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Chronic pain, chronic stress and substance use: overlapping mechanisms and implications

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Chronic pain is among the most common reasons adults in the U.S. seek medical care. Despite chronic pain's substantial impact on individuals' physical, emotional, and financial wellness, the biologic underpinnings of chronic pain remain incompletely understood. Such deleterious impact on an individuals' wellness is also manifested in the substantial co-occurrence of chronic stress with chronic pain. However, whether chronic stress and adversity and related alcohol and substance misuse increases risk of developing chronic pain, and, if so, what the overlapping psychobiological processes are, is not well understood. Individuals suffering with chronic pain find alleviation through prescription opioids as well as non-prescribed cannabis, alcohol, and other drugs to control pain, and use of these substances have grown significantly. Substance misuse also increases experience of chronic stress. Thus, given the evidence showing a strong correlation between chronic stress and chronic pain, we aim to review and identify overlapping factors and processes. We first explore the predisposing factors and psychologic features common to both conditions. This is followed by examining the overlapping neural circuitry of pain and stress in order to trace a common pathophysiologic processes for the development of chronic pain and its link to substance use. Based on the previous literature and our own findings, we propose a critical role for ventromedial prefrontal cortex dysfunction, an overlapping brain area associated with the regulation of both pain and stress that is also affected by substance use, as key in the risk of developing chronic pain. Finally, we identify the need for future research in exploring the role of medial prefrontal circuits in chronic pain pathology. Critically, in order to alleviate the enormous burden of chronic pain without exacerbating the co-occurring substance misuse crisis, we emphasize the need to find better approaches to treat and prevent chronic pain.

KEYWORDS

stress, chronic pain, ventromedial prefrontal cortex, sex differences, substance use

1. Introduction

While 1 in 5 Americans suffer with chronic pain (1), the understanding of why and how chronic pain develops remains ambiguous. Chronic pain is defined as pain that persists or recurs for over 3 months [per International Classification of Diseases, ICD-10 (2)] or 6 months [per National Pain Strategy and NIH Task Force (1, 3)]. Chronic pain significantly impacts individuals' ability to work and maintain relationships and is significantly associated with emotional distress or depressive symptoms (4–7). In the clinical setting, opioid analgesics remain the mainstay of chronic pain treatment (8), despite evidence that chronic opioid treatment for chronic pain is not an effective pain management approach and development of novel therapies for pain and chronic pain is a national priority (9). In patients whose chronic pain motivates them to use prescription

opioids for pain relief, there is an increased prevalence of comorbid mental health conditions including substance misuse and substance use disorders, emotional difficulties (e.g., depression, anxiety) and even suicidal ideation (10, 11). The prevalence and toll of chronic pain implore us to better understand the patterns and underlying pathophysiology of chronic pain in order to alleviate its burden.

2. Key features of chronic pain

We first look at patterns in chronic pain from an epidemiological perspective. Across studies, it has been shown that women are significantly more likely to develop chronic pain than men for certain types of pain syndromes (12–15). Additionally, mood and anxiety disorders commonly co-occur with chronic pain (4), and substance misuse tends to heighten individuals' experiences of pain. Exploring these features of the chronic pain population may help in identifying potential mechanisms that underly the development of chronic pain and uncover important targets for intervention.

2.1. Sex differences

There is a greater prevalence of chronic pain in women vs. in men in certain types of pain conditions (12). This greater prevalence of chronic pain in women has been reported for the following conditions: back pain, migraine, musculoskeletal pain, neuropathic pain, oral pain, osteoarthritis, and widespread pain (16). Such evidence suggests that evaluating sex differences in chronic pain development and experience can help parse potential biologic and psychologic underpinnings of chronic pain.

Animal models have shown the existence of physiological differences between males and females that affect pain sensation (14). For example, relative to male animals, females have slower recovery following chronic constriction injury, have earlier pain presentation in a model of femoral cancer, and have more fatigue-induced hypersensitivity to pain (17–19). Furthermore, female mice require more morphine to achieve an equal analgesic effect to male mice (20). This sex difference in opioid analgesic tolerance in preclinical studies is consistent with findings in clinical studies of women and men (21).

Previous studies have shown sex differences in the endogenous opioid system and the cannabinoid system (22, 23). Both pathways are involved in processing pain, pain coping and self-regulation of pain (22, 24). It has been shown that female sex is associated with lesser activation of anti-nociceptive signaling through mu opioid receptors, which could mediate their greater sensitivity to pain (25). Studies on sex differences in the endocannabinoid system reveal significantly greater CB1 activation in female vs. male hippocampus (26), greater sensitivity in response to cannabinoid ligand in females than males (27), and faster development of tolerance to cannabinoid ligands in females vs. males (28). Changes in protein expression in the endogenous cannabinoid pathway coincide with development of chronic pain conditions

(29). In addition, the endocannabinoid system is also involved in stress regulation and coping (30) and animal studies have shown that increased levels of the two main endocannabinoids—2-Arachidonoylglycerol (2-AG) and anandamide (AEA)—promote resilient coping following stress (31, 32).

