Psychological stress in early-life as a predisposing factor for the development of chronic pain: clinical and preclinical evidence and neurobiological mechanisms

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Abstract

A wealth of research over the past two decades has expanded our understanding of the impact of early-life adversity on physiological function and, consequently, health and well-being in later life. Early-life adversity increases the risk of developing a number of disorders such as chronic pain, fibromyalgia or irritable bowel syndrome. While much of this research has examined the impact of physical maltreatment, an increasing number of studies have been published over the past few years examining the effect of childhood psychological stress and trauma on the development of various types of chronic pain conditions. This manuscript reviews the clinical and preclinical data examining the link between early-life psychological stress, altered nociceptive behavior and chronic pain in later life. Evidence supporting a role for certain key neurobiological substrates including the hypothalamic-pituitary-adrenal axis, monoaminergic, opioidergic, endocannabinoid and immune systems, and epigenetic mechanisms in the association between early-life psychological stress and chronic pain is provided. Greater understanding of the impact of early-life stress may inform the development of personalized treatments for chronic pain in later life and strategies to prevent its onset in susceptible individuals.

Significance statement: Increasing evidence supports a significant association between early-life stress and adversity with an increased incidence of chronic pain in later life. This manuscript reviews the clinical and preclinical data linking early-life psychological stress to the risk of chronic pain in later life, examines possible mechanisms underlying this association, and provides directions for future research. Greater understanding of the impact of early-life stress may inform the development of personalized treatments for chronic pain in later life and strategies to prevent its onset in susceptible individuals.

Introduction

Chronic pain is defined as pain lasting for longer than 3 months and the average duration of pain in chronic pain patients is 7 years (Breivik et al., 2006). The protracted nature of chronic pain results in substantial emotional distress and reduced quality of life (Hart et al., 2000). The cardinal signs of chronic pain typically include persistent pain, hyperalgesia (enhanced pain to a normally painful stimulus), and allodynia (pain to a normally innocuous stimulus). Increasing evidence supports a significant association between early-life stress and adversity with an increased incidence of chronic pain in later life (Afari et al., 2014; Barreau et al., 2007; Fillingim and Edwards, 2005; Low and Schweinhardt, 2012). One of the challenges in interpreting these studies, however, is that of disaggregating the effects of physical versus psychological stress. This is an exceptionally difficult task as physically stressful, traumatic or painful events can have a profound psychological impact. Even when discrete events can be separated into physical or psychological impacts, it is virtually impossible to control all potential confounds that may subsequently occur – ranging from further (cumulative) trauma, to the effects of substance use, nutrition, activity level, other medical conditions and so on. These events occur against a backdrop of varying levels of inherited vulnerability for chronic pain and a social and cultural context. Thus, we are reliant on population-level studies to identify macro-level indicators of risk, while we look to clinical and animal studies to understand potential mechanisms to explain these associations. This review examines the clinical and preclinical data linking early-life psychological stress to the risk of chronic pain in later life, the proposed neurobiological mechanisms underlying this association and directions for future research. We do not believe it is possible to state that psychological stress is the sole causal agent in the development of subsequent chronic pain. Almost all clinical and population studies have multiple confounds; however, here we present

evidence of possible mechanisms to link psychological stress and adversity in childhood with an increased risk of chronic pain in adult life.

Does early-life psychological adversity alter pain processing and/or confer a risk for chronic pain?

It is well established that painful physical events and procedures in neonates induce long-lasting alterations in pain processing which extend into adulthood (for reviews see Beggs, 2015; Fitzgerald and Beggs, 2001; LaPrairie and Murphy, 2010; Schwaller and Fitzgerald, 2014), with increasing evidence indicating that stress also plays a key role. A meta-analysis by Davis and colleagues revealed that individuals who report childhood abuse or neglect have more pain symptoms compared to those not exposed to such trauma, and similarly, that chronic pain patients are more likely to report childhood trauma (Davis et al., 2005). A range of psychologically-traumatic experiences has been studied such as childhood neglect, emotional abuse, poverty, and familial separation or parental death. However, across these studies, there is considerable variation in the age at which the experience occurs, the nature of the event, and the frequency and duration of these experiences.

If childhood psychological adversity is associated with more physical pain complaints and an increased incidence of chronic pain in later life, does this mean that there is a fundamental perturbation in nociceptive processing in these individuals? There are limited and often conflicting data on whether childhood trauma results in altered pain processing in later life, and studies to date often group psychological and physical stress together. Females with a history of sexual abuse exhibited lower pressure pain thresholds and a characteristic tendency to set lower standards for judging stimuli as noxious compared to those without a history of abuse (Scarinci et al., 1994). Patients with a functional gastrointestinal disorder and a history of sexual (but also physical) trauma exhibited greater temporal summation (increased pain to repetitive painful stimuli: an index of central sensitization), increased number of pain sites

and greater disability compared to patients without a history of trauma and healthy controls (Sherman et al., 2015). Yet, it has been reported that healthy individuals (no pain disorder) with a history of sexual and physical abuse had decreased sensitivity to repetitive noxious thermal stimulation (i.e. *less* temporal summation) (Fillingim and Edwards, 2005). These studies highlight differences in pain processing between patients with and without a functional painful (gastrointestinal) disorder but had been exposed to childhood trauma.

