

ANIMAL SENTIENCE

AN INTERDISCIPLINARY JOURNAL ON ANIMAL FEELING

Demin, Konstantin A.; Lakstygai, Anton M.; and Kalueff, Allan V. (2018) [Time to \(finally\) acknowledge that fish have emotionality and pain.](#) *Animal Sentience* 21(13)

DOI: 10.51291/2377-7478.1356

Date of submission: 2018-07-02

Date of acceptance: 2018-07-10



This article has appeared in the journal *Animal Sentience*, a peer-reviewed journal on animal cognition and feeling. It has been made open access, free for all, by WellBeing International and deposited in the WBI Studies Repository. For more information, please contact wbisr-info@wellbeingintl.org.



Time to (finally) acknowledge that fish have emotionality and pain

Commentary on [Sneddon et al.](#) on *Sentience Denial*

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Abstract: The increasing work using fish as a model organism calls for a better understanding of their sentience. While growing evidence suggests that pain and emotionality exist in zebrafish, many deniers continue to ignore the evidence. Here we revisit the main conceptual breakthroughs in the field that argue clearly for pain and emotionality. We call for an end to denial and a focus on studying the mechanisms of fish pain and emotionality, and their translational relevance to human conditions.

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As the use of fish as model objects in biomedicine is rapidly growing, some concerns merit further consideration and critical discussion. Recent studies suggest that fish, like mammals, appear to have sentience (Brown, 2015; Rey et al., 2015), including mounting evidence that fish feel pain, respond to it behaviourally, and have all the requisite pain mechanisms and pathways (Malafoglia, Bryant, Raffaelli, Giordano, & Bellipanni, 2013). Fish behavior is complex and emotionality-driven (Kalueff et al., 2012). Some skepticism remains, however, as to whether zebrafish are sentient (Diggles et al., 2017; Key, 2015, 2016; Rose, 2002, 2007, 2016; Rose et al., 2014), and whether, from a bioethical perspective, they should be protected (similarly to the way mammals are). A recent study (Sneddon et al., 2018) rigorously challenges such views through a thorough discussion of nociception and analgesia studies in zebrafish (*Danio rerio*).

Today, zebrafish are widely used in biomedical research as a powerful tool for translational research in various fields, including neuroscience. Despite their simpler central nervous system (CNS) organization relative to mammals, zebrafish have complex, well-described behavior which is emotionally driven and extends far beyond simple instinctive/reflexive reactions to different stimuli (Broom, 2007; Kalueff, Stewart, & Gerlai, 2014). The high level of genetic homology between zebrafish and humans is another argument in support of their sentience. Zebrafish have 26,206 protein-coding genes, and a large share of these genes (71,4%) are human gene orthologs (Howe et al., 2013). Pharmacological effects and molecular targets of various drugs are also highly conserved in zebrafish and humans (Milan, Peterson, Ruskin, Peterson, & MacRae, 2003), especially for receptors and enzymes (Schaaf et al., 2008). Neurochemistry in zebrafish and humans is evolutionarily conserved, with all major neurotransmitter systems (glutamate, GABA, catecholamines, acetylcholine) present in both fish and human CNS (Panula et al., 2010). Fish also possess a well-established nociceptive system strikingly paralleling that in mammals (Sneddon, 2002, 2003, 2009). For example, fish display aversive behavioral and physiological reactions to noxious stimuli that cause pain in other animals and humans (Sneddon, 2009). Fish also respond to a wide range of analgesics, including both opioid (e.g., morphine) and non-opioid drugs (e.g., aspirin and ibuprofen) (Malafoglia et al., 2013), further bridging the ostensible physiological and neurochemical gap between fish and mammals. Various experimental models of pain have been developed in zebrafish (Currie, 2014), fostering anti-pain medication screening and the investigation of genetic mutations involved in nociceptive pathways. Among the common pain response, the pain-inducing drugs cause altered motor activity in zebrafish that can be assessed using automated track records (Kalueff et al., 2013) and corrected by anti-pain medication.

