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Chronic Pain and Psychiatric Conditions

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Chronic pain · Psychiatric conditions · Genetic correlation · Comorbidity

Abstract
Introduction: Chronic pain is a common condition with high socioeconomic and public health burden. A wide range of psychiatric conditions are often comorbid with chronic pain and chronic pain conditions, negatively impacting successful treatment of either condition. The psychiatric condition receiving most attention in the past with regard to chronic pain comorbidity has been major depressive disorder, despite the fact that many other psychiatric conditions also demonstrate epidemiological and genetic overlap with chronic pain. Further understanding potential mechanisms involved in psychiatric and chronic pain comorbidity could lead to new treatment strategies both for each type of disorder in isolation and in scenarios of comorbidity. ***Methods:*** This article provides an overview of relationships between DSM-5 psychiatric diagnoses and chronic pain, with particular focus on PTSD, ADHD, and BPD, disorders which are less commonly studied in conjunction with chronic pain. We also discuss potential mechanisms that may drive comorbidity, and present new findings on the genetic overlap of chronic pain and ADHD, and chronic pain and BPD using linkage disequilibrium score regression analyses. ***Results:*** Almost all psychiatric conditions listed in the DSM-5 are associated with increased rates of chronic pain. ADHD and BPD are significantly genetically correlated with chronic pain. Psychiatric conditions aside from major depression are often underresearched with respect to their relationship with chronic pain. ***Conclusion:*** Further understanding relationships between psychiatric conditions other than major depression (such as ADHD, BPD, and PTSD as exemplified here) and chronic pain can positively impact understanding of these disorders, and treatment of both psychiatric conditions and chronic pain.
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Introduction

Chronic pain, broadly defined as pain persisting beyond a period of 3 months, is a highly prevalent condition [1, 2] with significant negative socioeconomic and quality-of-life impact [3]. Chronic pain is a core feature of a range of conditions, as well as presenting as a primary disorder (as recently outlined for the ICD-11, [4, 5]). Mechanisms of development, and factors contributing to increased likelihood of development of chronic pain, are not fully understood, and treatment and management can be less effective as a result. Chronic pain is often comorbid with psychiatric conditions, with one of the most well-studied psychiatric conditions in relation to chronic pain being major depressive disorder (MDD). However, almost every psychiatric diagnosis in the DSM-5 is also

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associated with increased rates of chronic pain, and for many psychiatric disorders, this chronic pain relationship is understudied, particularly in personality disorders and neurodevelopmental disorders such as attention-deficit hyperactivity disorder (ADHD).

Importantly, comorbid psychiatric disorder and chronic pain can often contribute to worse outcomes for the individual, as compared to having chronic pain in the absence of psychiatric disorder and vice versa. For example, treatment of chronic pain with SNRI monotherapy [6] in a person with comorbid bipolar disorder can be dangerous and induce mania [7, 8].

Comorbidity between chronic pain and psychiatric disorder could indicate shared neurobiological mechanisms, and so understanding this overlap can inform effective, safe treatment and add to understanding of both chronic pain and psychiatric disorder etiology. In this review, we discuss the relationship between psychiatric disorders and chronic pain, presenting broad evidence for co-occurrence of chronic pain and a range of psychiatric disorders, and discussing potential underlying biological mechanisms of these comorbidities. We focus in particular on three psychiatric disorders with as yet understudied relationships with chronic pain: post-traumatic stress disorder (PTSD), borderline personality disorder (BPD), and ADHD. This knowledge gap may have particularly devastating consequences in cases of chronic pain comorbidity.

Section 1: Epidemiology of Psychiatric Disorders and Chronic Pain

Prevalence of chronic pain and chronic pain disorders is higher in populations with a range of psychiatric disorders compared to those without (Table 1; online suppl. information; for all online suppl. material, see www.karger.com/doi/10.1159/000527041). Some of these relationships are more well studied and understood than others – e.g., there is a large body of literature on the relationship between major depression and chronic pain [1, 9–18]. In contrast, chronic pain comorbid with personality disorders, such as BPD, and neurodevelopmental disorders, such as ADHD and autism spectrum disorder, is less well understood. Although neurological disorders and associated neurocognitive disease are referenced in the DSM-5, the relationship between neurological disorders and chronic pain has been reviewed elsewhere [19–21], and is beyond the scope of this article.