2.2. Role of chronic stress in vulnerability for chronic pain

Chronic stress has been shown to predict development of chronic pain (33, 34). Chronic stress occurs when an individual experiences sustained emotional or physiological challenges continuously over a significant period of time, leading to “wear and tear on the body” (35). Long-term stress has been shown to sensitize individuals to pain, a phenomenon known as stress-induced hyperalgesia (36–39). Bolstering this hypothesis, Ide et al. showed that unpredictable chronic mild stress reduced the pain-relieving effects of morphine in mice (40). Clinically, it has been shown (41) that a greater number of adverse events increases the risk for chronic pain development, as well as the experience of chronic stress. Furthermore, recent evidence suggests a biological link between stress experience and pain; individuals with a history of Adverse Childhood Experience (ACE) were found to have specific epigenetic changes involving a gene associated with setting individual pain thresholds (42). However, the relationship between chronic stress, chronic pain, and relationship of both to opioid use has not been explored within the same samples and we present secondary data below to illustrate this association.

2.3. Chronic stress and pain co-occurrence in a large community sample

In a large sample of 947 young-mid age community adults [18–55 years of age; 56% women; mean age 30.7 (s.d. = 9.95) years] who were not acutely ill psychiatrically or medically, and did not have current or past opioid use disorder (OUD) as assessed by the Structured Clinical Interview for DSM-IVTR [SCID-I (43)], we assessed chronic stress using the Cumulative Adversity Index, a structured interview assessment of cumulative adversity and stressful life events [CAI (44)], and also number of pain symptoms using the Cornell Medical Index (45). The Chronic Stress Subscale of the Cumulative Adversity Interview (CAI) consisted of 62 items relating to the subjective experience of continuous stressors or ongoing stressful life events and problems. Items were rated as not true, some to very true for perceived difficulties with specific ongoing interpersonal, social, and financial relationships and responsibilities including difficulties in the work and home environment and relationships with family and significant others. The Cumulative Adversity Interview and its chronic stress subscale has high reliability ranging from an overall 0.86 and 0.82 for the chronic stress subscale (46).

Cornell Medical Index is a questionnaire that poses “yes” or “no” questions about individuals’ current occurrence of physical and emotional health symptoms, including specific types of pain symptoms. In addition to current symptoms, it also asks subjects to indicate whether they have been diagnosed with specific illnesses, and about health habits, like smoking (45). The CMI is verified across multiple studies as a good indicator of general health (47, 48).

In this large community sample, we found that women reported greater average number of pain symptoms ($t = 5.6$, $p < 0.001$) and higher levels of chronic stress ($t = 5.5$, $p < 0.001$) compared to men (Figure 1A). In all participants, higher chronic stress was positively associated with greater pain symptoms [Figure 1B; incidence rate ratio (IRR) = 1.08, $p < 0.001$]. Further, greater likelihood of taking opioids was predicted by both greater number of pain symptoms (Opioids: OR = 1.52, $p < 0.026$) and high chronic stress (Opioids: OR = 1.58, $p < 0.001$) (Figure 1C).

These patterns of high co-occurrence of chronic stress with chronic pain are consistent with previously cited research on the association between stress and chronic pain and further highlight that each is associated with an increased risk of opioid use in a large community sample. Moreover, female sex was associated with experiencing more chronic stress and pain, supporting previously reported vulnerability of women to related chronic stress and pain dysfunction and association with opioid misuse. While these are cross-sectional data from a large non-clinical

community sample, they point to a need to further examine the basis of the associations between chronic pain and chronic stress in a longitudinal manner and assess sex differences in order to further understand the mechanisms underlying the development of chronic pain.

2.4. Comorbidities with negative affect and depressive disorders

It has been well-established that chronic stress can produce long-term emotional distress (49–51). As there is a positive correlation between chronic stress and physical distress, it is important to explore the interaction between incidence of long term emotional and physical pain. Data from the World Mental Health surveys show that pain conditions strongly correlate with negative affect in communities across the world (4, 5). Furthermore, Gerrits et al. have shown that individuals with current or history of anxiety or depression report experiencing more severe pain and pain in more locations than healthy controls (52). The relationship is reciprocal: within pain populations, there is greater prevalence of depressive symptoms, and within clinically depressed populations, there is more chronic pain (53). Comorbid mood disorder and chronic pain lead to poorer prognosis in both conditions than in patients with one of the two conditions alone (54). Long-term use of opioids

