has long
been known that direct electrical stimulation of V1 elicits the subjective experience
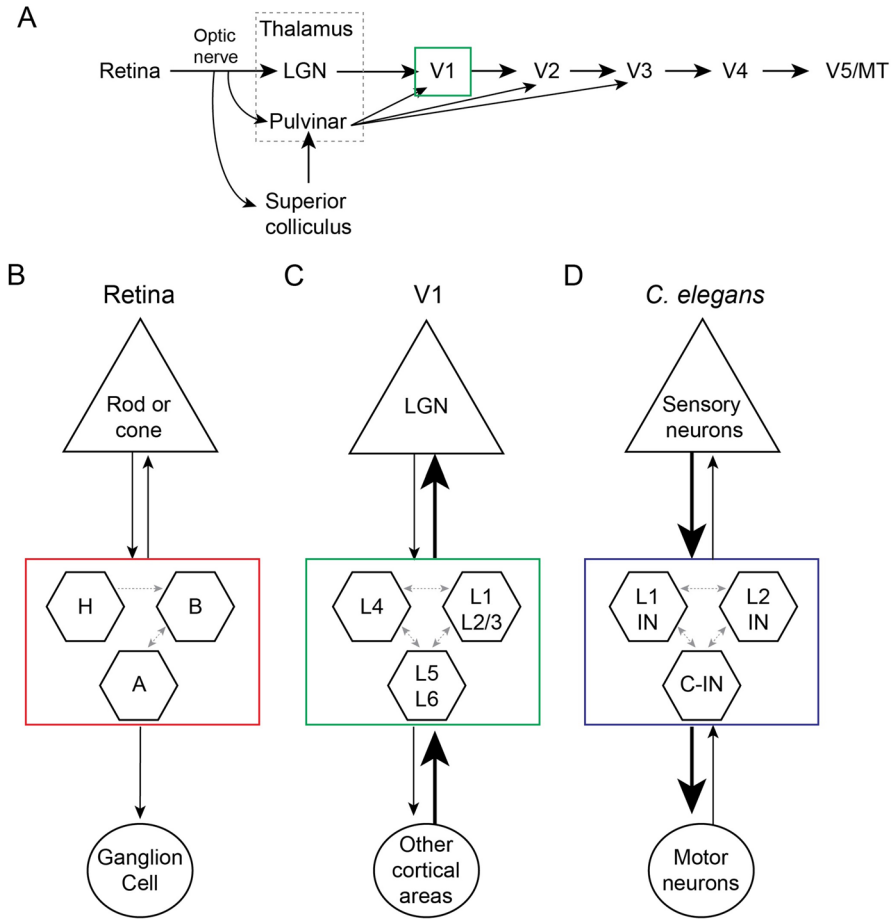
of pinpoint flashes of brightness referred to as phosphenes (Brindley and Lewin 1968). When electrical stimulation is patterned and applied dynamically, subjects can identify multiple independent phosphenes as forming complex visual percepts such as letters (Beauchamp et al. 2020). These results reveal that the feedforward retino-thalamo-cortical trajectory is not necessary for subjective visual experience.

In rare cases, electric stimulation of the human brainstem (Tasker et al. 1980) and specifically of the superior colliculus (Nashold 1970) produces phosphenes—but this seems to be mediated indirectly by pulvinar connections from these regions and subsequent pulvino-cortical pathways. The direct role of the superior colliculus is best assessed by ablation. When the superior colliculus and frontal eye fields in the cortex in monkeys are ablated, they are unable to saccade their eyes to appropriate visual targets (Schiller et al. 1979). Despite these motor deficits, their visual ability remains intact since monkeys instead move their heads and/or bodies to reorient their visual attention. Although the data from pathological insults to the human pulvinar is limited, evidence suggests a role for the pulvinar in visual attention

mechanisms rather than in subjective experience (Fischer and Whitney 2012; Froesel et al. 2021; Lucas et al. 2019). Further evidence that the pulvinar and superior colliculus do not generate subjective experience comes from patients with lesions to the optic tract downstream of the thalamus. These patients may lose sight in half of the visual fields of both eyes (called homonymous hemianopsia; Pambakian and Kennard 1997). Given that the pulvinar and superior collicular visual pathways are unaffected in those conditions with specific optic tract lesions, subcortical brain regions are clearly not sufficient for subjective visual experience.