Interestingly, in a community-based sample of 62 females, emotional abuse (but not physical abuse or neglect, sexual abuse or emotional neglect) resulted in reduced heat pain tolerance, reported as an affective component of pain, but no change in pain intensity ratings, a sensory measure of pain (Pieritz et al., 2015). In contrast, it has been reported that the perception of pain associated with rectal distension did not differ between women with a history of sexual abuse and controls (Whitehead et al., 1997) and that thermal or ischemic pain tolerance or thresholds are unchanged in individuals with a history of sexual and physical abuse compared to controls with no abuse history (Fillingim and Edwards, 2005). Thus, the relationship between childhood adversity and pain processing remains unclear. Future studies should assess the emotional/affective component of pain when measuring experimental pain in individuals with a history of childhood adversity. In addition, further studies comparing the effects of psychological vs. physical stress on pain responding are required. Although experimental pain studies can be useful to detect alterations in sensory and nociceptive processing, this measure of pain differs significantly from the experience of clinically-reported chronic pain. Experimental pain is predictable; subjects are informed that no tissue damage will occur and maintain control over stopping the stimulation; and acute experimental pain does not have the emotional, cognitive, social and behavioral factors that accompany a chronic pain condition (Moore et al., 2015).

A number of retrospective studies have identified that childhood adversity is associated with chronic pain in later life. Using the World Mental Health Survey, Von Korff et al (2009) reported progressively increased risk of adult arthritis based on the number of childhood psychosocial stressors (including sexual and physical abuse, death of a parent, divorce, and family violence) in a population across the Americas, Europe and Asia. This study showed that sexual abuse was associated with the greatest risk of adult onset arthritis (1.64 hazard ratio) and physical abuse was associated with a (1.42 hazard ratio); as sexual and physical abuse both have physical and psychological components, it is difficult to delineate the contribution of each type of trauma. Scott et al (2011) investigated whether childhood adversity and early-onset mental disorders are associated with increased risk of a range of chronic conditions (asthma, diabetes, arthritis, chronic spinal pain, chronic headache) in a sample of more than 18,000 people across 10 countries. A history of three or more childhood adversities was associated with greater susceptibility to these conditions, even when controlling for current mental disorder. In particular, neglect, family violence, abuse or family criminal behavior were strongly associated with symptomatic pain conditions. Furthermore, Stickley and colleagues (2015) recently reported significant associations between child sexual abuse and adult onset chronic pain in a Japanese population, with a greater number of childhood adversities being associated with a higher risk of adult chronic pain. These studies indicate a cumulative risk of developing painful conditions arising from repeated adverse experiences during childhood. The strengths of these retrospective studies include the large sample size, the range of childhood adversities surveyed, and the culturally diverse population examined.

However, a significant limitation of retrospective studies identifying a correlation between childhood adversity and adult ill-health is the possibility of recall bias (McBeth et al., 2001). However, this bias is not that people with adult ill-health tend to over-report

childhood adversities. Rather, those free of pain tend to under-report the occurrence of childhood adversity, thus magnifying the observed relationship between childhood events and subsequent chronic pain (McBeth et al., 2001) and highlighting the importance of well-controlled prospective studies. One such prospective study used the 1958 British Cohort Study to examine the impact of life experiences before the age of 7 on subsequent chronic widespread pain at 45 years of age (Jones et al., 2009). Several psychologically-stressful events in early childhood (such as having resided in institutional care, maternal death and familial financial hardship) predicted chronic pain later in life. Of interest, children who had been hospitalized following a car accident were significantly more likely to have chronic widespread pain, although other physical trauma such as surgery, was not associated with chronic pain in adulthood (Jones et al., 2009). The authors of this study suggest that the psychological sequelae associated with traffic accidents may play a role in the development of chronic pain (Jones et al., 2009). However, while prospective studies address the issue of recall bias, there are still major challenges associated with studies of this nature. The quality of data may vary; attrition is typically very large; and multiple other life events may have contributory effects that are difficult to identify, define and measure. Although it must be acknowledged that much more research is required, the current clinical data do indicate support for an association between early-life psychological stress and increased risk of chronic pain in later life.

Preclinical evidence for a long-lasting effect of early-life stress on nociceptive behavior

Rodent models provide an important means of examining potential neurobiological mechanisms underlying the association between early-life stress and pain in later life [see Table 1 for summary of the literature]. Animal studies are particularly useful as the age at which the stress occurs, the nature of the event(s), and the frequency and duration of these episodes can be controlled for. Mother-infant interactions provide a fundamental role in