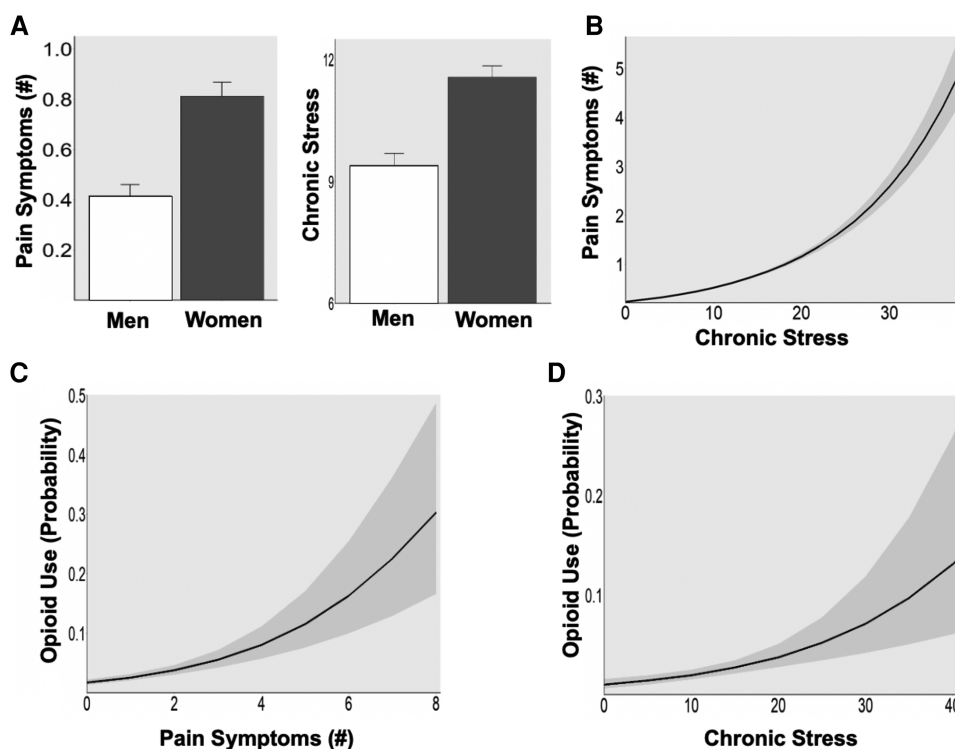


FIGURE 1

(A) Sex difference in pain symptoms and chronic stress. Women showed greater pain symptoms ($p < 0.001$) and higher chronic stress ($p < 0.001$) than men in a large community sample ($N = 947$). (B) Association between stress and pain. High chronic stress was associated with greater pain symptoms in all participants ($p < 0.001$). (C) Pain and opioid use. The probability of opioid use increased with greater pain symptoms ($p < 0.001$). (D) Stress and opioid use. The probability of opioid use increased with higher levels of chronic stress ($p < 0.001$).

for pain conditions correlates with an increased probability of new-onset depression (55). In the reverse direction, chronic pain patients with comorbid mood disorders are more likely to escalate long-term opioid use than chronic pain patients without mood disorders (56). This comorbidity further highlights the need to understand the emotional aspects of chronic pain in order to effectively prevent and treat chronic pain and associated mental illnesses.

2.5. Coping with pain and stress: relationship to pain catastrophizing

In the face of stress and pain, the methods by which different individuals cope can alleviate or aggravate pain. Over time, researchers have studied the relationship between the pain experience and catastrophizing, the latter being defined as an “exaggerated negative ‘mental set’ brought to bear during painful experiences” (57). Across pain conditions, catastrophizing proves to exacerbate intensity and emotional distress accompanying pain (57–59), and also increases the risk of developing chronic pain (60–62). Importantly, multiple sub-populations of individuals who tend to catastrophize overlap with those overrepresented in the chronic pain population. Women tend to catastrophize more than men (63, 64). Patients with depression and anxiety show higher levels of catastrophizing in the face of distress (65), and catastrophizing has been shown to play a mediating role in the relationship between depression and pain (66). Patients reporting higher adverse childhood events exhibited greater levels of catastrophizing and perceived lower confidence in their ability to cope with their pain (33). The latter highlights the need to consider domains of coping and self-regulation in exploring the neural mechanisms of chronic pain and to develop not only a greater understanding of chronic pain, but also to identify specific components that must be addressed in its treatment.

2.6. Chronic pain and substance misuse

Substances of abuse have been shown to induce hyperalgesia, a state of hypersensitivity to pain. In opioid misuse, specifically, the phenomenon of opioid-induced hyperalgesia has been shown across preclinical and clinical models (67). In addition to hypersensitivity to pain, periods of withdrawal from chronic substance misuse creates a state of “hyperkatifeia”, or increase in intensity of negative emotional state (68, 69). The combination of heightened pain state and worsened negative emotional state may then motivate drug use dose escalation, a path by which many patients progress from opioid use to dependence (70). Furthermore, chronic pain is associated with social isolation, and opioid use has been shown to temporarily alleviate such loneliness (11, 71). However, chronic opioid use can exacerbate social isolation, contributing to the negative emotional state that then drives opioid dependence and contribute to the drug overdose mortality rate (71).

In addition to opioid use, chronic alcohol use sensitizes users’ nociception (72). As with opioid-induced hyperalgesia, this alcohol-produced painful state has been shown to motivate escalation of alcohol use in models assessing vulnerability for alcohol use disorders (73). Similarly, when individuals with cannabis use disorder attempt to stop using cannabis, many experience withdrawal involving heightened states of emotional and physical pain that can drive cannabis dependence (74). This cyclic pattern of chronic pain leading to drug use, and drug use leading to heightened physical and emotional pain states highlights the need to develop better assessment of substance-related hyperalgesia in individuals with chronic pain. Furthermore, understanding how substance misuse may facilitate development of heightened pain states can provide insight into pathways that may mediate the development of chronic pain and how best to treat such co-morbidity.

