

Is it pain if it does not hurt? On the unlikelihood of insect pain

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Abstract—Whether insects (Insecta) have the subjective experience of pain is difficult to answer. Recent work in humans demonstrated that the experience of pain occurs due to the activation of a “pain network” that integrates nociceptive sensory information, memory, emotion, cognition, and self-awareness. In humans, the processing of nociceptive sensory information alone does not produce the subjective experience of pain. Insect nociception is processed largely in parallel in two higher-order areas in the brain: the mushroom bodies and the central complex. There is little evidence of a coordinated pain network that would integrate these two areas with each other along with other traits thought to be important for a pain experience in humans. However, it is difficult to exclude the possibility that insects could have a modest pain experience using a less integrated neural circuit. This possibility seems unlikely, however, because even a modest experience would require some neuronal investment. It is unclear whether insects would benefit from such an investment. Recent work in artificial intelligence suggests that relatively simple, cost-efficient circuits can produce adaptive behaviours without subjective experience. Given our current understanding of insect behaviour, neurobiology, and evolution, the likelihood that insects experience pain is low.

Introduction

Recent debate over whether lobsters (Decapoda: Nephropidae) feel pain has heightened interest in the question of whether insects (Insecta) feel pain. Concerns about lobsters have resulted in new regulations about their transport and containment, on the assumption that they experience distress (Browman *et al.* 2018). Should we have the same concerns about insects? Although all animals (Animalia) deserve our respect (*e.g.*, see Mather 2011; Adamo 2016), not all animals may experience pain.

Pain is a negative subjective experience (Allen *et al.* 2005) that is complex and multifaceted (Garcia-Larrea and Jackson 2016). It encompasses feelings such as discomfort and despair. It differs from nociception, which is the ability to sense damaging stimuli (Allen *et al.* 2005). All organisms have some form of nociception, even Bacteria (Berg 1975). It is possible to have nociception without pain (Hardcastle 1997).

People with complete spinal transection still exhibit nociceptive reflexes below the level of the injury (*e.g.*, flexion of the ankle in response to an electric shock of the foot), but these reflexes occur without pain (Andersen *et al.* 2004). Therefore, exhibiting short-term or long-term behavioural responses to harmful stimuli does not mean that an animal feels pain. The behavioural change could be part of a response to nociception. Because pain is a private, subjective experience, it is difficult to determine which animal species experience pain. Some philosophers suggest using the “argument by analogy” to answer this question (*e.g.*, Allen *et al.* 2005). This method compares the behaviour and neurobiology of the animal in question with that of humans, who are known to feel pain. If the behaviour of an animal is consistent with how humans behave when in pain, and the animal has the appropriate neuroanatomical areas, then it is concluded that the animal would

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experience some form of pain. However, insect behaviour and neurobiology differ substantially from that of humans, making it difficult to use the argument by analogy. Nevertheless, it is possible to consider more broadly what behavioural and neurobiological attributes we would expect in an organism that experiences pain (Sneddon *et al.* 2014).

Behaviour

Insects respond to damaging stimuli with a variety of avoidant behaviours (Eisemann *et al.* 1984). Moreover, noxious stimuli, such as electric shock, promote learning (*e.g.*, Waddell and Quinn 2001), demonstrating that nociception is motivating in insects. Insects can also inhibit nociceptive behaviour, depending on the context. For example, some insects exhibit sexual cannibalism; the male allows the female to eat him during mating (*e.g.*, *Cyphoderris strepitans* Morris and Gwynne (Orthoptera: Prophalangopsidae); Sakaluk *et al.* 1995). Noxious stimuli (*e.g.*, a pinch) can have long-lasting effects on behaviour (*e.g.*, McMackin *et al.* 2016). Therefore, the insect response to damaging stimuli is far more complex than a reflex. Additionally, behavioural studies have shown that insects have impressive learning abilities (Perry *et al.* 2017). Social insects, for example, show sophisticated forms of behavioural plasticity that appear similar to observational learning (Alem *et al.* 2016), numeracy (Skorupski *et al.* 2018), and having complex emotional states (Perry and Baciadonna 2017). Social insects are also rightly famous for their communication abilities (*e.g.*, Dyer *et al.* 2002). These phenomena raise the possibility that insects may have neural circuits that are capable of subjective experience.