providing optimal conditions for normal brain development, regulating the behavior and physiology of the pup by influencing sensorimotor, thermal and nutrient-based processes (Hofer, 1994). The manipulation of mother-pup interactions is widely used to model early-life stress in rodents and is performed during the first 2 weeks of life (Cirulli et al., 2009; Marco et al., 2011), a critical period in the development of nociceptive, sensory, and emotional functions (Ellenbroek et al., 2005; Fitzgerald, 2005). During this sensitive developmental window, but not later, adverse events have long-lasting programming effects, as neuronal pathways are shaped by experience and are vulnerable to abnormal perturbations (Hensch, 2004; Rice and Barone, 2000). The most commonly used models of early-life stress are maternal separation (MS), which involves repeated episodic removal of the pup from the dam for 2-3h period from P1-14, and maternal deprivation (MD), which involves a single 24 hour period of separation typically at PND 9 (Ellenbroek et al., 2005; Vetulani, 2013; Viveros et al., 2009). Both paradigms result in disruptions of maternal care thus involving a social/emotional insult, as well as a nutritional and temperature challenge. An alternative method of examining early-life stress, without the confounding variables of nutritional and temperature deficits, is the neonatal limited bedding (NLB) model. This is performed by providing reduced nesting material to mother and pups from P2-9 resulting in unpredictable and variable maternal care, thus proposed to mimic a neglectful parent (Avishai-Eliner et al., 2001; Ivy et al., 2008). Such disruptions of mother-offspring interactions during the critical first 2 postnatal weeks induce alterations in neuroendocrine, behavioral and neurochemical processes in the offspring that can be observed post weaning through to adulthood (for review see De la Fuente et al., 2009; Levine, 2005; Schmidt et al., 2011; Viveros et al., 2009).

A paucity of studies has investigated the effects of early-life neonatal stress on nociceptive processing and responding. Nociceptive behaviour is evaluated in rodents primarily using reflexive-based assays that measure the latency to respond to a thermal (e.g.

heat source) or mechanical (e.g. von Frey hair) stimulus applied to the hind-paw or tail. Visceral pain is commonly assessed using colorectal distension, which involves expansion of a balloon inserted into the colorectal cavity and measurement of the threshold pressure and number of contractions. Inflammatory persistent/chronic pain is most commonly modeled in rodents by intraplantar administration of a noxious substance (e.g. formalin, Complete Freund's Adjuvant, prostaglandin or carrageenan) and assessment of spontaneous pain behavior (e.g. licking of injected paw) or hypersensitivity to mechanical or thermal stimuli. Neuropathic pain is a devastating, intractable condition arising from damage or dysfunction of the nervous system that can be modeled in rodents by inducing experimental trauma (e.g. ligation) to peripheral or spinal nerves. [For an in-depth review of animal models of pain, see Burma *et al.* in the current issue]. In the sections that follow, we will review the current literature on the effects of early-life psychological stress on nociceptive responding during adulthood in rodents.

- *Prolonged early-life psychological stress and nociceptive processing*

Maternal deprivation (MD) or separation (MS) models of early-life psychological stress induce sensorimotor-, thermal- and nutrient-deprivation, which may influence the development of nociceptive pathways. For example, low intensity tactile inputs play a role in the development of nociceptive pathways in early-life (Waldenstrom et al., 2003) and as such, the lack of stimulation during the separation period and altered maternal care in the post-separation period may adversely affect such nociceptive circuits. Studies employing MS or MD have primarily examined sensory or visceral nociceptive thresholds (Table 1). Work from our group has demonstrated that MD results in heat hypoalgesia and mechanical allodynia in adult female, but not male, rats, and has no effect on nociceptive responding to a cold innocuous stimulus in either sex (Burke et al., 2013). These data indicate possible sexually-dimorphic changes in nociceptive circuitry and/or the processing of nociceptive

stimuli following this form of early-life stress. In comparison, a greater number of studies have examined the effect of MS on nociceptive thresholds with reports of increased (Coutinho et al., 2002) and decreased (Stephan et al., 2002) thermal heat thresholds in the tail-flick and hot-plate tests, respectively, although a number of studies indicate no effect of MS on thermal or mechanical nociceptive behavior during adulthood (Bernardi et al., 1986; D'Amato et al., 1999; Kalinichev et al., 2001; Lariviere et al., 2006; Uhelski and Fuchs, 2010). Brief MS plus a mild but repeated pain (saline i.p. injection) has been shown to result in increased thermal nociceptive thresholds (Pieretti et al., 1991). Taken together and including the results of a recent comprehensive meta-analysis, the data indicate that MS in rodents primarily results in heat hypoalgesia in later life (Chen and Jackson, 2016). In comparison, neonatal isolation, which in contrast to MS, involves separating the pups individually from the dam for a period 1 hour per day from PND 2–9, results in unchanged (although tended to be reduced) (Imanaka et al., 2006) or reduced (Imanaka et al., 2008) latency to respond in the hot plate test (Table 1), indicating that this type of early-life stress results in slight thermal hyperalgesia in adult rats. Thus, the effects of early-life stress on nociceptive thresholds to thermal stimuli in adulthood may depend on the model under investigation (MD, MS or neonatal isolation) and the means of nociceptive assessment (tail flick, hotplate etc.). Only one study has compared the effect of MS in two different rat strains, revealing MS-induced thermal hyperalgesia in Lewis, but not Fisher 344, rats (Stephan et al., 2002), indicating a possible contribution of genotype to altered thermal nociceptive threshold in animals exposed to MS.

In comparison to the varied effect of early-life stress on somatic sensory thresholds, MS consistently results in visceral hypersensitivity in rodents. As such, the MS model is now considered a clinically-relevant model of irritable bowel syndrome (IBS) (O'Mahony et al.,

2011), allowing in-depth investigation into the brain-gut axis, the mechanisms mediating visceral hypersensitivity, and potential pharmacological interventions. This review will refrain from providing an appraisal of visceral hypersensitivity in the MS model as this has been covered in detail in several excellent reviews (Chaloner and Greenwood-Van Meerveld, 2013; O'Mahony et al., 2011; Theodorou, 2013). However, relatively few studies have examined the effect of early-life stress on nociceptive behavior in other persistent pain models.