PTSD occurs following exposure to traumatic or stressful life events [97, 98], and presents with symptoms grouped (following DSM-5 diagnostic criteria) into 4 categories: intrusion, avoidance, negative changes to mood and cognition, and arousal/reactivity changes. Lifetime prevalence of PTSD in adult Americans has been estimated at ~6–7% [97, 98] and at 15.3–26.53% in conflict-affected populations [99, 100]. Other studies have shown similar rates of PTSD between US civilian and veteran populations [101, 102]. PTSD in both veterans and civilians is associated with increased rates of chronic pain [103, 104]. Chronic pain may also represent a significant stressor and inciting event for an adjustment disorder [105] or development of PTSD [106], particularly if the pain is associated with (or caused by) an injury sustained at the time of the index trauma – direct exposure (e.g., injury on 9/11) has been found to be a significant risk factor for subsequent PTSD [107–109]. Higher pain levels in the early post-injury period are also associated with increased risk of later PTSD symptoms [110, 111].

BPD is characterized by affective dysregulation and an unstable sense of self, in addition to chronic self-destructive behaviors [112–115]. BPD is common in both general population and clinical settings, with point prevalence and lifetime prevalence in US general population samples found to be 1.6% and 5.9%, respectively [116]. In populations meeting criteria for personality disorder diagnosis of all kinds, chronic pain is more prevalent compared to populations without personality disorder diagnoses [117], and having BPD comorbid with a chronic pain condition is associated with worsening chronic pain symptoms [118]. Those with BPD also report more pain and chronic pain compared to the general population [119–121]. BPD has also been associated with worse pain symptoms even in comparison with other personality disorders [122]. BPD also shares significant diagnostic cross-over with complex PTSD [123, 124], and both conditions often occur together [125].

Finally, ADHD is a common neurodevelopmental disorder, with symptoms of developmentally inappropriate inattention, impulsivity, and hyperactivity, with diagnosis according to DSM-5 requiring symptom onset before age 12 [114, 126]. Prevalence is estimated at 2.8% in adult populations [127]. As well as pain perception changes in adolescents with chronic pain, higher rates of neuropsychiatric conditions, including ADHD, are present in those with chronic pain [128]. Other studies also found a sex-related relationship, where adolescent girls were more likely to have a neurodevelopmental disorder go undiagnosed or misdiagnosed if they also had a chronic pain condition [129]. High rates of ADHD have also been observed in populations with fibromyalgia, a chronic pain condition [130, 131].

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Table 1. Summary of relationships between psychiatric conditions and chronic pain

Psychiatric diagnosis	Specific sub-type (if any)	Comorbidity patterns	Evidence for dysregulation of pain perception?	Specific areas or types of chronic pain?
Schizophrenia spectrum disorders	Schizophrenia	↑ [22] ⇓ [23–25]	Yes [23, 26–29]	
	Other schizophrenia spectrum disorders	↑ [30]		
Bipolar disorder		↑ [10, 31–35]		Migraine [34] General chronic pain [10, 33]
Obsessive-compulsive and related disorders	OCD	↑ [36–38]	Yes [39, 40]	Fibromyalgia [36, 41] General chronic pain [37]
	Body dysmorphic disorder	?		
	Excoriation disorder	?	Yes [42, 43]	
	Hoarding disorder	↑ [44, 45]		
	Trichotillomania	?	Yes [42]	
Neurodevelopmental disorders	Autism spectrum disorder	↑	Yes [46–50]	Gastrointestinal [51–54] Joint pain (hypermobility spectrum disorder) [55, 56]
	Intellectual disability	Mixed [57–61]		
	Other neurodevelopmental disorders*	?		
Feeding and eating disorders	Anorexia nervosa	↑ [62, 63]	Yes [64–67]	Endometriosis-low BMI relationship [68–71]
	Bulimia nervosa	↑ [65, 72]	Yes [67, 73, 74]	Abdominal [74] Migraine, IBS, facial pain [65]
	Binge eating disorder	↑ [75–77]		
	General disordered eating	↑ [72, 78]		
	ARFID	↑ [65, 79]		Abdominal [79]
	Pica	? [80, 81]		Sickle cell [82, 83]
	Rumination disorder	↑ [84]		
Anxiety disorders	Generalized anxiety disorder	↑ [85]		
	Any anxiety disorder	↑ [1, 86, 87]		
	Panic disorder	↑ [36]		
	Social anxiety disorder	↑ [36]		
Depressive disorders other than MDD	Premenstrual dysphoric disorder	? [88–90]		
Substance-related/addictive disorders	Opioid use disorder	↑ [91–94]		
	Alcohol use disorder	↑ [95, 96]		

Arrows pointing upward indicate positive relationship between rates of chronic pain and/or chronic pain conditions and psychiatric disorder; arrows pointing downward indicate negative relationship between chronic pain/chronic pain conditions and this psychiatric disorder. Question marks indicate lack of available research on relationships between chronic pain/chronic pain conditions and this psychiatric disorder. *Other neurodevelopmental disorders were childhood onset fluency disorder, specific learning disorders, motor disorder, tic disorder, stereotypic movement disorder. More in-depth discussion is shown in online supplementary Table 1.