However, some behaviour that denote advanced cognitive or emotional capacity in humans are mediated by simpler mechanisms in insects (*e.g.*, Alem *et al.* 2016). For example, a phenomenon known as “learned helplessness” has been used in dogs (*Canis lupus familiaris* Linnaeus (Carnivora: Canidae) and other Mammalia; Maier and Watkins 1998) as an animal model of depression (Seligman and Maier 1967). Learned helplessness is induced by exposing dogs to unavoidable shocks in a training cage. After this

experience, dogs have difficulty learning that a flashing light warns them of a shock that they can avoid by jumping over a barrier. A dog that has never been shocked learns this lesson quickly. Insects also exhibit learned helplessness (*e.g.*, Batsching *et al.* 2016). In learned helplessness studies on insects, one group of insects is able to escape an electric shock, while the other group cannot. The group that cannot escape the shock shows a reduced ability to learn to avoid subsequent shocks (*e.g.*, Batsching *et al.*, 2016). However, in insects (*e.g.*, *Drosophila melanogaster* Meigen (Diptera: Drosophilidae)), learned helplessness is very context-specific and does not appear to generalise to other behaviours (Batsching *et al.* 2016). In mammals, learned helplessness leads to a reduction in a range of motivated behaviours (Maier and Watkins 1998), which is why it has been considered an animal model for depression. In insects, even a cockroach (*Periplaneta americana* (Linnaeus) (Blattodea: Blattidae) leg attached to a thoracic ganglion can show plasticity operationally similar to learned helplessness (Eisenstein and Carlson 1997). Either a ganglion of about 1000 neurons is capable of depression, or learned helplessness can occur without a psychological experience in insects. In another example, male courtship behaviour in *D. melanogaster* is modulated by both internal and external cues (Ellenderson and von Philipsborn 2017). However, neural stochasticity plays a role in producing variable male courtship behaviour (Zhang *et al.* 2018), preventing *D. melanogaster* from becoming a “reflex machine” without using complex neural processes.

Other aspects of insect behaviour are incongruent with mammalian pain behaviour. Although larval insects show sensitisation of nociception after damage that resembles both hyperalgesia (Walters *et al.*, 2001; Babcock *et al.* 2009) and allodynia (Babcock *et al.* 2009; McMackin *et al.* 2016), adult insects of a number of species will walk on damaged limbs (Eisemann *et al.* 1984). Some insects will continue to feed while being eaten themselves (Eisemann *et al.* 1984). Damaged cockroaches (S.A.A., personal observation) and Mormon crickets (*Anabrus simplex* Haldeman (Orthoptera: Tettigoniidae) (Lockwood 2012) will consume their own internal organs. They appear to respond to the protein stimulus of their

own guts and eat them, even if they are not food-deprived.

Neurobiology of nociception and pain

Differentiating between nociception and pain requires human subjects, because humans can communicate their subjective experience. Humans have sensory neurons (nociceptors) that respond to damaging stimuli (Purves *et al.* 2012). Nociceptive sensory information follows well-studied tracts through the spinal cord and into the brain (Purves *et al.* 2012). Intracranial electrical recordings and noninvasive imaging studies demonstrate that there is a difference between nociception and pain (Chatelle *et al.* 2016). Humans initially process incoming nociceptive stimuli preconsciously in two parallel pathways that assess the sensory and emotional aspects of pain (Bastuji *et al.* 2018; Hagiwara *et al.* 2018). These pathways consist primarily of subcortical regions; the thalamus is a key area in the sensory pathway, while the amygdala is important for the emotional processing pathway (Bastuji *et al.* 2018). From the thalamus, nociceptive stimuli are transferred to a cortical nociceptive network consisting of primary and secondary somatosensory cortices, as well as the posterior insula (Lu *et al.* 2016; Bastuji *et al.* 2018; Garcia-Larrea and Bastuji 2018). The activation of this nociceptive network, which includes both cortical and subcortical structures, is not sufficient for the subjective experience of pain (Bastuji *et al.* 2016; Garcia-Larrea and Bastuji 2018). Nevertheless, the activation of the nociceptive network can produce long-lasting effects on behaviour (Garcia-Larrea and Bastuji 2018). The perception of pain occurs a fraction of a second after activation of the nociceptive network with the activation of a “pain network”; *i.e.*, circuits that combine the sensory and emotional aspects of nociception along with other factors such as memory (Garcia-Larrea and Bastuji 2018). This network includes the activation of sensorimotor and fronto-parieto-insular cortical areas (Garcia-Larrea and Bastuji 2018). The full sensation of pain occurs when these regions are joined by activity in the posterior cingulate and medial temporal cortical areas (Garcia-Larrea and Bastuji 2018). These conclusions were based on studies (*e.g.*, Bastuji

