The pain echo chamber: how barren environments amplify pain in captive animals

frontiers in Animal Science

TYPE Review
PUBLISHED 24 March 2026
DOI 10.3389/fanim.2026.1736142

OPEN ACCESS

EDITED BY
Pavan Kumar,
Guru Angad Dev Veterinary and Animal Sciences University, India

REVIEWED BY
Sebastian Gaston Alvarado,
Queens College (CUNY), United States
Jacquelyn Tubbs,
National Institutes of Health (NIH), United States

*CORRESPONDENCE
Cynthia Schuck-Paim
cynthia.schuck@welfarefootprint.org

RECEIVED 30 October 2025
REVISED 24 February 2026
ACCEPTED 27 February 2026
PUBLISHED 24 March 2026

CITATION
Schuck-Paim C, Alonso WJ, Hartcher K, Chiang C, Pereira PA, Veit W, Mendl M, Nicol CJ and Lecorps B (2026) The pain echo chamber: how barren environments amplify pain in captive animals.
Front. Anim. Sci. 7:1736142.
doi: 10.3389/fanim.2026.1736142

The pain echo chamber: how barren environments amplify pain in captive animals

Cynthia Schuck-Paim[1]*, Wladimir J. Alonso[1], Kate Hartcher[1], Chiawen Chiang[1,2], Patricia Alves Pereira[1,3], Walter Veit[4], Michael Mendl[5], Christine J. Nicol[6] and Benjamin Lecorps[5]

[1]Welfare Footprint Institute, Winter Springs, FL, United States, [2]Department of Environmental Studies, New York University, New York, NY, United States, [3]Department of Biology, University of Crete, Crete, Greece, [4]Department of Philosophy, University of Reading, Reading, United Kingdom, [5]Bristol Veterinary School, University of Bristol, Bristol, United Kingdom, [6]Department of Pathobiology and Population Sciences, Royal Veterinary College, London, United Kingdom

Pain is not solely a function of tissue damage but can be strongly shaped by environmental context. Its perceived intensity, duration, and likelihood—the core features of affective experience—are modulated by factors including opportunities for behavioral engagement, control over environmental conditions, social environment, physical activity, sleep quality, maternal stress and pain early in life. All of these factors affect pain responses of captive animals, yet most welfare assessments and mitigation protocols treat pain as if it were context-invariant. Here, we review multiple lines of evidence indicating that environmental and rearing conditions modulate pain processing and healing in captive animals. We show that barren, confined environments disable multiple endogenous analgesic mechanisms, while simultaneously activating several neurobiological pathways that intensify nociceptive signaling and delay healing. Pain perception amplification and impaired healing are particularly likely when captivity is associated with intensive and barren environments. The implications of these findings are substantial. First, they highlight the need for animal welfare assessment models, and animal welfare research in general, to take environmental modulation of pain explicitly into account. Likewise, certification and regulatory frameworks must acknowledge that seemingly identical ailments or procedures can produce fundamentally different welfare experiences depending on the environment where they take place. Additionally, analgesic dosing protocols and laboratory-based pain models must be reevaluated for translational validity. More broadly, these findings challenge the acceptability of barren housing systems ubiquitous in farms, laboratories, and other settings. Given the substantial evidence that barren environments amplify and prolong painful states from common routine procedures and ailments, the transition to higher welfare housing systems becomes an ethical and scientific imperative.

KEYWORDS
barren housing, endogenous analgesia, environmental enrichment, intensive animal farming, pain amplification, pain echo chamber, pain modulation, pain suppression

Introduction

Pain is a conscious experience that emerges from adaptive signaling mechanisms, alerting organisms to actual or potential tissue damage and threats, and guiding protective behaviors. By its very nature, it is designed by natural selection to capture an organism's attention, serving to interrupt ongoing behavior and redirect focus toward the source of possible harm (Walters and Williams, 2019). This subjective experience emerges from complex interactions between ascending nociceptive signals—the detection and transmission of noxious stimuli—and descending modulatory influences, rather than being a simple reflection of actual tissue damage itself (Hoskin et al., 2019).

However, while individual differences in pain sensitivity are increasingly recognized (Nielsen et al., 2009; Ijichi et al., 2014; Lecorps et al., 2020), pain is largely treated as a fixed response to noxious stimuli, tissue damage and threat level—a signal that varies in intensity based on severity but that remains consistent regardless of an animal's environment or behavioral opportunities. While individual differences in pain sensitivity are increasingly recognized (Nielsen et al., 2009; Ijichi et al., 2014; Lecorps et al., 2020), the assumption of environmental invariance pervades multiple fields. For instance, animal welfare frameworks assign identical severity scores to identical painful conditions whether animals are housed in barren cages or enriched environments (Bracke et al., 2001; EFSA, 2012; Mellor, 2017) an inflamed hock is typically assumed to elicit the same pain and welfare impact independently of the housing and environment context in which it happens, and the same is the case for fractures, diseases, mutilations and other painful events. Likewise, veterinary analgesic protocols assume uniform dosing requirements regardless of housing conditions (Percie du Sert and Rice, 2014; Abboud et al., 2021); and laboratory pain models generalize findings from animals in restrictive housing to predict clinical efficacy in humans or other animals. Hence, whether an animal experiences inflammatory pain from arthritis, visceral pain from colic, neuropathic pain from nerve damage, or acute pain from a surgical procedure, the experience is assumed to be comparable regardless of whether the animal can engage in highly motivated behaviors, has social companions, or is under chronic physiological stress (Bracke et al., 2002; Welfare Quality® Consortium, 2009; Honess and Wolfensohn, 2010; Teng et al., 2018).

Still, mounting evidence challenges this assumption. Consider, for instance, the striking observation that chickens with experimentally-induced joint inflammation show complete suppression of pain behaviors when engaged in feeding after food deprivation—an effect entirely reversed by opioid antagonists (Gentle and Corr, 1995). Or that rodents housed in enriched environments require significantly less self-administered analgesia following surgery than those in barren cages (Pham et al., 2010). Or that in humans, distraction techniques can reduce pain perception by 30-45% (Morris et al., 2009; Moont et al., 2010; Verhoeven et al., 2011; Jensen et al., 2012), while chronic stress and sleep deprivation increase pain sensitivity by similar magnitudes (Jennings et al., 2014; Haack et al., 2020). These observations reveal that pain is not simply a reflection of nociceptive input, but rather emerges from complex interactions between ascending nociceptive signals and multiple modulatory systems. Environmental factors such as housing, and their effects on neurophysiology, can change how these signals are processed, amplifying or suppressing the pain experience substantially. Moreover, many of the environmental and physiological factors that modulate pain perception also seem to influence healing capacity and recovery times (Gentle and Tilston, 1999).

Despite its fundamental importance, the environmental influence on pain processing has been largely overlooked in the animal welfare and veterinary sciences. This oversight has profound implications, as the welfare impact of any given ailment or source of harm cannot be assessed in isolation from environmental context. More troublingly, it suggests that animals in barren, restrictive environments may experience pain that is not merely unrelieved but biologically amplified beyond what would occur in more naturalistic settings. This is concerning for captive animals broadly, but particularly pronounced in intensive farming systems where barren environments converge with many additional stressors (Lecorps et al., 2021) that may further amplify pain pathways. While pain serves adaptive functions by promoting protective behaviors during healing, the environmental amplification documented here extends far beyond any protective benefit, particularly for chronic pain which frequently serves no adaptive function in captive settings (Walters, 2019).

In this review, we synthesize evidence from neuroscience, animal welfare and veterinary science, to examine how environmental factors modulate pain perception and healing in captive environments. We show that animals raised in barren environments are deprived of nearly all modulatory influences that enable endogenous pain suppression, while being simultaneously exposed to multiple pain-amplifying conditions.

We begin by briefly outlining the neurobiological mechanisms through which pain can be modulated, as understanding these pathways is crucial for recognizing how and why environmental factors can change the pain experience. We then examine common factors that trigger these mechanisms, and demonstrate how barren captive environments—particularly those seen in intensive farming systems—engage pain-amplifying and disable pain-suppressing pathways. This convergence, we argue, creates what we term a "Pain Echo Chamber"—an environment that fundamentally changes the phenomenology of pain itself, making many painful experiences more likely, more intense, and more prolonged than they would be otherwise.

Mechanisms of environmental pain modulation

Multiple neurobiological systems mediate how environmental factors influence pain processing, operating across anatomical levels and temporal scales. They are summarized in Table 1. The following sections examine these mechanisms to enable understanding and predicting which environmental factors modulate pain and healing, the magnitude of potential effects, why experiences may vary across housing conditions, as well as allow generalization from specific observations to broader principles of pain modulation.

TABLE 1 Summary of pain-amplifying and pain-suppressing mechanisms.

Category	Pain effect	Mechanism	Brief description
Spinal (Bottom- Up)	Amplify	Central sensitization (wind-up)	Persistent nociceptive input increases spinal neuron excitability, amplifying pain.
		Structural rewiring (sprouting)	Chronic inflammation or injury leads to long-term spinal reorganization, leading to allodynia.
	Suppress	Gate control	Non-painful sensory input from movement or touch can inhibit nociceptive signaling at the spinal level.
Supra-spinal (Top- Down)	Amplify	Affective facilitation	Fear, anxiety or negative expectations heighten the emotional salience of pain and its perceived intensity.
	Suppress	Descending inhibition	Purposeful engagement or motivational states activate pathways that reduce nociceptive transmission.
		Cognitive distraction	Motivated activities divert attention away from pain processing.
Neuro-chemical	Amplify	Substance P & CGRP	Inflammatory sensitization, enhanced nociceptive signaling.
		BDNF-mediated central sensitization	Persistent stress or injury elevates BDNF, strengthening pain circuits and heightening sensitivity
		Serotonin influence	Depending on context, serotonergic signaling can facilitate or inhibit nociceptive transmission.
	Suppress	Endogenous opioids	Released during motivated behaviors, inhibit pain transmission.
		Oxytocin	Positive social contact triggers oxytocin release, reducing sensory and affective components of pain.
		Noradrenaline release	Behavioral engagement increases monoamine release, contributing to descending pain inhibition.
Neuro-Immune	Amplify	Pro-inflammatory cytokines	Inflammatory mediators sensitize nociceptors and promote prolonged pain responses.
		Pro-inflammatory microglial activation	Chronic stress locks microglia in a pro-inflammatory state that sustains central sensitization.
	Suppress	Anti-inflammatory cytokines	Anti-inflammatory mediators resolve nociceptor sensitization and support pain reduction.
		Reparative microglial activation	Microglia in a recovery-oriented state promote healing and reduce neuronal hyperexcitability.
Develop-mental	Amplify	Developmental programming	Early-life injury or stress alters nociceptor numbers and circuit wiring, heightening adult pain.
		Epigenetic modification	Chronic pain or stress induces epigenetic changes that promote long-term pain hypersensitivity.
		Gray matter changes	Prolonged pain leads to structural changes, weakening endogenous pain regulation.
	Suppress	Enrichment- induced neurogenesis	Enriched environments promote neurogenesis and support neural circuits involved in pain control.

Peripheral and spinal ('bottom-up') pathways

Environmental factors first influence pain where signals enter the nervous system—at the spinal level. Gate control theory (Melzack and Wall, 1965) describes how non-painful sensory input can block pain transmission: when animals engage in movement or exploration, touch and vibration signals activate inhibitory neurons in the spinal cord that prevent nociceptive signals from reaching the brain—effectively "closing the gate" to pain. This explains why restricted movement removes a fundamental form of endogenous pain control. Where movement restriction is medically indicated—such as following orthopedic procedures—this loss of spinal-level pain modulation underscores the importance of optimizing other analgesic pathways. Conversely, repeated or intense pain, as caused by painful husbandry procedures or common ailments, can cause central sensitization—spinal neurons become hyperexcitable and amplify all incoming signals (Latremoliere and Woolf, 2009). Through a process referred to as "wind-up", each successive pain signal produces a larger response, progressively amplifying pain (Herrero et al., 2000). Eventually, even light touch can be perceived as painful (allodynia) and mild pain as severe (hyperalgesia) (Sandkühler, 2009). These functional changes can persist long after healing—a process documented across vertebrates, suggesting ancient evolutionary origins (Pinsker et al., 1973; Walters et al., 2023).

Beyond these functional changes, peripheral nerve injury arising, for example, from traumatic lesions (e.g., bodily mutilations) and chronic inflammation, can induce long-term structural reorganization within the spinal cord. First, following tissue damage, touch-sensing nerve fibers may sprout into areas normally reserved for nociceptive signals, creating new circuits

through which non-painful inputs trigger pain responses (Woolf et al., 1992). Second, sustained injury can change the balance of synapses, increasing excitatory connections and reducing inhibitory ones, resulting in a permanent bias toward pain transmission (Miletic and Miletic, 2008). These changes help maintain chronic pain even after the injury has healed.

Supraspinal ('top-down') pathways

Pain is also modulated by descending supraspinal pathways that adjust nociceptive transmission according to cognitive, emotional, and motivational states (Millan, 2002). In mammals, for example, these pathways originate in midbrain regions and project to the spinal cord, where they modulate incoming pain (Fields, 2004). This system mediates diverse forms of analgesia—from pain suppression induced by acute fear (Fanselow and Baackes, 1982) to relief from rewarding experiences. While specific anatomical structures vary, functionally similar descending controls appear conserved across vertebrates and even invertebrates (Gentle, 2011; Sneddon, 2015; Khuong et al., 2019).

Critically, activation of descending modulation is activity-dependent. Passive exposure to the environment engages it weakly, whereas purposeful engagement—such as goal-directed movement or attentionally salient behavior—recruits endogenous analgesic systems more effectively (Tracey and Mantyh, 2007; Heinricher et al., 2009; Ossipov et al., 2010). Thus, environments that limit movement and engagement are likely to blunt activation of these pain-suppressing pathways (see 'Physical Exercise' section).