In summary, the key features associated with development of chronic pain include chronic stress and cumulative adversity experiences, mood and anxiety comorbidity, substance misuse risk and sex differences in pain experience for certain types of pain conditions and in the development of chronic pain. Additionally, specific types of pain coping may also increase risk of development of chronic pain. Notably, adverse stressful experiences in early life or during vulnerable periods of illness or adversity may increase chronic pain via epigenetic mechanisms by changing stress genes and changes in genes that support microglia during neuronal development (75, 76). Such epigenetic changes may alter the structure and function of neural circuits involved in regulating stress and pain, thereby reducing stress coping and increasing nociception. Thus, the next section explores the overlap in functional neural mechanisms of chronic stress and chronic pain and discusses the clinical implications.

3. Overlapping neural circuits in chronic pain and chronic stress

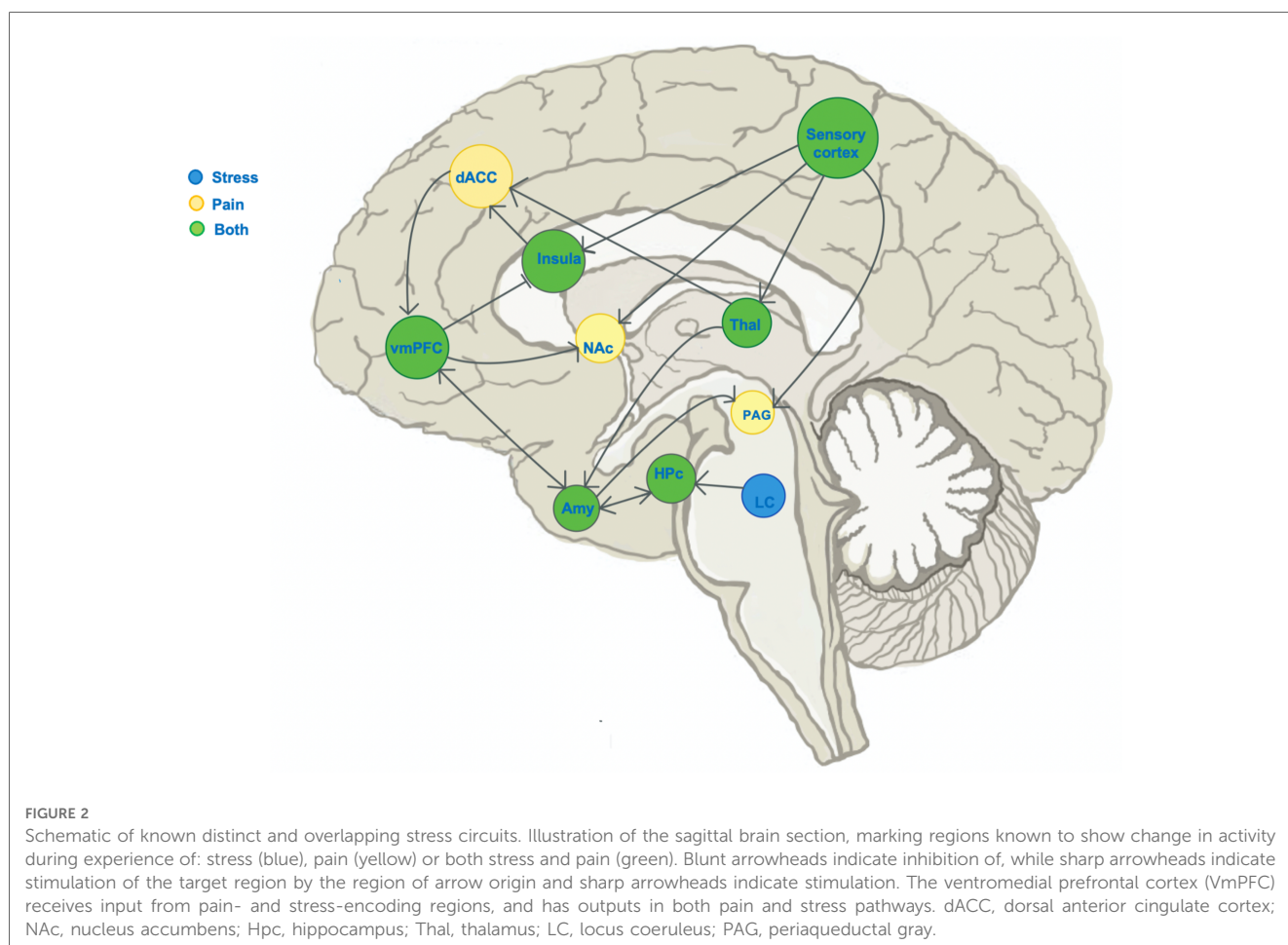
Recent evidence focusing on understanding the pain experience in humans, has identified a Neurologic Pain Signature (NPS), a defined pattern of brain functional magnetic response imaging (fMRI) activity underlying the pain experience (77). Evidence shows the NPS can be divided into a nociceptive component and a self-regulatory component (78–81). While regions such as the somatosensory cortices, dorsal anterior cingulate cortex (dACC), and thalamus are known to react to noxious stimuli and to signal pain experience, fronto-striatal circuits have been shown to mediate top-down self-regulation of pain (78, 79). Specifically, the nucleus accumbens (NAc)-ventromedial prefrontal cortex (VmpFC) pathway has been shown to act as an anti-nociceptive region (80), with increased blood-oxygen-level-dependent (BOLD) activity in the VmpFC inversely relating to pain (81). Recent research has also shown significant abnormalities in functional connectivity of the VmpFC and NAc and other fronto-striatal regions during resting state in individuals with chronic pain on prescription opioids compared to drug free

controls, further supporting the importance of this circuit in regulating nociception (82). Importantly, studies from animal models and clinical research show that dysfunction of the medial prefrontal cortex, a key component of this self-regulatory pathway, mediates the development and persistence of chronic pain (83–86).

