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Understanding early-life pain and its effects on adult human and animal emotionality: Translational lessons from rodent and zebrafish models

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ABSTRACT

Critical for organismal survival, pain evokes strong physiological and behavioral responses in various sentient species. Clinical and preclinical (animal) studies markedly increase our understanding of biological consequences of developmental (early-life) adversity, as well as acute and chronic pain. However, the long-term effects of early-life pain exposure on human and animal emotional responses remain poorly understood. Here, we discuss experimental models of nociception in rodents and zebrafish, and summarize mounting evidence of the role of early-life pain in shaping emotional traits later in life. We also call for further development of animal models to probe the impact of early-life pain exposure on behavioral traits, brain disorders and novel therapeutic treatments.

1. Introduction

Pain is an important biological process that influences physiological systems in humans and other sentient species [1-3], strongly affecting their emotional responses and behavior [4,5]. While pain often evokes *immediate* physiological and psychological effects [6-8], such influences can also be *long-lasting*. For example, chronic pain sufferers often display high harm avoidance, difficulty with defining and setting goals, poorer motivation or adaptive coping [9], aggressive behavior and negative affect [10,11], see Fig. 1.

Animal experimental models are extensively utilized in neuroscience and central nervous system (CNS) disorder research [12-14], in-

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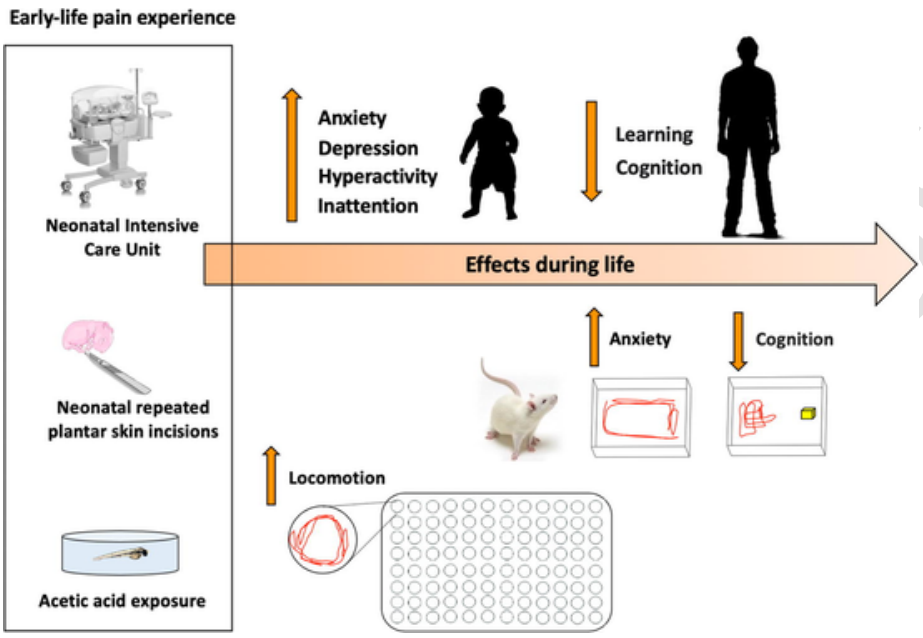

Fig. 1. Selected examples of potential neurobehavioral effects of early-life pain experience (also see Table 2). In humans, exposure to Neonatal Intensive Care Unit increases risks of developing anxiety, depression, inattention/hyperactivity [42,43], cognitive impairments and poorer school performance [39] later in life, including as adults [44]. In rodents, neonatal repeated plantar skin incisions similarly impair long-term memory and spatial learning [48,53,116] and increase anxiety-like behavior [49] in adults. In zebrafish, exposure to acetic acid increases locomotor activity in larvae [33], which can be associated with an anxiogenic-like behavior [117].

cluding studying both *physical* (e.g., pain [15,16]) and *psychological* stress [17,18]. Rodent models are particularly useful for studying pain mechanisms [19,20] and treatment [21,22], and typically involve hyperalgesia and allodynia assays utilizing thermal, mechanical, electrical or chemical noxious stimuli [23,24] (Table 1). Complementing rodent models, zebrafish (*Danio rerio*) are widely used in neuroscience research, due to high (>70%) genetic and physiological homology to humans [25], shared neural circuits and neurotransmitter systems [26,27], and a potential for high-throughput *in-vivo* CNS drug screening [28-32]. There also multiple well-established and sensitive zebrafish pain models, usually based on exposing adult or larval fish to acetic acid, formalin [33-35] and hyper- or hypothermia [36] (Table 1).

