Targeting the stress response in pediatric pain: current evidence for psychosocial intervention and avenues for future investigation

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Abstract
Nonpharmacological treatments for chronic pain in youth have been identified as first-line treatments over and above medication. Therapies such as cognitive-behavioral therapy and mindfulness-based stress reduction have shown good efficacy in reducing the psychological correlates (eg, anxiety, depression, and stress) and social or behavioral sequelae (eg, limited physical activity and lack of school engagement) associated with pediatric chronic pain. However, minimal research has examined the physiological mechanism(s) of action for these interventions. A recent review (Cunningham, et al., 2019) emphasized the need for objective (ie, physiological) assessment of treatment response in pediatric pain populations. The current review adds to this literature by identifying the physiological stress response as a particular target of interest in interventions for pediatric pain. Research indicates that youth with chronic pain report high rates of psychological stress, posttraumatic stress symptoms, and exposure to adverse childhood experiences (abuse/neglect, etc). In addition, a host of research has shown strong parallels between the neurobiology of pain processing and the neurobiology of stress exposure in both youth and adults. Interventions such as narrative or exposure therapy (eg, trauma-focused cognitive-behavioral therapy) and mindfulness-based or meditation-based therapies have shown particular promise in alleviating the neurobiological impact that stress and pain can have on the body, including reduction in allostatic load and altered connectivity in multiple brain regions. However, no study to date has specifically looked at these factors in the context of pediatric pain treatment. Future research should further explore these constructs to optimize prevention in and treatment of these vulnerable populations.

Keywords: Pediatric pain, Stress response, Psychosocial intervention, Treatment outcomes

1. Introduction
The central and peripheral nervous systems have long been identified as primary intervention targets to address pain chronicity in youth.\textsuperscript{23,112} Many providers immediately turn to pharmacological interventions such as neuropathic pain medication or atypical antidepressants (eg, tricyclics) to modify or tamp down nervous system sensitization associated with pain chronicity.\textsuperscript{29} However, the efficacy in youth is not well documented in receiver operating characteristic analysis trials.\textsuperscript{40} Moreover, the engagement of other treatment options has often been shown to be useful. Combining physical therapy and psychosocial intervention (eg, cognitive-behavioral therapy [CBT]) independently or concomitantly with drug therapy has been found to optimize or outperform the pharmacological impact on these outcomes by addressing the psychological and social aspects of pain-related disability, such as decreased pain tolerability, decreased social interaction, and increased functional impairment and fear of pain.\textsuperscript{22} Emerging research has started to indicate that these nonpharmacological interventions, much like the above noted classes of medication, may directly and indirectly modify nervous system sensitivity.\textsuperscript{17} However, the literature on the objective (ie, neurobiological) responses to these interventions for youth with chronic pain remains limited. While psychosocial interventions have shown variable engagement due to their required duration of implementation,\textsuperscript{26,110} pharmacological therapies may also take time and produce side effects. The natural evolution of brain changes through brain-brain interactions induced by these therapies may produce adaptive
therapeutic changes. Such approaches need rigorous comparative evaluation akin to the standards used to evaluate new medications, alone or in combination. Measures of the neurobiological stress response (eg, hypothalamic–pituitary–adrenal [HPA] axis and autonomic nervous system) have been proposed to be unique predictors of pain chronicity in youth given the frequent occurrence of psychological stress (herein referred to as "stress"). Posttraumatic stress symptoms (PTSS) and adverse childhood experiences (ACEs; abuse, neglect, violent/conflictual home environment, parent/guardian separation or divorce, etc.) documented in pediatric pain populations. Outside of pain, a large body of research highlights the malleability of the stress response and the ensuing "wear and tear" that stress can impose on the nervous system, most notably in youth (vs. adults). Several interventions exist that address the unique biopsychosocial (BPS) correlates of stress in youth. Some of these interventions have not been performed in pediatric pain populations (eg, trauma-focused cognitive-behavioral therapy [TF-CBT]) but many have, including mindfulness-based stress reduction (MBSR) and biofeedback. However, only a few of these studies have specifically examined the efficacy of these interventions in modifying the physiological stress response. Furthermore, evidence suggests that many youth with chronic pain do not respond to treatment (eg, decrease in disability or increase in adaptive coping) after engaging in traditionally used psychosocial therapies (eg, CBT). One reason for such treatment failure may be that currently accepted interventions for chronic pain do not adequately target the stress response as a major factor in pain maintenance. However, this hypothesis remains untested. Accordingly, the aims of the current review are to (1) propose the stress response as a unique target for psychosocial intervention to alleviate chronic pain and (2) outline new avenues for future research.

