

Contents lists available at [ScienceDirect](https://www.sciencedirect.com)

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Review

Stressful experiences in youth: “Set-up” for diminished resilience to chronic pain

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ARTICLE INFO

Keywords:

Pediatric pain
Stress
Immunological
Cortisol
Brain
Pain chronification

ABSTRACT

Chronic pain in youth is common, with prevalence rates in some reports exceeding 50%. Given the plasticity of brain systems in youth and their general level of activity, the underlying processes relating to the evolution of chronic pain may be different from that observed in adults. One aspect that affects brain development is childhood stress. Preliminary research indicates that maladaptive responses to stressful events that induce biological and psychological inability to adapt may be related to pain chronicity in youth. This relationship is particularly notable given the high rates of exposure to stressful events in pediatric pain populations. A review of the literature was performed in the areas of biological, cognitive, psychological and social processes associated with chronic pain and psychological stress and trauma in youth and adult populations. The current review presents a theoretical framework, adapted from McEwen's model (1998) on stress and allostatic load, which aims to outline the potential connection between exposure to stressful events and pediatric chronic pain. Avenues for future investigation are also identified.

1. Introduction

Physiological adaptation to stress, known as allostasis, is a complex process by which multiple physiological systems are involved, including neuroendocrine, neurological, cardiovascular, and metabolic, among others, and respond to a stressor to adapt and reverse the individual to a homeostatic state (i.e., physiological stability). For most individuals, a certain level of stress is expected, and the body is successfully able to adapt in order to maintain homeostasis. However, with repeated exposure to stressful or traumatic experiences, the body's response to stress can turn maladaptive (McEwen, 1998a) and fail to produce a reversal of normally adaptive processes back to baseline. Maladaptive response to stress is known as allostatic load (AL); a concept representing the physiological “wear and tear” that the stress may exert on the body over time (Juster et al., 2010). Such maladaptation to stress may lead to increased risk for disease and/or mortality across a wide spectrum of diseases (i.e., cancer, diabetes, asthma, etc (Danese and McEwen, 2012)). Recent research indicates that chronic pain (a potential stressor itself) may be among those disease states stemming from AL. Several neuroendocrine

and brain-based mechanisms, known to be affected by chronic stress, also play a significant role in pain processing. For example, adults with chronic pain have increased biomarkers of stress such as cortisol as well as altered brain systems that may contribute to or be affected by stress hormones (see (Vachon-Presseau et al., 2013a; Vachon-Presseau et al., 2013b)). Similarly, research in non-pain youth populations indicates that trauma and stress-exposed youth evidence altered physiological stress reactivity (Carion et al., 2007; Jessop and Turner-Cobb, 2008). However, the potential role of brain-based mechanisms of stress in pediatric pain remains poorly understood.

Within the past several years, various reports (Abdallah and Geha, 2017; Romero-Grimaldi et al., 2015; Borsook et al., 2012) have highlighted aspects of how stressful events and chronic pain may interact in youth or adult populations, such as via glucocorticoid release and/or altered cognitive processes (i.e., threat learning) (Timmers et al., 2019; Nelson et al., 2016), HPA-axis variability (Nelson et al., 2016; McInnis et al., 2019), hippocampal volume (Vachon-Presseau et al., 2013a), etc. However, no research to-date has put forth a comprehensive model of stress and pain, taking into account psychosocial, cognitive,

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¹ Dr. Bruce McEwen passed away on January 2nd, 2020.