With most psychiatric disorders, comorbid chronic pain negatively impacts treatment and management of both psychiatric and chronic pain symptoms. These negative impacts can be due to more general factors shared across several psychiatric disorders such as differences in communication, or clinician biases, or may be related to factors that are more specific to each psychiatric disorder. Factors can also be loosely described as "above the skin" or "below the skin," with above the skin including social epidemiologic factors such as interactions with others, individual behaviors, and higher level factors such as environment at the neighborhood or country level, and government policies and their implementation and below the skin including genetic and molecular factors [132, 133]. An example of an above-the-skin factor in the relationship between schizophrenia and chronic pain could be differences in access to healthcare for people with schizophrenia [134–136], which then influences chronic pain development. Here, chronic pain is subsequent to schizophrenia in a causal pathway and is related to individual behavior and social epidemiologic factors (healthcare access). In comparison, a potential below-the-skin factor in chronic pain and schizophrenia could be crosstalk between the dopaminergic and immune systems. In the following section, mostly below-the-skin factors are discussed, but impacts on successful treatment involving more above-the-skin type factors are also briefly covered.

Section 2: Potential Causes for and Mechanisms of Overlap with Chronic Pain

Post-Traumatic Stress Disorder

Psychological Factors

Several psychological models to explain chronic pain and PTSD comorbidity have been proposed. These include the shared vulnerability, mutual maintenance, fear avoidance, and the triple vulnerability models. The shared vulnerability model suggests that certain individual differences, such as increased anxiety sensitivity (fear of anxiety-related bodily sensations and the belief these sensations are physically harmful), increase risk of co-occurring PTSD and chronic pain [103, 137], specifically due to increased likelihood of intense emotional reaction to traumatic incidents involving physical injury [138]. Mutual maintenance theory outlines seven components as drivers of comorbid chronic pain and PTSD: anxiety sensitivity, pain acting as a reminder of the traumatic event, attentional bias (where attention is focused on pain and/or trauma cues), avoidance as a coping mechanism, fatigue/lethargy contributing to depression, general fear in both conditions, and finally overwhelming cognitive demands in both conditions, which limit energy and use of healthy coping mechanisms [139]. With fear avoidance, the individual seeks to avoid potentially beneficial movement in fear of pain, exacerbating both chronic pain and PTSD [140, 141]. The triple vulnerability model suggests that three vulnerabilities are required to be present in order to develop a disorder: biological, generalized psychological, and specific psychological vulnerabilities [137, 142, 143] – these could be shared between chronic pain and PTSD, or elements of either disorder could represent one or more vulnerabilities for the other.

Across models, catastrophizing represents a key component and important link between chronic pain and PTSD. Related to this, PTSD networks in the brain representing information about fear become "highly elaborated and accessible," changing attentional bias and interpretation of neutral stimuli (reviewed by [144]) – this is similar to being in a chronic pain state, where networks involved in fear and distress also show increased activity [145–147], and previously neutral sensory stimuli may become noxious and painful (allodynia). Additional theories suggest comorbidity in pain and PTSD could be driven by "pain flashbacks" [148], though this moreso describes pain from injuries happening at the time of trauma.

Genetic Correlation

There is evidence of a shared genetic basis for PTSD and multisite chronic pain (0.41 [149]) and with having at least one chronic pain condition (0.61, men only [150]). In comparison, genetic correlation between schizophrenia and PTSD, and between MDD and PTSD, is ~0.34 [151], and bipolar disorder and PTSD is 0.65 [152]. However, research into potential pathways driving comorbidity is generally scarce (reviewed by [153]).