In inflammatory pain models, MS rats were shown to not differ from controls in terms of symptom development or severity in the adjuvant-induced arthritis model (Lariviere et al., 2006), nor was mechanical allodynia altered following intraplantar carrageenan administration (Uhelski and Fuchs, 2010). However, in the formalin test of inflammatory pain, MS rats exhibit either no change (Lariviere et al., 2006) or enhanced (Uhelski and Fuchs, 2010) nociceptive behavior. Differences in duration and timing of separation, strain of rat, or concentration of formalin used may account for the discrepancy between these latter studies. Due to the limited number of studies in this area, it is difficult to draw definitive conclusions. However, it would appear that early-life stress enhances nociceptive behavior in some, but not all, inflammatory pain models – thus, further studies are required to clarify the effect of early-life stress on inflammatory nociception.

Recently, pain research has been shifting in focus from examining only the sensory component of pain, towards the emotional component of pain, arguably the more debilitating aspect of pain. The combination of the formalin test of inflammatory pain and place escape avoidance paradigm (PEAP) allowed Uhelski and colleagues to evaluate the effect of MS on the affective/supraspinal processing of inflammatory nociception (Uhelski and Fuchs, 2010). MS rats tended to spend more time in the aversive light side of the PEAP chamber and exhibited enhanced formalin-evoked nociceptive behavior in the latter part of the trial when

compared to non-MS counterparts, results which the authors used to conclude that early-life stress results in enhanced negative affective behavior to noxious inflammatory stimuli. Such an effect may not be altogether surprising given that MS rodents exhibit enhanced negative affective behavior under non-noxious aversive conditions (Millstein and Holmes, 2007; Slotten et al., 2006). Future research should aim to characterize the impact of early-life stress on emotional pain using operant-conditioning paradigms, such as conditioned place avoidance, which may clarify whether early-life stress preferentially enhances affective-motivational vs. sensory-discriminative aspects of pain.

Even fewer studies have investigated the effect of early-life stress on neuropathic pain-related behavior. Our group provided the first evidence that when compared to non-stressed controls, adult female, but not male, MD rats exhibit enhanced mechanical and cold allodynia following L5-L6 spinal nerve ligation (Burke et al., 2013), a well recognized model of neuropathic pain (Kim and Chung, 1992). These data indicate sexually-dimorphic effects of early-life stress on neuropathic pain-like behavior. More recently, it has been shown that male and female mice exposed to the combination of MS and social isolation exhibit enhanced thermal and mechanical hypersensitivity following peripheral nerve injury in adulthood (Nishinaka et al., 2015). While these two studies were carried out in rats and mice, respectively, and thus the impact of MD/MS on each species may be slightly different, it is possible that females may be more susceptible to the sensitizing effects of early-life psychological stress on nociceptive processing and/or that males may require additional stress (i.e. social isolation) to induce long-term alterations in nociceptive pathways. Further studies are required to determine if similar effects are observed in other models of early-life psychological stress, however, the current data indicate that the combination of early-life stress and peripheral nerve injury results in enhanced pain-related behavior in both rats and mice.

The neonatal limited bedding (NLB) model is a naturalistic model of early-life stress, induced by providing reduced nesting material that results in unpredictable and variable maternal care (Avishai-Eliner et al., 2001). Several studies have demonstrated that similar to MS, NLB results in enhanced visceral hyperalgesia in adulthood (Guo et al., 2015; Holschneider et al., 2016; Prusator and Greenwood-Van Meerveld, 2015), with limited studies examining the effect on somatic nociceptive thresholds or in chronic pain models. Adult males, but not females, exposed to NLB exhibit mechanical hyperalgesia (Prusator and Greenwood-Van Meerveld, 2015). Administration of the inflammatory mediator prostaglandin E2 into the skin or muscle resulted in an enhanced and prolonged hyperalgesic response in adult NLB rats (Green et al., 2011). NLB rats exhibit lower mechanical thresholds of the skeletal muscle and enhanced conduction velocity of muscle nociceptors (Green et al., 2011). Interestingly, sound stress during adulthood exacerbates NLB-induced muscle hyperalgesia, an effect dependent on adrenal medullary hormones and cytokine signaling (Alvarez et al., 2013). Given that early-life stress predisposes to the development of musculoskeletal pain such as fibromyalgia (Low and Schweinhardt, 2012), and that stressful events exacerbate symptoms of this condition (Van Houdenhove et al., 2005), the NLB model may provide a useful and clinically-relevant model that will facilitate examination of the neurobiological mechanisms and identification of novel therapeutic targets for this chronic pain disorder.

Neurobiological mechanisms underlying the association between early-life stress and chronic pain (clinical and preclinical evidence)

Although the neurobiological mechanisms mediating the relationship between early-life stress and chronic pain in later life are unknown, clinical and preclinical data have

suggested a role for several systems in this association. Several excellent reviews have described a variety of potential mechanisms (including sex hormones, structural and functional alterations, and allostasis) by which psychological stress in childhood may lead to pain disorders in adulthood (Barreau et al., 2007; Chaloner and Greenwood-Van Meerveld, 2013; Low and Schweinhardt, 2012; Tietjen, 2016; Tietjen and Peterlin, 2011; Von Korff et al., 2009). As such, this review will highlight the data supporting a role of some of the most widely regarded intermediaries such as the hypothalamic-pituitary-adrenal (HPA) axis-stress response, monoamines, endogenous opioids, endocannabinoids, inflammatory mediators and epigenetic mechanisms, in the relationship between early-life psychological stress and chronic pain.