Similar to pain encoding in the brain, stress processing involves both stress-sensing components as well as top-down regulation of stress circuits and the stress experience. Acute stress activates the hypothalamic-pituitary-adrenal axis, which receives top-down regulatory input from the VmPFC (35, 87). Flexible and adaptive VmPFC function is necessary to “turn off” stress once fearful stimuli are gone (88, 89), and impaired VmPFC function is observed in patients with post-traumatic stress disorder (90). The VmPFC’s role in top-down control of both emotional and physical distress makes this region a key area of interest when studying the development of chronic pain, given the simultaneous epidemiological overlaps in emotional and physical pain. We focus specifically on the self-regulatory component of pain and stress circuits because of the clear anatomical and functional overlap in brain circuits across both stress and pain. (See **Figure 2** illustration of the known neural circuits of pain and stress and their overlap.)

3.1. Ventromedial PFC (VmPFC) and the self-regulation of pain and stress

Activity in the ventromedial prefrontal cortex has been shown to function as an anti-nociceptive neural signal (80). Chronic back pain patients were found to have reduced medial PFC (mPFC) gray matter volume (91). In a study that tasked participants with utilizing strategies to regulate their pain experience, activity in the VmPFC and nucleus accumbens were greatest when participants were actively trying to down-regulate pain (78). In a separate study of brain activity and the effects of opioid analgesia during experimental pain, baseline striatal activity was correlated with greater opioid-induced pain relief (92). As cited earlier, McConnell et al. (82) also show dysfunction in this corticostriatal circuit in chronic pain patients using prescription opioids and such dysfunction related to greater negative affect. Other work has bolstered this finding showing that using cognitive strategies that rely on mPFC circuits to distract attention from painful experiences relies on opioid-ergic networks that gate nociceptive input at the level of the spine (93). In the context of the previously noted sex differences in the endogenous opioid system, and its relation to pain processing, it will be important to explore these neurobiological circuits as it relates to predisposition to chronic pain in men and women.



If the VmPFC is necessary in self-regulation of pain, we may expect that factors known to increase the risk of developing chronic pain—like chronic stress—do so by contributing to VmPFC dysfunction. In addition to pain regulation, the VmPFC is a crucial region for adaptive coping (94) and emotion regulation (95, 96). It is involved in the self-control and regulation of emotions of both stressful (97) and rewarding nature (98). Studies on the effects of chronic stress—a known predisposing factor of chronic pain—on brain structure and function reveal that chronic stress is associated with anatomical and functional changes in the VmPFC. Chronic stress is associated with lower gray matter volume in the mPFC, VmPFC, striatum and insula (46). Chronic stress is known to increase inflammation through the peripheral and central nervous systems (76), and such inflammation is thought to contribute to the development of psychiatric disorders in patients who endured chronic stress (99). Furthermore, stress-induced inflammation is associated with disruptions in functional connectivity in the VmPFC in patients with depression (100). VmPFC and other prefrontal disruption has also been documented in patients with alcohol use disorder and substance use disorders (101–104). Taken together, these findings suggest that pathology of the VmPFC may mediate the effects of chronic stress on self-regulatory pain mechanisms.

3.2. Stress, pain, and hypoactive VmPFC response

In a previous study, we examined the association between cumulative adversity, including chronic stress, health symptoms and neural responses to stress vs. no-stress neutral cues in 75 healthy community adults with no history of depression, anxiety or substance use disorder (105). Cumulative adversity and chronic stress were assessed using the Cumulative Adversity Index (CAI) along with the Chronic Stress Subscale, and physical and emotional health symptoms were assessed using the Cornell Medical Index (CMI) and each of these are described in Section B3 above. In those with a history of cumulative stress and adversity, findings revealed a key neurofunctional link such that higher CAI scores corresponded to greater limbic-striatal (e.g., regions of the amygdala, hippocampus, insula, and striatum) responses to acute stress stimuli, but reduced stress-related activity in the orbitofrontal cortex (OFC), a region of the VmPFC, involved in emotion, pain, and reward self-regulation. Furthermore, hyperactivation of the hippocampus and hypoactivation of the OFC/VmPFC region was each significantly associated with greater overall number of health symptoms.