2. Neurobiological underpinnings of pain and potential targets of intervention

Chronic pain in youth is diagnosed when pain lasts for 3 months or longer in the absence of a primary medical issue. The underlying neurobiology of chronic pain is frequently conceptualized as the product of central sensitization, which is the increase in activity and responsiveness in nociceptive pathways in the central and peripheral nervous systems after a painful event. However, up to 50% of youth with chronic pain fail to report a recognizable inciting incident for their chronic pain for a number of reasons, including when minor injuries and unknown or undiagnosed disease processes (eg, rare disease) are involved. The diagnostic conceptualization of pediatric chronic pain is often formulated using the BPS model of pain. This model asserts that pain chronicity occurs because of the interaction between central sensitization or centralization of pain and HPA axis hyperactivity, in conjunction with psychological (eg, anxiety, depression, pain catastrophizing, and fear of pain) and social (eg, decreased social engagement and school attendance) factors contributing to functional disability and, in turn, pain chronicity. The pain feedback loop is exacerbated by these sociobiological loads, producing a failure of homeostasis and increased allostatic load (AL), ie, wear and tear on regulatory systems, including the nervous system, in response to repeated or prolonged stress.

Aspects of neurological functioning relevant to both the physiological stress response and pain processing in youth are highlighted in Figure 1. The HPA axis (depicted in red) is one of the primary moderators of the neuroendocrine and neurobiological stress response, comprising the hypothalamus, pituitary gland, and adrenal cortex and releasing adrenal hormones (eg, epinephrine/norepinephrine) and corticosteroids (eg, cortisol) in response to stress. Major brain areas implicated in the stress response and pain processing (depicted in green) include the prefrontal cortex, hippocampus, amygdala, and locus coeruleus (LC). Finally, constructs representing the broader impact of stress on neurobiology (depicted in blue) include, as mentioned above, increased AL.

