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Emotional component of pain perception in the medicinal leech?

Commentary on **Crump et al.** on *Decapod Sentience*

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Abstract: Crump et al. have provided a series of criteria to assess animal sentience that is focused on the perception of pain, which is known to have both sensory and emotional components. They also provide a qualitative scoring system to assess data that address the eight criteria and apply this paradigm to decapod crustaceans. The criteria laid out have the potential to be applied to other invertebrates typically thought to have sensory response to tissue damage, but no emotional component to pain perception.

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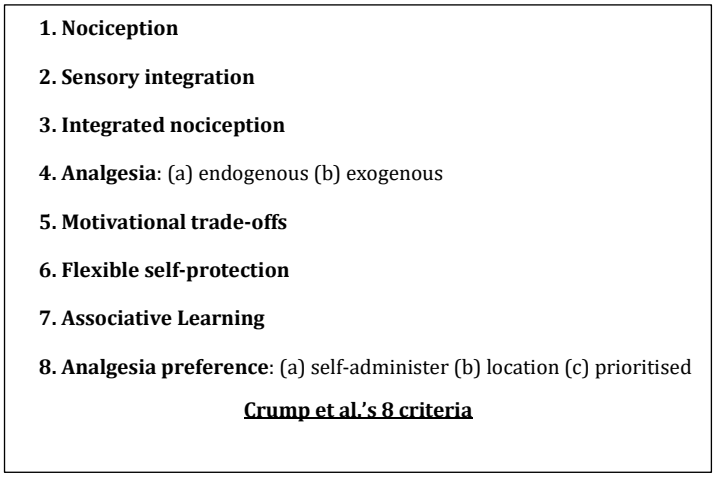
The idea of invertebrates possessing affective/emotional responses to noxious stimuli, and thereby meeting the IASP definition of pain, has been controversial for quite a while (Crook and Walters, 2011; de Waal and Andrews, 2022; Mesa, 2022; Walters, 2016). I will confess that this is an issue that I have struggled with in my studies of nociception in the medicinal leech. It simply seemed a very difficult nut to crack. However, a number of recent studies have begun to provide more evidence that invertebrates do have affective behaviours related to pain. With this in mind, the target article by Crump et al. (2022) provides a useful framework to guide the interpretation of past studies as well as future experiments. What follows are some thoughts regarding the future use of these criteria to assess pain in invertebrates beyond crustaceans.

1. Modulatory neurotransmitters. Crump et al. (2022) provide an important update on previous criteria that had focused on the presence of endogenous opioids in the central nervous system (CNS) as evidence of an affective component of pain in a given species. Evidence of an endogenous opioid system in invertebrates is pretty weak in terms of identifying actual endogenous neuropeptides and receptors that have clear homology to those found in mammals. The authors have expanded this criterion to include other neurotransmitters with anxiolytics and/or antidepressant properties, e.g., serotonin and dopamine. There is clear evidence of these transmitters in a variety of invertebrates and some studies have shown potential anxiolytic and analgesic properties (Fossat et al., 2014; Gaudry and Kristan, 2009). This inclusion of a broader range of neurotransmitters systems converges nicely with the increased use of selective serotonin re-uptake inhibitors and tricyclic antidepressants as treatment for chronic pain in people as an alternative to using opioids (Finnerup et al., 2015; Gustavsson et al., 2013).