<https://doi.org/10.1016/j.bbih.2020.100095>

Received 4 June 2020; Accepted 7 June 2020

Available online 11 June 2020

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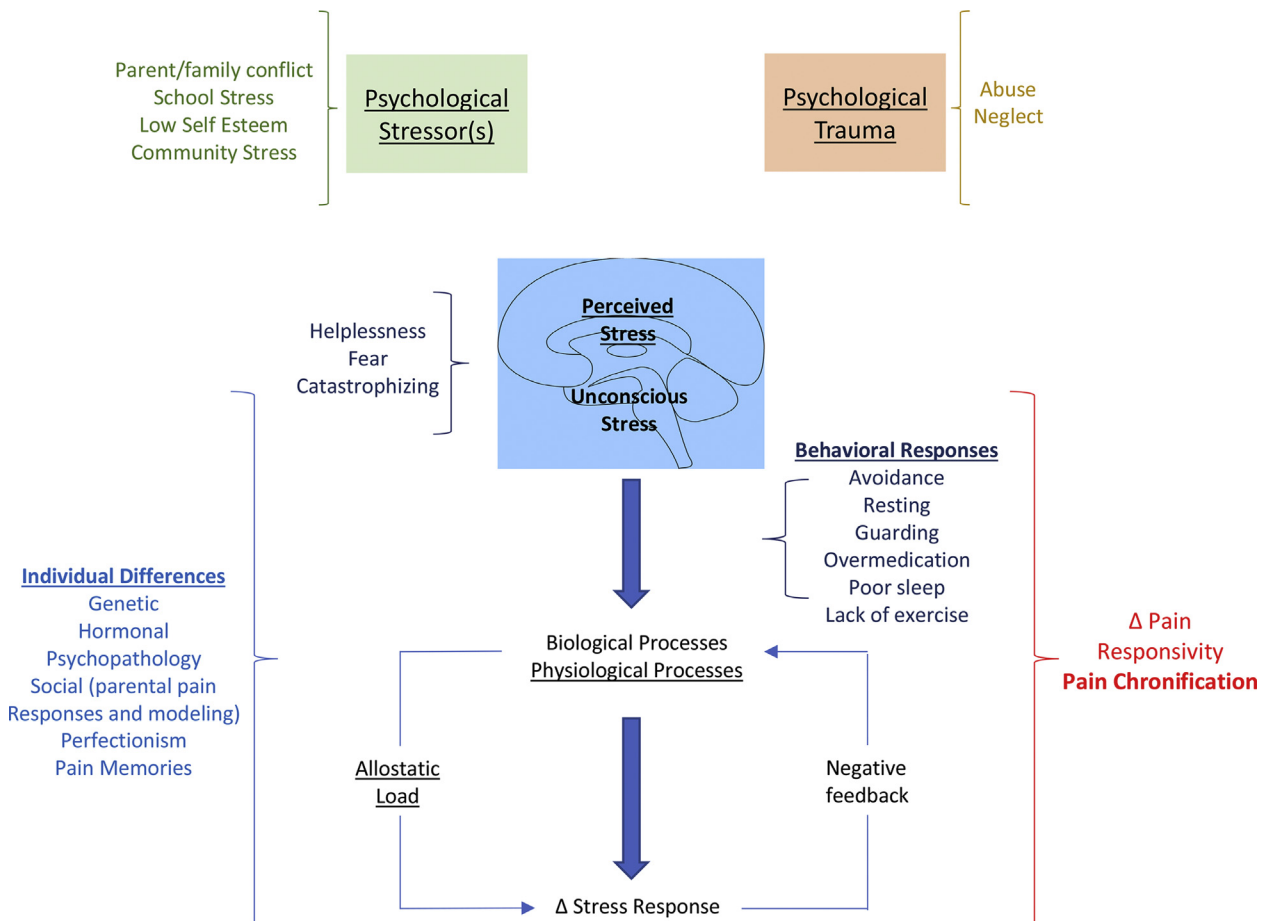
neuroendocrine, and neurobiological indices. The stress response and allostatic load model put forth by Bruce McEwen (McEwen, 1998b) provides an integrative model of how major life events, stress, and individual factors (e.g., biological, environmental, etc.) can contribute to the development of allostatic load, and in turn, poorer physical health. Several models have also been proposed outlining the potential association between stress and pain (Abdallah and Geha, 2017; Timmers et al., 2019; Hannibal and Bishop, 2014; Chapman et al., 2008; McEwen and Kalia, 2010) in adult and pediatric populations. However, to-date these models have failed to comprehensively identify the unique interplay between physiological, individual, behavioral, and environmental factors and how they may impact levels of adaptation to stress and pain in youth. Applying a theoretical framework to combine these parallel lines of research on the potential association between stressful experiences and pediatric pain and related impairment will provide researchers and clinicians with a greater and more complete understanding of the role that these mechanisms may play in future pain prevention and intervention efforts and guide future research to further this knowledge.

This review is divided into the following sections: (1) Overview of search methods utilized in this review; (2a) Physiological Stress and Adaptation – evaluates the state of the current research on how the experience of psychological stress via subjective experiences of stress and/or objective history of stressful events in childhood may relate to the manifestation and/or chronification of pain in youth using a multifactorial framework; and (2b) A review of psychological stress and

adaptations where we interrogate the concept of how pain itself is a stressor and may contribute to maladaptive processes as a result of allostatic load ; (3) Pain as a Model of Ongoing Stress; (4) We then provide a theoretical model of the interactions of pain and stress where we discuss aspects such as psychological stressors or traumatic life events; conscious and unconscious processes involved in perception of stress and how these may differ across individuals; and (5) Conclude with providing some thoughts on future directions.