Cognitive and emotional appraisal also influence descending modulation. Perceived predictability or control over aversive events reduces stress-related pathology and pain responses, whereas unpredictability or uncontrollability promotes heightened pain sensitivity and persistent negative expectations (Weiss, 1972; Apkarian et al., 2005; Lecorps and Weary, 2024). Likewise, while acute fear may suppress pain, anxiety about future pain can amplify its salience (Neugebauer et al., 2004). Stress-induced elevations in corticosteroids further contribute to pain potentiation by acting on regions such as the amygdala, enhancing fear learning and the emotional dimension of pain (Korte, 2001). Glucocorticoid signaling is itself subject to epigenetic regulation: chronic stress can alter methylation of genes governing HPA axis function (Dion et al., 2022), potentially locking the stress-pain axis into a state of sustained activation even after the original stressor is removed.

Pain perception is also shaped by attentional resource allocation. When animals engage with competing stimuli, fewer cognitive resources remain available for pain processing, reducing pain perception depending on its intensity and the motivational salience of competing activity (Villemure and Bushnell, 2002; Sprenger et al., 2012). Conversely, where few competing demands exist, pain is more likely to dominate conscious experience. Still, when pain becomes sufficiently intense relative to other priorities, it can monopolize attention, disrupt responsiveness to external stimuli (Sneddon et al., 2003), impair memory formation (Moriarty et al., 2011) and disrupt most aspects of an animal's life (Weary 2014; Olsson et al., 2020). This principle also applies when multiple pain sources coexist. For example, lame chickens showed higher thermal nociceptive thresholds than non-lame birds (Hothersall et al., 2014), suggesting that a dominant pain source can attenuate perception of additional pain. Alternatively, intense ongoing pain may recalibrate nociceptive sensitivity, rendering milder stimuli less salient (Lecorps and Weary, 2024).

Importantly, pain may also create a self-reinforcing dynamic, impairing the very cognitive capacities (attention, executive function, working memory) that enable top-down pain suppression. In humans, for example, chronic pain is associated with widespread cognitive deficits, which correlate with both pain duration and intensity (Rong et al., 2021; Bell et al., 2022; Chen et al., 2023; Patel et al., 2025). If similar impairments occur in animals experiencing pain in barren environments, they would progressively erode the capacity for attentional and cognitive pain modulation discussed above, contributing to an escalating cycle of pain amplification.

Neurochemical mediators

Pain modulation ultimately depends on the actions of specific neurochemicals that either inhibit or facilitate nociceptive transmission. Among these, the endogenous opioid system is central to pain suppression. The body's natural opioids—including endorphins and enkephalins—produce powerful analgesia by binding to opioid receptors distributed throughout pain-processing pathways (Fields, 2004). These opioids inhibit the release of pro-nociceptive (pain-promoting) neurotransmitters, effectively blocking pain signals. Importantly, opioid receptor sensitivity is not fixed—chronic stress can downregulate these receptors, compromising the body's natural analgesic capacity (Corder et al., 2018). Endogenous opioids analgesia is highly conserved across vertebrates and invertebrates (Scharrer et al., 1988).

Monoaminergic pathways—involving neurotransmitters like noradrenaline and serotonin— provide additional pain modulation. Noradrenaline generally produces robust analgesia and mediates pain relief from behavioral engagement and cognitive distraction like grooming and environmental exploration (Ossipov et al., 2010). Serotonin itself can also directly modify gene expression through an epigenetic route: in the brain, serotonin is chemically attached to histone proteins, where it promotes a more permissive transcriptional state (Farrelly et al., 2019). This raises the possibility that serotonergic dysregulation in barren environments could alter pain-related gene expression in ways that outlast the original conditions.

In contrast, other neurochemicals consistently amplify pain. Neuropeptides like substance P and calcitonin gene-related peptides drive inflammatory responses and acute pain sensitization (Julius and Basbaum, 2001), while neurotrophins—particularly Brain-Derived Neurotrophic Factor (BDNF)—contribute to the long-term sensitization of pain circuits. Under persistent injury or stress, BDNF enhances synaptic efficiency in pain circuits, lowering their activation threshold and leading both to allodynia and hyperalgesia (Pezet and McMahon, 2006; Sandkühler, 2009). Notably, BDNF expression is itself subject to epigenetic regulation (Uchida et al., 2013), raising the possibility that stress- and pain-

driven increases in BDNF signaling are not merely transient but can become epigenetically consolidated.

Finally, oxytocin may lead to pain attenuation through social context. Released during positive social interactions like grooming or maternal care, oxytocin has both analgesic and anxiolytic effects, reducing the sensory and emotional components of pain (Neumann, 2008; Boll et al., 2018), an effect sometimes referred to as social analgesia (Mekhael et al., 2023). Animals deprived of positive social contact thus lose access to this endogenous analgesic pathway.

Neuroimmune and inflammatory modulation

While the neural mechanisms previously described operate on a timescale of milliseconds to minutes, immune-inflammatory processes induce more persistent alterations in pain sensitivity lasting days to months. Pain involves bidirectional communication between the nervous and immune systems: inflammatory mediators sensitize the pain pathways, while neural signals modulate these inflammatory responses.

Following injury, immune cells release cytokines that modulate pain perception. Pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 sensitize nociceptors and amplify pain signals—an initially adaptive response that ensures protection of damaged tissue. Anti-inflammatory cytokines, including IL-10, IL-4, and TGF-β, later resolve this sensitization by suppressing pro-inflammatory mediators (Scholz and Woolf, 2007).

Chronic stress shifts this balance toward persistent pro-inflammatory states that maintain pain long after healing. This disruption occurs partly through microglia, the nervous system's resident immune cells. These cells normally cycle between pro-inflammatory states (enhancing pain during acute injury) and anti-inflammatory states (promoting resolution). However, chronic stress locks microglia in pro-inflammatory activation (Inoue and Tsuda, 2018), bathing injury sites in inflammatory mediators that continuously sensitize nociceptors (Marchand et al., 2005). The result is a self-perpetuating cycle of pain: pain drives inflammation and inflammation maintains pain, with the system locked in a sensitized state (Ji et al., 2013).

Developmental plasticity

Experiences during sensitive developmental periods can induce lasting changes that can affect pain processing throughout life, including structural changes in the brain itself. Chronic pain can induce such changes, including reduced gray matter volume in pain-modulating regions (Apkarian et al., 2004). Conversely, factors such as enrichment and exercise, can promote neurogenesis (May, 2008). Additionally, environmental deprivation and thwarting of behavioral motivations have been shown to lead to aberrant or maladaptive brain functions (Würbel, 2001). Underlying many of these changes are epigenetic modifications—molecular mechanisms that regulate gene expression without changing the DNA sequence. Chronic stress and persistent pain can induce DNA methylation and/or histone modification that act as "dimmer switches", increasing the expression of pro-nociceptive genes while suppressing anti-nociceptive ones (Descalzi et al., 2015). These epigenetic marks can lock the nervous system into a state of heightened pain sensitivity that may persist even if conditions improve. Direct evidence for pain-related epigenetic remodeling now exists in controlled models. In mice subjected to peripheral nerve injury, global DNA methylation in the prefrontal cortex decreased from 60% to 48% six months after injury, accompanied by chronic hypersensitivity and anxiety-like behavior (Tajerian et al., 2013). Critically, environmental enrichment reversed both the pain behaviors and the prefrontal methylation changes, and the degree of methylation recovery correlated with the magnitude of pain attenuation (Tajerian et al., 2013). At the gene-specific level, chronic neuropathic pain altered methylation of over 3,900 unique genes in the frontal cortex, affecting pathways involved in intracellular signaling, cell motility, and cytoskeletal structure (Topham et al., 2021). That these changes are genuinely epigenetic (rather than downstream correlates of pain) was confirmed by the finding that approximately one-third of them, spanning over 1,000 genes including genes with known pain-related function, were reversed when the DNA methylation pathway was targeted pharmacologically, concurrent with pain relief (Topham et al., 2021). Together, these two lines of evidence show that pain can be "memorized" in the brain through epigenetic mechanisms, and that this memory can be erased by improving the environment. These epigenetic effects have also been demonstrated in farmed animals. Piglets born to sows kept in barren environments during late gestation showed distinct DNA methylation profiles in the hippocampus, frontal cortex, and amygdala compared to piglets from enriched sows (Tatemoto et al., 2023). Consistent with this, differentially methylated regions associated with chronic social isolation stress were identified in the red blood cells of chickens across genetically distinct populations reared in different biomes (Pértille et al., 2020). Together, these findings indicate that the environmental modulation of pain discussed operates, at least in part, through epigenetic mechanisms that can sustain heightened pain sensitivity across time and generations, but that are potentially reversible when environmental conditions improve.

During neonatal and juvenile periods, the nervous system itself is also exceptionally plastic. Painful injuries or significant stress early in life can permanently change the trajectory of the pain circuit development, increasing the number of nociceptive nerve terminals, neurons with lower activation thresholds, and reorganizing synaptic connections (Schwaller and Fitzgerald, 2014). Functionally, early adversity can recalibrate stress and pain systems in ways that persist into adulthood, changing HPA-axis function, increasing anxiety-like behavior, and heightening nociceptive sensitivity, often leading to long-term hyperalgesia (Coffman et al., 2022). Critically, these adjustments are non-linear: across humans and animal models, repeated mild, controllable challenges are associated with more resilient later responses to stress and experimental pain, whereas both very low adversity (under-stimulation) and high or chronic adversity are linked to poorer regulation and increased pain sensitivity—a U-shaped "stress inoculation" or "toughening" pattern (Macrì et al., 2009; Seery et al., 2013).

These developmental effects are not restricted to the directly exposed individual. For instance, maternal environmental enrichment before and during gestation in rats has been shown to reduce anxiety-like behaviors in the offspring (Zuena et al., 2016). Likewise, pre-reproductive maternal enrichment has been reported to increase maternal licking/grooming and nursing, leading to increased social interaction and reduced social avoidance in the next generation (Cutuli et al., 2019). Although these studies focus primarily on stress reactivity rather than nociception, changes in stress regulation are known to influence pain modulation, suggesting possible downstream, secondary effects on pain sensitivity (Bell and Hellmann, 2019).

The consequences of early or prenatal stress also depend on timing and severity: in primate models, brief, controllable stress exposures early in development enhanced later coping abilities, whereas prolonged or intense disruptions, such as maternal separation, increased vulnerability (Parker and Maestripieri, 2011). From an evolutionary perspective, such calibration may be adaptive when early adversity reliably signals a harsh environment, potentially favoring heightened vigilance or increased pain sensitivity (Veit and Browning, 2023). However, changes in pain sensitivity are not necessarily adaptive and may instead reflect side-effects of broader neuroendocrine plasticity. Moreover, early painful experiences may recalibrate reference points such that individuals develop a higher tolerance to pain, even if neural sensitization increases nociceptive processing. In captivity, this may give rise to a developmental mismatch if individuals shaped by barren or noxious early conditions remain hyper-reactive or hypersensitive despite later exposure to enriched environments.

Healing modulation

Many factors that modulate pain perception also directly influence healing capacity, with both processes regulated by the same neuro-immune-endocrine systems. Healing is not passive but an active biological cascade that can be profoundly impaired by environmental stressors. Sustained activation of the HPA/I axis due to repeated or prolonged stress chronically elevates glucocorticoid hormones that directly impair healing by suppressing the immune system, dysregulating inflammation, and inhibiting cellular repair processes (Sapolsky et al., 2000; Glaser and Kiecolt-Glaser, 2005). As a result, injuries may not only feel more painful under chronic stress but also take longer to heal (Gentle and Hunter, 1993; Gentle and Tilston, 1999).

High levels of glucocorticoids also compromise immune function by inhibiting T-cell and macrophage proliferation, impairing pathogen clearance and debris removal. For example, pigs housed in barren, stressful environments exhibit slower viral clearance and more severe lung pathology than pigs in enriched environments (van Dixhoorn et al., 2016). Likewise, in chickens, stress-induced immunosuppression reduces responses to vaccination (Yunis et al., 2000; Cheema et al., 2003; Quinteiro-Filho et al., 2010), increases susceptibility to pathogens (Calefi et al., 2017; Hofmann et al., 2020) and delays wound healing (Quinteiro-Filho et al., 2010).

Beyond immunosuppression, chronic stress dysregulates the inflammatory cascade. Effective healing requires a rapid initial pro-inflammatory phase followed by an anti-inflammatory phase that resolves inflammation and promotes tissue rebuilding. Chronic stress prolongs the pro-inflammatory stage and delays the onset of the restorative phase (Glaser and Kiecolt-Glaser, 2005). Studies confirm this dysregulation, with chronically stressed animals showing significantly delayed wound closure compared to non-stressed controls (Padgett et al., 1998; Christian et al., 2006).

Finally, glucocorticoids directly inhibit cellular repair by suppressing fibroblast proliferation and the synthesis of collagen, essential for tissue rebuilding (Kruse et al., 1978). These mechanisms work together: chronically stressed animals experience enhanced pain perception, compromised immune defense, dysregulated inflammation, and inhibited tissue repair—making injury and disease more likely, more painful and slower to heal.

Common factors triggering modulatory mechanisms

Having established the neurobiological mechanisms through which pain can be modulated, in this section we examine and illustrate common environmental and physiological factors that engage these pathways. This distinction serves two purposes. First, it acknowledges that individual factors rarely map onto single mechanisms, activating multiple pain-modulatory pathways simultaneously. Second, identifying common environmental factors provides targets for intervention, allowing the identification and modification of housing conditions, management practices, and experiences that can shape pain outcomes. Table 2 maps how these factors activate specific modulatory mechanisms.

Opportunities for motivated behaviors and cognitive engagement

Active participation in motivated, goal-directed activities can activate top-down pathways that reduce pain perception. These activities typically involve highly motivated behaviors, such as nesting, feeding, foraging, and environmental exploration in general. For example, chickens with experimentally-induced arthritis showed pronounced limping, reduced weight-bearing on the affected leg, and decreased locomotor activity (Gentle and Corr, 1995). However, these impairments disappeared during feeding—an effect that scaled with hunger level. Birds deprived of food for 24 hours showed more complete suppression of limping than those deprived for only four hours, with normal locomotion persisting throughout feeding periods of up to thirty minutes (Gentle and Corr, 1995; Wylie and Gentle, 1998). In another set of experiments, chickens with induced arthritis in a familiar barren environment showed higher levels of cortisol, inflammation, and joint temperature than chickens placed in a novel pen (Gentle and

TABLE 2 Mapping of common factors in captive conditions to pain-modulatory mechanisms.