2. Role of activity-dependent modulatory processes. One element that might be added to the criteria (perhaps as 4c) is evidence of activity-dependent neuromodulation in neural circuits that process sensory and/or affective components of pain. Long-term potentiation (LTP) and long-term depression (LTD), the most highly studied forms of activity-dependent synaptic plasticity, have been observed in the context of pain in the mammalian spinal cord and CNS elements associated with emotions, e.g. cingulate gyrus, hippocampus, and amygdala (Klein et al., 2004; Kronschläger et al., 2016; Li et al., 2017; Liu and Sandkuhler, 1997; Sandkuhler, 2007). In addition, LTP and LTD may also contribute to learning and memory processes associated with pain (Price and Inyang, 2015; Walters and Moroz, 2009). The most-studied mechanism of LTP requires activation of NMDA type glutamate receptors (NMDARs), although NMDAR-independent forms also exist (Malenka and Bear, 2004). Examples of both NMDAR-dependent and -independent forms of LTP have been observed in *Aplysia* (Antonov et al., 2003; Clark et al., 1994; Lin and Glanzman, 1994a, b; Ludwar et al., 2017; Murphy and Glanzman, 1997; Walters and Byrne, 1985), Octopus (Hochner et al., 2003; Shomrat et al., 2008), crayfish (Tsai et al., 2005), and *Hirudo* (Burrell and Sahley, 2004; Grey and Burrell, 2010; Li, 2010). Relevant to the issue of pain invertebrates, *Hirudo* nociceptive synapses exhibit NMDAR-mediated LTP (Yuan and Burrell, 2019) as well as endocannabinoid-mediated LTD (Yuan and Burrell, 2010, 2013). There is also a form of endocannabinoid-mediated potentiation in *Hirudo* non-nociceptive pressure cell synapses that involves activity-dependent disinhibition and shares a number of features with endocannabinoid-mediated disinhibition observed in nociceptive and non-nociceptive circuits in the mammalian spinal cord (Paulsen and Burrell, 2019, 2021; Pernia-Andrade et al., 2009; Wang and Burrell, 2016, 2018). Such disinhibition mechanisms are known to play a critical role in both hyperalgesia and allodynia in vertebrates (Medlock et al., 2022; Pernia-Andrade et al., 2009; Petitjean et al., 2015; Torsney and MacDermott, 2006).

3. How much centralization is needed? The target article's Criteria 2 and 3 focus on brain regions that integrate sensory (including nociceptive) information with an (understandable) emphasis on crustacean and arthropod brains and brain structures. Some flexibility may be required to apply these criteria to a broad range of invertebrate species that do not have the degree of consolidation in the CNS as the crustacean examples discussed by Crump et al. or the cephalopods (Mather 2017) that have featured in pain research by Robyn Crook and colleagues (Crook, 2021; Crook et al., 2014; Crook et al., 2013; Howard et al., 2019). *Hirudo* may provide a constructive example. *Hirudo* have structures referred to as a head and tail "brain" that do have integrative elements related to behavioural choice (Esch et al., 2002;

Kristan et al., 2005; Mesce et al., 2008). However, integration in *Hirudo* also occurs in networks of neurons distributed throughout the chain of segmental ganglia that also make up the CNS (Briggman and Kristan, 2006; Mullins et al., 2011; Shaw and Kristan, 1997). The point is that the presence of integrative structures is an important criterion for evidence of pain, but these integrative elements may be more widely distributed in the CNS of other invertebrate phyla, e.g., Annelids, Nemertea, Platyhelminths, Nematodes, and even "lower" Arthropods and Molluscs.

4. Concluding statement: In addition to having importance in terms of animal welfare, I would argue that these criteria also have relevance in terms of pain research to benefit people. Chronic pain is a worldwide health emergency (Rice et al., 2016; Zimmer et al., 2021) but is also very difficult to treat. Opioids remain an indispensable treatment option, but opioid misuse has become its own public health crisis (Fields, 2011; Okie, 2010). Unfortunately, the record of developing new treatments for chronic pain is poor (Mogil, 2009; Woolf, 2020). There are multiple barriers in developing new analgesic treatments, e.g., the difficulty in interrogating pain in animals vs. people, but I would argue that an additional factor is that there is still a poor understanding of the basic biology of pain. This is an issue that can best be addressed through comparative approaches to pain. Studies across a broad range of species can potentially identify evolutionarily conserved processes mediating pain that may have a better chance of having translatable clinical relevance. This is not a new concept (Walters, 2019; Walters and Williams, 2019; Williams, 2016; Woolf and Walters, 1991), yet there is almost no interaction between people who study pain/nociception in mammals and those who work with non-mammalian vertebrates and invertebrates (for a notable and welcome exception, see *Evolution of mechanisms and behaviour important for pain* 2019). The appreciation that there are evolutionarily conserved emotional processes related to pain in invertebrates, or "emotion primitives" if one prefers (Anderson and Adolphs, 2014), may improve the face validity of pain research in invertebrate model organisms and this in turn may have benefits for pain research overall.

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