2. Methods

A review of the literature was performed in the areas of “chronic stress”; “psychological trauma”; “physiological effects of stress”; “neurobiology of pain”; and “pain and stress”. Primary search engines used included PubMed and Google Scholar. Studies were included in the review if they were completed within the past 10–15 years (to avoid outdated research findings) or if they were seminal works (e.g., one of few available articles on a certain topic, formative examinations of a certain construct/phenomenon, etc.). Studies using both pediatric and adult participants were included (and specified when appropriate in the text) due to the aim of the review being to provide a comprehensive overview of the current literature and due to the lack of extant research within certain areas (e.g., brain structure, physiology, prospective trauma or stress exposure, etc.) in pediatric populations. Results of the literature review are first presented more generally, with an overview of



Note: Original elements of McEwen’s allostatic load model (1998) denoted as underlined text.

Fig. 1. Nelson et al.

Note: Original elements of McEwen’s allostatic load model (1998) denoted as underlined text.

the definitions of stress, psychological trauma, and adverse childhood experiences (ACEs). Research on the physiological effects of stress were then pooled and are delineated in subcategories of neuroendocrine/immunologic and brain structure and function. Finally, the proposed theoretical framework is presented by topic as first outlined in McEwen's model (McEwen, 1998b) and in accordance with the adapted model (Fig. 1).

3. Results

3.1. Psychological stress and adaptation

Stress is generally defined as the subjective experience of an event during which an individual is usually conscious of emotional distress or discomfort (Bijlsma and Loeschke, 2005). Stressful experiences have been conceptualized in the literature across a spectrum of severity to range from the most severe of events: *psychological trauma*, defined by the Diagnostic and Statistical Manual (DSM-5) as “*actual or threatened death, serious injury, or sexual violence*” (Association, 2013) to discrete but less impactful or severe events called *psychosocial “stressors”*, defined as situations in life that may contribute to (e.g., anxiety, depression) or directly precipitate (i.e., Adjustment Disorder) psychological issues. Examples of psychological stressors include divorce (either directly experienced as an adult or as a child with parents who are divorcing), bereavement, geographical move, prolonged health issues, etc (Association, 2013). *Adverse Childhood Experiences (ACEs)* have also become more common in the literature and encompass both psychological trauma such as abuse or neglect and certain stressors such as parent/guardian separation or divorce, mental illness, drug use, or incarceration, or a violent or conflictual home environment (Felitti et al., 1998). It has been well established in the literature that stressful experiences can be significantly associated with a host of psychological issues in youth including anxiety and depression (Pechtel and Pizzagalli, 2011; Hanson et al., 2015) or posttraumatic stress disorder (PTSD) (Wilson and Keane, 2004; Scheeringa and Zeanah, 2001). As a combination of both traumatic and stressful experiences, the concept of ACEs particularly evidences the broad impact of the stress spectrum. Exposure to stressful experiences can also lead to what is known as “diminished resilience”, which is the decreased ability of an individual to emotionally and/or physiologically adapt to or “bounce back” from stressors or external threats (Hawkey et al., 2005).

3.2. Neuroendocrine/immunological changes

Human adaptation to psychological stress or trauma involves a number of physiological processes, including immunological, cardiovascular, pulmonary, metabolic, and neurological systems (McEwen, 1998a; Juster et al., 2010). The prevailing model of physiological adaptation to stress is called *allostasis*, which was first described by Sterling and Eyer in 1988 (McEwen, 1998a; Ramsay and Woods, 2014). It encompasses the process by which the body's neural and neuroendocrine networks successfully adapt to stressful experiences (Ramsay and Woods, 2014) in order to maintain homeostasis, which is the body's physiological stability or equilibrium (i.e., maintenance of regulatory systems (Romero et al., 2009; McEwen and Wingfield, 2010)). However, the ongoing unabated (ongoing - constant or intermittent) physiological demand of stress may contribute to physical illness, via allostatic load, or physiological wear and tear of multiple regulatory systems in response to stress (Juster et al., 2010; McEwen, 2015; Yaribeygi et al., 2017). More generally, exposure to psychological stress or trauma can lead to hyperarousal of the HPA-axis, regulated by the autonomic nervous system. This hyperarousal of the HPA-axis manifests as hyper-responsiveness to stress, both acutely and chronically, a process known as *cross-sensitization* (Belda et al., 2016).

In terms of immunological processes, the brain increases production of pro-inflammatory cytokines such as c-reactive protein (CRP), interleukin-6, tumor necrosis factor-alpha (TNF-a), etc., in response to

acute or prolonged stressors in both children and adult populations (Pay and Shaw, 2019; Slavish and Szabo, 2019; Sibille et al., 2016). Interestingly, retrospective studies in adults also specifically indicate that stressful experiences in youth are significantly associated with systemic inflammation as adults (Slopen et al., 2013) and may predispose individuals to the development of psychopathology, such as depression via release of inflammatory cytokines (Miller et al., 2009). It may be that childhood is a sensitive period that, when combined with significant stress, increases risk for poorer psychosocial and physical health long-term. Few studies have been performed that prospectively examine the predictive power of stressful experiences in childhood. Of the studies that have been done, evidence suggests that even acutely stressful event in middle childhood are predictive of increased inflammation in pre-adolescent and adolescent years (Slopen et al., 2013).