et al. 2016) in which patients with intracranial electrodes were given nociceptive-specific stimuli (*e.g.*, laser pulses). The exact timing of activity in different brain regions was recorded and compared with the timing of a voluntary muscle movement that patients were asked to make as soon as they felt pain. The time required to make the movement was taken into account to determine the time when pain was perceived (Bastuji *et al.* 2016). Activity in the insula cortex and the amygdala occurred more than 120 ms before the earliest motor reaction, suggesting that this brain activity was occurring prior to conscious awareness (Bastuji *et al.* 2016). These results suggest that the subjective experience of pain is the product of a complex and dynamic neural network, although a definitive pain “connectome” is still missing (see Mouraux and Iannetti 2018). Nevertheless, the evidence in humans shows that pain is not created by activity in a single brain area (Bastuji and Lavigne 2016; Chatelle *et al.* 2016; Garcia-Larrea and Bastuji 2018), and this is likely true in other mammals as well (*e.g.*, laboratory mice (*Mus musculus* Linnaeus; Rodentia: Muridae); Corder *et al.* 2019).

Human studies show that pain experience requires the combination of different inputs (*e.g.*, emotional, sensory, cognitive), and that this combination occurs in cortical structures (Garcia-Larrea and Bastuji 2018). However, other animals could use different neural structures to create a subjective experience of pain. Could insect brains support a pain network? Insects clearly have the neural machinery for nociception. They have multimodal nociceptors (Guo *et al.* 2014) that tile the body wall (Grueber *et al.* 2001). Just as mammalian nociceptors send information to the brain via dorsal horn neurons in the spinal cord (Purves *et al.* 2012), insect nociceptors synapse onto neurons that reach the brain (*e.g.*, larval *D. melanogaster*; Gerhard *et al.* 2017). Although the entire nociceptive pathway has not yet been delineated in any insect, it is known that nociceptive information is processed in two higher-order integratory areas, the mushroom bodies (Waddell 2013; Konig *et al.* 2018) and the central complex (Hu *et al.* 2018). These two areas are among the most complex in the insect brain, and are key for navigation, learning, memory, and other complex cognitive tasks (Barron and Klein 2016; Kinoshita and Homberg 2017). A peripheral

electric shock activates neurons in both the fan-shaped body of the central complex, and the mushroom bodies in *D. melanogaster* (Hu *et al.* 2018). The fan-shaped body is necessary for both innate and conditioned escape behaviours in response to nociceptive stimuli (Hu *et al.* 2018). Unfortunately, the details of how nociceptive sensory information reaches the fan-shaped body, and how the fan-shaped body activates its motor targets, remain unknown (Hu *et al.* 2018). Nociceptive information (*i.e.*, electric shock) also activates dopaminergic cells in the protocerebrum, and these neurons encode the saliency of a sensory input, *i.e.*, whether it is rewarding or aversive (Waddell 2013). These dopaminergic neurons innervate both the mushroom bodies and the central complex (Galili *et al.* 2014). The dopaminergic input to the mushroom bodies is critical for nociception to have reinforcing effects and stimulate learning (Waddell 2013).