Zebrafish, being relatively homologous to humans in terms of amino acid sequences in key genes in the opioid system (Gonzalez-Nunez, Barrallo, Traynor, & Rodriguez, 2006; Pinal-Seoane et al., 2006), represent a valuable tool for the study of the central opioid system and its role in pain regulation (Demin et al., 2018). Not only do all mammalian opioid receptor genes have counterparts in the zebrafish genome (Klee et al., 2012), but the zebrafish opioid system can be described as more complex than in mammals in terms of the number of opioid genes and their more diverse physiological functions (see Demin et al. (2018) for a recent comprehensive discussion). Thus, zebrafish models enable the use of this organism not only as a simple “copy” of mammalian models of pain, but as a complementary tool to further assess the nature of the opioid system *in vivo* and its role in pain physiology.

In general Darwinian terms, the existence of a fast-acting physiological system that informs individuals about potentially harmful stimuli is crucial for animal survival. It is hence

unsurprising that fish (like mammals) have such a system and express specific behaviors in response to pain. It is naïve, however, to focus on the description of the nociceptive system and pain-associated behavior in zebrafish and ignore conceptual “hard problems”. For example, the discussion of animal sentience is over-focused on the potential existence of subjective perceptual experience. No branch of science has reliable knowledge about the true nature of consciousness; and no methods exist to prove or disprove pain awareness for any organism except humans. In disputing fish sentience, another concern of Diggles et al. (2017) is the methods used to activate nociceptors. The study of nociception in zebrafish does need further investigation at the level of receptors, neurons and nerves involved in pain sensation, which is crucial for confirming the validity of the currently available fish-based main models. However, it is unfair to negate zebrafish nociception models based on this argument since we need more such research, not less (see also Woodruff, 2018).

At the same time, some questions raised by a relatively more developed critique of fish sentience by Key (2016) do remain open. Despite being widely criticized (Balcombe, 2016; Braithwaite & Droege, 2016; Broom, 2016; Brown, 2016; Derbyshire, 2016; Dinets, 2016; Elwood, 2016; Manzotti, 2016; Seth, 2016), Key notes the lack of precise brain correlates of feeling pain that can be used to translate nociception from human to fish. We agree that identifying such easy-to-translate correlates is an important step for today’s translational research in the field of nociception. Moreover, sensory systems for pain in fishes can potentially vary physiologically (by analogy with vision in different taxa); hence such cross-taxa correlates with humans may not be as straightforward as might be expected (Elwood, 2016).

Finally, we argue that fish not only have the ability to experience pain per se, but also drive their behaviors accordingly, as part of complex emotionality-driven behavioral phenotypes that in many domains resemble mammalian emotionality (Kalueff et al., 2012).

Zebrafish nociception, relatively well-studied recently, is close to becoming universally accepted despite resistance from some authors whose views are dated and unsupported by modern objective scientific evidence (Angoa-Perez et al., 2014; Rose, 2002, 2007, 2016; Rose et al., 2014). The field of bioethics has a powerful enough basis for granting the protection deserved by species proved to have pronounced avoidance reactions to harmful stimuli and cognitive skills. Using fish models can be regulated by applying the bioethical laws already applied to other sentient animals involved in biomedical research, such as mammals. Our knowledge of animal sentience is fundamental to many disciplines and imperative to animal welfare (Proctor, Carder, & Cornish, 2013). Therefore, in recognizing fish sentience, we should also promote fish welfare (Martins et al., 2012; Webster, 2014). For example, mounting evidence suggests that zebrafish need environmental enrichment (Collymore, Tolwani, & Rasmussen, 2015; Giacomini et al., 2016; Marcon et al., 2018) as part of their husbandry standards and experimental procedures, as in the widely recognized use of environmental enrichment in mammals. Despite all arguments about the large phylogenetic distance between fish and mammals, it is necessary to provide an equal level of protection in research in order to avoid methodological and conceptual obstacles that may significantly impede scientific progress and discovery.

In summary, whereas the denial of fish nociception and emotionality (Diggles et al., 2017; Key, 2015, 2016; Rose, 2016; Rose et al., 2014) continues to ignore the rapidly growing body of positive empirical evidence (Kalueff et al., 2012; Lopez-Luna, Al-Jubouri, Al-Nuaimy, & Sneddon, 2017; Sneddon, 2002, 2003, 2009; Sneddon et al., 2018; Stewart et al., 2015), the field should also adapt and reshape in response. Specifically, it can turn away from discussing dated and unsupported views and move full speed ahead to focusing on what really matters:

studying the mechanisms of fish pain and emotionality and their translational relevance to human conditions in order to build a reliable, reproducible and ethically sound line of research using these sentient aquatic species.

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LE PROBLÈME DES
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