Prominent neuroendocrine hormones that play a role in the adaptation of psychological stress or trauma are glucocorticoids such as cortisol and dehydroepiandrosterone (DHEA) and catecholamines such as epinephrine (E) and norepinephrine (NE) (Juster et al., 2010; McCaffery et al., 2012). Cortisol and DHEA are known to regulate HPA axis activity, which is the mobilizing system for the sympathetic nervous system and immune system when the body is first exposed to psychological stress or trauma (Aschbacher et al., 2013; Mouthaan et al., 2014). Both hormones have also been implicated in varying degrees to the manifestation and maintenance of PTSD in adults (Mouthaan et al., 2014; Olf et al., 2007). In fact, evidence in certain patient populations (e.g., cardiovascular, car accident, etc.) suggests that the application of hydrocortisone (cortisol in medication form) immediately following a traumatic event can significantly decrease the incidence of PTSD when compared to those who did not receive hydrocortisone (Schelling et al., 2004, 2006). E/NE are the primary hormones relating to the adrenal system, which regulates autonomic nervous system activity, in particular the “fight or flight” response after being presented with a stressor or “threat”, including increasing heart rate and perspiration, etc. (Juster et al., 2010; Welch, 1992). Notably, in individuals who have been exposed to chronic stress or trauma, the noradrenergic system, which controls the regulation of E/NE, has been found to be more active overall, with resulting strengthening of amygdala or fear-response functioning ((Arnsten et al., 2015); see below).

3.3. Brain structure and function

Several neurological structures play a significant role in the body's adaptation to stressful experiences (McEwen and Gianaros, 2010). One of the most prominent areas of the brain studied in stress and trauma research is the hippocampus (Carrion et al., 2007; McEwen, 2001). Evidence indicates that the hippocampus is particularly vulnerable to the effects of glucocorticoid release in response to stress and that youth with repeated or prolonged stress (i.e., ACEs, PTSD) evidence decreased hippocampal volume (Carrion et al., 2007; McEwen, 2001). Other prominent areas within the brain that aid in stress adaptation are the amygdala, frontal lobe, and locus coeruleus, among others (Carrion et al., 2007; De Kloet et al., 2005). The amygdala is most commonly associated with emotional fear and aggression and is a primary area for threat detection and response (van Marle et al., 2009). When viewed specifically in the context of stress or trauma exposure (e.g., PTSD), research indicates that this area of the brain is acutely and chronically impacted. For example, evidence suggests that serotonin binding in the amygdala is reduced in adults with PTSD, which may underlie affected fear learning and threat detection (Murrough et al., 2011), as highlighted in a recent review (Timmers et al., 2019). A history of psychological trauma in childhood has also been found to affect normal amygdala reactivity in adults; increasing sensitivity and blunting specificity in responding to a perceived threat or stressor (Grant et al., 2011). The frontal lobe or, more specifically, prefrontal cortex is primarily involved in higher cognitive processes, including executive functioning and complex decision making (Blakemore and Robbins, 2012; Robbins, 1996). In response to stress and

the resulting flood of catecholamines (see above), the prefrontal cortex has been found to “go off-line,” with significantly impaired cognitive functioning, including the reduction in neuron firing, and strengthened emotional responses stemming from the amygdala and basal ganglia (Arnsten et al., 2015). In fact, exposure to prolonged stress or trauma, potentially in a dose-response relationship (i.e., greater adversity leads to greater impairment) may lead to atrophy in the prefrontal cortex (Arnsten et al., 2015) and/or smaller volume of gray matter (Ansell et al., 2012), which can manifest as impaired processing, working memory, attention/concentration, self-control, etc. (Arnsten et al., 2015; Arnsten, 2009).