The most striking difference between the central processing of nociception in insects compared with that in mammals is the apparent lack of a higher-order network combining brain regions involved in nociception (*e.g.*, the mushroom bodies and central complex). Both the mushroom bodies (Aso *et al.* 2014a, 2014b) and the central complex (Franconville *et al.* 2018) have few output neurons, restricting the type of information they can transmit (Collett and Collett 2018; Franconville *et al.*, 2018). For example, although the mushroom bodies can have 170 000 intrinsic neurons (*e.g.*, in honey bees – *Apis mellifera* Linnaeus (Hymenoptera: Apidae)) and have a complex neural architecture (Aso *et al.* 2014a, 2014b), the number of output neurons is three orders of magnitude lower, about a few hundreds in honey bees (Peng and Chittka 2017) to < 100 in other insects (Aso *et al.* 2014a, 2014b). Similarly, the central complex is a densely recurrent sensorimotor hub, but it has few output neurons (Franconville *et al.* 2018). The central complex is connected to a limited number of other brain regions (Franconville *et al.* 2018), while the mushroom bodies are connected to neuropils across the brain (Aso *et al.* 2014a, 2014b). This reduction in dimensionality (*i.e.*, few neuronal outputs) is also observed in some mammalian subcortical brain structures. For example, the mammalian basal ganglia, which carry out some of the same tasks as the insect central

complex, also demonstrate a similar dimension reduction (Fiore *et al.* 2015). However, this degree of dimension reduction is not a prominent feature of the cortical areas important for producing the pain network (*e.g.*, prefrontal cortex; Fuster 2001). In humans, white matter tracts comprise 47% of total cortical mass (grey + white matter), demonstrating considerable investment in network capacity (Herculano-Houzel *et al.* 2010). Data from laboratory mouse (Oh *et al.* 2014), macaque (*Simia inuus* Linnaeus (Primates: Cercopithecidae)) (Markov *et al.* 2014), and human (Yeh *et al.* 2018) suggest that cortical areas are well connected in mammals.

Not only do mushroom bodies and the fan-shaped body have few output neurons, there are no direct connections between them (Pfeiffer and Homberg 2014; Collett and Collett 2018; Hu *et al.* 2018), and they are not in the same hub of interconnected neuropils (Chiang *et al.* 2011; Shih *et al.* 2015). The lack of direct connections between these two important information integration centres in the insect brain raises question about how insects perform cognitive tasks (Collett and Collett 2018). For example, during navigation, the lack of a major connecting pathway between these two areas suggests that the mushroom bodies and central complex work in parallel, as opposed to working together as part of an integrated network (Collett and Collett 2018). In ants (Hymenoptera: Formicidae), this organisation suggests that during navigation, ants switch back and forth between using landscape memories (stored in the mushroom bodies) and celestial cues (stored in the central complex) to find their way home (Collett and Collett 2018). Collett and Collett (2018) postulate that the mushroom bodies transfer an attraction signal only to the central complex via a still unknown indirect pathway; this organisation reduces the amount of integration required between the two areas for accurate navigation. Nociception appears to be analysed in the same way, with parallel sensory inputs processed separately by the mushroom bodies and central complex (Hu *et al.* 2018).

In humans, pain perception requires the integration of the parallel sensory and emotional pathways that process nociceptive information, as well as the integration of this combined input with other inputs, such as from areas important for memory and cognition (Garcia-Larrea and Bastuji 2018).

It is this integrative step that seems to be missing in insects. Insects have something like a nociceptive network, with nociception integrated in parallel in different brain regions, but they do not appear to have a pain network that integrates nociception processing across brain areas with higher-order functions. A similar conclusion has been suggested for Mollusca (Key and Brown 2018).

However, there is a great deal we do not know about nociception, even in the best studied insect, *D. melanogaster* (Hu *et al.* 2018). For example, both the mushroom bodies and the fan-shaped bodies are strongly connected to neuropils in the superior protocerebrum. The function of the superior protocerebrum is poorly understood (Strausfeld 2012). Although there is no evidence that nociceptive information is integrated in this brain region, it has not been well studied, and may play a larger role in nociception than is currently appreciated. There are also other areas of convergence (see van Swinderen 2005); for example, some mushroom body output neurons have axon terminals in the same region that contain the dendrites of neurons projecting to the fan-shaped body (Aso *et al.* 2014b). Although the central complex has few direct connections to other brain areas, it is indirectly connected to many of them (Hanesch *et al.* 1989). Therefore, there are connections between the mushroom bodies and the central complex, but they are indirect and mediated by few neurons. Studies on whole-brain networks in the insect (*e.g.*, Yap *et al.* 2017) should help clarify our understanding of nociceptive processing. Such studies may demonstrate that there is more integration of nociceptive processing in insects than is currently thought.