3. Stress—the great arbiter of homeostasis or allostatic load

Stress has been well established as an inciting factor of homeostatic disruption and neurobiological dysfunction in youth and adults. Primary neurobiological processes involved in the stress response also have been concretely identified and involve several aspects of the neurological system, including the HPA axis brain structures that help regulate the HPA axis and manage emotional aspects and interpretation of stressful events and, more globally, AL. For a comprehensive review of the neurobiological impact of stress, refer to the study by Nelson, et al., in short, stress exposure effects include changes in brain structures in conjunction with dysregulation of...
the HPA axis. The HPA axis is a primary stress response system involving the hypothalamus, pituitary gland, and adrenal glands, and is a system commonly measured as part of the larger construct of AL (see below). Key biomarkers reflecting HPA axis functioning are levels of glucocorticoids such as cortisol and dehydroepiandrosterone (DHEA). Regulation of the HPA axis is, in part, controlled by the hippocampus. Results from several studies indicate that prolonged glucocorticoid release in response to stress exposure can lead to decreased hippocampal volume. Other areas affected by prolonged or significant stress and pain include (but are not limited to) the amygdala, prefrontal cortex (PFC), and LC. The amygdala is part of the fear network and shares connectivity across brain regions. Research indicates that in response to stress, dendrites in the amygdala expand, which causes increased activity in the area. In the PFC, endocannabinoids are partially responsible for dampening or blocking the stress response in the HPA axis. Remodeling can occur in the PFC in response to stress but can be alleviated after the source of stress is removed. Finally, chronic sources of stress have been shown to induce changes in the physiology and function of the LC, such as dendritic growth by exposure to corticotropin-releasing factor after HPA axis activation. Across these processes, the experience of varying degrees and types of stress (e.g., psychological stress, abuse, or toxic stress) has been associated with a host of health-related issues in adulthood, including obesity, cancer, diabetes, and chronic pain. However, research on the impact of stress on health-related functioning and disease susceptibility in youth is limited, although ongoing. One of the more prominent health conditions being proposed as related to or exacerbated by stress in pediatric populations is chronic pain. The first conceptual framework published on the potential relation between stressful experiences and chronic pain in youth proposed AL as a unique contributor to pain chronicity. A more recent review expanded on this framework by identifying other shared neurobiological mechanisms across stress and pain, including biomarkers of AL such as maladaptive levels of glucocorticoids (e.g., flattened cortisol and increased DHEA—representative of HPA axis functioning), catecholamines (e.g., increased epinephrine [E] or norepinephrine [NE]—representative of sympathetic nervous system functioning), and inflammatory cytokines (e.g., increased C-reactive protein) and altered connectivity in brain structures implicated in the stress response (as described above). The experience of chronic pain may, in fact, fall under the category of “toxic stress” or significant or prolonged exposure to stress, with accompanying activation of the neurobiological stress response, given the lengthy average duration of experienced pain and functional disability in these youth. That is, chronic pain may not only be initiated or exacerbated by stress exposures but also be itself a form of toxic stress with consequent neurobiological effects. Exposure in childhood to toxic stress, such as trauma or ACEs, has been linked to lifelong consequences for physical and mental health through the neurobiological correlates described above (e.g., AL and HPA axis dysfunction) and is an important consideration in the context of long-term outcomes in youth with chronic pain.

4. Psychosocial intervention and chronic pain—what is the current evidence?

The Centers for Disease Control and Prevention released a report in 2016 that outlined best practices for chronic pain treatment. In this report, nonpharmacological treatments, most notably psychosocial interventions such as CBT, were identified as first-line treatments for chronic pain in youth. Cognitive-behavioral therapy has been found to be beneficial for chronic pain through targeting decreased levels of activity in relation to emotional distress and functional disability (e.g., behavioral activation) and addressing altered cognitions surrounding the pain experience (e.g., reframing catastrophizing pain thoughts). More recently, mindfulness-based interventions such as MBSR and acceptance and commitment therapy have shown promise in addressing cognitive and behavioral aspects of the pain experience by focusing on observing one’s present state in a nonjudgmental manner. Although there is societal demand for nonpharmacological treatments, their fidelity and quality still need to be defined.

Multiple articles have reviewed the efficacy of psychotherapy in the treatment of pediatric pain (e.g., Palermo, et al., 2010; Fisher, et al., 2014; and Eccleston, et al., 2014), with heaviest focus on randomized clinical trials using CBT interventions, biofeedback, and relaxation training. Results of these systematic reviews and meta-analyses generally reveal a significant positive effect of interventions on pain intensity and functional disability. Individual studies on the efficacy of psychosocial interventions also have shown a strong short-term positive impact on psychological (e.g., anxiety, depression, fear of pain, and pain catastrophizing) and social (e.g., peer engagement and school attendance) factors commonly observed in pediatric pain patients. Efforts to examine the impact of combining physical training with psychosocial intervention have also begun, with promising results. However, research indicates that a significant subset of youth fails to respond to traditional psychosocial interventions geared towards alleviating chronic pain. Initial factors identified as barriers to successful treatment include patient anxiety and other psychological symptoms and parent factors, such as pain history and pain catastrophizing. However, few studies have objectively examined changes (or lack thereof) that may occur in aspects of neurobiological pain processing (e.g., HPA axis dysregulation: cortisol/DHEA and autonomic nervous system function: E/NE) in response to psychosocial intervention. Consequently, data are limited as to whether traditional targets of intervention, including psychological impairment (e.g., anxiety and depression), disability, and pain intensity, contribute to or are representative of physiological or neurobiological changes in the individual. A recent review emphasized the need for the objective assessment of pain treatment outcomes and identified several brain mechanisms to consider, including those involved in the attention network, cognitive control (e.g., prefrontal cortex), nociceptive processing (e.g., thalamus and insula), and the fear network and emotional processing (e.g., amygdala and hippocampus). Research assessing the responsiveness of these areas, including areas intrinsic to the physiological stress response, to available psychosocial interventions for pain remains limited.