Factor	Effect on pain	Mechanism triggered
Opportunities for motivated behaviors and engagement	Suppression	Activates descending inhibition of nociceptive signals, stimulates endogenous opioid release, and induces attentional distraction that reduces pain processing.
Physical exercise and movement	Suppression	Induces endogenous opioid-mediated analgesia, reduces pro-inflammatory cytokines through improved circulation, and supports neuroplasticity that strengthens pain regulation.
Lack of physical exercise and movement (restriction/immobility)	Amplification	Reduces spinal gate control, sustains inflammatory sensitization, and increases baseline pain sensitivity.
Positive and stable social contact	Suppression	Triggers oxytocin-mediated analgesia and reduces stress-related activation of pain pathways.
Social isolation or unstable social conditions	Amplification	Promotes stress-induced central sensitization and delays healing through sustained hyperactivation of pain pathways.
Disrupted sleep and rest	Amplification	Increases pro-inflammatory cytokine activity and impairs descending pain inhibition, leading to heightened pain sensitivity and delayed healing.
Painful and stressful procedures in early life	Amplification	Induces central sensitization, structural rewiring, and long-term developmental programming of nociceptive pathways, including epigenetic modifications.
Maternal stress (additional factor)	Amplification	Changes offspring nociceptive and stress regulation via prenatal developmental programming, reducing endogenous pain suppression capacity.
Presence of control and environmental choice	Suppression	Engages descending modulation of pain through expectancy-based relief and supports adaptive neurochemical regulation of nociception.
Lack of control or unpredictable aversive exposure	Amplification	Sustains pro-inflammatory microglial activation and central sensitization through chronic stress-induced HPA/HPI overactivation.

Tilston, 1999; Gentle, 2001). A similar effect occurred during nesting: broody hens with induced joint pain showed normal weight-bearing and locomotion while building nests or brooding eggs, yet exhibited pronounced limping and one-legged standing when not engaged in these activities (Gentle, 2001). Critically, naloxone administration (a drug that blocks opioid receptors) reversed all pain suppression effects, indicating the involvement of endogenous opioids (Wylie and Gentle, 1998; Gentle, 2001).

This phenomenon extends across species. In cats, the temperature threshold for withdrawal responses to heat increases during feeding (51 °C during feeding versus 47 °C not feeding), indicating reduced pain sensitivity during behavioral engagement (Casey and Morrow, 1983). Similarly, rodents exploring novel environments showed reduced pain behaviors on formalin-injected paws (licking, biting, reduced weight-bearing), with effects mediated by changes in monoamines (Ford et al., 2008). In turn, opioid-mediated analgesia was found with prolonged exposure to a predator threat (Kavaliers and Colwell, 1991), while with short exposure (30 sec) to the threat, analgesia was insensitive to naloxone but blocked by a serotonin agonist, suggesting involvement of serotonergic pathways (Kavaliers and Colwell, 1991). Overall, the magnitude of pain suppression appears to scale with motivational salience, with highly motivated behaviors like nest-building and maternal care producing stronger analgesia (Bridges and Grimm, 1982; Gentle and Tilston, 1999). Additionally, some behavioral changes might reflect attentional reallocation. In cattle, oral distraction devices reduced struggle during freeze branding (Aitken et al., 2013). In humans, active task engagement was shown to reduce pain ratings in scenarios including a cold pressor task (Verhoeven et al., 2011) and during dressing in burn injury patients (Morris et al., 2009).

Overall, these findings indicate that behaviors that are motivated and engage attention activate multiple pain-suppressing pathways, including opioid systems, serotonergic pathways, and cognitive-attentional processes, with their relative contributions depending on the salience of competing demands, the temporal dynamics of the experience and the intensity of pain.

Physical exercise

Physical activity can suppress pain through both immediate and long-term mechanisms. Exercise induces analgesia through pathways including endogenous opioid release (Koltyn, 2000) and modulation of inflammatory responses. Regular joint movement maintains synovial fluid circulation and lymphatic drainage, reducing pro-inflammatory cytokine levels that would otherwise accumulate (Castrogiovanni et al., 2019). In humans, for example, increased physical activity improves pain ratings in a broad range of painful clinical conditions including low back pain, osteoarthritis, and fibromyalgia (Gowans et al., 2004; Smith and Grimmer-Somers, 2010). These effects have been shown to persist long after the exercise period (Naugle et al., 2012), likely reflecting continued circulation of endogenous opioids and anti-inflammatory factors.

Conversely, sedentary animals often develop chronic pain (reversible only through exercise-induced opioid release) (Bement and Sluka, 2005; Sluka et al., 2013), and those prevented from voluntary running show greater pain sensitivity (Stagg et al., 2011; Grace et al., 2016). In rodents, voluntary wheel running can reduce neuropathic pain behaviors and inflammation after sciatic nerve compression (Bertolini et al., 2011; Stagg et al., 2011). Lack of physical activity or prolonged immobility after an injury can also lead to delayed healing (Bement and Sluka, 2005; Keylock et al., 2008).

These effects of exercise appear conserved across vertebrates. In Atlantic salmon, swimming has been shown to promote neuroplasticity, enhance social cohesion, and reduce plasma

cortisol (Spiliopoulos et al., 2025). For example, active swimming following crowding stress accelerated the return of cortisol and metabolic indicators to baseline levels (Veiseth et al., 2006). Although these studies did not directly measure pain, the observed effects of exercise on stress reactivity, social behavior, and cognitive modulation point to its involvement in supraspinal (top-down) pathways with possible downstream effects on pain perception. Exercise may also build resilience against pain through neuroplastic changes. By elevating BDNF levels, exercise promotes neurogenesis (Siuciak et al., 1995; Bekinschtein et al., 2011), which in humans has been associated with reduced chronic pain (Vachon et al., 2013).

Social contact

Evidence indicates that social context also modulates pain, yet its effects are complex and bidirectional, depending on factors including relationship quality and the nature of the interaction. For example, in rodents, socially enriched mice undergoing surgical cecal manipulation consumed less analgesic than mice in socially deprived environments (Pham et al., 2010). Accordingly, isolated mice show increased pain behaviors and delayed wound healing (Pyter et al., 2014). In lambs, the presence of a familiar partner reduced signs of pain such as rolling following a tail-docking procedure (Guesgen et al., 2014), whereas social isolation reduced mechanical pain thresholds (Clark et al., 2011).

In contrast, studies of disbudding in dairy calves have produced contradictory results: calves paired with conspecifics showed some signs of an improved ability to recover from disbudding in one study (Bučková et al., 2022), yet no social benefit was observed in another (Nogues et al., 2023). This variability may either reflect the influence of unmeasured contextual factors that determine whether social presence engages analgesic pathways, or the possibility that social buffering is not present in calves. Additionally, some animals may exhibit social withdrawal as an adaptive response to pain and inflammation (Gingerich et al., 2020; Zoltick et al., 2024), and forcing social contact in these cases may lead to aggression (Munsterhjelm et al., 2019) or loss of social status (Tansley et al., 2019). Finally, emotional contagion can create reciprocal welfare impacts, with pain in one individual reducing welfare in exposed conspecifics (Le Moëne and Larsson, 2025). The variability in outcomes indicates that implementing social housing requires careful consideration of species-specific behaviors, the stability of social hierarchies, and the severity of painful states.

Where beneficial effects occur, they appear mediated through oxytocin release and stress response modulation. While oxytocin's effects are most thoroughly documented in mammals, the oxytocin/vasotocin system and its role in social behavior is present across vertebrates (Akinrinade et al., 2023), suggesting potential parallel mechanisms for social pain modulation in other taxa. Epigenetic mechanisms also seem to underlie some of the effects mentioned. For example, maternal housing conditions during gestation have been shown to change DNA methylation in offspring brain regions governing emotionality and stress regulation (Tatemoto et al., 2023), suggesting that the consequences of social impoverishment may extend beyond the directly exposed individual.

Disrupted sleep and rest

Sleep disruption, whether due to insufficient duration, poor quality, or irregular patterns, seems to be a potent amplifier of pain perception, likewise impairing healing. In rodents, for example, even partial sleep deprivation consistently increases sensitivity to thermal and mechanical pain and exacerbates the severity of inflammatory pain states (Lautenbacher et al., 2006; Haack et al., 2020). The hyperalgesic effect of suboptimal sleep is linked to both inflammatory and neural pain-modulating systems. Sleep is essential for regulating immune function, with disruption increasing pro-inflammatory cytokines and contributing to a state of systemic inflammation that lowers pain thresholds (Roehrs et al., 2006). Simultaneously, sleep deprivation can impair the efficacy of the brain's top-down analgesic pathways (e.g., endogenous opioids), compromising the ability to suppress pain (Przewłocka et al., 1986; Hakki Onen et al., 2001). This combination of enhanced pro-inflammatory signaling and impaired endogenous analgesia can lead to a state where pain is both more easily triggered and less effectively controlled.

These effects are also evident in other vertebrates. In Atlantic salmon aquaculture, continuous light protocols are routinely applied (Mota et al., 2024). Under these conditions, melatonin release is suppressed, as the pineal organ in salmonids depends on proper light–dark cycles for secretion (Iigo et al., 2007). Melatonin acts directly on the interrenal tissue (the functional equivalent of the adrenal gland) to inhibit *de novo* cortisol synthesis, functioning as an anti-stress signal (Azpeleta et al., 2023). Elevated glucocorticoids are well known for their immunosuppressive effects (Tort, 2011), whereas melatonin is critical for synchronizing immune cell activity and enhancing innate defenses (Cuesta et al., 2008; Esteban et al., 2013; Ren et al., 2015). Accordingly, salmon kept under continuous light exhibited delayed wound healing compared to 12:12 light–dark cycles or continuous darkness (Oldham, 2025).

Painful experiences

Lasting changes in pain sensitivity that persist over life and across generations have been documented in multiple species and contexts. For example, exposure of gestating sows to an immune challenge has led to the downregulation of genes for key opioid receptors, impairing the offspring's natural pain-relief system (Rodriguez-Zas et al., 2024). This transgenerational downregulation of gene expression is consistent with epigenetic mediation, whereby maternal stress induces methylation changes in offspring that persist beyond the original challenge. Similarly, piglets of sows who experienced social mixing stress during mid-pregnancy showed significantly higher pain scores in response to tail-docking soon after birth, with average litter pain score correlated with the sow's cortisol levels during mid-gestation (Rutherford et al., 2009). These observations are in line with the hypothesis that maternal stress changes the developmental trajectory of nociceptive and immune regulation, leading to heightened pain responses and reduced resilience, possibly as an evolutionary adaptation to poor environments (Veit and Browning, 2023).

Similar effects are observed in fish. Although the effects of maternal stress on offspring pain sensitivity have not been directly investigated, maternal stress seems to affect offspring stress reactivity. In teleosts, cortisol is deposited into the oocyte and plays a critical role in embryonic development (Alsop and Vijayan, 2008). To prevent overexposure, ovarian follicles possess enzymatic mechanisms that restrict excessive cortisol incorporation into the eggs (Faught et al., 2016). However, whether this buffering capacity can compensate under chronic maternal stress remains unclear: high embryonic cortisol exposure can lead to dysregulated immune and stress function, and impaired tissue regeneration (Hartig et al., 2016), plausibly priming fish offspring for maladaptive responses to injury and pain.

Permanent changes in pain processing have also been demonstrated following painful procedures performed early in life. Rodents experiencing neonatal injury show substantially increased sensitivity to painful stimuli in adulthood (Ruda et al., 2000). Piglets castrated without analgesia displayed increased pain sensitivity weeks after the procedure (Hay et al., 2003), calves disbudded without pain relief showed heightened sensitivity to both thermal and mechanical stimuli months later (Adcock & Tucker, 2018) and, in sheep, female lambs that had been exposed to either tail-docking or a simulated infection during days 3–4 of their lives showed higher-levels of pain-related behavior when giving birth to their own first offspring (Clark et al., 2014). Beyond direct tissue damage, premature maternal separation has been associated with increased pain sensitivity in offspring across species (Vilela et al., 2017).

Opportunities for control and environmental choice

The effects of environmental control and expectations on pain perception have been documented in various contexts (Habermann et al., 2025). In humans, control over pain offset or treatment onset shows the most consistent hypoalgesic effects. Recent work demonstrated that self-initiated treatment (via button press to reduce painful heat) led to lower pain ratings compared to externally initiated treatment, suggesting that control shifts expectations toward more effective treatment rather than modulating sensory precision (Habermann et al., 2025). In animals, research has primarily focused on how lack of control amplifies pain rather than how control might reduce it. Prolonged exposure to inescapable stressors—such as social instability, confinement, overcrowding, or persistent pain—often triggers hyperalgesia (Jennings et al., 2014). In rodents, chronic unpredictable stressors increased sensitivity to pain and prolonged recovery from injury (Maile et al., 2025). The inability to predict or control aversive events is linked with chronic activation of stress systems, leading to central sensitization and heightened pain perception.

While these studies indicate that removing control amplifies pain, environmental choice may provide animals with behavioral means to manage painful or inflammatory states through different mechanisms. For example, fish exposed to pathogens or inflammatory challenges, for example, actively seek warmer water to induce behavioral fever (Huntingford et al., 2020). As ectotherms, fish cannot physiologically generate fever through internal metabolic processes as mammals do; instead, they must raise their body temperature behaviorally by moving to warmer areas. This thermoregulatory behavior enhances immune response and inhibits pathogen growth, allowing them to self-medicate through environmental navigation. While this represents management of the underlying inflammatory condition rather than direct pain modulation, it demonstrates how environmental choice enables animals to actively respond to painful or inflammatory states when such options are available. Additionally, environmental choice may support neurochemical systems involved in stress and pain regulation. For example, salmon reared in thermally enriched environments—where temperature gradients allowed thermal choice—exhibited higher levels of dopamine and serotonin (Sanhueza et al., 2018; Huntingford et al., 2020), neurotransmitters central to stress coping and pain modulation. When environmental choice is removed, animals lose both behavioral and neurochemical pathways for managing disease states and pain, potentially intensifying and prolonging it.