Opioid and Endocannabinoid Systems

One potential area of mechanistic overlap between PTSD and chronic pain is the opioid and endocannabinoid systems (ECSs). Interactions between adrenergic alpha2 receptors and mu-opioid receptors have an effect on morphine efficacy [154, 155]: when agonists for both receptors are administered together, this can have synergistic effects for pain relief [156]. These adrenergic receptors have also been found to be reduced in those with PTSD [157, 158], and agonists can be used off-label to treat hyperarousal in PTSD [159] and painful conditions [160]. Activation of cannabinoid and mu-opioid receptors in tandem increases efficacy of morphine pain relief, and this activation is also essential for fear extinction [161–163]. Models of PTSD involving conditioning and fear extinction have been outlined, where neutral cues become associated with danger, contributing to hyperarousal [164]. The ECS has also been investigated as a potential therapeutic target in PTSD [165].

Immune Factors

Immune factors also play a key role in both PTSD and chronic pain. Higher levels of inflammatory cytokines have been found in those with PTSD versus those without [157, 166–171], circulating both peripherally and centrally. Other studies show epigenetic changes sustained during trauma may have long-term effects on the immune system and inflammation [172–174]. The immune system and inflammation also play a key role in both acute and chronic pain [175–181].

GABAergic Neurosteroids and the HPA Axis

Another set of compounds that may represent a link between PTSD and chronic pain is GABAergic neurosteroids allopregnanolone (ALLO) and pregnanolone (reviewed by [182–184]). These steroids have an antinociceptive effect in studies of human and rodents [185–190], have been shown to be effective in reducing neuropathic pain [191], and are also found to be reduced in CSF [192, 193] in brain tissue samples [194], and serum [195] of those with PTSD. Some studies also show women with PTSD may have a "block" in the pathway from progesterone to conversion to neurosteroids [196]. ALLO has also been linked to fear extinction in studies of women with PTSD [197].

ALLO neurosteroids exert their action in part by modulation of the HPA axis. Stress activates the HPA, leading to the eventual release of stress hormones (glucocorticoids, cortisol in humans), regulating gene transcription and stress response. In those with PTSD, studies have shown HPA axis dysfunction, with reduced cortisol levels found in those with PTSD versus controls [198–201], which may be due to oversensitivity of the negative feedback loop [202, 203] following a period of chronic overactivation of the HPA axis [204]. Other studies found more mixed results for the relationship between cortisol and PTSD [205]. Evidence for HPA axis dysfunction is more mixed for chronic pain [206–214], and it is not clear whether HPA axis dysfunction in chronic pain is a cause or consequence.

Bone-Derived Neurotrophic Factor

Bone-derived neurotrophic factor (BDNF) expression is altered in a range of brain regions in response to stress (reviewed by [215]), including PTSD, as well as being expressed in many different tissues outside the CNS and playing a part in development [216], and with BDNF-mediated neuroplasticity linked to maintenance of the hippocampus [217–219]. Function and structure of the hippocampus have been shown to be negatively impacted by stress from trauma exposure, and PTSD symptoms have been associated with hippocampal activity (reviewed by [220]). BDNF is also involved in neuroglial proliferation in response to injury and as part of normal development [216, 219, 221].

Treatment and Management Impacts of Comorbidity

PTSD has been found to make painful symptoms worse in veterans [222] and in civilians [223], and those with PTSD and comorbid chronic pain tend to use more analgesic medication (including opioids) than those with chronic pain who do not have PTSD [224, 225] – since risk of substance misuse is higher in populations with PTSD [226–230], this can also have a detrimental impact on successfully treating PTSD and comorbid chronic pain. Also, if chronic stress without achieving hormone homeostasis is associated with PTSD, this can directly impact drug processing and so treatment efficacy [231–233], negatively impacting success of treatments for both conditions.

Comorbidity and potential shared underlying mechanisms can also be positive in terms of treatment: some studies show treatment for PTSD can be helpful in chronic pain, e.g., eye movement desensitization reprocessing [234, 235]. Cognitive behavioral therapy treatment for PTSD has also been found to improve chronic pain symptoms [227, 236], as have a range of other nonpharmaceutical treatments such as narrative exposure therapy, yoga programs, and emotional freedom techniques [227, 237].

Borderline Personality Disorder

Psychological Factors

There are theories that chronic pain is individual failure to self-regulate pain [238], or that a "pain personality" exists [119, 238], referring to specific personality traits that may increase risk of chronic pain development such as reduced self-directedness and increased harm avoidance [239]. Similarly, BPD has been characterized as a pathological inability to self-regulate emotion – these potentially stigmatizing conceptualizations of BPD and chronic pain and their impact on treatment are discussed further below. More recent work conceptualizes BPD as a consequence of stressful or traumatic life events – BPD can be "latent," with severe symptoms only brought on by sufficient stress [240] – developing chronic pain could be this stressor.