5. Psychosocial and narrative-based interventions focused on stress or trauma exposure

Several evidence-based interventions exist for youth with a history of trauma or posttraumatic stress disorder (PTSD) that may be relevant to consider in the context of treating youth with chronic pain. One of the most robust interventions for children and adolescents is TF-CBT. Trauma-focused cognitive-behavioral therapy operates under the framework “PRACTICE,” which represents several common tenets across typical CBT therapies, such as psychoeducation and parenting skills (P),
relaxation training (R), affective modulation (A), and cognitive coping (C). Trauma-focused cognitive-behavioral therapy also includes elements of intervention specifically catered to trauma, including gradual emotional and cognitive exposure to the trauma (eg, asking the child to name the trauma directly: “when I was abused” vs “when that happened to me”), trauma narrative construction and processing (T), and in vivo mastery of the trauma (I). The goal of engaging trauma-exposed children and adolescents in therapy with emotional exposure and narrative work is to desensitize them to the fear or distress that they associate with memories or situations connected to the trauma (eg, seeing people or going places that remind them of the traumatic event).51,74 Talking through specific details of the event in the form of a narrative can also help correct negative or inaccurate thoughts or beliefs about the traumatic experience (eg, “I could have done something to stop it”) that may be perpetuating the fear or distress.21,74 Evidence indicates that pediatric interventions that include a trauma narrative lead to greater reductions in trauma-related fear and general anxiety as well as parent-related distress relative to treatments that do not include a trauma narrative component.37 Recent studies among traumatized youth also indicate that narrative therapy, whether as part of TF-CBT or independently, produces more robust and stable treatment outcomes, including reductions in PTSD symptoms and improvements in sleep, when compared with treatment as usual.91

5.1. Mindfulness

One of the other major categories of intervention geared towards addressing the impact of stress and trauma is mindfulness-based interventions. As mentioned above, the basic tenet of mindfulness is teaching individuals to observe their experience in a nonjudgmental manner37 and has been used successfully in the context of chronic pain. In the context of trauma, similar to TF-CBT and narrative or exposure work, mindfulness practice can lead individuals to view their traumas or stress with kindness and nonjudgment rather than fear or avoidance.7 This is exemplified in one of the tenets of MBSR that teaches “stress + resistance = suffering.”36 Most often studied in traumatized or highly stressed adults, an abundance of evidence suggests that mindfulness can lead to sustained improvement in mood and PTSS and increases in resilience.33,51 Preliminary work in traumatized or at-risk pediatric populations also indicates that MBSR leads to greater feelings of competence with stress management and enhanced self-awareness.42