However, the putative lasting effects of early-life pain (ELP) exposure remain poorly understood. Specifically, it is unclear whether individual pain experience, especially ELP exposure, may affect, define or otherwise shape human and animal behavioral traits as adults. It is also unclear whether ELP exposure contributes to long-term behavioral deficits in a way similar (or distinct) to other, non-pain early-life stressors (ELS), and whether these responses are similar between fish and mammals.

Addressing this problem, here we summarize common experimental models of pain in mammals and zebrafish, and outline mounting evidence of how ELP experience may shape neurobehavioral traits later in life. Recognizing the growing importance of zebrafish models in neuroscience and pain research, we also discuss various zebrafish pain models and evaluate potential effects of ELP experience on fish emotional behaviors as adults.

2. Effects of ELP exposure on human and animal emotional responses

2.1. Human phenotypes

Mounting clinical evidence shows that ELP exposure modulates later-life affective states [37]. For example, prematurely born children (commonly exposed to pain due to daily injections in neonatal Intensive Care Units) often display greater negative affect [38], cognitive deficits [39] and internalizing behaviors later in life, as toddlers [40] or schoolers [41]. Such preterm children also develop greater anxiety [42], depression and attention deficit/hyperactivity disorder (ADHD) as adolescents [43], and educational disadvantages as adults [44]. In addition to lasting *psychological* effects (i.e., emotional dysregulation), ELP also exerts long-term effects on various physiological mechanisms. For instance, preterm children (<26 weeks of gestation) display aberrant somatosensorial sensitivity and reduced sensitivity to thermal modalities at middle childhood [45] (also see Table 2 for further clinical evidence implicating ELP in altered CNS traits). Children born preterm at low gestational age (24–28 weeks) have higher cortisol levels and a different pattern of cortisol response to cognitive assessment stress, compared to full-term children [46]. Likewise, exposure of preterm infants to neonatal procedural pain is accompanied by reduced white and subcortical grey matter [47], collectively suggesting that neonatal pain in vulnerable (e.g., preterm) infants may contribute to impaired brain development [47] and, thus, further contribute to lasting physiological and emotional consequences [37,46].

2.2. Selected rodent and zebrafish ELP models

Common preclinical rodent ELP models include paw injection of inflammatory agents (e.g., 10% formalin and 0.25–2% carrageenan), needle prick in hindpaw or plantar skin incisions (see Table 2 for details). Neonatal pain (e.g., caused by local peripheral tissue injury) impacts not only exploration and motivation in rodents, but also their acute pain sensitivity as adults [48] (Table 2). For example, ELP increases rodent nociception, alcohol preference, neophobia and defensive 'withdrawal' behavior as adults [49]. Chronic neonatal hindpaw inflammation (induced by complete Freund's adjuvant injection) causes adult rodent hyperalgesia, allodynia and higher Fos protein expression in the dorsal horn of the spinal cord [50]. Neonatal hindpaw inflammation also attenuates conditioned freezing behavior in rodents during the postweaning period [51]. Neonatal pain evokes lasting changes in central orexinergic pathways (known to modulate the mesolimbic dopaminergic reward circuits) [48,52], and impairs long-term memory and brain-derived neurotrophic factor (BDNF) activity in adult rat hip-

Table 1
Selected pain models in rodents and zebrafish.