Expectations can also modulate responses to pain and generate placebo- and nocebo-like effects. This phenomenon is well-documented in humans (Bingel et al., 2011; Büchel et al., 2014; Hoskin et al., 2019) and may also exist in non-human animals (Nolan et al., 2012; Lecorps and Weary, 2024). For example, one study demonstrated placebo analgesia in rats that had learned to endure thermal stimuli to obtain a reward (Nolan et al., 2012). After experiencing pain relief from morphine during this task, the animals continued accessing the reward even when given saline injections instead, suggesting that anticipation of analgesia alone was sufficient to modulate their pain. Similarly, heifers trained using positive reinforcement to enter a headlock voluntarily showed reduced aversion to the headlock after it was associated with a mild subcutaneous injection, demonstrating that positive expectations engineered via positive training can reduce pain perception (Lomb et al., 2021).

Conversely, negative expectations may amplify pain through nocebo-like effects. For instance, animals that have experienced heightened pain may develop persistent negative expectations about painful stimuli, potentially maintaining hyperalgesia even after transfer to enriched environments. This learned anticipation of greater pain could represent an additional mechanism through which pain amplification persists beyond the immediate housing conditions, leading to a form of expectation-based sensitization.

Systemic pain amplification under intensive conditions

While natural settings can offer a balance of factors that can either suppress or enhance pain perception, intensive and barren settings substantially reduce opportunities for the activation of the endogenous analgesic mechanisms discussed, while simultaneously promoting most of the pathways that heighten pain sensitivity and

TABLE 3 Mapping of pain-modulating factors to intensive rearing for caged egg-laying hens, breeding sows in crates, dairy calves, and salmon reared in recirculating aquaculture Systems, illustrating how common husbandry factors are predicted to inhibit pain-suppressing mechanisms while activating pathways known to amplify and prolong pain.

Conditions under conventional intensive farming	Laying hens in conventional cages	Breeding sows in crates	Dairy calves	Farmed salmon
Characterization: Stocking density, space availability	High stocking density; very limited floor and vertical space per bird (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	Metal enclosures; insufficient to turn or change posture normally (Marchant-Forde, 2008; EFSA, 2022)	Individual hutches or small pens; limited space; high densities in group pens (Marcé et al., 2010; Hötzel et al., 2014; USDA, 2014)	Extremely high in hatcheries, limited horizontal/vertical swimming space (Stien et al., 2013)
Characterization: Barreness	Barren cages, no perches, nests or substrate (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	Concrete/slatted floors; no manipulable substrate (Marchant-Forde, 2008; EFSA, 2022)	Barren housing (Mandel et al., 2016), wire/solid floors with bedding	Barren tanks, no substrate/shelter); const flow & light (Reiser et al., 2025)
Opportunities for motivated behaviors and engagement	None: foraging, nesting, dust-bathing, exploration impossible (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	None: nesting, foraging, exploration, wallowing prevented (Godyń et al., 2019; Mkwanazi et al., 2019)	Often no opportunities for grazing or social & maternal interaction (Marcé et al., 2010; Hötzel et al., 2014; USDA, 2014; Costa et al., 2016)	Very limited: no shelter, substrate, current or temperature choice (Martins et al., 2012)
Physical exercise and movement	Walking, wing-flapping and other movements not possible (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	Extreme confinement, no possibility of movement.	Kept in small pens; restricted locomotion (Costa et al., 2016; Mandel et al., 2016)	Abnormal swimming, natural and individual variation prevented (Martins et al., 2012)
Social contact	Small group sizes, competition for limited resources, inability to escape aggression (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	Social isolation; abrupt weaning, mixing of unfamiliar piglets, inability to escape aggression (Marchant-Forde, 2008; EFSA, 2022).	Social isolation for young animals (individual housing), early maternal separation (Costa et al., 2016)	Fin-nipping, aggression, and establishment of rigid, stressful hierarchies (Martins et al., 2012)
Disrupted sleep and rest	Inability to roost, constant disruption from cage mates (Lay et al., 2011; Freire and Cowling, 2013; Hemsworth, 2021)	Crate prevents comfortable resting postures, constant noise (Marchant-Forde, 2008; EFSA, 2022).	Inadequate dry bedding & drafts/ heat; disturbed lying bouts, constant lighting (Tucker et al., 2021)	Constant lighting, currents and noise; no quiescent zones (Bassi et al., 2022)
Painful and stressful procedures in early life	Beak-trimming, sexing, hatchery processing, immunization, transport (Hedlund et al., 2019)	Tail-docking; teeth clipping in some systems; injections; repeated handling (Sutherland, 2015; Ison et al., 2016; Adcock, 2021).	Maternal deprivation (Beaver et al., 2019), disbudding (Marquette et al., 2023a), castration (Marquette et al., 2023b), acute hunger after weaning (Weary et al., 2008)	Stressful hatchery and early rearing, repeated crowding/grading, transport/handling (Hoem and Tveten, 2023)
Maternal stress (additional factors)	Breeders in non-cage systems. Hens can be subject to repeated and sometimes aggressive attention from males. Bone fractures during laying (EFSA, 2023)	Chronic hunger, confinement, repeated farrowing; piglet removal, mixing (Marchant-Forde, 2008; EFSA, 2022).	Stress in gestation (heat, lameness), mastitis in lactation, peripartum practices (von Keyserlingk et al., 2009)	Crowding/handling, photoperiod/temperature manipulation, stripping of eggs/milt, spawning induction (Barton, 2000)
Control & Choice	No control over the environment or own behavior.			
Common painful conditions	Reduced bone strength and fractures (Sherwin et al., 2010), peritonitis, pecking wounds, vent and cloaca issues, footpad dermatitis (Lay et al., 2011; Freire and Cowling, 2013; Blatchford et al., 2016)	Lameness, pressure and gastric ulcers, mastitis-metritis, UTI, reproductive tract pain (Marchant-Forde, 2008; EFSA, 2022).	Navel infections, abdominal pain, sole, hock, joint & claw lesions, pneumonia, pleuritis (Thomsen et al., 2023; Roche et al., 2024)	Skeletal and jaw deformities, skin injuries, eye damage, gill pathologies, respiratory distress (Stien et al., 2013)

delay healing. These conditions are present in various captive settings, particularly those used for research animals, and in industrial animal farming, which typically involves the confinement of large numbers of animals at high stocking densities under barren conditions.

Overcrowding can amplify pain through most modulatory systems examined in this review. It often reduces the possibility of movement and physical exercise, hence the activation of afferent fibers that can inhibit nociceptive transmission, as well as exercise-induced analgesia. It also reduces engagement in motivated activities such as exploration, that would normally activate descending analgesic pathways. It creates persistent social tension through the inability to establish stable hierarchies or escape agonistic encounters, degrades air quality through concentrated waste production, disrupts rest through constant disturbances, and generates chronic competition for resources. These factors engage, and sustain, the pathways that promote the chronic upregulation of the HPA/HPI axis, leading to a pro-inflammatory state that drives central

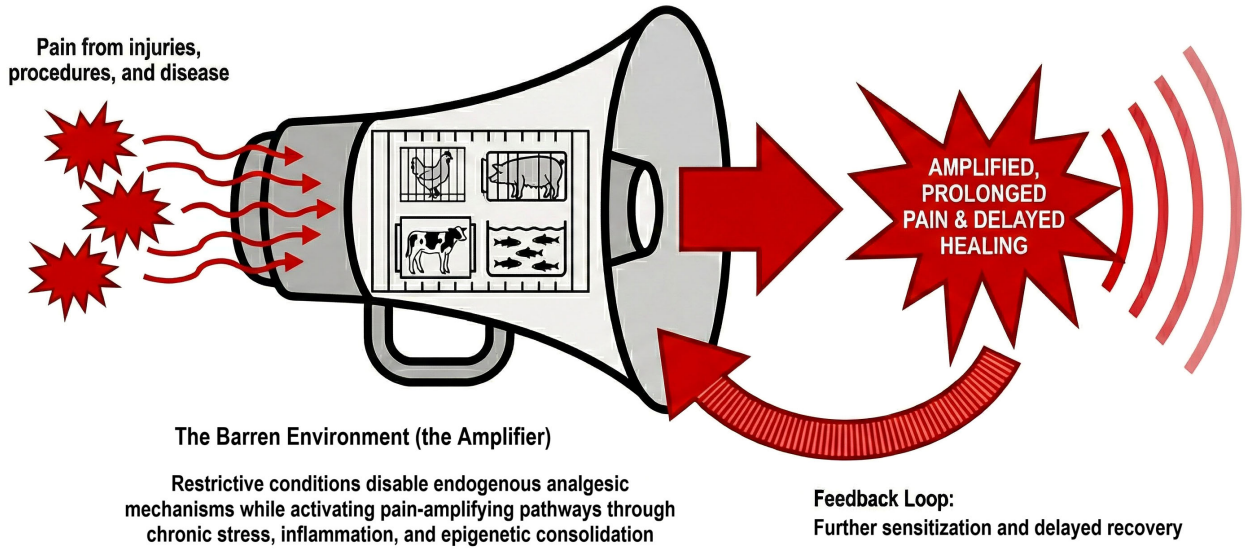

FIGURE 1
Conceptual illustration of the pain echo chamber. Pain from injuries, procedures, and disease enters a barren environment that functions as an amplifier — disabling endogenous analgesic mechanisms (including those triggered by movement, behavioral engagement, social contact, and sleep) while simultaneously activating pain-amplifying pathways — resulting in amplified, prolonged pain and delayed healing. A feedback loop of further sensitization and impaired recovery sustains the cycle.

sensitization, resulting in allodynia and hyperalgesia. Impaired immune competence also delays healing and increases vulnerability to additional welfare challenges. Concurrently, barren conditions are similarly associated with the chronic deprivation of highly motivated behaviors, most of which can trigger the endogenous analgesic pathways discussed. Cognitive and sensory deprivation further remove attentional competition that would otherwise direct focus away from (mild and moderate) pain signals. Barren environments also remove opportunities to cope with these challenges, such as refuge areas and environmental choice.

These pain-amplifying conditions converge most severely in female breeders, who typically endure longer production cycles than animals raised for meat. They face repeated reproductive procedures including artificial insemination, pregnancy diagnosis, and parturition, alongside reproduction-related pathologies (e.g., mastitis, metritis, egg peritonitis). Chronic feed restriction, standard practice to ensure reproductive efficiency in breeders of fast-growing lines, also maintains these animals in states of persistent hunger (D'Eath et al., 2009), and the metabolic demands of reproduction create additional physiological stress. Housing systems for breeders often impose greater space restriction (e.g., gestation crates, farrowing crates, battery cages), and at least in the case of mammals repeated maternal separation adds psychological stress that further sensitizes pain pathways. The extreme conditions experienced by female breeders have cascading effects that go beyond pain amplification, creating intergenerational effects that amplify pain perception in the offspring too. Prenatal stress from mothers experiencing chronic pain, feed restriction, and confinement changes HPA axis development and nociceptive processing in the offspring. These effects compound when offspring themselves undergo painful procedures in early life and premature maternal separation, potentially establishing pain hypersensitivity for life.

Table 3 illustrates common husbandry practices associated with both pain amplification and suppression of endogenous analgesia in four farm animal groups: caged egg-laying hens, crated breeding sows, dairy calves and intensively reared Atlantic salmon. As shown in the table, multiple are the factors that act synergistically to create an environment of systemic pain amplification—a "Pain Echo Chamber"—where the likelihood, intensity and duration of painful experiences are magnified beyond what would be expected based on the underlying pathology (Figure 1).

Implications and recommendations

The evidence that environmental context fundamentally modulates pain perception has profound consequences for welfare assessment and translational science. Welfare assessment frameworks that treat painful events as context-invariant risk systematically underestimating pain in barren conditions, and overestimating it under meaningfully enriched conditions. The solution requires either using housing-matched pain indicators—deriving intensity and duration estimates from animals in the specific system being assessed—or applying environmental correction factors when such data are unavailable. The latter will require investigating the magnitude of environmental modulation on pain salience and healing rates across species and conditions. Certification schemes and regulatory processes must also incorporate environmental modulation when evaluating severity. For instance, schemes that assign identical welfare scores to footpad dermatitis across all broiler systems will fail to account for how environmental context shapes this condition's impact. Different approaches could address this effect, including different outcome thresholds or welfare impact scales for different housing systems.

Until research can establish magnitude differences in the severity and duration of pain, a conservative approach is to derive pain indicators from the least enriched systems, so assessments capture worst-case scenarios where pain is maximal. Likewise, pain models built on barren laboratory housing may not accurately reflect drug efficacy or clinical relevance, requiring housing-based recalibration of analgesic testing and dosing. This aligns with calls to increase variability in animal housing and external validity of research findings (Voelkl et al., 2020).

The dynamic modulation of pain by environmental context bears practical implications. Critically, the provision of meaningful opportunities for behavioral engagement, agency, social interactions, and exercise must become a core feature of welfare standards. The emerging evidence that many environmentally driven changes in pain processing are mediated by epigenetic mechanisms, which are reversible with environmental improvement (Tajerian et al., 2013; Topham et al., 2021), also suggests that the benefits of enrichment extend beyond preventing future harm: they may actively reverse molecular changes that sustain heightened pain sensitivity in currently housed animals.

Importantly, enrichment should not be about maximizing stimulation, but rather choice and control. Some painful conditions will be compatible with social contact, movement, or cognitive engagement, while more severe states may adaptively motivate withdrawal, rest, and isolation (Proudfoot et al., 2014; Sundman et al., 2024). For instance, when movement restriction is medically necessary — such as during post-surgical recovery from orthopedic procedures — the temporary removal of exercise-induced analgesia makes it all the more important to optimize remaining modulatory pathways, including adequate pharmacological analgesia, comfortable resting conditions, and, where appropriate, choice of social contact.