Together these approaches indicate that cortical rather than subcortical pathways generate subjective visual experience in humans. Which part of the visual processing hierarchy generates subjective visual experience? Our purpose here is not to canvass each brain region along the visual pathway and discuss its role in conscious vision— a huge undertaking! Rather, consideration of the sufficient neural architectures for conscious vision will facilitate a comparison with *C. elegans'* neural circuitry to better understand the neural basis of subjective experience. The first cortical region in the visual processing hierarchy is V1 (Fig. 6A). Although pathological lesions to V1 produce blindness, electrical stimulation of upstream visual cortex reveals that V1 is not necessary for subjective experience of phosphenes (Mazzi et al. 2014). Despite the elaborate neural circuitry present in V1 (Sincich and Horton 2005), V1 does not play a direct role in subjective experience (Leopold 2012). Subjective visual experience arises in cortical areas upstream of V1 in the visual pathway (Fahrenfort et al. 2007; Juan et al. 2004; Juan and Walsh 2003; Koivisto et al. 2010; Lamme 2004; Lamme and Roelfsema 2000; Liu et al. 2019; Pascual-Leone and Walsh 2001; Pollen 1999, 2003; Ro et al. 2003; Silvanto et al. 2005; Super et al. 2001).

How does the circuitry of the retina and V1, both of which are neither necessary nor sufficient for subjective visual experience, compare with the worm's ASH/AWC-AIB-RIM-AVA circuit? The retina and V1 are hierarchically organised and broadly organised into three layers (Fig. 6B, C). In the retina, photoreceptors (rods or cones) are sensory neurons, interneuron populations comprise horizontal cells, amacrine cells and bipolar cells and ganglion cells represent the output neurons (Carlson 2019; Fig. 6B). While this retinal topology grossly matches the worm circuit (compare Fig. 6B, D), there are some differences in local connectivity i.e., the interneuron populations of the retina are less interconnected and there are generally fewer feedback connections within the retina compared to the worm. The six layered V1 is classically partitioned into three processing laminae consisting of L1–3, L4 and L5–6 which are interconnected in much the same way that three layers of interneurons in the worm circuit are organised (compare Fig. 6C, D). As already noted, both circuit architectures contain feedback connections, but they differ in the relative strength of these connections. Feedback connections outnumber feedforward connections in the visual pathway (Briggs 2020) whereas in the worm, connectivity is dominated by feedforward projections (Witvliet et al. 2021).

Given that the spinal cord, retinal and V1 processing is neither necessary nor sufficient for subjective experience and yet, overall, their neural architectures are like that of the worm's ASH/AWC-AIB-RIM-AVA circuit, we must question the likelihood that this latter circuit can generate subjective experience of repellent odours and rewarding food as claimed for motivational trade-off behaviours in worms. The

idea that an isolated circuit in worm has subjective experience seems to be bolstered by suggestions that isolated patches of cerebral cortex (Bayne et al. 2020) as well as in vitro cerebral organoids may be conscious (Niikawa et al. 2022). However, such propositions can be dismissed given that Nakamura and Mishkin (1986) convincingly demonstrated that rhesus monkeys became blind when large portions of the cerebral cortex beyond the visual cortex and inferior temporal lobe were ablated. The remaining isolated regions of cortex processing visual information were not sufficient for subjective experience, making it highly improbable that a small, isolated circuit in worms is conscious. Similar conclusions have been reached regarding the necessity of widespread and co-ordinated activation of cortical regions in the mouse brain during vision (Goldbach et al. 2021).