Pain models	Treatment	Doses	Effects/Models	References
Models to evoke pain				
Rodents				
Adult	Axotomy (complete sciatic nerve transection)		Neuropathic pain	[99]
Adult	Chronic constriction injury		Neuropathic pain	[100]
Adult	Partial sciatic nerve ligation		Neuropathic pain	[101]
Adult	Caudal trunk resection		Neuropathic pain	[101, 102]
Adult	Acetic acid injection	0.6%, 10 mg/kg	Visceral pain (writhes)	[103, 104]
Adult	Prostaglandins	100 ng/50 µl/paw	Mechanical hyperalgesia	[105]
Adult	Formalin	50 µl 1%/paw	Mechanical hyperalgesia and altered time perception	[106]
Adult	Interleukin-1β	100 ng intrathecally	Thermal hyperalgesia	[107]
Adult	Formalin	25 µl 5%/paw	Mechanical and thermal hyperalgesia	[108]
Zebrafish				
Larvae (5dpf)	Acetic acid	0.0025–0.025%	Hyperlocomotion and higher expression of COX-2*	[33]
Larvae (5dpf)	Acetic acid	0.1% and 0.25%	Hypolocomotion	[109]
Larvae (5dpf)	Acetic acid	0.01%	Hyperlocomotion	[109]
Larvae (5dpf)	Citric acid	0.1%, 1% and 5%	Hyperlocomotion	[109]
Adult		2.5–10%, injected	Hypolocomotion and abdominal constrictions	[34,35]
Larvae (5dpf)	Hyperthermia	40 °C, for 1 min	Hypolocomotion	[36]
Larvae (5dpf)	Hypothermia	7–10 °C, for 1 min	Hypolocomotion	[36]
Adult	Formalin	0.1%; 3 and 5 µl	Hypolocomotion	[110]
Pharmacological modulation of pain				
Rodents				
Adult	4-aminoantipyrine	8–320 µg/paw	Attenuated hyperalgesia caused by prostaglandin	[105]
Adult	Amylin	0.03–1 mg/kg, and 0.3–10 µg/mouse intrathecally	Fewer writhes	[103]
Adult	Morphine	0.25–5 mg/kg	Fewer writhes	[104]
Adult	Pregabalin	2–200 mg/kg	Fewer writhes	[104]
Adult	N-(3-(Aminomethyl) benzyl) acetamidine	10 and 50 µg	Prevented thermal hyperalgesia	[107]
Adult	Duloxetine	3–30 mg/kg	Mechanical and thermal hyperalgesia following formalin administration	[108]
Adult	Naltrexone	20 mg/kg	Prevented neonatal pain-induced long-term memory deficits and hippocampal BDNF reduction*	[53]
Zebrafish				
Larvae (5dpf)	Buprenorphine	0.1 mg/L	Prevented hyperlocomotion induced by acetic acid	[33]
Larvae (5dpf)	Aspirin	2.5 mg/L	Prevented behavioral changes induced by acetic acid	[109]
Larvae (5dpf)	Lidocaine	5 mg/L	Prevented behavioral changes induced by acetic acid	[109]
Larvae (5dpf)	Morphine	48 mg/L	Prevented behavioral changes induced by acetic acid	[109]
Larvae (5dpf)	Morphine	48 mg/L	Ameliorated hypoactivity caused by high (40 °C) temperature	[36]
Larvae (5dpf)	Lidocaine	5 mg/L	Ameliorated hypoactivity caused by high (40 °C) temperature	[36]
Adult	Morphine	6 mg/kg	Attenuated hypolocomotion induced by 10% acetic acid	[34]
		0.2 mg/mL	Inhibited formalin-induced nociception	[110]
Adult	Indomethacin	0.2 mg/mL	Inhibited formalin-induced nociception	[110]

*Abbreviations: BDNF - brain-derived neurotrophic factor; COX-2 - cycloxigeanse-2; dpf - days post fertilization.

Table 2
The impact of early-life pain experience on emotional traits in humans and rodents.