- *The HPA axis and the stress response*

A wealth of clinical and preclinial animal studies demonstrates that early-life stress is associated with long-term alterations in the responsiveness of the hypothalamic-pituitary-adrenal (HPA) axis, including decreased glucocorticoid receptor (GR) binding, impaired negative feedback sensitivity, increased central corticotrophin-releasing hormone (CRH) levels, increased plasma adrenocorticotrophic hormone (ACTH) and corticosterone responses to stress (for review see Heim et al., 2008; Maccari et al., 2014). Elegant studies by Grunau *et al.* have revealed that higher neonatal pain-related stress in pre-term infants is associated with altered HPA axis functioning at 3, 8 and 18 months and 7 years of age (Brummelte et al., 2015; Grunau et al., 2013; Grunau et al., 2007; Grunau et al., 2005) and the number of neonatal invasive procedures was associated with reduced white and gray matter development (Brummelte et al., 2012), highlighting the legacy of such noxious events in early life on the stress response and the developing brain. Dysfunction of the HPA axis, ranging from increased cortisol to hypocortisolemia, has also been reported in chronic pain patients such as those suffering from fibromyalgia, chronic back pain and rheumatoid arthritis

(Catley et al., 2000; Riva et al., 2010; Vachon-Presseau et al., 2013). Thus, dysfunction of the HPA-stress response following early-life stress may impact on nociceptive circuitry leading to enhanced susceptibility to the development of chronic pain in later life.

Acute stress, HPA axis activation and elevated levels of CRH are well known to elicit analgesia both in humans and rodents (for review see Butler and Finn, 2009; Schafer et al., 1997). Thus, in contrast to reports of heightened nociceptive behavior in rodent models of early-life stress, elevated CRH/HPA axis activity associated with these models may be expected to induce an analgesic rather than pro-nociceptive effect. However, chronic (rather than acute) stress tends to be pro-nociceptive (Jennings et al., 2014; Olango and Finn, 2014). For example, rodents chronically treated with corticosterone exhibit cold allodynia and heat hyperalgesia (Hache et al., 2012) and prior corticosterone administration enhances mechanical allodynia to a noxious inflammatory stimulus (Loram et al., 2011). As such, altered programming of the HPA axis by early-life stress may result in chronically elevated CRH/corticosterone and heightened pain responses, or compromised stress-induced analgesia under acutely stressful conditions.

Removal of the adrenal medulla has been shown to not alter NLB-induced hyperalgesia but prevent its exacerbation by sound stress in adulthood, an effect mimicked by chronic administration of adrenaline to NLB rats (Alvarez et al., 2013). Recent studies have highlighted a role for corticosterone in the amygdala in mediating mechanical allodynia and visceral hypersensitivity in rats (Myers and Greenwood-Van Meerveld, 2010, 2012). In addition, MS results in an up-regulation of thalamic CRH mRNA, protein and receptor levels in response to noxious colorectal distension (Tjong et al., 2010), and a number of alterations in HPA axis-related genes in the hypothalamus and hippocampus in response to noxious vaginal distension (Pierce et al., 2014). Thus, via modulation of neural substrates of the pain

matrix, enhanced HPA axis activation in response to early-life psychological stress may program pain circuitry towards heightened nociceptive processing in later life.

- *The monoamine neurotransmitters: classical mediators of stress and pain*

The monoamine system has a well-recognized role in the modulation of stress, emotion and nociception, and thus is a likely mediator in the relationship between early-life stress and pain. Accordingly, in addition to elevating mood and treating depression, tricyclic antidepressants are one of the first line treatments for chronic neuropathic pain (Finnerup et al., 2005). Furthermore, recent clinical data has demonstrated higher methylation of the serotonin transporter gene (SLC6A4) promoter in children that were born very pre-term compared to full-term controls at age 7, an effect associated with neonatal pain-related stress and behavioral problems (Chau et al., 2014), highlighting how early life events may epigenetically imprint on neurotransmitter function and behavior. The stress hyporesponsive period during which preclinical early-life stress paradigms are performed is also a critical window in the development of dopaminergic and serotonergic systems (Galineau et al., 2004). Numerous studies have reported effects of MS/MD on monoamine levels, receptor function, receptor density and turnover both peripherally and centrally, although several brain-region specific changes have been reported. MD leads to increased serotonergic (Rentesi et al., 2010) and dopaminergic (Ellenbroek et al., 1998) activity in adulthood and in adolescence (Llorente et al., 2010). MS leads to increased serotonin and its metabolites in the dorsal raphe nucleus and nucleus accumbens of females (Arborelius and Eklund, 2007) and increased the serotonin ratio in the brainstem, but not in the frontal cortex, hippocampus or hypothalamus (O'Mahony et al., 2008). In nociceptive paradigms, serotonin levels have been shown to be higher in the spinal cord of MS rats after noxious colorectal distension (Ren et al., 2007) and administration of imipramine, a tricyclic antidepressant that increases monoamine levels, reversed thermal hyperalgesia induced by MS (Stephan et al., 2002).