3.4. Pain as a Model of Ongoing Stress in youth

Prior research has proposed a strong connection between stress exposure and chronic pain. Predominantly examined in adult populations, Vachon-Preseu et al. outlined a stress model of chronic pain in adults which posits that the resulting neuroendocrine response following stress exposure leads to pain chronicity via reduced hippocampal volume (Vachon-Preseu et al., 2013a). Burke et al., recently published a review that identifies neurobiological mechanisms of psychological stress experienced in childhood such as HPA-axis, immune, monoaminergic, endocannabinoid, and epigenetic, among others, that may lead to chronic pain in adulthood (Burke et al., 2017). However, little research has examined the potential role of these neurobiological mechanisms in pain processing while individuals are still in childhood, despite the high rate of chronic pain among pediatric populations (King et al., 2011). Moreover, these existing models do not fully acknowledge physiological factors in the context of childhood/adolescence as a particularly sensitive developmental period (Knudsen, 2004), nor do they take into account the unique individual factors that have been found to contribute to pain chronicity in youth such as parent factors, child psychopathology, pain memories, etc (Chow et al., 2016; Noel et al., 2012; Cunningham et al., 2016). Preliminarily, Nelson et al. published a conceptual framework that identified potential shared mechanisms such as nervous system sensitization, HPA axis activity, and allostatic load underlying the association between ACEs and chronic pain in pediatric populations (Nelson et al., 2016). Other investigations by Timmers and colleagues (Timmers et al., 2019) and McInnis and colleagues (McInnis et al., 2019) have highlighted specific aspects of the stress response, mainly cortisol via cognitive threat detection (the former) and HPA-axis activity (the latter), in relation to chronic pain in youth. However, these models do not fully capture the complexities of the human stress response (i.e., neuroendocrine, neurobiological) and the vast array of ways in which stress, trauma, or ACEs can impact the biopsychosocial functioning of youth. The current paper adds to this body of literature by proposing a more comprehensive theoretical model (Fig. 1) that not only encompasses neuroendocrine and neurobiological structures related to stress and pain but also acknowledges the complex interplay between these constructs, ACEs or other stressful experiences, and intrinsic cognitive, environmental, and behavioral factors that have been found to contribute to the chronicity of pain in youth. This framework is adapted from McEwen’s model detailing the stress response and allostatic load (McEwen, 1998b). Specific sections of the model are outlined below. In each section, associations between aspects of the model in both pain and stress or trauma research in youth and/or adults are presented. These results are presented broadly in order to highlight trends in the current literature and potential avenues for future research relevant to pediatric pain populations.

3.5. A proposed theoretical model

3.5.1. Psychological stressors or traumatic life events

Recent research has indicated that youth with chronic pain are frequently exposed to ACEs, such as psychological trauma (e.g., abuse), parental separation/divorce, or conflictual home or community

environments (Nelson et al., 2017a, 2017b), and report symptoms of posttraumatic stress (PTSS) at a high rate (Holley et al., 2016; Noel et al., 2016). Retrospectively, a significant amount of research also shows a strong association between ACEs in childhood and various chronic pain conditions in adulthood such as fibromyalgia/widespread pain, pelvic pain, migraines, and backpain among others (Jones et al., 2009; Tietjen et al., 2010). Preliminary prospective research on young adults also indicates that maltreatment (e.g., physical, emotional, sexual abuse, etc.) experienced as a child increases risk for higher pain intensity and more pain locations as an adult (Beal et al., 2019). Outside of ACEs or specific incidences of maltreatment, many youth with chronic pain generally identify stressful experiences relating to family, school, or social functioning as either inciting or exacerbating factors for pain intensity (White and Farrell, 2005; Varni et al., 1996).

3.5.2. Conscious (perceived) processing of stress

Cognitive factors surrounding the perception of how stressful an experience is or the impact that stress has on life may be significantly important in the association between stress exposure and chronic pain. To begin, the Lazarus and Folkman model of stress and coping has been applied in this context, with Nelson et al., 2016 positing that youth with a history of chronic stress or ACEs may engage in cognitive distortions surrounding threat appraisal of perceived stress (i.e., pain), which may then influence coping styles and overall impairment (Nelson et al., 2016). More recently, Timmers et al., 2019 expanded upon this line of inquiry by proposing that threat detection via cortisol release and related brain networking may mediate the relationship between chronic stress and chronic pain in youth (Timmers et al., 2019). In both child and adult research studies, perception of the danger or inherent risk surrounding the experience of a traumatic event has been identified as a salient factor in the development of PTSD following psychological trauma (McKeever and Huff, 2003). For example, an individual may be in a potentially or actually life-threatening situation without experiencing feelings of intense fear/horror, victimization, or loss of control (Yehuda, 1999). Accordingly, the subjective experience surrounding a stressful event may be as impactful for the development of PTSD as the underlying biology or diathesis (e.g., HPA-axis involvement, neuroendocrine networks, etc.) (McKeever and Huff, 2003). Similarly, cognitive processes uniquely connected to the subjective experience of pain such as fear of pain and pain catastrophizing (i.e., the interpretation of pain as negative and/or dangerous (Pielech et al., 2014)) have been repeatedly implicated in pain intensity and functional disability (Pielech et al., 2014; Turk and Wilson, 2010) in addition to being associated with the presence of ACEs in youth (Nelson et al., 2016). Given the strong connection between perception of threat and/or the magnitude of a stressful experience, it may be that youth who experience stressful or traumatic events are at greater risk for more negative cognitive appraisals of pain, but this has yet to be objectively examined.