These findings suggest that higher levels of adversity and chronic stress may sensitize individuals to higher neural stress reactivity in emotional- and distress-sensing regions while simultaneously compromising responses of the VmPFC self-regulation region during acute stress with significant impact on health. This pattern is most clearly revealed in a direct comparison of those with the highest cumulative stress levels (High Stress—top one third of the sample, $N = 25$) as compared

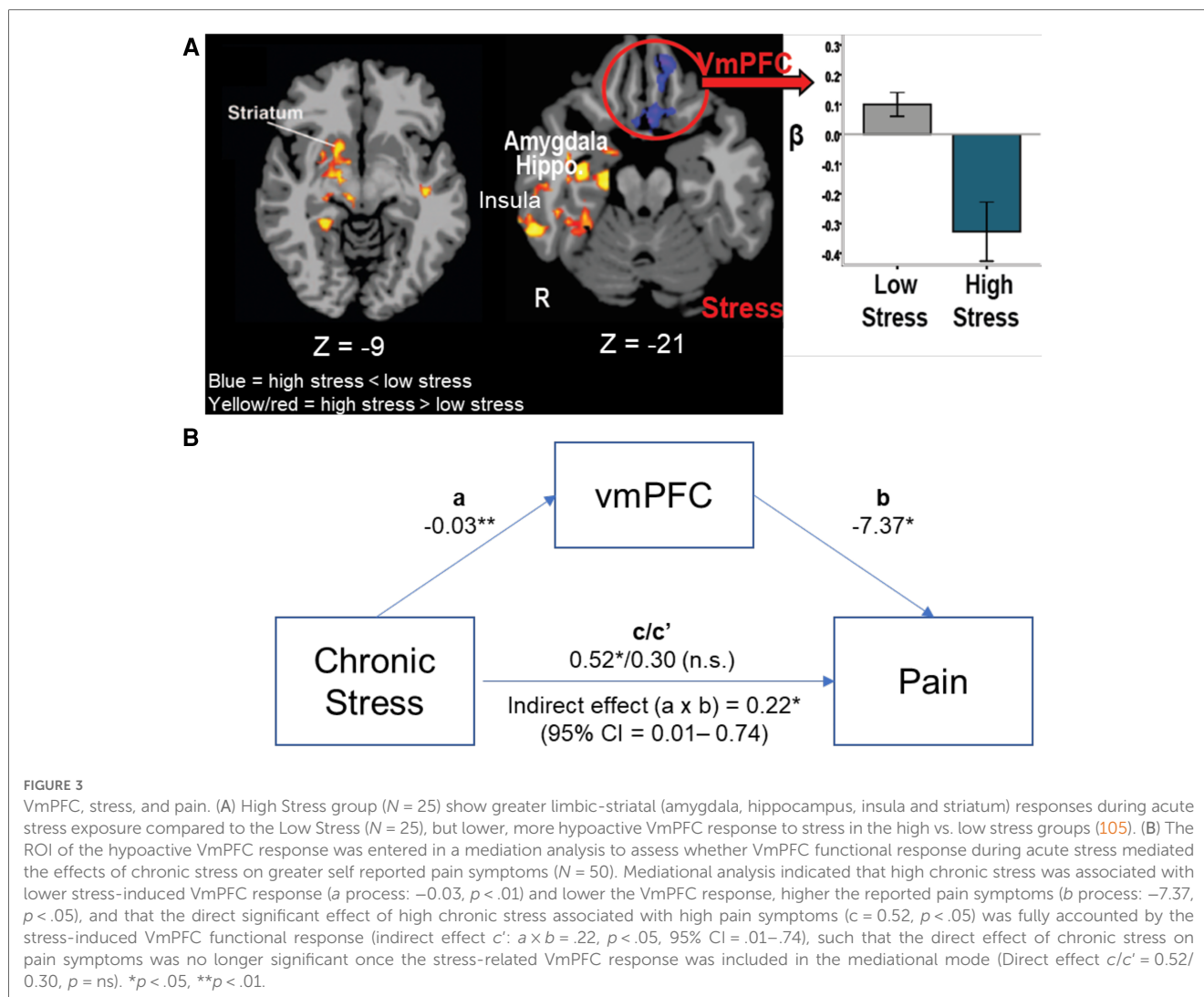
to those who report lowest cumulative stress levels (Low Stress—bottom one third of the sample, $N = 25$) as shown in **Figure 3A** [from Seo et al. (105)]. Furthermore, in a separate study of 30 community adults, we assessed the functioning of the VmPFC over several continuous minutes of sustained stress exposure and demonstrated that dynamic and flexible activity in the VmPFC during stress mediates active coping in stressful situations (106). Thus, it could be expected that deficient VmPFC engagement, as shown in **Figure 3A**, among high stress individuals may interfere with not only active stress coping, but also with active top-down regulation of pain.

To follow up on the hypothesis presented above, we conducted secondary whole brain analyses of the data presented in Seo et al. (97) to specifically examine whether the VmPFC is involved in predicting pain symptoms in the high and low stress stress groups described above, and tested its specific role in mediating the link between chronic stress and pain symptoms by conducting a mediational analysis. The VmPFC region of interest (ROI) beta values were extracted from the whole brain analysis (results shown in **Figure 3A**) for the High Stress and Low Stress groups ($N = 50$). The chronic stress scores from the CAI and the number of physical pain symptoms in the sample of High and Low stress groups from the Cornell Medical Index (CMI, described above in Section 2.2) were included in a mediational analysis to assess whether chronic stress predicts physical pain symptoms and whether the acute stress response of the VmPFC mediates the link between high chronic stress and higher pain symptoms. Indeed, the findings of this secondary follow-up analyses reveal that the blunted acute stress-induced VmPFC response significantly mediated the relationship between chronic stress and self-reported pain symptoms (**Figure 3B**).