Thus, disruptions in monoaminergic neurotransmission in CNS areas that modulate both pain and mood following early-life stress may account, at least in part, for the altered nociceptive responding observed in later life.

- *Endogenous Opioid System*

A number of studies have implicated opioid signaling in the altered nociceptive behavior associated with early-life stress. The endogenous opioidergic system is a well-recognized modulator of both pain and emotion (Filliol et al., 2000; Herz and Millan, 1990), and endogenous opioids and their receptors are present in the brain at birth (Rius et al., 1991; Tsang et al., 1982). Long-lasting alterations in endogenous opioid tone have been reported following MS. For example, MS rats exhibit reduced overall brain opioid receptor binding (Bernardi et al., 1986), although increased μ-opioid receptor expression in the medial preoptic area and increased δ-receptor density in the basomedial amygdala of MS rats has also been reported (Ploj and Nylander, 2003; Weaver et al., 2007). Furthermore, MS rats exhibit altered expression of the endogenous opioids dynorphin and enkephalin in the hypothalamus, substantia nigra, amygdala and periaqueductal gray (Ploj et al., 2003), key brain areas in the modulation of emotional and nociceptive processes. In response to exogenous opioid administration, MS rats exhibit higher levels of morphine tolerance and more withdrawal symptoms (Kalinichev et al., 2001) and morphine is less potent at inducing thermal antinociception in adult male MS rats (Bernardi et al., 1986; Kalinichev et al., 2001; Weaver et al., 2007). The opioid receptor antagonist naloxone exacerbates stress-induced visceral hyperalgesia in MS rats and can prevent stress-induced analgesia in control, but not MS, rats (Coutinho et al., 2002). Similarly, the combination of a mild but repeated stress (brief MS for 10 min PND 0-21) plus a mild but repeated pain (saline injection) results in increased thermal pain thresholds, accompanied by increased plasma endorphin levels, effects prevented by pretreatment with the opioid antagonist naloxone (Pieretti et al., 1991). Thus,

the data suggest that long-term alterations in opioidergic tone may in part underlie enhanced nociceptive behavior in rodents following MS and other forms of early-life stress, and may explain pain hypersensitivity in individuals exposed to childhood adversity.

- *The endocannabinoid system*

The endogenous cannabinoid (endocannabinoid) system is developed at birth in humans and rodents and evidence suggests a role for this system in brain development and maturation (Berrendero et al., 1999; Long et al., 2012; Mato et al., 2003). Although no studies to date have implicated the endogenous cannabinoid system in altered nociceptive responding associated with early-life stress, it is an important neural substrate that warrants investigation. Increasing evidence over the past two decades has shown that the endocannabinoid system regulates pain and is modulated by stress, and cannabinoid ligands are antinociceptive in acute, inflammatory and neuropathic pain models [for reviews see (Corcoran et al., 2015; Fitzgibbon et al., 2015; Hill, 2015; Hohmann and Suplita, 2006; Jennings et al., 2014; Manzanares et al., 2006). Thus, deficits in endogenous cannabinoid tone have been suggested to underlie hyperalgesia in several conditions. Early-life stress has been shown to result in immediate and long-lasting alterations in the endocannabinoid system. For example, MD results in sexually-dimorphic decreases of cannabinoid receptor type 1 (CB_1) receptor expression and increases in CB_2 receptor expression and altered levels of enzymes involved in the biosynthesis and degradation of endocannabinoids in the hippocampus of P13 rodents (Suarez et al., 2009; Suarez et al., 2010). In adolescence, a number of genes encoding components of the endocannabinoid system were increased in the frontal cortex of males and the hippocampus of females exposed to MD (Marco et al., 2014) and changes in the endocannabinoid system have been reported in the nucleus accumbens and frontal cortex of MS rats (Romano-Lopez et al., 2015). Furthermore, early life stress is well

known to induce depressive- and anxiety-like behavioral phenotypes in adulthood (Daniels et al., 2004; Llorente et al., 2007; Marco et al., 2015) and recent studies from our laboratory have demonstrated an important role for anandamide activation of CB_1 receptors in the rostral ventromedial medulla in a rat model of hyperalgesia associated with depression/anxiety (Rea et al., 2014). Thus, although further studies are required it is possible that early-life stress-induced changes in the endocannabinoid system in pain-related brain regions may lead to alterations in nociceptive responding and the enhanced susceptibility to chronic pain.