3.5.3. Unconscious processing of stress

Outside of consciously perceived stress, evidence suggests that a large amount of stress-based physiological activation may be caused by *unconscious stress*. Termed “unconscious perseverative cognition”, researchers have found that individuals often unconsciously activate cognitive representations (e.g., memories, thoughts) of past stressful events or future events that elicit fear or anxiety (Brosschot et al., 2010, 2014). Further, evidence in similar lines of research indicates that autonomic nervous system arousal continues for several hours and even during sleep after the initial activation of a conscious stressful event (Brosschot et al., 2010). In parallel lines of research, evidence has delineated a strong association between physiological arousal (e.g., autonomic nervous system, HPA activation) and sleep disruption in both chronic pain and traumatized pediatric and adult populations (Harrison et al., 2016; Kobayashi et al., 2016). It may be that physiological arousal, activated by conscious and/or unconscious processes associated with stress puts youth with chronic pain at greater risk for impairment,

including sleep disturbance. However, this has never before been examined.

3.5.4. Individual differences

Many individual characteristics in youth in particular have been identified as potential risk factors for maladaptive physiological effects of stress or trauma, including chronic pain. From an epigenetic standpoint, evidence highlights the potential for translation of stress or trauma-based disease or dysfunction in adults to a genetic predisposition in offspring. For example, research indicates that the offspring of adults who have experienced maltreatment in childhood are significantly more likely to exhibit psychopathology (i.e., depression, behavioral issues) and altered physiology (e.g., DNA methylation), despite an upbringing that does not contain trauma or stress (Franklin et al., 2010; Yehuda and Lehrner, 2018). Irrespective of parent trauma, research also indicates that HPA-axis vulnerability in the context of PTSD is significantly associated with certain genetic polymorphisms in youth, including those genes that encode glucocorticoid receptors (Mehta and Binder, 2012). In parallel lines of research, genetic predispositions exist for the development of chronic pain in youth. For example, having a parent with a chronic pain syndrome significantly increases risk for a child to develop chronic pain as well (Stone and Wilson, 2016). This may manifest either as the same chronic pain syndrome between parent and child (e.g., migraines, fibromyalgia) or as more generally, altered pain processing such as central sensitization (i.e., pain hypersensitivity via altered sensory responses elicited by normal inputs (Latremoliere and Woolf, 2009; Woolf, 2011)) in offspring (Stone and Wilson, 2016). Hormonal processes have also been proposed to play a role in the manifestation and/or maintenance of pediatric chronic pain. In youth, females are observed to have chronic pain in significantly higher rates than males (King et al., 2011) and chronic pain syndromes average age of onset in youth (surrounding age 14) often follows puberty (King et al., 2011; Kløven et al., 2017).

Outside of individual differences in physiology that may increase risk for chronic pain, research indicates that several psychological factors or environmental influences within a youth's environment may increase risk for chronic pain. First and foremost, a significant body of literature indicates that the presence of psychopathology, including (for example) depression and PTSD, contributes to poorer functioning in youth. For example, Miller, et al., released a model indicated that the release of inflammatory cytokines following psychological stress contributes to the development of depression (Miller et al., 2009), which is associated with poorer functioning in pediatric pain populations in related research (Arnou et al., 2009; Goldberg, 1994). Additionally, Holley, et al., published a mutual maintenance model implicating the presence of PTSD in pain chronicity in youth (Holley et al., 2016). Aside from diagnostically relevant psychopathology, preliminary evidence is coming out that identifies memories of painful experiences, such as a painful injections or blood draws, as a predisposing factor to pain chronicity in youth in particular (Noel et al., 2012, 2015). This shows strong parallels to youth with a history of ACEs or chronic stress and a history of PTSD in that PTSD by nature involves emotionally painful memories and/or altered cognitions/emotions surrounding a traumatic event (Association, 2013). Perfectionism (e.g., socially-prescribed beliefs, non-disclosure of perceived imperfections (Hewitt et al., 2011)) as a personality trait has also been commonly seen in youth with chronic pain and found to be significantly related to pain chronicity and increased disability (Randall et al., 2018). Individual characteristics may compound risk for psychopathology in response to stress as well. For example, evidence suggests that female gender and psychopathology prior to trauma exposure (e.g., anxiety) increases risk for PTSD and symptom chronicity (Hamblen and Barnett, 2016). Similarly, it has been proposed in the trauma literature that poor physical health (e.g., asthma, irritable bowel syndrome) increases risk for PTSD and symptom chronicity (Nooner et al., 2012), a fact which may be particularly relevant for youth with pain and a history of exposure to adverse childhood experiences.