This underscores why housing systems should provide animals with meaningful choices: opportunities to engage or withdraw, to move or rest, to seek social contact or isolation. Withholding such resources from animals, particularly those in chronic pain, constitutes a clear failure of adequate care. Additionally, enriched environments expand behavioral repertoires, allowing subtle behavioral deviations (e.g., reduced play, exploration) to signal emerging pain or disease earlier than in barren settings (Littin et al., 2008). This enhanced detectability is relevant in the context of early infectious disease detection (Nicol, 2025), and helps prevent painful conditions from progressing into chronic, amplified pain states.

These provisions are particularly relevant during early development, when nociceptive systems and stress–pain interactions are calibrated for life. Preventing sensitization caused by painful husbandry procedures and maternal or early-life stress is essential to avoid long-term hyperalgesic trajectories.

Conclusion

Pain perception is not a fixed consequence of tissue damage but a dynamic phenomenon shaped by an animal's environment and history. As demonstrated in this review, the same injury can produce profoundly different affective experiences depending on whether an animal can move, interact socially, engage in rewarding activities, rest properly, exercise control and access cognitive buffering. Barren housing, particularly under intensive conditions, systematically disables endogenous analgesic systems while simultaneously activating multiple pathways that amplify the perception of pain and delay healing. Pain in these conditions—what we describe as a Pain Echo Chamber—is not only unrelieved; it is amplified and prolonged beyond what the underlying pathology would otherwise induce. This is additionally concerning considering that pain can lead to longer-term affective disturbances, including depressive-like states such as negative mood and anhedonia, as shown in farm animals subjected to painful husbandry procedures or chronic injuries (Lecorps et al., 2021).

The consistency of findings across vertebrates, and even some invertebrates, suggests that environmental modulation of pain represents a fundamental biological principle rather than isolated phenomena. These findings challenge assumptions across animal welfare science, veterinary medicine, and translational research, suggesting that we may have systematically underestimated the pain experiences of animals in barren housing systems ubiquitous in farms, laboratories, and other captive settings. Given the evidence that barren and intensive conditions change the phenomenology of pain itself, the transition to higher welfare housing systems becomes an ethical and scientific imperative.

Author contributions

CS-P: Conceptualization, Writing – review & editing, Writing – original draft, Methodology, Investigation. WA: Writing – original draft, Writing – review & editing. KH: Writing – original draft, Writing – review & editing. CC: Writing – original draft, Writing – review & editing. PP: Writing – review & editing, Writing – original draft. WV: Writing – original draft, Writing – review & editing. MM: Writing – original draft, Writing – review & editing. CN: Writing – original draft, Writing – review & editing. BL: Writing – review & editing, Writing – original draft.

Funding

The author(s) declared that financial support was received for this work and/or its publication. CS-P, WA, KH, CC, WV, and PP broader research is supported by Coefficient Giving, though it did not specifically request this project or have any say over methods or results.

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author CN declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

Abboud, C., Duveau, A., Bouali-Benazzouz, R., Massé, K., Mattar, J., Brochoire, L., et al. (2021). Animal models of pain: Diversity and benefits. *J. Neurosci. Methods* 348, 108997. doi: 10.1016/j.jneumeth.2020.108997

Adcock, S. J. J. (2021). Early life painful procedures: Long-term consequences and implications for farm animal welfare. *Front. Anim. Sci.* 2. doi: 10.3389/fanim.2021.759522

Adcock, S. J., and Tucker, C. B. (2018). The effect of disbudding age on healing and pain sensitivity in dairy calves. *J. Dairy Sci.* 101, 10361–10373. doi: 10.3168/jds.2018-14987

Aitken, B. L., Stookey, J. M., Noble, S., Watts, J., and Finlay, D. (2013). The effects of an oral distraction on cattle during a painful procedure. *Can. Vet. J.* 54, 588–590. Available online at: https://pmc.ncbi.nlm.nih.gov/articles/PMC3659455/.

Akinrinade, I., Kareklas, K., Teles, M. C., Reis, T. K., Gliksberg, M., Petri, G., et al. (2023). Evolutionarily conserved role of oxytocin in social fear contagion in zebrafish. *Science* 379, 1232–1237. doi: 10.1126/science.abq5158

Alsop, D., and Vijayan, M. M. (2008). Development of the corticosteroid stress axis and receptor expression in zebrafish. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 294, R711–R719. doi: 10.1152/ajpregu.00671.2007

Apkarian, A. V., Bushnell, M. C., Treede, R.-D., and Zubieta, J.-K. (2005). Human brain mechanisms of pain perception and regulation in health and disease. *Eur. J. Pain* 9, 463–484. doi: 10.1016/j.ejpain.2004.11.001

Apkarian, A. V., Sosa, Y., Sonty, S., Levy, R. M., Harden, R. N., Parrish, T. B., et al. (2004). Chronic back pain is associated with decreased prefrontal and thalamic gray matter density. *J. Neurosci.* 24, 10410–10415. doi: 10.1523/JNEUROSCI.2541-04.2004

Azpeleta, C., Delgado, M. J., Metz, J. R., Flik, G., and de Pedro, N. (2023). Melatonin as an anti-stress signal: Effects on an acute stress model and direct actions on interrenal tissue in goldfish. *Front. Endocrinol. (Lausanne)* 14. doi: 10.3389/fendo.2023.1291153

Barton, B. A. (2000). Salmonid fishes differ in their cortisol and glucose responses to handling and transport stress. *N. Am. J. Aquac.* 62, 12–18. doi: 10.1577/1548-8454(2000)062<0012:sfditc>2.0.co;2

Bassi, A., Love, O. P., Cooke, S. J., Warriner, T. R., Harris, C. M., and Madliger, C. L. (2022). Effects of artificial light at night on fishes: A synthesis with future research priorities. *Fish. Fish. (Oxf.)* 23, 631–647. doi: 10.1111/faf.12638

Beaver, A., Meagher, R. K., von Keyserlingk, M. A. G., and Weary, D. M. (2019). Invited review: A systematic review of the effects of early separation on dairy cow and calf health. *J. Dairy Sci.* 102, 5784–5810. doi: 10.3168/jds.2018-15603

Bekinschtein, P., Oomen, C. A., Saksida, L. M., and Bussey, T. J. (2011). Effects of environmental enrichment and voluntary exercise on neurogenesis, learning and memory, and pattern separation: BDNF as a critical variable? *Semin. Cell Dev. Biol.* 22, 536–542. doi: 10.1016/j.semcdb.2011.07.002

Bell, T., Franz, C. E., and Kremen, W. S. (2022). Persistence of pain and cognitive impairment in older adults. *J. Am. Geriatr. Soc* 70, 449–458. doi: 10.1111/jgs.17542

Bell, A. M., and Hellmann, J. K. (2019). An integrative framework for understanding the mechanisms and multigenerational consequences of transgenerational plasticity. *Annu. Rev. Ecol. Evol. Syst.* 50, 97–118. doi: 10.1146/annurev-ecolsys-110218-024613

Bement, M. K. H., and Sluka, K. A. (2005). Low-intensity exercise reverses chronic muscle pain in the rat in a naloxone-dependent manner. *Arch. Phys. Med. Rehabil.* 86, 1736–1740. doi: 10.1016/j.apmr.2005.03.029

Bertolini, G. R. F., do Nascimento, C. M., Artifon, E. L., Cunha, D. M., and Meireles, A. (2011). Swimming training and functional assessment of sciatic nociception in rats. *Rev. Bras. Reumatol.* 51, 249–257.

Bingel, U., Wanigasekera, V., Wiech, K., Ni Mhuircheartaigh, R., Lee, M. C., Ploner, M., et al. (2011). The effect of treatment expectation on drug efficacy: Imaging the analgesic benefit of the opioid remifentanil. *Sci. Transl. Med.* 3, 70ra14. doi: 10.1126/scitranslmed.3001244

Blatchford, R. A., Fulton, R. M., and Mench, J. A. (2016). The utilization of the Welfare Quality® assessment for determining laying hen condition across three housing systems. *Poult. Sci.* 95, 154–163. doi: 10.3382/ps/pev227

Boll, S., Almeida de Minas, A. C., Raftogianni, A., Herpertz, S. C., and Grinevich, V. (2018). Oxytocin and pain perception: From animal models to human research. *Neuroscience* 387, 149–161. doi: 10.1016/j.neuroscience.2017.09.041

Bracke, M. B. M., Metz, J. H. M., Dijkhuizen, A. A., and Spruijt, B. M. (2001). Development of a decision support system for assessing farm animal welfare in relation to husbandry systems: Strategy and prototype. *J. Agric. Environ. Ethics* 14, 321–337. doi: 10.1023/A:1012282207323

Bracke, M. B. M., Spruijt, B. M., Metz, J. H. M., and Schouten, W. G. P. (2002). Decision support system for overall welfare assessment in pregnant sows A: Model structure and weighting procedure. *J. Anim. Sci.* 80, 1819–1834.

Bridges, R. S., and Grimm, C. T. (1982). Reversal of morphine disruption of maternal behavior by concurrent treatment with the opiate antagonist naloxone. *Science* 218, 166–168. doi: 10.1126/science.7123227

Büchel, C., Geuter, S., Sprenger, C., and Eippert, F. (2014). Placebo analgesia: A predictive coding perspective. *Neuron* 81, 1223–1239. doi: 10.1016/j.neuron.2014.02.042

Bučková, K., Moravcsíková, Á., Šárová, R., Rajmon, R., and Špinka, M. (2022). Indication of social buffering in disbudded calves. *Sci. Rep.* 12, 2825. doi: 10.1038/s41598-022-15919-8

Calefi, A. S., Quinteiro-Filho, W. M., Ferreira, A. J. P., and Palermo-Neto, J. (2017). Neuroimmunomodulation and heat stress in poultry. *Worlds. Poult. Sci. J.* 73, 493–504. doi: 10.1017/S0043933917000472

Casey, K. L., and Morrow, T. J. (1983). Nocifensive responses to cutaneous thermal stimuli in the cat: Stimulus-response profiles, latencies, and afferent activity. *J. Neurophysiol.* 50, 1497–1515. doi: 10.1152/jn.1983.50.6.1497

Castrogiovanni, P., Di Rosa, M., Ravalli, S., Castorina, A., Guglielmino, C., Imbesi, R., et al. (2019). Moderate physical activity as a prevention method for knee osteoarthritis and the role of synoviocytes as biological key. *Int. J. Mol. Sci.* 20, 511. doi: 10.3390/ijms20030511

Cheema, M. A., Qureshi, M. A., and Havenstein, G. B. (2003). A comparison of the immune response of a 2001 commercial broiler with a 1957 randombred broiler strain when fed representative 1957 and 2001 broiler diets. *Poult. Sci.* 82, 1519–1529. doi: 10.1093/ps/82.10.1519

Chen, J., Wang, X., and Xu, Z. (2023). The relationship between chronic pain and cognitive impairment in the elderly: A review of current evidence. *J. Pain Res.* 16, 2309–2319. doi: 10.2147/JPR.S416253

Christian, L. M., Graham, J. E., Padgett, D. A., Glaser, R., and Kiecolt-Glaser, J. K. (2006). Stress and wound healing. *Neuroimmunomodulation* 13, 337–346. doi: 10.1159/000104862

Clark, C., Mendl, M., Jamieson, J., Arnone, A., Waterman-Pearson, A., and Murrell, J. (2011). Do psychological and physiological stressors alter the acute pain response to castration and tail docking in lambs? *Vet. Anaesth. Analg.* 38, 134–145. doi: 10.1111/j.1467-2995.2011.00594.x

Clark, C., Murrell, J., Fernyhough, M., O'Rourke, T., and Mendl, M. (2014). Long-term and trans-generational effects of neonatal experience on sheep behaviour. *Biol. Lett.* 10, 20140273. doi: 10.1098/rsbl.2014.0273

Coffman, J. A., Burman, M. A., and Duboué, E. R. (2022). Editorial: Early life stress and developmental programming of immune and nervous system responsivity. *Front. Cell Dev. Biol.* 10. doi: 10.3389/fcell.2022.897251

Corder, G., Castro, D. C., Bruchas, M. R., and Scherrer, G. (2018). Endogenous and exogenous opioids in pain. *Annu. Rev. Neurosci.* 41, 453–473. doi: 10.1146/annurev-neuro-080317-061522

Costa, J. H. C., von Keyserlingk, M. A. G., and Weary, D. M. (2016). Invited review: Effects of group housing of dairy calves on behavior, cognition, performance, and health. *J. Dairy Sci.* 99, 2453–2467. doi: 10.3168/jds.2015-10144

Cuesta, A., Cerezuela, R., Esteban, M. A., and Meseguer, J. (2008). *In vivo* actions of melatonin on the innate immune parameters in the teleost fish gilthead seabream. *J. Pineal Res.* 45, 70–78. doi: 10.1111/j.1600-079X.2008.00557.x

Cutuli, D., Berretta, E., Caporali, P., Sampedro-Piquero, P., De Bartolo, P., Laricchiuta, D., et al. (2019). Effects of pre-reproductive maternal enrichment on maternal care, offspring's play behavior and oxytocinergic neurons. *Neuropharmacology* 145, 99–113. doi: 10.1016/j.neuropharm.2018.02.015

D'Eath, R. B., Tolkamp, B. J., Kyriazakis, I., and Lawrence, A. B. (2009). Freedom from hunger" and preventing obesity: The animal welfare implications of reducing food quantity or quality. *Anim. Behav.* 77, 275–288. doi: 10.1016/j.anbehav.2008.10.028

Descalzi, G., Ikegami, D., Ushijima, T., Nestler, E. J., Zachariou, V., and Narita, M. (2015). Epigenetic mechanisms of chronic pain. *Trends Neurosci.* 38, 237–246. doi: 10.1016/j.tins.2015.02.001

Dion, A., Muñoz, P. T., and Franklin, T. B. (2022). Epigenetic mechanisms impacted by chronic stress across the rodent lifespan. *Neurobiol. Stress* 17, 100434. doi: 10.1016/j.ynstr.2022.100434

EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare), Nielsen, S. S., Alvarez, J., Bicout, D. J., Calistri, P., Canali, E., et al. (2022). Welfare of pigs on farm. *EFSA J.* 20, e07421. doi: 10.2903/j.efsa.2022.7421

EFSA AHAW Panel (EFSA Panel on Animal Health and Welfare), Nielsen, S. S., Alvarez, J., Bicout, D. J., Calistri, P., and Canali, E.. (2023). Welfare of laying hens on farm. *EFSA J.* 21, e07789. doi: 10.2903/j.efsa.2023.7789

EFSA Panel on Animal Health and Welfare (AHAW). (2012). Guidance on risk assessment for animal welfare. *EFSA J.* 10, 2513. doi: 10.2903/j.efsa.2012.2513

Esteban, M.Á., Cuesta, A., Chaves-Pozo, E., and Meseguer, J. (2013). Influence of melatonin on the immune system of fish: A review. *Int. J. Mol. Sci.* 14, 7979–7999. doi: 10.3390/ijms14047979

Fanselow, M. S., and Baackes, M. P. (1982). Conditioned fear-induced opiate analgesia on the Formalin test: Evidence for two aversive motivational systems. *Learn. Motiv.* 13, 200–221. doi: 10.1016/0023-9690(82)90021-2

Farrelly, L. A., Thompson, R. E., Zhao, S., Lepack, A. E., Lyu, Y., Bhanu, N. V., et al. (2019). Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. *Nature* 567, 535–539. doi: 10.1038/s41586-019-1024-7

Faught, E., Best, C., and Vijayan, M. M. (2016). Maternal stress-associated cortisol stimulation may protect embryos from cortisol excess in zebrafish. *R. Soc Open Sci.* 3, 160032. doi: 10.1098/rsos.160032

Fields, H. (2004). State-dependent opioid control of pain. *Nat. Rev. Neurosci.* 5, 565–571. doi: 10.1038/nrn1431

Ford, G. K., Moriarty, O., McGuire, B. E., and Finn, D. P. (2008). Investigating the effects of distracting stimuli on nociceptive behaviour and associated alterations in brain monoamines in rats. *Eur. J. Pain* 12, 970–979. doi: 10.1016/j.ejpain.2008.01.002

Freire, R., and Cowling, A. (2013). The welfare of laying hens in conventional cages and alternative systems: First steps towards a quantitative comparison. *Anim. Welf.* 22, 57–65. doi: 10.7120/09627286.22.1.057

Gentle, M. J. (2001). Attentional shifts alter pain perception in the chicken. *Anim. Welf.* 10, 187–194. doi: 10.1017/S0962728600023617

Gentle, M. J. (2011). Pain issues in poultry. *Appl. Anim. Behav. Sci.* 135, 252–258. doi: 10.1016/j.applanim.2011.10.023

Gentle, M. J., and Corr, S. A. (1995). Endogenous analgesia in the chicken. *Neurosci. Lett.* 201, 211–214. doi: 10.1016/0304-3940(95)12181-1

Gentle, M. J., and Hunter, L. N. (1993). Neurogenic inflammation in the chicken (Gallus gallus var domesticus). *Comp. Biochem. Physiol. C.* 105, 459–462. doi: 10.1016/0742-8413(93)90086-z

Gentle, M. J., and Tilston, V. L. (1999). Reduction in peripheral inflammation by changes in attention. *Physiol. Behav.* 66, 289–292. doi: 10.1016/s0031-9384(98)00297-2

Gingerich, K. N., Choulet, V., and Miller-Cushon, E. K. (2020). Disbudding affects use of a shelter provided to group-housed dairy calves. *J. Dairy Sci.* 103, 10519–10529. doi: 10.3168/jds.2020-18267

Glaser, R., and Kiecolt-Glaser, J. K. (2005). Stress-induced immune dysfunction: implications for health. *Nat. Rev. Immunol.* 5, 243–251. doi: 10.1038/nri1571

Godyń, D., Nowicki, J., and Herbut, P. (2019). Effects of environmental enrichment on pig welfare-a review. *Anim. (Basel)* 9, 383. doi: 10.3390/ani9060383

Gowans, S. E., Dehueck, A., Voss, S., Silaj, A., and Abbey, S. E. (2004). Six-month and one-year followup of 23 weeks of aerobic exercise for individuals with fibromyalgia: Followup study on exercise and fibromyalgia. *Arthritis Rheumatol.* 51, 890–898. doi: 10.1002/art.20828

Grace, P. M., Fabisiak, T. J., Green-Fulgham, S. M., Anderson, N. D., Strand, K. A., Kwilasz, A. J., et al. (2016). Prior voluntary wheel running attenuates neuropathic pain. *Pain* 157, 2012–2023. doi: 10.1097/j.pain.0000000000000607

Guesgen, M. J., Beausoleil, N. J., Minot, E. O., Stewart, M., and Stafford, K. J. (2014). Social context and other factors influence the behavioural expression of pain by lambs. *Appl. Anim. Behav. Sci.* 159, 41–49. doi: 10.1016/j.applanim.2014.07.008

Haack, M., Simpson, N., Sethna, N., Kaur, S., and Mullington, J. (2020). Sleep deficiency and chronic pain: potential underlying mechanisms and clinical implications. *Neuropsychopharmacology* 45, 205–216. doi: 10.1038/s41386-019-0439-z

Habermann, M., Strube, A., and Büchel, C. (2025). How control modulates pain. *Trends Cogn. Sci.* 29, 60–72. doi: 10.1016/j.tics.2024.09.014

Hakki Onen, S., Alloui, A., Jourdan, D., Eschalier, A., and Dubray, C. (2001). Effects of rapid eye movement (REM) sleep deprivation on pain sensitivity in the rat. *Brain Res.* 900, 261–267. doi: 10.1016/s0006-8993(01)02320-4

Hartig, E. I., Zhu, S., King, B. L., and Coffman, J. A. (2016). Cortisol-treated zebrafish embryos develop into pro-inflammatory adults with aberrant immune gene regulation. *Biol. Open* 5, 1134–1141. doi: 10.1242/bio.020065

Hay, M., Vulin, A., Génin, S., Sales, P., and Prunier, A. (2003). Assessment of pain induced by castration in piglets: behavioral and physiological responses over the subsequent 5 days. *Appl. Anim. Behav. Sci.* 82, 201–218. doi: 10.1016/S0168-1591(03)00059-5

Hedlund, L., Whittle, R., and Jensen, P. (2019). Effects of commercial hatchery processing on short- and long-term stress responses in laying hens. *Sci. Rep.* 9, 2367. doi: 10.1038/s41598-019-38817-y

Heinricher, M. M., Tavares, I., Leith, J. L., and Lumb, B. M. (2009). Descending control of nociception: Specificity, recruitment and plasticity. *Brain Res. Rev.* 60, 214–225. doi: 10.1016/j.brainresrev.2008.12.009

Hemsworth, P. H. (2021). Cage production and laying hen welfare. *Anim. Prod. Sci.* 61, 821–836. doi: 10.1071/an19609

Herrero, J. F., Laird, J. M., and López-García, J. A. (2000). Wind-up of spinal cord neurones and pain sensation: much ado about something? *Prog. Neurobiol.* 61, 169–203. doi: 10.1016/s0301-0082(99)00051-9

Hoem, K. S., and Tveten, A.-K. (2023). Sea transfer and net pen cleaning induce changes in stress-related gene expression in commercial Atlantic salmon (Salmo salar) gill tissue. *Aquac. Int.* 31, 2245–2262. doi: 10.1007/s10499-023-01084-w

Hofmann, T., Schmucker, S. S., Bessei, W., Grashorn, M., and Stefanski, V. (2020). Impact of housing environment on the immune system in chickens: A review. *Anim. (Basel)* 10, 1138. doi: 10.3390/ani10071138

Honess, P., and Wolfensohn, S. (2010). The extended welfare assessment grid: a matrix for the assessment of welfare and cumulative suffering in experimental animals. *Altern. Lab. Anim.* 38, 205–212. doi: 10.1177/026119291003800304

Hoskin, R., Berzuini, C., Acosta-Kane, D., El-Deredy, W., Guo, H., and Talmi, D. (2019). Sensitivity to pain expectations: A Bayesian model of individual differences. *Cognition* 182, 127–139. doi: 10.1016/j.cognition.2018.08.022

Hothersall, B., Caplen, G., Parker, R. M. A., Nicol, C. J., Waterman-Pearson, A. E., Weeks, C. A., et al. (2014). Thermal nociceptive threshold testing detects altered sensory processing in broiler chickens with spontaneous lameness. *PloS One* 9, e97883. doi: 10.1371/journal.pone.0097883

Hötzel, M. J., Longo, C., Balcão, L. F., Cardoso, C. S., and Costa, J. H. C. (2014). A survey of management practices that influence performance and welfare of dairy calves reared in southern Brazil. *PloS One* 9, e114995. doi: 10.1371/journal.pone.0114995

Huntingford, F., Rey, S., and Quaggiotto, M.-M. (2020). Behavioural fever, fish welfare and what farmers and fishers know. *Appl. Anim. Behav. Sci.* 231, 105090. doi: 10.1016/j.applanim.2020.105090

Iigo, M., Abe, T., Kambayashi, S., Oikawa, K., Masuda, T., Mizusawa, K., et al. (2007). Lack of circadian regulation of *in vitro* melatonin release from the pineal organ of salmonid teleosts. *Gen. Comp. Endocrinol.* 154, 91–97. doi: 10.1016/j.ygcen.2007.06.013

Ijichi, C., Collins, L. M., and Elwood, R. W. (2014). Pain expression is linked to personality in horses. *Appl. Anim. Behav. Sci.* 152, 38–43. doi: 10.1016/j.applanim.2013.12.007

Inoue, K., and Tsuda, M. (2018). Microglia in neuropathic pain: cellular and molecular mechanisms and therapeutic potential. *Nat. Rev. Neurosci.* 19, 138–152. doi: 10.1038/nrn.2018.2

Ison, S. H., Clutton, R. E., Di Giminiani, P., and Rutherford, K. M. D. (2016). A review of pain assessment in pigs. *Front. Vet. Sci.* 3. doi: 10.3389/fvets.2016.00108

Jennings, E. M., Okine, B. N., Roche, M., and Finn, D. P. (2014). Stress-induced hyperalgesia. *Prog. Neurobiol.* 121, 1–18. doi: 10.1016/j.pneurobio.2014.06.003

Jensen, K. B., Berna, C., Loggia, M. L., Wasan, A. D., Edwards, R. R., and Gollub, R. L. (2012). The use of functional neuroimaging to evaluate psychological and other non-pharmacological treatments for clinical pain. *Neurosci. Lett.* 520, 156–164. doi: 10.1016/j.neulet.2012.03.010

Ji, R.-R., Berta, T., and Nedergaard, M. (2013). Glia and pain: is chronic pain a gliopathy? *Pain* 154 Suppl 1, S10–S28. doi: 10.1016/j.pain.2013.06.022

Julius, D., and Basbaum, A. I. (2001). Molecular mechanisms of nociception. *Nature* 413, 203–210. doi: 10.1038/35093019

Kavaliers, M., and Colwell, D. D. (1991). Sex differences in opioid and non-opioid mediated predator-induced analgesia in mice. *Brain Res.* 568, 173–177. doi: 10.1016/0006-8993(91)91394-g

Keylock, K. T., Vieira, V. J., Wallig, M. A., DiPietro, L. A., Schrementi, M., and Woods, J. A. (2008). Exercise accelerates cutaneous wound healing and decreases wound inflammation in aged mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* 294, R179–R184. doi: 10.1152/ajpregu.00177.2007

Khuong, T. M., Hamoudi, Z., Manion, J., Loo, L., Muralidharan, A., and Neely, G. G. (2019). Peripheral straightjacket (α2δ Ca2+ channel subunit) expression is required for neuropathic sensitization in Drosophila. *Philos. Trans. R. Soc Lond. B. Biol. Sci.* 374, 20190287. doi: 10.1098/rstb.2019.0287

Koltyn, K. F. (2000). Analgesia following exercise: a review. *Sports Med.* 29, 85–102.