Early-life experience	Neurobehavioral effects	References
Humans	***Children and adolescents***	
Toddlers born preterm (Neonatal Intensive Care Unit)	Greater internalizing behaviors, higher temperamental negative affect (e.g., frustration, discomfort, motor activation, fear and sadness), higher risk of anxiety, depression and inattention/hyperactivity	[40,41] [38][42, 43]
	Higher somatization	[5]
	Temperament with less effortful control and attention problems	[111]
	Impaired cognitive ability and school performance	[39]
	Adults	
	Lower IQ and academic achievement scores	[44]
Rodents	***Pups***	
Neonatal paw injection of 5 µl 10% formalin	Increased neuronal apoptosis	[112]
Neonatal intraplantar injection of an inflammatory agent, 2% carrageenan	Attenuated conditioned freezing during the postweaning period	[51]
Needle prick in hindpaw	Decreased anxiety-like behavior	[113]
	Adults	
Neonatal paw subcutaneous injections of 4% formalin	Reduced exploration in males and poorer learning in females	[114]
Neonatal hindpaw injection of 0.25% carrageenan	Reduced emotional responsiveness to stress	[115]
Neonatal repeated plantar skin incisions	Increased motivation to explore, impaired long-term memory	[48,53]
	Increased anxiety-like behavior	[49]
	Impaired spatial learning	[116]
Neonatal intraplantar injection of 1% carrageenan	Blunted anxiety-like and stress responses	[98]

Table 3
Selected open questions related to early individual pain experience and its potential effects on human and animal emotionality.

Questions
General
• Do human, rodent and zebrafish pain behaviors represent stable traits across ages and emotional contexts?
• Do human, rodent and zebrafish pain phenotypes correlate with their respective behavioral traits?
• To what extent does early-life pain experience contribute to emotional traits?
• Can non-pharmacological approaches (e.g., environmental enrichment or social contexts) revert or modify the effects of early-life pain exposure in adult animals?
• What is a better therapy (e.g., both pharmacological and non-pharmacological) for long-lasting (delayed) emotional consequences of early-life pain exposure?
• What are epigenetic mechanisms underlying such long-term (delayed) consequences, and their putative therapies?
• How strongly can the early-life pain exposure contribute to the development of various affective CNS disorders as adults?
• What are other (e.g., non-affective) CNS disorders that can be associated (or comorbid) with early-life pain exposure?
• What are the effects of early-life pain exposure on sociability?
Zebrafish-related
• What are the effects of early-life pain exposure on zebrafish personality?
• Do the effects of early-life pain exposure differ across sexes and strains of zebrafish?
• What are the effects of early-life pain pharmacotherapy (e.g., non-steroidal vs steroidal anti-inflammatory drugs with analgesic properties) on personality in zebrafish?
• Does early-life pain exposure present specific (or shared with human and rodent) epigenetic consequences in zebrafish?
• What are reliable experimental protocols to induce early-life pain exposure in zebrafish?
• How does early-life pain exposure affect adult response to pain, and how is this effect modulated pharmacologically (analgesia)?

pocampus [53], thus further implicating animal ELP in neurobehavioral alterations later in life. However, the exact impact of ELP exposure on adult zebrafish CNS traits remains unclear, warranting further studies and consideration.

3. Shared CNS pathways for ELS and ELP

3.1. Shared effects of stress and pain on selected physiological biomarkers

Recent evidence suggests that ELS and ELP may overlap pathophysiologically [54-56]. For example, ELS activates the mammalian hypothalamic–pituitaryadrenal (HPA) and the fish hypothalamic-pituitary-interrenal (HPI) 'stress' axes [57,58], both regulating nociception [59,60]. Hypothalamic corticotropin-releasing hormone (CRH), the primary trigger of stress response in these taxa [61], acts on multiple brain areas involved in nociception [62] (e.g., activating rodent hippocampus [63]). Produced during stress, CRH triggers the pituitary adrenocorticotropic hormone (ACTH) signaling that stimulates the release of HPA/HPI glucocorticoids, such as cortisol in humans and zebrafish, and corticosterone in rodents [64,65]. ACTH and glucocorticoids, in turn, are not only directly involved in stress, but also mediate acute pain-related responses. For example, administering ACTH and glucocorticoids in adult male rats with normal levels of HPA hormones reduces nociceptive tail-flick reflex after injection [66].