Given the growth in our understanding of the neurobiology of pain in humans (*e.g.*, Garcia-Larrea and Bastuji 2018) and nociception in insects (*e.g.*, Hu *et al.* 2018) in the last two years, it is not surprising that an earlier paper (Barron and Klein 2016) was more optimistic about insects having subjective experiences such as pain. Their conclusion was based, in part, on an earlier paper (Merker 2007) that argued that subcortical areas in humans were both necessary and sufficient for subjective experience. However, a decade later, the consensus appears to be that a complex neural ensemble that includes

cortical areas is required for the subjective experience of pain in humans (Garcia-Larrea and Bastuji 2018).

Evolutionary perspective

Insects are unlikely to invest in the neural machinery required to feel pain unless there is an evolutionary advantage in doing so (Adamo 2016). Whether pain would be an advantage depends on whether the fitness benefits would outweigh the costs.

Costs of having the subjective experience of pain

Brains of all animals appear to be organised to minimise wiring costs (Arnatkeviciute *et al.* 2018; Liang *et al.* 2018). Large-scale integration of information across a brain is not cheap (Collin *et al.* 2014; Liang *et al.* 2018). High interconnectedness results in high levels of wiring volume, leading to high metabolic energy use (Collin *et al.* 2014). The pain network identified by Garcia-Larrea and Bastuji (2018) requires extensive (*i.e.*, expensive) wiring. Insects have modest connections across brain regions, possibly because of the high cost of large neurons (Chittka and Niven 2009). Moreover, small insect brains may not provide the room required for the parallel and serial processing pathways (Chittka and Niven 2009) needed for a pain network. Given the current hypotheses of what is required for the subjective experience of pain (Garcia-Larrea and Bastuji 2018), the sparser interconnections within the insect brain may be unable to support pain perception.

In humans, subjective experience appears to require the investment of both additional neurons as well as additional wiring (Garcia-Larrea and Bastuji 2018). But how many neurons are needed for a minimal subjective experience of pain? Would 100 neurons be sufficient? In the lobster, *Homarus americanus* Milne-Edwards (Decapoda: Nephropidae), approximately 30 neurons are dedicated to maintaining two rhythms in the digestive tract (*i.e.*, the stomatogastric ganglion; Marder and Bucher 2007). It is possible that subjective experience requires only two or three times as many neurons as stomach churning, but this seems unlikely. Even if subjective experience requires only 100 additional neurons, this would increase the cost of the brain by 0.1% in insects such as

D. melanogaster that have about 100 000 neurons in their brain (Zheng *et al.* 2018). Neurons are energetically expensive cells (Niven 2016). In both vertebrates and invertebrates, the nervous system consumes a significant portion of the energy budget of the animal (Niven and Laughlin 2008). Therefore, the increase in neural investment needed to produce the subjective experience of pain in insects would probably lead to a reduction in other traits such as reproduction.

However, neurons do not act alone, but as part of neural circuits. These circuits are dynamic, and an individual neuron can participate in more than one circuit (Marder *et al.* 2015). Insect nervous systems share neurons across circuits (Niven and Chittka 2010). If the neurons needed to experience pain were shared with other circuits, then the costs could be reduced. However, they would not be zero. The insect brain squeezes a wide range of cognitive tasks out of a small number of neurons, and neurons are already “multitasking” (Chittka and Niven 2009; Vogt *et al.* 2014). Computational models suggest that as neurons participate in more tasks, the performance of the network eventually degrades (Caruana 1997). Moreover, regardless of the number of neurons required for subjective experience, there would be additional costs due to the neuronal wiring needed to create the appropriate network. Therefore, although the subjective experience of pain is an emergent property of a neural network, the ability to experience pain is not cost-free.

Even if only a few additional neurons are needed for a very modest pain experience, every neuron an insect adds to its brain is proportionately more expensive than the cost of adding an additional neuron to the human brain (about one million times more expensive for *D. melanogaster*). Nevertheless, a high cost does not prevent a trait from evolving if the benefits outweigh the costs.