Korte, S. M. (2001). Corticosteroids in relation to fear, anxiety and psychopathology. *Neurosci. Biobehav. Rev.* 25, 117–142. doi: 10.1016/s0149-7634(01)00002-1

Kruse, N. J., Rowe, D. W., Fujimoto, W. Y., and Bornstein, P. (1978). Inhibitory effects of glucocorticoids on collagen synthesis by mouse sponge granulomas and granuloma fibroblasts in culture. *Biochim. Biophys. Acta Gen. Subj.* 540, 101–116. doi: 10.1016/0304-4165(78)90439-7

Latremoliere, A., and Woolf, C. J. (2009). Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J. Pain* 10, 895–926. doi: 10.1016/j.jpain.2009.06.012

Lautenbacher, S., Kundermann, B., and Krieg, J.-C. (2006). Sleep deprivation and pain perception. *Sleep Med. Rev.* 10, 357–369. doi: 10.1016/j.smrv.2005.08.001

Lay, D. C., Fulton, R. M., Hester, P. Y., Karcher, D. M., Kjaer, J. B., Mench, J. A., et al. (2011). Hen welfare in different housing systems. *Poult. Sci.* 90, 278–294. doi: 10.3382/ps.2010-00962

Lecorps, B., Nogues, E., von Keyserlingk, M. A. G., and Weary, D. M. (2020). Pessimistic dairy calves are more vulnerable to pain-induced anhedonia. *PloS One* 15, e0242100. doi: 10.1371/journal.pone.0242100

Lecorps, B., and Weary, D. (2024). Animal affect, welfare and the Bayesian brain. *Anim. Welf.* 33, e39. doi: 10.1017/awf.2024.44

Lecorps, B., Weary, D. M., and von Keyserlingk, M. A. G. (2021). Captivity-induced depression in animals. *Trends Cogn. Sci.* 25, 539–541. doi: 10.1016/j.tics.2021.03.010

Le Moëne, O., and Larsson, M. (2025). Social avoidance of mice in pain in naturalistic conditions. *Affect. Sci.* 6, 159–170. doi: 10.1007/s42761-024-00276-8

Littin, K., Acevedo, A., Browne, W., Edgar, J., Mendl, M., Owen, D., et al. (2008). Towards humane end points: behavioural changes precede clinical signs of disease in a Huntington's disease model. *Proc. Biol. Sci.* 275, 1865–1874. doi: 10.1098/rspb.2008.0388

Lomb, J., Mauger, A., von Keyserlingk, M. A. G., and Weary, D. M. (2021). Effects of positive reinforcement training for heifers on responses to a subcutaneous injection. *J. Dairy Sci.* 104, 6146–6158. doi: 10.3168/jds.2020-19463

Macrì, S., Granstrem, O., Shumilina, M., Antunes Gomes dos Santos, F. J., Berry, A., Saso, L., et al. (2009). Resilience and vulnerability are dose-dependently related to neonatal stressors in mice. *Horm. Behav.* 56, 391–398. doi: 10.1016/j.yhbeh.2009.07.006

Maile, L., Mercado, K., Baig, L., and Davidson, S. (2025). Chronic unpredictable stress produces hyperalgesia and promotes inhibitory drive in medial prefrontal cortex. *J. Pain* 33, 105452. doi: 10.1016/j.jpain.2025.105452

Mandel, R., Whay, H. R., Klement, E., and Nicol, C. J. (2016). Invited review: Environmental enrichment of dairy cows and calves in indoor housing. *J. Dairy Sci.* 99, 1695–1715. doi: 10.3168/jds.2015-9875

Marcé, C., Guatteo, R., Bareille, N., and Fourichon, C. (2010). Dairy calf housing systems across Europe and risk for calf infectious diseases. *Animal* 4, 1588–1596. doi: 10.1017/S1751731110000650

Marchand, F., Perretti, M., and McMahon, S. B. (2005). Role of the immune system in chronic pain. *Nat. Rev. Neurosci.* 6, 521–532. doi: 10.1038/nrn1700

Marchant-Forde, J. N. (2008). *The welfare of pigs*. Ed. J. N. Marchant-Forde (New York, NY: Springer). doi: 10.1007/978-1-4020-8909-1

Marquette, G. A., Ronan, S., and Earley, B. (2023a). Calf disbudding – animal welfare considerations. *J. Appl. Anim. Res.* 51, 616–623. doi: 10.1080/09712119.2023.2264912

Marquette, G. A., Ronan, S., and Earley, B. (2023b). Review: castration – animal welfare considerations. *J. Appl. Anim. Res.* 51, 703–718. doi: 10.1080/09712119.2023.2273270

Martins, C. I. M., Galhardo, L., Noble, C., Damsgård, B., Spedicato, M. T., Zupa, W., et al. (2012). Behavioural indicators of welfare in farmed fish. *Fish Physiol. Biochem.* 38, 17–41. doi: 10.1007/s10695-011-9518-8

May, A. (2008). Chronic pain may change the structure of the brain. *Pain* 137, 7–15. doi: 10.1016/j.pain.2008.02.034

Mekhael, A. A., Bent, J. E., Fawcett, J. M., Campbell, T. S., Aguirre-Camacho, A., Farrell, A., et al. (2023). Evaluating the efficacy of oxytocin for pain management: An updated systematic review and meta-analysis of randomized clinical trials and observational studies. *Can. J. Pain* 7, 2191114. doi: 10.1080/24740527.2023.2191114

Mellor, D. J. (2017). Operational details of the five domains model and its key applications to the assessment and management of animal welfare. *Animals* 7, 60. doi: 10.3390/ani7080060

Melzack, R., and Wall, P. D. (1965). Pain mechanisms: a new theory. *Science* 150, 971–979. doi: 10.1126/science.150.3699.971

Miletic, G., and Miletic, V. (2008). Loose ligation of the sciatic nerve is associated with TrkB receptor-dependent decreases in KCC2 protein levels in the ipsilateral spinal dorsal horn. *Pain* 137, 532–539. doi: 10.1016/j.pain.2007.10.016

Millan, M. J. (2002). Descending control of pain. *Prog. Neurobiol.* 66, 355–474. doi: 10.1016/s0301-0082(02)00009-6

Mkwanazi, M. V., Ncobela, C. N., Kanengoni, A. T., and Chimonyo, M. (2019). Effects of environmental enrichment on behaviour, physiology and performance of pigs - A review. *Asian-Australas. J. Anim. Sci.* 32, 1–13. doi: 10.5713/ajas.17.0138

Moont, R., Pud, D., Sprecher, E., Sharvit, G., and Yarnitsky, D. (2010). Pain inhibits pain" mechanisms: Is pain modulation simply due to distraction? *Pain* 150, 113–120. doi: 10.1016/j.pain.2010.04.009

Moriarty, O., McGuire, B. E., and Finn, D. P. (2011). The effect of pain on cognitive function: a review of clinical and preclinical research. *Prog. Neurobiol.* 93, 385–404. doi: 10.1016/j.pneurobio.2011.01.002

Morris, L. D., Louw, Q. A., and Grimmer-Somers, K. (2009). The effectiveness of virtual reality on reducing pain and anxiety in burn injury patients: a systematic review. *Clin. J. Pain* 25, 815–826. doi: 10.1097/AJP.0b013e3181aaa909

Mota, V. C., Verstege, G. C., Striberny, A., Lutfi, E., Dessen, J.-E., Sveen, L., et al. (2024). Smoltification, seawater performance, and maturation in Atlantic salmon (Salmo salar) fed different fat levels. *Front. Aquac.* 3. doi: 10.3389/faquc.2024.1323818

Munsterhjelm, C., Nordgreen, J., Aae, F., Heinonen, M., Valros, A., and Janczak, A. M. (2019). Sick and grumpy: Changes in social behaviour after a controlled immune stimulation in group-housed gilts. *Physiol. Behav.* 198, 76–83. doi: 10.1016/j.physbeh.2018.09.018

Naugle, K. M., Fillingim, R. B., and Riley, J. L. (2012). A meta-analytic review of the hypoalgesic effects of exercise. *J. Pain* 13, 1139–1150. doi: 10.1016/j.jpain.2012.09.006

Neugebauer, V., Li, W., Bird, G. C., and Han, J. S. (2004). The amygdala and persistent pain. *Neuroscientist* 10, 221–234. doi: 10.1177/1073858403261077

Neumann, I. D. (2008). Brain oxytocin: a key regulator of emotional and social behaviours in both females and males. *J. Neuroendocrinol.* 20, 858–865. doi: 10.1111/j.1365-2826.2008.01726.x

Nicol, C. J. (2025). *Behavioural indicators of infectious disease in managed animals*. doi: 10.1016/j.applanim.2025.106573

Nielsen, C. S., Staud, R., and Price, D. D. (2009). Individual differences in pain sensitivity: measurement, causation, and consequences. *J. Pain* 10, 231–237. doi: 10.1016/j.jpain.2008.09.010

Nogues, E., Ede, T., Woodroffe, R. E., Weary, D. M., and von Keyserlingk, M. A. G. (2023). Can a social partner alleviate conditioned place aversion caused by isolation and pain in dairy calves? *Appl. Anim. Behav. Sci.* 269, 106092. doi: 10.1016/j.applanim.2023.106092

Nolan, T. A., Price, D. D., Caudle, R. M., Murphy, N. P., and Neubert, J. K. (2012). Placebo-induced analgesia in an operant pain model in rats. *Pain* 153, 2009–2016. doi: 10.1016/j.pain.2012.04.026

Oldham, T. (2025). "The influence of environmental conditions on wound healing in Atlantic salmon," in *22nd International Conference on Diseases of Fish and Shellfish - Abstract Book* (Bergen, Norway: Institute of Marine Research, Norway).

Olsson, A. S., Nicol, C. J., Niemi, S. M., and Sandøe, P. (2020). From unpleasant to unbearable—why and how to implement an upper limit to pain and other forms of suffering in research with animals. *ILAR J.* 60, 404–414. doi: 10.1093/ilar/ilz018

Ossipov, M. H., Dussor, G. O., and Porreca, F. (2010). Central modulation of pain. *J. Clin. Invest.* 120, 3779–3787. doi: 10.1172/JCI43766

Padgett, D. A., Marucha, P. T., and Sheridan, J. F. (1998). Restraint stress slows cutaneous wound healing in mice. *Brain Behav. Immun.* 12, 64–73. doi: 10.1006/brbi.1997.0512

Parker, K. J., and Maestripieri, D. (2011). Identifying key features of early stressful experiences that produce stress vulnerability and resilience in primates. *Neurosci. Biobehav. Rev.* 35, 1466–1483. doi: 10.1016/j.neubiorev.2010.09.003

Patel, M., Hasoon, J., Diez Tafur, R., Lo Bianco, G., and Abd-Elsayed, A. (2025). The impact of chronic pain on cognitive function. *Brain Sci.* 15, 559. doi: 10.3390/brainsci15060559

Percie du Sert, N., and Rice, A. S. C. (2014). Improving the translation of analgesic drugs to the clinic: animal models of neuropathic pain: Improving models of neuropathic pain. *Br. J. Pharmacol.* 171, 2951–2963. doi: 10.1111/bph.12645

Pértille, F., Ibelli, A. M. G., Sharif, M. E., Poleti, M. D., Fröhlich, A. S., Rezaei, S., et al. (2020). Putative epigenetic biomarkers of stress in red blood cells of chickens reared across different biomes. *Front. Genet.* 11. doi: 10.3389/fgene.2020.508809

Pezet, S., and McMahon, S. B. (2006). Neurotrophins: mediators and modulators of pain. *Annu. Rev. Neurosci.* 29, 507–538. doi: 10.1146/annurev.neuro.29.051605.112929

Pham, T. M., Hagman, B., Codita, A., Van Loo, P. L. P., Strömmer, L., and Baumans, V. (2010). Housing environment influences the need for pain relief during post-operative recovery in mice. *Physiol. Behav.* 99, 663–668. doi: 10.1016/j.physbeh.2010.01.038

Pinsker, H. M., Hening, W. A., Carew, T. J., and Kandel, E. R. (1973). Long-term sensitization of a defensive withdrawal reflex in Aplysia. *Science* 182, 1039–1044. doi: 10.1126/science.182.4116.1039

Proudfoot, K. L., Jensen, M. B., Weary, D. M., and von Keyserlingk, M. A. G. (2014). Dairy cows seek isolation at calving and when ill. *J. Dairy Sci.* 97, 2731–2739. doi: 10.3168/jds.2013-7274

Przewłocka, B., Mogilnicka, E., Lasón, W., van Luijtelaar, E. L. J. M., and Coenen, A. M. L. (1986). Deprivation of REM sleep in the rat and the opioid peptides β-endorphin and dynorphin. *Neurosci. Lett.* 70, 138–142. doi: 10.1016/0304-3940(86)90452-0

Pyter, L. M., Yang, L., McKenzie, C., da Rocha, J. M., Carter, C. S., Cheng, B., et al. (2014). Contrasting mechanisms by which social isolation and restraint impair healing in male mice. *Stress* 17, 256–265. doi: 10.3109/10253890.2014.910761

Quinteiro-Filho, W. M., Ribeiro, A., Ferraz-de-Paula, V., Pinheiro, M. L., Sakai, M., Sá, L. R. M., et al. (2010). Heat stress impairs performance parameters, induces intestinal injury, and decreases macrophage activity in broiler chickens. *Poult. Sci.* 89, 1905–1914. doi: 10.3382/ps.2010-00812

Reiser, S., Illing, B., Pohlmann, D. M., and Focken, U. (2025). *Environmental enrichment during early rearing of salmonids*. doi: 10.1016/j.aquaculture.2025.742995

Ren, D.-L., Li, Y.-J., Hu, B.-B., Wang, H., and Hu, B. (2015). Melatonin regulates the rhythmic migration of neutrophils in live zebrafish. *J. Pineal Res.* 58, 452–460. doi: 10.1111/jpi.12230

Roche, S. M., Renaud, D. L., Saraceni, J., Kelton, D. F., and DeVries, T. J. (2024). Invited review: Prevalence, risk factors, treatment, and barriers to best practice adoption for lameness and injuries in dairy cattle-A narrative review. *J. Dairy Sci.* 107, 3347–3366. doi: 10.3168/jds.2023-23870

Rodriguez-Zas, S. L., Nowak, R. A., Antonson, A. M., Rund, L., Bhamidi, S., Gomez, A. N., et al. (2024). Immune and metabolic challenges induce changes in pain sensation and related pathways in the hypothalamus. *Physiol. Genomics* 56, 343–359. doi: 10.1152/physiolgenomics.00134.2023

Roehrs, T., Hyde, M., Blaisdell, B., Greenwald, M., and Roth, T. (2006). Sleep loss and REM sleep loss are hyperalgesic. *Sleep* 29, 145–151. doi: 10.1093/sleep/29.2.145

Rong, W., Zhang, C., Zheng, F., Xiao, S., Yang, Z., and Xie, W. (2021). Persistent moderate to severe pain and long-term cognitive decline. *Eur. J. Pain* 25, 2065–2074. doi: 10.1002/ejp.1826

Ruda, M. A., Ling, Q.-D., Hohmann, A. G., Peng, Y. B., and Tachibana, T. (2000). Altered nociceptive neuronal circuits after neonatal peripheral inflammation. *Science* 289, 628–630. doi: 10.1126/science.289.5479.628

Rutherford, K. M. D., Robson, S. K., Donald, R. D., Jarvis, S., Sandercock, D. A., Scott, E. M., et al. (2009). Pre-natal stress amplifies the immediate behavioural responses to acute pain in piglets. *Biol. Lett.* 5, 452–454. doi: 10.1098/rsbl.2009.0175

Sandkühler, J. (2009). Models and mechanisms of hyperalgesia and allodynia. *Physiol. Rev.* 89, 707–758. doi: 10.1152/physrev.00025.2008