Conclusions

Feelings of pain and pleasure are widely assumed to drive flexible behaviours such as motivational trade-offs in non-human animals and yet, the only evidence supporting this belief comes from first-person experiences in humans. Despite the confidence afforded to this premise, the assumption that if A (i.e., a feeling) causes B (i.e., a behaviour) in animal C (i.e., a human), then A must also cause B in animal D (e.g., a worm) constitutes a causal fallacy. This line of reasoning fails to consider that more than one causal factor may be responsible for B. We initially ignored this problem and hypothetically accepted the premise (as many others do) that flexible behaviours are evidence for subjective experience in worms. Doing so allowed us to identify a circuit that should (were the premise true) elicit subjective experience associated with the motivational trade-off between rewards of food and aversion to noxious odours. This circuit consisted of two olfactory chemosensory neurons (AWC and ASH) that detect attractive and aversive odours and a downstream network of three highly interconnected interneurons (AIB-RIM-AVA). The behavioural flexibility produced by this circuit depends on feedback mechanisms (involving both innately wired connections and "wireless" humoral neuromodulators) that fine-tune neural activity at each hierarchical level so that the final output to motoneurons generates appropriate motor responses. This worm circuit is unremarkable and like that in many regions of the mammalian nervous system which lack subjective experience. This observation leads us to reject the idea that motivational trade-offs are sufficient evidence for subjective experience that is often claimed by some in the literature on animal sentience. Such a conclusion is consistent with recent concerns about the weakness of criteria typically employed to determine sentience (Briffa 2022; Butlin 2022; Dawkins 2022).

One may challenge whether the flexible behaviour exhibited by worms is indeed the right kind of behaviour that demands subjective experience. While shifting the goalposts around definitions of flexible behaviours may appear to explain why the worm circuit fails to account for subjective experience, all it really does is change the underlying premise to "the cause of flexible behaviours in humans is the same as the cause of the *same* flexible behaviours in any

non-human animals". Imposing this more stringent "sameness" constraint does not change the fact that the premise constitutes a causal fallacy.

Although it is beyond the scope of this paper to examine the matter, there is a further question how much the flexible behaviour of humans relies on the subjective quality of experiences associated with it. When a circuit is revealed as both necessary and sufficient for flexible behaviour, questions arise as to what explanatory role is left for subjective experience—whether it has been explained or explained away? The possibility of redundancy is an often-overlooked consequence of generating detailed neural wiring diagrams (e.g., Felleman and Van Essen 1991; Sewards and Sewards 2002) and, as shown here, nowhere is this more evident than in the complete worm connectome.

Hunger in mammals is an interesting case study given its relevance to the motivational trade-offs associated with the flexibility exhibited by worms when either on or off food. While the neural basis of motivational drive underpinning hunger is far from understood in mammals, transgenic approaches have exposed some important circuits. For instance, the projection of a subpopulation of arcuate neurons in the hypothalamus expressing the gene agouti related protein (AGRP) to the paraventricular hypothalamus is both necessary and sufficient to motivate food search and consumption when mice are food deprived (Atasoy et al. 2012). These AGRP neurons are directly activated by hormones such as ghrelin that are secreted from the stomach in starved conditions (Alcantara et al. 2022). Thus, a simplified interpretation is that lack of food in the stomach causes the stomach to secrete a circulating hormone that activates AGRP neurons projecting to the paraventricular nucleus which in turn stimulates downstream motor programs for food search. This does not mean that upstream circuits in the cerebral cortex (perhaps associated with subjective experience) do not modulate these hypothalamic circuits. There are many cortical regions which act on hypothalamic feeding circuitry because of both exteroceptive and interoceptive sensory inputs (Azevedo et al. 2022). However, the characterisation of this cortical circuitry and any associated neuromodulators will, like in the worm, only reinforce the notion that this circuitry and not the subjective quality of the experience that explains motivationally driven behaviours.

We do not mean to imply that subjective experience has no function, but its role in motivated trade-offs cannot be assumed once the necessary and sufficient neural circuitry driving that behaviour is understood and that circuitry is known to operate below the threshold of consciousness. Given this, how does the field move forward in relation to understanding the neural basis of subjective experience? Since behaviour has limitations as a measure of animal consciousness (Richer 2021) just as it does in humans (LeDoux 2020, 2021), one approach is to first, focus on identifying those neural computations that are necessary for subjective experience in any creature and second, on characterising neural circuits capable of executing these computations (Key and Brown 2018; Key et al. 2021; Key et al. 2022; LeDoux 2022). Those animals lacking the capacity to perform such computations cannot be sentient. We do the field no favours and potentially some harm by extending the causal role of subjective experience based on superficial similarities in behaviours without this kind of critical examination of the underlying circuitry.

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