As stress alters rodent BDNF levels [67-70], pain also affects this key biomarker. For example, peripheral nerve injury in adult rodents upregulates mRNA expression of microglial BDNF [71]. Acute immobilization stress increases the expression of BDNF in rat hypothalamic paraventricular nucleus (PVN) [72], which also plays a role in pain responses [73]. Likewise, brain oxytocin may also play a role in both ELS and ELP responses. For instance, PVN stimulation or intrathecal oxytocin administration reduce the ability of spinal long-term potentiation (a hyperalgesia model) to facilitate nociceptive responses in rodents, hence implicating the PVN and the oxytocinergic system in pain [74].

3.2. Overlapping effects of ELS and ELP on the endocannabinoid and opioidergic systems

Endocannabinoids have also been implicated in both stress [75] and pain. For example, in neonatal rats, endocannabinoids protect against sciatic nerve injury-induced apoptosis [76], whereas maternal deprivation (a strong ELS) lowers brain endocannabinoid ligand and receptor expression [77]. Exposure to cannabinoids in early life also modulates behavioral responses later in life, as rats exposed during lactation demonstrate hyperactivity at infancy and adolescence [78,79]. Perinatal exposure to tetrahydrocannabinol (THC) induces lasting deficits in social interaction in adolescent and adult rats [80]. Early-life THC treatment increases *c-fos* expression at 14 hpf and *bdnf* at 48–96 hpf in whole-body zebrafish larvae samples, whereas cannabidiol (CBD) upregulates *c-fos* and *bdnf* at 24 hpf [81]. Collectively, this supports potentially overlapping role of endocannabinoids in both stress and pain, also suggesting that ELP and ELS may influence emotional and other behavioral phenotypes in a similar manner across species, including humans [82].

3.3.

While humans with neonatal injury display increased pain and injury-induced hyperalgesia when adults [56], ELP is associated with altered opioid system, as well as increased axonal sprouting, nerve growth factor (NGF)-induced neuronal plasticity and elevated glucocorticoids in young and adult rodents and humans [48,83,84]. While mammalian limbic system plays a critical role in stress behavior and learning [54,85], patients with chronic pain display depression and reduced gray matter in various brain regions [86]. Physiological and structural remodeling of learning circuitry in mammals also occurs in both pain and stress [54], thereby supporting pathobiological commonality of ELS and ELP, as they interact to shape neurobehavioral traits.

3.4. Shared effects of ELS and ELP on emotional behaviors

Shared effects of ELS and ELP also include altered human and animal emotional behaviors [87-90]. For example, early-life social deprivation (e.g., institutionalization in children or social isolation in primates) exerts long-term consequences in their emotional functioning and social behavior later in life [91-93]. ELS potently affects rodent emotionality, increasing anxiety-like behavior [94] and vulnerability for stress-related psychopathology as adults [95]. In zebrafish, ELS (e.g., hypoxia during the first 120 hpf) evokes slower swimming as adults [96].

ELP exposure also causes complex, long-term emotional and behavioral effects from young to adult age. For example, human ELP (e.g., in premature-born infants in neonatal Intensive Care Units) reduces amygdalar volume and increases social anxiety when adults [97]. Adult rats experiencing neonatal intraplantar injections of an inflammatory agent, carrageenan, display blunted anxiety- and despair-like responses [98], whereas repetitive ELP exposure increases alcohol preference, anxiety-like and defensive 'withdrawal' behaviors as adults [49].

4. Concluding remarks

Overall, mounting evidence summarized here suggests potentially overlapping mechanisms of ELS and ELP, whose lasting impact affects human and animal behavior later in life. As multiple questions regarding the role of ELP in human and animal emotional traits remain open (Table 3), this calls for further novel animal models (e.g., zebrafish) and

assays to probe the putative evolutionarily conserved role of ELP in shaping adult affective behavioral deficits and their therapeutic treatments.

Conflict of interest

The authors declare no conflicts of interest.

CRediT authorship contribution statement

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