Finally, several parent factors have been found to be significantly

related to pain chronicity in youth. In particular, if youth have parents with chronic pain, they may be at greater risk (in addition to the genetic aspects identified above) for developing chronic pain via parent modeling of pain. For example, if parents with chronic pain are sedentary and mainly rely on medication to respond to chronic pain flares vs. active coping strategies such as exercise, cognitive coping, or biobehavioral relaxation then youth with pain may be more likely to gravitate to passive strategies, which will in turn, increase risk for pain chronicity (Logan and Scharff, 2005; Palermo et al., 2014; Sieberg et al., 2016).

3.5.5. Behavioral responses

Common behavioral responses that youth employ in the context of trauma or stress (e.g., PTSD) hold striking similarities with frequently observed responses to chronic pain. The main behavioral response, originally identified in McEwen's model (McEwen, 1998b), is "fight or flight". Fight or flight refers to either staying and "fighting" or running away (i.e., "flight") when presented with a threat. While this term has traditionally been used in survival situations, it has become more mainstream in contexts of stress or psychological trauma to describe the biological underpinnings of being presented with a perceived threat (Jacobs, 2001). In the context of stress or trauma, this innate fight or flight response can become maladaptive (i.e., PTSD) whereas the body will often misinterpret ambiguous or neutral situations as threatening and automatically mobilize that fight or flight response (Lanius et al., 2017). This can often result in additional behavioral responses such as avoidance, or purposefully no longer going into situations that have been previously deemed threatening or triggering for PTSD (e.g., if an individual previously felt unsafe in a grocery store, they would not go back, etc.) (Lanius et al., 2017), which will then prolong or worsen the maladaptive fight or flight response and PTSD symptomatology.

Similar behavioral responses have been observed in the context of chronic pain in youth. Most saliently, research indicates that the experience of pain often mobilizes the fight or flight response which can lead to the body interpreting pain sensations as dangerous or threatening, even when the pain is chronic and acute injury or illness has been ruled out (Timmers et al., 2019; Lipani and Walker, 2006). This initial appraisal of pain as a threat then produces a host of behaviors designed to avoid or mitigate the experience of pain such as guarding (i.e., not using the affected body area to its full function), resting (i.e., not using the affected body area at all), or overuse of medication (i.e., acute relief of the symptom but not addressing the long-term functional limitations) (Asmundson et al., 2012). The maintenance of these avoidance behaviors can then worsen chronic pain symptoms via strengthening of maladaptive cognitive pathways (i.e., perception of pain as dangerous) and physical deconditioning of the affected and surrounding areas via lack of consistent exercise (Asmundson et al., 2012). Across both contexts (i.e., pain and psychological stress or trauma), health-related behaviors such as sleep (e.g., lack of sleep due to pain and/or PTSS) and lack of exercise are frequently and significantly observed and can further perpetuate the maladaptive fight or flight response and related symptomatology (Kovachy et al., 2013).

3.5.6. Biological and physiological processes

As mentioned above, the experience of stress initiates a host of physiological responses, including HPA-axis and autonomic nervous system activation via release of glucocorticoids and adrenal hormones. This may manifest in a variety of ways, including increased heart rate or blood pressure, muscle tension, fatigue, dizziness, abdominal pain or nausea, etc. (Allen et al., 2014). Many youth with pain report that the experience of stress intensifies or exacerbates their pain symptoms (Varni et al., 1996). By way of increases in pain intensity and behavioral responses of resting or guarding and avoidance noted above, many youth with chronic pain experience an increase in symptoms as time passes. Often interpreted as a worsening in their pain syndrome, it may be that the increase in symptoms as many families fear is instead due, in part, to general muscle deconditioning (Cunningham and Kashikar-Zuck, 2013).

Less frequently, muscle contractures may also occur which is where muscles in the affected limb tighten or shorten and can occur with prolonged lack of movement or guarding in the affected limb (Clinch and Eccleston, 2009). This perceived worsening of symptoms and/or increasing functional disability is often accompanied by increased stress (and in conjunction, prolonged physiological stress response), which may continue to interact with pain physiology in a bidirectional manner.