Sanhueza, N., Donoso, A., Aguilar, A., Farlora, R., Carnicero, B., Míguez, J. M., et al. (2018). Thermal modulation of monoamine levels influence fish stress and welfare. *Front. Endocrinol. (Lausanne)* 9. doi: 10.3389/fendo.2018.00717

Sapolsky, R. M., Romero, L. M., and Munck, A. U. (2000). How do glucocorticoids influence stress responses? Integrating permissive, suppressive, stimulatory, and preparative actions. *Endocr. Rev.* 21, 55–89. doi: 10.1210/edrv.21.1.0389

Scharrer, B., Stefano, G. B., and Leung, M. K. (1988). Opioid mechanisms in insects, with special attention to Leucophaea maderae. *Cell. Mol. Neurobiol.* 8, 269–284. doi: 10.1007/BF00711169

Scholz, J., and Woolf, C. J. (2007). The neuropathic pain triad: neurons, immune cells and glia. *Nat. Neurosci.* 10, 1361–1368. doi: 10.1038/nn1992

Schwaller, F., and Fitzgerald, M. (2014). The consequences of pain in early life: injury-induced plasticity in developing pain pathways. *Eur. J. Neurosci.* 39, 344–352. doi: 10.1111/ejn.12414

Seery, M. D., Leo, R. J., Lupien, S. P., Kondrak, C. L., and Almonte, J. L. (2013). An upside to adversity?: moderate cumulative lifetime adversity is associated with resilient responses in the face of controlled stressors: Moderate cumulative lifetime adversity is associated with resilient responses in the face of controlled stressors. *Psychol. Sci.* 24, 1181–1189. doi: 10.1177/0956797612469210

Sherwin, C. M., Richards, G. J., and Nicol, C. J. (2010). Comparison of the welfare of layer hens in 4 housing systems in the UK. *Br. Poult. Sci.* 51, 488–499. doi: 10.1080/00071668.2010.502518

Siuciak, J. A., Wong, V., Pearsall, D., Wiegand, S. J., and Lindsay, R. M. (1995). BDNF produces analgesia in the formalin test and modifies neuropeptide levels in rat brain and spinal cord areas associated with nociception. *Eur. J. Neurosci.* 7, 663–670. doi: 10.1111/j.1460-9568.1995.tb00670.x

Sluka, K. A., O'Donnell, J. M., Danielson, J., and Rasmussen, L. A. (2013). Regular physical activity prevents development of chronic pain and activation of central neurons. *J. Appl. Physiol.* 114, 725–733. doi: 10.1152/japplphysiol.01317.2012

Smith, C., and Grimmer-Somers, K. (2010). The treatment effect of exercise programmes for chronic low back pain: Treatment effect of LBP exercise. *J. Eval. Clin. Pract.* 16, 484–491. doi: 10.1111/j.1365-2753.2009.01174.x

Sneddon, L. U. (2015). Pain in aquatic animals. *J. Exp. Biol.* 218, 967–976. doi: 10.1242/jeb.088823

Sneddon, L. U., Braithwaite, V. A., and Gentle, M. J. (2003). Novel object test: examining nociception and fear in the rainbow trout. *J. Pain* 4, 431–440. doi: 10.1067/s1526-5900(03)00717-x

Spiliopoulos, O., Brown, C., Hilder, P., Tilbrook, A., and Descovich, K. (2025). The path to resilience: Improving welfare in aquaculture through physical exercise and stressor predictability training. *Rev. Aquac.* 17, e70051. doi: 10.1111/raq.70051

Sprenger, C., Eippert, F., Finsterbusch, J., Bingel, U., Rose, M., and Büchel, C. (2012). Attention modulates spinal cord responses to pain. *Curr. Biol.* 22, 1019–1022. doi: 10.1016/j.cub.2012.04.006

Stagg, N. J., Mata, H. P., Ibrahim, M. M., Henriksen, E. J., Porreca, F., Vanderah, T. W., et al. (2011). Regular exercise reverses sensory hypersensitivity in a rat neuropathic pain model: role of endogenous opioids. *Anesthesiology* 114, 940–948. doi: 10.1097/ALN.0b013e318210f880

Stien, L. H., Bracke, M. B. M., Folkedal, O., Nilsson, J., Oppedal, F., Torgersen, T., et al. (2013). Salmon Welfare Index Model (SWIM 1.0): a semantic model for overall welfare assessment of caged Atlantic salmon: review of the selected welfare indicators and model presentation. *Rev. Aquacult.* 5, 33–57. doi: 10.1111/j.1753-5131.2012.01083.x

Sundman, E. R., Dewell, G. A., Dewell, R. D., Johnson, A. K., Thomson, D. U., and Millman, S. T. (2024). The welfare of ill and injured feedlot cattle: a review of the literature and implications for managing feedlot hospital and chronic pens. *Front. Vet. Sci.* 11. doi: 10.3389/fvets.2024.1398116

Sutherland, M. A. (2015). Welfare implications of invasive piglet husbandry procedures, methods of alleviation and alternatives: a review. *N. Z. Vet. J.* 63, 52–57. doi: 10.1080/00480169.2014.961990

Tajerian, M., Alvarado, S., Millecamps, M., Vachon, P., Crosby, C., Bushnell, M. C., et al. (2013). Peripheral nerve injury is associated with chronic, reversible changes in global DNA methylation in the mouse prefrontal cortex. *PloS One* 8, e55259. doi: 10.1371/journal.pone.0055259

Tansley, S. N., Tuttle, A. H., Wu, N., Tohyama, S., Dossett, K., Gerstein, L., et al. (2019). Modulation of social behavior and dominance status by chronic pain in mice. *Genes Brain Behav.* 18, e12514. doi: 10.1111/gbb.12514

Tatemoto, P., Pértille, F., Bernardino, T., Zanella, R., Guerrero-Bosagna, C., and Zanella, A. J. (2023). An enriched maternal environment and stereotypies of sows differentially affect the neuro-epigenome of brain regions related to emotionality in their piglets. *Epigenetics* 18, 2196656. doi: 10.1080/15592294.2023.2196656

Teng, K. T.-Y., Devleesschauwer, B., Maertens De Noordhout, C., Bennett, P., McGreevy, P. D., Chiu, P.-Y., et al. (2018). Welfare-Adjusted Life Years (WALY): A novel metric of animal welfare that combines the impacts of impaired welfare and abbreviated lifespan. *PloS One* 13, e0202580. doi: 10.1371/journal.pone.0202580

Thomsen, P. T., Shearer, J. K., and Houe, H. (2023). Prevalence of lameness in dairy cows: A literature review. *Vet. J.* 295, 105975. doi: 10.1016/j.tvjl.2023.105975

Topham, L., Gregoire, S., Kang, H., Salmon-Divon, M., Lax, E., Millecamps, M., et al. (2021). The methyl donor S-adenosyl methionine reverses the DNA methylation signature of chronic neuropathic pain in mouse frontal cortex. *Pain Rep.* 6, e944. doi: 10.1097/PR9.0000000000000944

Tort, L. (2011). Stress and immune modulation in fish. *Dev. Comp. Immunol.* 35, 1366–1375. doi: 10.1016/j.dci.2011.07.002

Tracey, I., and Mantyh, P. W. (2007). The cerebral signature for pain perception and its modulation. *Neuron* 55, 377–391. doi: 10.1016/j.neuron.2007.07.012

Tucker, C. B., Jensen, M. B., de Passillé, A. M., Hänninen, L., and Rushen, J. (2021). Invited review: Lying time and the welfare of dairy cows. *J. Dairy Sci.* 104, 20–46. doi: 10.3168/jds.2019-18074

Uchida, H., Matsushita, Y., and Ueda, H. (2013). Epigenetic regulation of BDNF expression in the primary sensory neurons after peripheral nerve injury: implications in the development of neuropathic pain. *Neuroscience* 240, 147–154. doi: 10.1016/j.neuroscience.2013.02.053

USDA. (2014). "Animal and dairy cattle management practices in the United States," in *United States Department of Agriculture* (Fort Collins, CO: USDA–APHIS–VS–CEAH, National Animal Health Monitoring System (NAHMS)). Available online at: https://www.aphis.usda.gov/sites/default/files/Dairy14_dr_PartI_1.pdf (Accessed January 15, 2026).

Vachon, P., Millecamps, M., Low, L., Thompsosn, S. J., Pailleux, F., Beaudry, F., et al. (2013). Alleviation of chronic neuropathic pain by environmental enrichment in mice well after the establishment of chronic pain. *Behav. Brain Funct.* 9, 22. doi: 10.1186/1744-9081-9-22

van Dixhoorn, I. D. E., Reimert, I., Middelkoop, J., Bolhuis, J. E., Wisselink, H. J., Groot Koerkamp, P. W. G., et al. (2016). Enriched housing reduces disease susceptibility to co-infection with porcine reproductive and respiratory virus (PRRSV) and Actinobacillus pleuropneumoniae (A. pleuropneumoniae) in young pigs. *PloS One* 11, e0161832. doi: 10.1371/journal.pone.0161832

Veiseth, E., Fjaera, S. O., Bjerkeng, B., and Skjervold, P. O. (2006). Accelerated recovery of Atlantic salmon (Salmo salar) from effects of crowding by swimming. *Comp. Biochem. Physiol. B. Biochem. Mol. Biol.* 144, 351–358. doi: 10.1016/j.cbpb.2006.03.009

Veit, W., and Browning, H. (2023). Developmental programming, evolution, and animal welfare: A case for evolutionary veterinary science. *J. Appl. Anim. Welf. Sci.* 26, 552–564. doi: 10.1080/10888705.2021.2014838

Verhoeven, K., Van Damme, S., Eccleston, C., Van Ryckeghem, D. M. L., Legrain, V., and Crombez, G. (2011). Distraction from pain and executive functioning: an experimental investigation of the role of inhibition, task switching and working memory. *Eur. J. Pain* 15, 866–873. doi: 10.1016/j.ejpain.2011.01.009

Vilela, F. C., Vieira, J. S., Giusti-Paiva, A., and Silva, M. L. (2017). Experiencing early life maternal separation increases pain sensitivity in adult offspring. *Int. J. Dev. Neurosci.* 62, 8–14. doi: 10.1016/j.ijdevneu.2017.07.003

Villemure, C., and Bushnell, C. M. (2002). Cognitive modulation of pain: how do attention and emotion influence pain processing? *Pain* 95, 195–199. doi: 10.1016/S0304-3959(02)00007-6

Voelkl, B., Altman, N. S., Forsman, A., Forstmeier, W., Gurevitch, J., Jaric, I., et al. (2020). Reproducibility of animal research in light of biological variation. *Nat. Rev. Neurosci.* 21, 384–393. doi: 10.1038/s41583-020-0313-3

von Keyserlingk, M. A. G., Rushen, J., de Passillé, A. M., and Weary, D. M. (2009). Invited review: The welfare of dairy cattle–key concepts and the role of science. *J. Dairy Sci.* 92, 4101–4111. doi: 10.3168/jds.2009-2326

Walters, E. T. (2019). Adaptive mechanisms driving maladaptive pain: how chronic ongoing activity in primary nociceptors can enhance evolutionary fitness after severe injury. *Philos. Trans. R. Soc Lond. B. Biol. Sci.* 374, 20190277. doi: 10.1098/rstb.2019.0277

Walters, E. T., Crook, R. J., Neely, G. G., Price, T. J., and Smith, E. S. J. (2023). Persistent nociceptor hyperactivity as a painful evolutionary adaptation. *Trends Neurosci.* 46, 211–227. doi: 10.1016/j.tins.2022.12.007

Walters, E. T., and Williams, A. C. C. (2019). Evolution of mechanisms and behaviour important for pain. *Philos. Trans. R. Soc Lond. B. Biol. Sci.* 374, 20190275. doi: 10.1098/rstb.2019.0275

Weary, D. M. (2014). "What is suffering in animals?" In: *Dilemmas in Animal Welfare*, edsM. C. Appleby, D. M. Weary and P. Sandøe (Wallingford: CABI), 188–202. doi: 10.1079/9781780642161.0000

Weary, D. M., Jasper, J., and Hötzel, M. J. (2008). Understanding weaning distress. *Appl. Anim. Behav. Sci.* 110, 24–41. doi: 10.1016/j.applanim.2007.03.025

Weiss, J. M. (1972). Psychological factors in stress and disease. *Sci. Am.* 226, 104–113. doi: 10.1038/SCIENTIFICAMERICAN0672-104

Welfare Quality® Consortium. (2009). *Welfare Quality® Assessment Protocol for Poultry (Broilers, Laying Hens)* (Lelystad, Netherlands: Welfare Quality® Consortium).

Woolf, C. J., Shortland, P., and Coggeshall, R. E. (1992). Peripheral nerve injury triggers central sprouting of myelinated afferents. *Nature* 355, 75–78. doi: 10.1038/355075a0

Würbel, H. (2001). Ideal homes? Housing effects on rodent brain and behaviour. *Trends Neurosci.* 24, 207–211. doi: 10.1016/s0166-2236(00)01718-5

Wylie, L. M., and Gentle, M. J. (1998). Feeding-induced tonic pain suppression in the chicken: reversal by naloxone. *Physiol. Behav.* 64, 27–30. doi: 10.1016/s0031-9384(98)00020-1

Yunis, R., Ben-David, A., Heller, E. D., and Cahaner, A. (2000). Immunocompetence and viability under commercial conditions of broiler groups differing in growth rate and in antibody response to Escherichia coil vaccine. *Poult. Sci.* 79, 810–816. doi: 10.1093/ps/79.6.810

Zoltick, A. H., Mann, S., and Coetzee, J. F. (2024). Pain pathophysiology and pharmacology of cattle: how improved understanding can enhance pain prevention, mitigation, and welfare. *Front. Pain Res. (Lausanne)* 5. doi: 10.3389/fpain.2024.1396992

Zuena, A. R., Zinni, M., Giuli, C., Cinque, C., Alemà, G. S., Giuliani, A., et al. (2016). Maternal exposure to environmental enrichment before and during gestation influences behaviour of rat offspring in a sex-specific manner. *Physiol. Behav.* 163, 274–287. doi: 10.1016/j.physbeh.2016.05.010