- *Inflammation and immune mediators*

Increasing evidence indicates that childhood adversity is associated with activation of the immune system. A recent systematic review of the literature supports the presence of a proinflammatory profile in individuals with a history of early-life adversity (Coelho et al., 2014). Furthermore, microglial cells and immune mediators such as cytokines are well-recognized modulators in the development of central sensitization, hyperalgesia and allodynia (Latremoliere and Woolf, 2009; Watkins et al., 1995). Investigating the relationship between early-life adversity, alterations in immune mediators and pain has revealed that in a study of 92 individuals, levels of C-reactive protein were directly associated with somatic pain complaints; however, this relationship was not impacted by self-reported early-life adversity (Carpenter et al., 2012). However, further studies are required to determine whether other inflammatory markers may mediate the impact of early-life adversity on pain, in healthy individuals and in those with chronic pain conditions. Recent clinical studies have also shown that the minor allele of the inflammatory gene *NFKBIA rs2233409* was associated with higher secretion of inflammatory cytokines, and boys born very preterm with this minor allele for *NFKBIA* exhibited greater neonatal pain-related stress and lower cortisol at 7 years old compared with full-term equivalents (Grunau et al., 2013). Furthermore, imaging studies

have revealed that early-life stress is associated with thinning of the subgenual cingulate cortex in females who had both irritable bowel syndrome and the minor IL-1β allele (Gupta et al., 2015). Taken together, these studies indicate a likely link between genetics, early-life stress, inflammation, and altered brain structure; however, further studies are required to clarify this relationship.

Preclinical studies allow for the in-depth investigation of this association and a large body of data now supports a dysregulation of the immune system following early-life stress in several animal models. A recent review of the literature concluded that early-life stress results in a suppression of inflammatory markers during development but causes a shift towards a proinflammatory state in later life (Ganguly and Brenhouse, 2015). Such a dysregulation in inflammatory responses in early-life may sensitize the immune system via "priming" or "activation" of microglia, resulting in exaggerated and prolonged responses to ensuing noxious stimulation in later life. Support for this theory arises from literature demonstrating that neonatal intracerebral LPS exposure results in long-lasting hyperalgesia and increased microglial activation in the CNS in adulthood (Wang et al., 2011), and chronic hind-paw inflammation in early-life results in enhanced nociceptive behavior to inflammatory stimuli in later life (Hohmann et al., 2005). Furthermore, MS animals exhibit enhanced immunological and behavioral responses to endotoxin administration (Avitsur et al., 2013; Avitsur and Sheridan, 2009; Meagher et al., 2010; O'Mahony et al., 2009), and MS and MD enhance susceptibility to experimental colitis (Milde et al., 2004; Veenema et al., 2008) and experimental autoimmune encephalitis (Teunis et al., 2002). Taken together, these data show that early-life stress primes the immune system and enhances susceptibility to inflammatory disease. It is therefore possible that early-life stress may prime glial cells for exaggerated responding to injury in later life.

Alternatively, dysregulation of immune function and the proinflammatory state

observed following early-life psychological stress (Barreau et al., 2004; Dimatelis et al., 2012; Musholt et al., 2009; O'Malley et al., 2011; Reus et al., 2013) may directly impact on peripheral nociceptive processing. Accordingly, NLB rats exhibit increased circulating IL-6 levels, and antisense directed to the IL-6-receptor subunit gp130 prevents NLB-induced muscle hyperalgesia (Alvarez et al., 2013). Genetic silencing of protein kinase C epsilon type (PKC)ε, an important mediator in neuronal plasticity and signaling in activated macrophages, partially reversed the reduction in muscle mechanical thresholds and completely reversed the prolongation of inflammatory prostaglandin E_2-mediated hyperalgesia (Green et al., 2011). MS-induced visceral hyperalgesia has been associated with increased neuronal nitric oxide synthase in the distal colon (Tjong et al., 2011) and increased expression of the astrocytic excitatory amino acid transporter (EAAT)-1 in the spinal cord (Gosselin et al., 2010), suggesting alterations in glial cell functionality in the MS model that may underlie the visceral hyperalgesia observed in these animals. Supraspinally, work from our group has demonstrated sexually-dimorphic alterations in neuroinflammatory gene expression in brain regions associated with pain and mood in MD rats following the induction of neuropathic pain in adulthood (Burke et al., 2013). MD females with peripheral nerve injury exhibited enhanced mechanical and cold allodynia, an effect associated with reduced TNFα mRNA in the prefrontal cortex and increased IL-6 and TNFα mRNA in the hippocampus. In comparison, MD males with peripheral nerve injury developed allodynia and hyperalgesia to an equal degree as non-stressed males, but displayed reduced IL-6 mRNA in the prefrontal cortex with increased astrocyte activation and IL-1β expression in the hippocampus compared to non-stressed controls (Burke et al., 2013). This study revealed interactions between early-life stress, persistent pain and neuroimmune processes, and highlights the importance of examining sex differences in preclinical research.

While further research is required, these data indicate that stressful experiences in early life adversely impact on a range of physiological processes that may sensitize or modulate emotional and nociceptive circuits, resulting in an enhanced vulnerability towards the development of stress-related illnesses and chronic pain in later life.