3.5.7. Pain chronicity as a function of allostatic load and structural brain changes

Previous research has posited that allostatic load (described above) following repeated/prolonged exposure to stressful experiences may contribute to pain chronicity in youth (Nelson et al., 2016). Specifically, nervous system (i.e., sympathetic/parasympathetic) reactivity in relation to allostatic load may lead to poorer pain processing via heightened central sensitization (Nelson et al., 2016). Evidence of this has been found in targeted studies examining various biomarkers of the stress-response and/or allostatic load in youth populations. For example, a recently published study found higher rates of early life stress concomitantly with increased activation of the autonomic nervous system (e.g., heart rate, electrodermal activity) and immune response (i.e., c-reactive protein) in youth with chronic pain vs. healthy controls (McInnis et al., 2019). Cortisol, a primary stress hormone, regulator of HPA-axis function, and biomarker for allostatic load, has also been identified as a pain-related outcome and target for intervention in pediatric pain populations (Chadi et al., 2016). Research in adults has found an association between stress exposure and HPA axis and glucocorticoid involvement (e.g., cortisol) in the maintenance of chronic pain conditions (Hannibal and Bishop, 2014; McEwen and Kalia, 2010).

Within respect to brain structure, the hippocampus may be particularly associated with pain chronicity in youth with a history of psychological stress or trauma. For example, evidence in adults suggests that hippocampal dysfunction (i.e., reduced volume, metabolic dysregulation) is greater in individuals with musculoskeletal pain compared to controls (Vachon-Presseau et al., 2013a; Emad et al., 2008) and may lead to altered pain processing across conditions (Liu and Chen, 2009). Research also indicates that decreased hippocampal volume is associated with increased pain sensitivity in adults (Ziv et al., 2010; Grunau et al., 2006). Connecting this to allostatic load, a study performed in adults with chronic pain found elevated cortisol when compared to controls and that higher cortisol was associated with decreased hippocampal volume and increased pain (Vachon-Presseau et al., 2013a). In the hippocampus, the release of glucocorticoids in response to stress is also associated with the induction of long-term potentiation, which is primarily associated with memory formation (De Kloet et al., 2005). This may be particularly relevant to pediatric chronic pain and pain chronicity, as it was previously mentioned (see above) that the nature of memories surrounding painful experiences are associated with the development of chronic pain (Noel et al., 2015; Nijs et al., 2015).

Additional brain structures implicated in stress exposure also play central roles in pain processing. As mentioned above, the amygdala is commonly impacted in psychological stress or trauma exposure (Murough et al., 2011; Grant et al., 2011). Concomitantly, the amygdala is one of the most studied areas of the brain in pain processing. Given its central role in emotion and fear, the amygdala has been consistently identified as a primary region of interest in modulating the affective aspect of the pain experience (Thompson and Neugebauer, 2017). Nociceptive pathways have been found leading to the amygdala and several imaging studies have shown increased activity in the amygdala in response to mechanical or thermal stimulation (Thompson and Neugebauer, 2017). It may be that the negative effects of stressful or traumatic experiences and/or PTSD symptomatology compounds or strengthens these pathways and increases risk for pain chronicity. However, little research has examined this specifically. The prefrontal cortex is also commonly connected to the stress-response in that this area is frequently impaired and may atrophy in response to chronic stress or

trauma exposure (Arnsten et al., 2015). The prefrontal cortex has also been found to be highly involved in multiple aspects of pain processing, including sensory, cognitive, emotional, and integrative (Peng et al., 2018). Increased brain activation in the frontal lobe has also been found in adults with chronic pain (Molina et al., 2017). Despite this, no research to-date has examined the association between stress or trauma exposure, brain functioning in these areas, and pain behavior and/or symptomatology in pediatric populations.

4. Conclusions/future directions

Findings from this comprehensive review suggest that biological and physiological responses to stress may contribute to the maintenance or exacerbation of pediatric chronic pain. However, no research has examined these processes in a comprehensive and systematic manner in youth. Systematically examining stress-based neurological mechanisms in youth with chronic pain and their association with pain and related outcomes would likely increase our understanding of the etiology and maintenance of pediatric pain conditions. Determining such relations is also critical for identifying brain mechanisms of effective treatments in these youth. For example, if neuroendocrine risk factors are high in youth with chronic pain and are associated with increased pain, this mechanistic evidence would offer further support for the importance of targeting the physiological stress-response using a mind and body approach in these youth. The results of these investigations may lead to more targeted mechanistic studies on the effects of stress on the brain and its relationship to pain. For example, research indicates that chronic stress via glucocorticoids deleteriously affects endocannabinoid receptors in the brain (Morena et al., 2016), which holds direct implications in the processing and treatment of pain in youth and adult populations. However, this has never before been examined. Finally, objective physiological evidence of the role of stress in pain is critical for adoption and support by patients, health care providers, and health care payers and will pave the way for tailored and mechanistically informed treatments.

Funding source

The Cathedral Fund.

Declaration of competing interest

None.

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