Benefits of having the subjective experience of pain

The standard argument for the value of pain is that it aids animals in making adaptive behavioural choices (Sneddon *et al.* 2014). In other words, it prevents insects from becoming mere “reflex machines”. However, recent advances in artificial intelligence suggest that the subjective experience of pain is not necessary to achieve these benefits.

Robots can now be designed with “emotional architecture” that allows them to adapt their behaviour to changing environments (Dominguez *et al.* 2017). Negative emotions can be programmed to have long-lasting effects on the behaviour of a robot (Lee-Johnson and Carnegie 2010). These robots display the same or similar behaviours as those that have been used as evidence that insects have subjective experiences. For example, honey bees become less sensitive to positive stimuli and more sensitive to negative stimuli after shaking (*i.e.*, ambiguous stimuli are more likely to be rejected; Bateson *et al.* 2011). Although interpreted as an emotional response in honey bees, “emotional” robots show a similar phenomenon. For example, when programmed to have both feeding and survival goals, “food” became motivationally ambiguous in the presence of an artificial predator (Parisi and Petrosino 2010). When predator cues were present, the robot would accept only high-quality food, avoiding the low-quality food that it would normally accept when predator stress was absent. A robotic rat has been programmed to feel “discomfort” when wet, providing it with a motivational drive (Ames *et al.* 2012). This robotic rat can learn to solve a Morris water maze, just like a real laboratory rat (Rodentia: Muridae) (Ames *et al.* 2012). The robot rat is “rewarded” by the lack of discomfort, similar to pain relief learning in *D. melanogaster* (Yarali *et al.* 2008). Robots can also exhibit pain-like behaviour that is more like our own than any insect (Stiehl *et al.* 2004). Robots can have flexible responses to damaging stimuli (*i.e.*, modifiable pain responses; Matsunaga *et al.* 2005). Artificial intelligence-generated characters can respond to simulated damage with limps and wound guarding (*e.g.*, Fallout 4; www.youtube.com/watch?v=Znn1EwpfOgA). Robots are also capable of observational learning (Reggia *et al.* 2018). These abilities suggest that subjective experience is not required for complex, motivated behaviour. Robots and computer simulations show that relatively simple, cost-efficient circuits can produce adaptive behaviours (*e.g.*, Parisi and Petrosino 2010). Moreover, our partial understanding of the central neural circuits mediating nociceptive behaviour in *D. melanogaster* (*e.g.*, Hu *et al.* 2018) suggests that subjective experience is not required to explain the adaptive behaviour of *D. melanogaster* to damaging stimuli (also see Gutfreund 2017). In other words, present models

can explain how nociception can motivate learning (Waddell 2013; Hu *et al.* 2018) without requiring the subjective experience of pain. If insects can produce complex, motivated behaviour without paying for the additional neuronal resources required for experiencing pain, then evolution should select this cheaper option.

Caveats

An unfortunate side effect of using the human brain as the gold standard for the neural requirements for subjective experience means that all other brains are likely to be found wanting simply because they are different. It is possible that insects have a more modest experience using a relatively basic network, although, in humans, a less complex network results in a nociceptive network that appears to be devoid of the subjective experience of pain. However, studies in humans do not illuminate the circuitry required for a minimal subjective experience. The subjective experience of pain is unlikely to be an all-or-none phenomenon. But this issue forces us to consider what we would accept as a subjective experience of pain. What if it was devoid of emotional content? What if cognition is not involved? If insects have any type of subjective experience of pain, it is likely to be something that will be very different from our pain experience. It is likely to lack key features such as distress, sadness, and other states that require the synthesis of emotion, memory, and cognition.

Conclusion

We can never know with certainty whether insects feel pain, but given our current understanding of insect behaviour, neurobiology, and evolution, the likelihood is low. The main issue is not even the small number of neurons in insects (several orders of magnitude less than in humans; Herculano-Houzel 2012). The more important difference is the lack of connections between relevant brain areas. If the subjective experience of pain is produced by a network composed of brain regions that integrate sensory information processing, emotions, cognition, and memory, then it does not appear that insects have their relevant areas wired up in this way.

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