These findings support the hypothesis that cumulative and chronic stress may negatively impact the VmPFC, compromising self-regulatory control over the stress-pain circuit, leading to risk of greater physical pain symptoms. Together, these findings also support the hypothesis that VmPFC may serve as a common overlapping neural region that may underlie the high association between chronic stress and increased vulnerability to chronic pain. On the basis of this neurobiological overlap, a heuristic *feed-forward* model on the overlap of chronic pain, chronic stress and substance misuse risk is proposed in **Figure 4**, wherein chronic stress states alter VmPFC related circuits that regulate stress, reward and pain. A dysfunctional VmPFC circuit then results in risk of greater acute pain experience and poor self-regulation of pain that, in turn, increases the risk of sustained pain symptoms and development of chronic pain (**Figure 4**).

3.3. Summary on overlapping processes of chronic stress and chronic pain

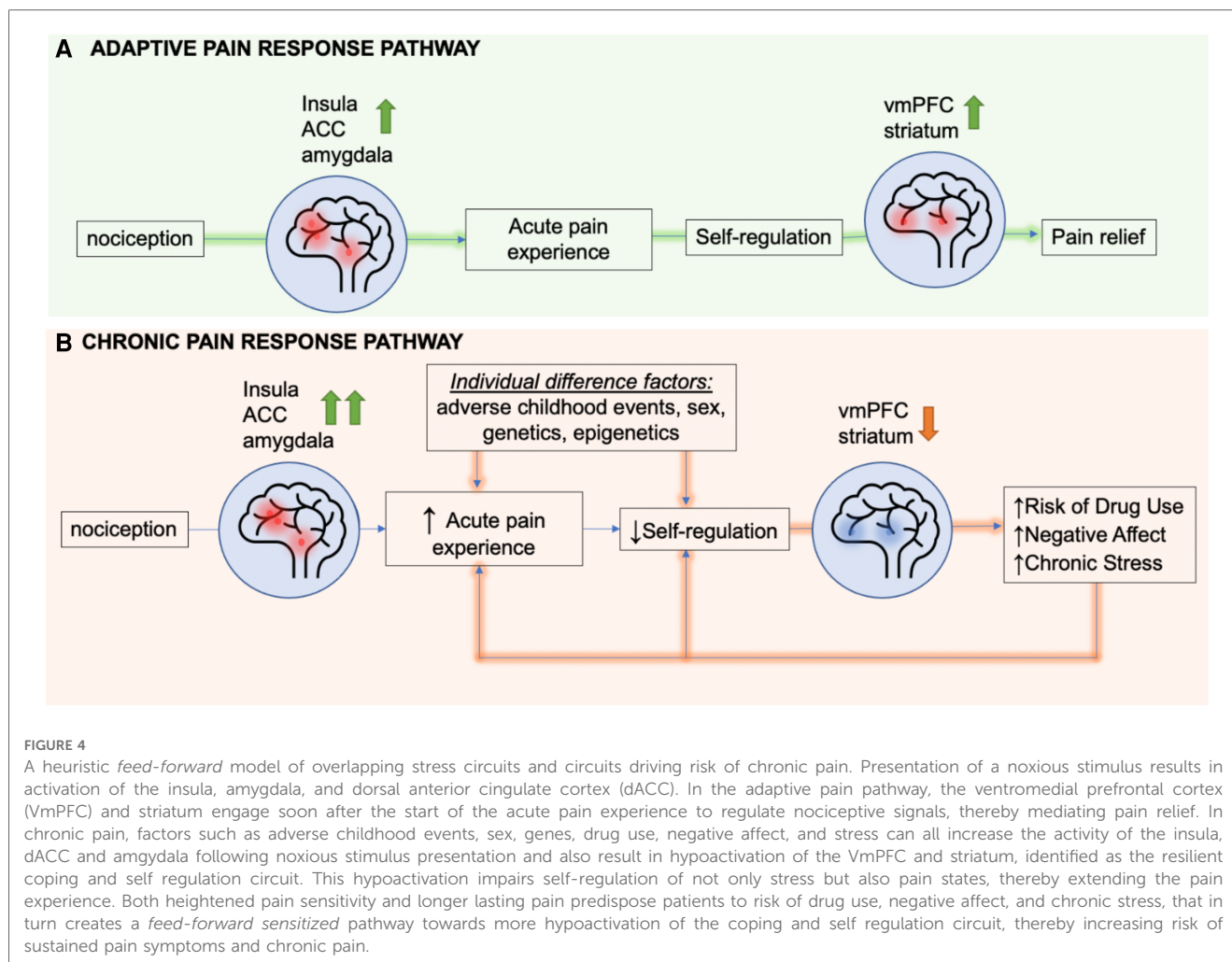
In this section, we address the neurobiological link between pain and stress, substance use, and sex differences. Critically, the VmPFC is a neurobiological focus in the neural circuits underlying each of these conditions and appears to be a key region mediating the relationships amongst these variables. Many