- Epigenetic mechanisms

Converging lines of evidence indicate that complex interactions between early life events and gene expression alter brain development (Murgatroyd and Spengler, 2011) and such interactions have been proposed to underlie the association between early-life stress and pain in later life (Low and Schweinhardt, 2012; Tietjen, 2016; Tietjen and Peterlin, 2011). As highlighted in previous paragraphs, early-life stress is associated with alteration in the expression of several genes such as those of the monoamine, opioid, immune and cannabinoid systems. However, epigenetics mechanisms refer to changes in gene function in the absence of DNA sequence changes, and increasing evidence indicates that these mechanisms may influence the phenotypic outcomes of adverse events in early life. Processes carried out by the epigenome include histone modifications (deacetylation or phosphorylation), DNA methylation, and chromatin remodeling. These modifications are stable and may be transferred across generations, but may also be reversed by certain pharmacological agents. Accordingly, histone deacetylase (HDAC) inhibitors have shown promise in the treatment of several clinical pain conditions (Chiechio et al., 2009; Lin et al., 2007). Neonatal pain-related stress and behavioral problems in children that were born very pre-term have been shown to be associated with enhanced methylation of the serotonin transporter gene (SLC6A4) promoter when compared to full-term control children at age 7 (Chau et al., 2014). Trauma-induced demethylation of the gene FKBP5, an important functional regulator of the GR, was found to occur only if trauma occurred in childhood, but

not adulthood (Klengel et al., 2013). This demethylation resulted in increased expression of FKBP5 and an enhanced risk of developing PTSD (Klengel et al., 2013) and FKBP5 which codes for FKBP51 protein, has recently been found to be a critical mediator of chronic pain (Maiaru et al., 2016).

Recent preclinical data has shown that visceral hypersensitivity following MS is accompanied by alterations in histone acetylation in the spinal cord (Moloney et al., 2015). Administration of a HDAC inhibitor in adulthood normalized spinal histone acetylation and the heightened visceral nociceptive response in MS rats (Moloney et al., 2015). Further studies are required to determine if HDAC inhibitors would modulate other changes in nociceptive processing observed following MS or in different models of early-life stress. Low maternal care has been shown to result in anxiety-like behavior, reduced stress-induced corticosterone and altered histone acetylation and transcription factor binding to the GR promoter in the hippocampus (Caldji et al., 2000; Liu et al., 1997; Weaver et al., 2004). Furthermore, these naturally occurring variations in maternal behavior can alter thermal thresholds in adulthood, such that high maternal care increases thresholds to a noxious thermal stimulus when compared to low maternal care counterparts (Walker et al., 2008). Promisingly, the epigenetic changes, i.e. altered histone acetylation and transcription factor binding to the GR promoter in the hippocampus, could be attenuated by pharmacological manipulation of methylation, which resulted in decreased stress-induced HPA axis activation (Weaver et al., 2004; Weaver et al., 2005). Together, epigenetic processes may be a mechanism by which early life events contribute to long-term consequences of psychological early-life stress and may underlie the susceptibility to developing chronic pain in later life.

Synopsis of evidence and directions for future research

Clinical and preclinical evidence demonstrates that early-life stress results in a number of abnormalities that may account for maladaptive development and/or functionality within pain circuitry, enhancing susceptibility to the development of chronic pain in later life. For example, a correlation between early-life events and resting state activity in the salience/executive control network, a network implicated in the pathophysiology of central pain amplification, has been shown in individuals with IBS (Gupta et al., 2014). Furthermore, childhood adversity is associated with altered structure and function of certain brain regions, and changes in stress reactivity (Faravelli et al., 2012; Krugers and Joels, 2014; Maniam et al., 2014; Tottenham and Sheridan, 2009), and thus future studies should assess the emotional/affective component of pain when measuring experimental pain in individuals with a history of childhood adversity. However, investigating the mechanisms responsible for the increased incidence of adult pathologies following early-life stress in the clinical population is difficult given ethical considerations and the inability to control for confounding factors. As such, animal models have proved useful in this regard, revealing a role for a host of neurobiological substrates including the HPA axis, endogenous opioids, endocannabinoids, epigenetic mechanisms and immune mediators. The preclinical data indicate that the effects of early-life psychological stress on nociceptive responding depend on the model under investigation, the intensity of the stress and the context under which nociceptive behavior is examined. In particular, this review has highlighted the limited data examining the impact of early-life stress on the development and expression of clinically-relevant neuropathic and inflammatory pain conditions, an area that warrants further investigation. To facilitate translation to the clinic, it is critical to consider sex differences, a move toward non-reflexive pain assays, and the use of transgenic mice to identify genetic underpinnings. Moreover, further research is required to fully decipher the influence of additional stressful life experiences, sex hormones, and other neurobiological processes in combination with early-

life stress, on nociceptive processing and development, and treatment of chronic pain. Greater understanding of the impact of early-life stress may inform the development of personalized treatments for chronic pain in later life and strategies to prevent its onset in susceptible individuals.

In order to definitively address this issue in future research, a paradigm shift to a "bottom up approach" may be needed, thereby moving away from top-down epidemiological studies to more individual risk-targeted research. Since there is significant variability in individual responses to stress arising from a complex interplay of vulnerability and protective mechanisms, we are in effect aiming to identify a phenotype for subsequent development of chronic pain following exposure to psychological stress. This will require the identification of children who experience psychological adversity, following those children longitudinally and looking for neurobiological changes that can be causally implicated in the development of chronic pain in the same individuals. Such neurobiological alterations could then (a) provide a basis for biomarker-based prediction, diagnosis or stratification of chronic pain associated with early life stress or (b) be targeted directly by personalized medicines that can be tailored to reverse or prevent the specific neurobiological alterations in individual patients. Personalized treatments take account of epigenetic variables, lifestyle and environment and offer the potential to both identify personalized risk of future illness and personalized likelihood of responding to a therapy or combination of therapies (Bruehl et al., 2013). This is a radical shift in how these questions have been addressed until now, but may ultimately be a more productive line of inquiry.

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