6. Neuropsychological perspectives on stress-focused or trauma-focused interventions

Given that the neuropsychological areas of interest described above (eg, HPA axis dysregulation: cortisol/DHEA, sympathetic nervous system dysregulation: E/NE, and altered brain connectivity) are proposed mechanisms of pain,76,78,107 they may also be considered as intervention outcomes to be assessed through objective measurement (eg, saliva assay, urine analysis, and functional magnetic resonance imaging) over the course of treatment. The functioning of the HPA axis is already studied in the context of psychosocial intervention. Generally, HPA axis dysfunction can manifest as dysregulated glucocorticoid release, sleep disruption, blood pressure issues, and immunosuppression.19,32 Admittedly, evidence has been inconsistent on the ability of psychosocial interventions to target HPA axis dysregulation through normalized cortisol or DHEA levels. In the context of PTSD, a recent review indicated that certain trauma-focused interventions, including TF-CBT, prolonged exposure (PE), and eye-movement desensitization reprocessing, performed on adults with PTSD, are effective in mitigating dysregulation in basal cortisol levels and the cortisol awakening response in certain subsamples; however, more broad results from these studies remain mixed.86,99,107 In youth particularly, evidence suggests that certain aspects of HPA axis functioning (eg, basal cortisol levels) may be indicative of who may be more or less responsive to TF-CBT113 and MBSR83 and, moreover, may be a more reliable measure of treatment response than subjective measures such as psychological questionnaires.63 This latter finding supports the rationality of efforts to objectively measure treatment response through biological measures such as saliva assay rather than rely on traditional pain measures such as (self-reported) disability and pain intensity.

As discussed above, changes in brain structures, such as the hippocampus, amygdala, PFC, and LC, have been shown to take place in conjunction with exposure to stress and the ensuing dysregulation of the HPA axis.4,5,39,69,70,72 However, few studies have directly measured functional connectivity in these brain regions preintervention and postintervention. Findings from the few relevant studies, mostly in adults, suggest that certain exposure-based trauma interventions (eg, PE) enhance connectivity in the amygdala and hippocampus.114 These enhanced connections may improve an individual’s inhibition, memory encoding and retrieval, and ability to re-evaluate threats.114 Some adult studies have also observed volumetric changes in the amygdala34 and decreased activation of the PFC3 after certain psychotherapies (eg, eye-movement desensitization reprocessing and exposure-based interventions). Evidence in the context of stress-related disorders generally indicates that trauma-focused interventions are more effective at producing brain changes than basic cognitive-behavioral or supportive psychotherapy without an exposure component.3

More global outcomes of stress on the body that may be influenced by interventions include AL. As described above, AL is a construct that represents the multisystem wear and tear and long-term vulnerability to illness or disease that repeated or prolonged stress can impose.66 Once present, AL is maintained through continued exposure to stress and consequent health-related behaviors, such as disrupted sleep, poor nutrition, and sedentary behaviors or reduced physical exercise.66,68,70 Several studies, predominantly in adults, highlight the responsibility of AL, measured through a multifactorial composite of individual mechanisms, to psychosocial intervention. For example, preliminary evidence suggests that MBSR or CBT can help mitigate AL after significant or prolonged stress exposure.87,88 Complementary interventions such as yoga or tai chi also have shown preliminary effectiveness in their ability to mitigate AL.16,17 However, our current understanding on how psychosocial interventions and AL may interact is lacking, and more research in both pediatric and adult populations is needed.

7. Implications for future pediatric pain interventions

A stress-focused or trauma-focused approach to intervention may be the logical next step in optimizing psychosocial intervention for these youth. This argument is further strengthened by preliminary evidence suggesting that youth with chronic pain and PTSD experience decreased response to non–trauma-focused CBT intervention.77 Applying a trauma-focused lens to chronic pain intervention may include adapted elements of trauma therapies (eg, TF-CBT and narrative exposure) or streamlining care to mindfulness-based strategies. A strong
body of research indicates that the nature of pain memories is highly predictive of long-term pain outcomes in youth. Accordingly, youth with chronic pain may benefit from the general framework of TF-CBT adapted to apply to the context of pain. This could include psychoeducation about MPS aspects of stress or trauma and chronic pain (P), relaxation training (R) and affective modulation (A) put into the context of pain and pain-related distress, and cognitive coping (C) applied to pain catastrophizing and fear of pain. Trauma-focused aspects of the intervention, including trauma narrative construction and processing (T) and in vivo mastery of the trauma (I), may involve constructing and processing a narrative surrounding a particularly stressful or intense pain memory. Working with youth, with or without a history of other stressful experiences, to deconstruct or build a narrative surrounding their memory of pain (eg, examine cognitive biases and emotions surrounding the event) as one would a traumatic memory may contribute to desensitizing the strong emotional or fear-based response to pain that many youth experience. In this context, regulation of the HPA axis through trauma-focused or narrative work may optimize overall health and sleep patterns, which could then mitigate AL after connectivity in various brain areas affected by stress, and decrease the associated pain response. Longitudinally, these interventions may also protect the individual from known effects of chronic toxic stress, including AL and increased risk for poor health and early death. More research in pediatric pain populations is needed that implements objective measures (eg, functional magnetic resonance imaging and saliva assay), in conjunction with traditionally measured pain outcomes (eg, disability and pain intensity), to assess the neurobiological effects of interventions on the stress response and on pain.