studies have pointed to the overlap between stress and pain circuits (7). In individuals with a history of early life stress, as well as those with current diagnoses of post-traumatic stress disorder, imaging studies show a blunted VmPFC stress response (107, 108, 109). Early life stress has been linked specifically to VmPFC hypoactivation (38, 110). Patients with alcohol use disorder show a similar VmPFC dysfunction in response to stress (101). These same circuits are also dysfunctional in patients with chronic pain using prescription opioids (82). A decrease in prefrontal activity has also been shown to be correlated with increased levels of pain catastrophizing (111). Conversely, an increase in VmPFC responding during stress has been associated with higher levels of active coping (106). Furthermore, the VmPFC is a key region regulating limbic and striatal regions, regions responsive to stress and reward stimuli respectively. As reviewed in above sections, substantial neurobiological evidence indicate that the VmPFC- limbic-striatal circuit may underlie the pathology of co-occurring chronic pain and chronic stress. Given that the VmPFC exerts regulatory control over subcortical regions involved in stress (e.g., amygdala) and reward (striatum) processing, VmPFC dysfunction in individuals with chronic pain may increase risk of

common comorbid conditions including depression, anxiety, prescription opioid misuse and other substance use disorder (SUD). Initially, individuals with chronic pain may experience pain symptoms alone. However, as their symptoms worsen, they are likely to experience pain, distress, and emotional difficulties (e.g., depressed and anxious mood) resulting from sensitized VmPFC- limbic-striatal circuit governing both pain and stress as shown in Figure 4. Continued chronic pain and distress are likely to further compromise this circuit, weakening the VmPFC control over the striatal regions (reward system). The subsequently disinhibited striatal system may result in difficulties controlling an urge to use substances (e.g., opioid, alcohol, and other substances), and to cope with pain and emotional distress, further increasing the risk of other comorbid conditions including depression, anxiety, and SUD in individuals with chronic pain.

Although this pattern can occur in both men and women, given some evidence of sex differences in prevalence of chronic pain subtypes (12) and high prevalence of affective disorders in women (112, 113), it is likely that there are sex differences in the manifestation of this pathology, and therefore further research in



both men and women is needed to understand pain-related dysfunction in the VmPFC-limbic-striatal circuit. In support of this, our group has shown that sex differences in stress responding are mediated by the VmPFC. While dorsomedial activity tends to attenuate the stress response in men, VmPFC activity seems to dampen stress reactivity in women (114). Thus, hypoactivity of the VmPFC in women may lead to difficulties with controlling striatal and limbic response to stress and reward stimuli, which may explain high prevalence of chronic pain, and co-occurring emotional disorders in epidemiological studies.

4. Clinical implications

Our current pharmacological approaches to treating chronic pain target the opioid, gamma-aminobutyric acid (GABA), and cannabinoid systems (115–117). As noted earlier, opioid agonists are commonly prescribed for chronic pain conditions, but chronic opioid use itself may exacerbate chronic pain. We have reviewed findings on opioid-induced hyperalgesia, and the processes by which opioids may hypersensitize individuals to risk of chronic pain. In addition, our group has shown that opioid-dependent individuals are less likely to employ adaptive coping

strategies (118), and report higher chronic stress and traumatic experiences (119) which may further exacerbate hyperalgesic responses. As we have also reviewed, self-regulation of pain relies on neural mechanisms involved in adaptive coping. Thus, chronic opioid use may in fact simultaneously exacerbate the nociceptive aspect of pain while inhibiting individuals' ability to self-regulate pain. Notably, opioids may be creating a feed-forward cycle that ultimately worsens, rather than alleviates, the experience of chronic pain (shown in Figure 4).

Alternatives to opioid treatment include medications that alter neurotransmitter signaling upstream of, downstream of, or in parallel with endogenous opioid pain-gating (120). For example, serotonin noradrenergic reuptake inhibitors (SNRIs) are often used to treat chronic pain comorbid with anxiety and emotional distress (121–123). Gabapentinoids, whose effect is mediated directly by binding to voltage-gated calcium channels, but perhaps indirectly by altering GABAergic and glutamatergic activity (124–126), are first-line treatment for neuropathic pain (121, 127). Additionally, cannabinoid agonists are rising in popularity for pain treatment, and self-motivated use of medicinal cannabis for pain and stress relief is increasing in the US (128, 129). There is also some evidence that tetrahydrocannabinol can reduce dysfunctional corticomesolimbic

connectivity in those with chronic pain (130). However, there is a desperate need for testing of medicinal cannabis products that are non-addictive and for novel non-addictive agents and approaches for pain treatment. As more analgesic agents are introduced, it is crucial that we understand how these substances may interact with the pain circuitry in the brain, and especially pain regulatory pathways of the VmPFC and striatal circuits and their impact on the risk of developing chronic pain. In addition, pain management combined with stress management will be beneficial for the treatment for chronic pain given the substantial overlap between stress and pain pathways. Recent work has shown the effectiveness of mindfulness-based stress reduction, acceptance and commitment therapy (ACT) and cognitive behavioral therapy in chronic pain treatment (131–133). Both psychological strategies and carefully studied pharmacologic solutions may ultimately provide more successful pathways to managing chronic pain without exacerbating the condition or creating new adversities.

Author contributions

JS and RS conceptualized, planned and wrote the review. NF and DS conducted secondary analyses and provided feedback and editing to finalize the manuscript. All authors contributed to the article and approved the submitted version.

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