Although mindfulness-based approaches have been studied in adult chronic pain populations and show promise in the treatment of chronic pain, these types of interventions have been examined only recently in pediatric pain populations. Minimal research has specifically examined the ability of mindfulness practice to directly affect the neurobiological processes (eg, altered functional connectivity and AL) common to the experiences of both stress and pain in youth. Based on the strong evidence in adults that mindfulness-based practice can have a host of protective effects on psychosocial and neurobiological functioning, this intervention may be an important choice to optimize treatment in youth with chronic pain who report stress or trauma exposure. In fact, in light of the proposed categorization of chronic pain as an instigator or form of toxic stress, mindfulness-based approaches may be a more effective intervention choice than basic CBT approaches for chronic pain rehabilitation in youth with or without a trauma history. However, to date, no study has directly examined this nor the potential implications of combining aspects of mindfulness within the CBT framework for pediatric pain management. In these contexts, more research is needed, particularly treatment studies that incorporate neurobiological mechanism and outcome measurements, to determine the most effective interventions for these vulnerable youth.

8. Conclusions
A host of research has identified strong overlap between neurobiological correlates of stress and of pain. In addition, evidence suggests that youth with chronic pain report high rates of ACEs, PTSS, and general psychological stress when compared with the general population or to matched nonpain peers. However, research remains limited on how a history or ongoing experiences of stress or trauma may influence the manifestation of chronic pain (eg, neurobiology) in youth or the course of and response to treatment. In parallel, evidence indicates that a subset of youth with chronic pain fail to respond to traditional psychotherapy for pain management (eg, CBT). Given that stress-exposed youth are at increased risk for altered brain connectivity, HPA axis activation, and AL, trauma-focused therapies, such as TF-CBT, narrative exposure, or mindfulness-based interventions, may be more appropriate interventions for youth experiencing chronic pain than current therapies. Specifically, these intervention approaches, above and beyond traditional modalities, may better interrupt any ongoing stress response and directly target and desensitize the emotional response, memories, and neurobiological mechanisms surrounding the experience of stress and maintenance of pain.

9. Future directions
Research is only just beginning to elucidate links between stress and pain in youth. Currently, we do not have evidence demonstrating the extent to which the overlap in neurobiological mechanisms of stress and pain contributes to one another, particularly in youth. Studies are needed to confirm the existence of these associations. However, given the preliminary evidence that stress-based neurological processes may be implicated in pain chronicity, modifying existing psychosocial treatments to acknowledge and actively address stress histories and their sequelae is critical. For example, randomized clinical trials performed with CBT vs TF-CBT or MBSR in these youth are an important next step. Preassessments and postassessments with brain imaging and neuroendocrine biomarkers (eg, salivary cortisol) should be conducted to confirm the impact of these interventions at the biological level. Evidence is also currently unclear on which stress-based neurobiological mechanism(s) (eg, AL or altered brain connectivity) may be the optimal intervention target(s), especially given their strong associations and bidirectional effects on each other. Future research should pursue this line of inquiry because such information will inform the development of therapeutic approaches that maximize effectiveness and enhance decision-making around best methods for assessing treatment outcomes. Alternative and complementary measures of physiological effects of stress, such as telomere attrition and DNA methylation, also should be explored in this context. The results from these studies may inform the development of new research and treatment avenues with the goal of optimizing care for these vulnerable youth.

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