Genetic Correlation

In contrast to PTSD and chronic pain, genetic correlations have not previously been calculated between chronic pain, chronic pain disorders, and BPD. This may in part be due to the fact that GWAS and other genetic studies of BPD are relatively small in sample size in comparison with GWAS of, e.g., MDD – recent GWAS sample sizes in BPD range from 2,750 (with 1075 BPD cases) [241] to 8,426 participants in GWAS analyses of borderline personality features (as opposed to diagnosed BPD) [242]). For the purposes of this review, genetic correlation between multisite chronic pain and BPD was calculated using summary statistics from the 2017 GWAS of BPD (see online suppl. Table 2) carried out by Witt et al. [241] and was found to be 0.39 (SE 0.095), comparable to genetic correlation values found between chronic pain and PTSD, and chronic pain and neuroticism [149].

HPA Axis Dysfunction

HPA axis dysfunction has also been implicated in BPD, as "acute" BPD symptoms tend to be stress-reactive (reviewed by [243]). HPA axis dysfunction has also been linked to BPD through its effects on memory (reviewed by [244]). A recent large meta-analysis also found HPA axis changes in individuals with BPD, measured through cortisol levels [245]. Early life stress and childhood trauma, experienced extremely commonly by those with BPD, also affect HPA axis function [246, 247], to the extent that BPD could be conceptualized as a "stress-related neurodevelopmental disorder" [247], with cortisol-related dysfunction worsening with age and BPD chronicity [248].

Opioid and ECS

Similar to PTSD, studies have also highlighted the endogenous opioid system in BPD pathophysiology. The brain opioid theory of social attachment refers to observations that those addicted to narcotics and those involved in "intense" social relationships show similar emotional and behavioral qualities [249], and suggests that feelings of pleasure from social interaction are due to activity of the endogenous opioid system [250]. Degree of opioid receptor availability has been linked to adult attachment styles [251], and administering naltrexone (an opioid antagonist) has been found to reduce feelings of social connection [252]. In BPD, the endogenous opioid system may be dysregulated, contributing to unstable relationships, chronic feelings of emptiness, and increased susceptibility to substance use disorders – an underactive endogenous opioid system, with reduced receptor density, could explain BPD-associated pathological behavior as a way of seeking exogenous opioid satiety [253]. Symptoms may also be explained by an underactive endogenous opioid system leading to an upregulation of opioid receptors [254], leading to lower baseline levels of pleasure being achievable and hyper-sensitized opioid receptor populations [255, 256].

Opioid drug treatments and the endogenous opioid system play a key role in pain, chronic pain, and treatment of pain (reviewed by [257]), emotional pain has been shown to be neurally similar to physical pain (reviewed by [258, 259]), and emotional euphoria associated with, e.g., romantic relationships has been shown to reduce pain [260]. In addition, opioid receptors can be thought of generally as representing the interface between nervous and immune systems in hyperalgesia (reviewed by [261]). Taken together, evidence suggests dysregulation in the endogenous opioid system could contribute to the relationship between BPD and chronic pain.

BDNF

Changes in neurotrophic factors such as BDNF, and associated changes in neuroplasticity, have also been linked to BPD (reviewed by [246]). Changes to methylation at specific promoters of the BDNF gene have been associated with a range of psychiatric disorders including BPD (reviewed by [262, 263]). These neuroplastic changes may alter the way the brain is able to process and react to various stimuli including stress. Neuroplasticity has also been implicated in the transition from acute to chronic pain [264–271].

Treatment and Management Impacts of Comorbidity

Chronic pain has been found to worsen personality disorder symptoms [272], and in the case of BPD clinical severity of pain symptoms is worse for patients who have both chronic pain and BPD [118]. Another concern in the impact of chronic pain on BPD treatment (and vice versa) is increased risk of substance use issues in those with BPD [273–275], particularly if chronic pain treatment involves drug treatment(s) associated with addiction and dependency. This is of particular importance as the overlap between BPD and chronic pain is understudied, and so clinicians and healthcare professionals may be less likely to screen for PDs including BPD in those with chronic pain compared to screening, e.g., MDD or depressive symptoms. BPD is estimated to be 15 times more common in populations with chronic pain compared to those who are pain-free, and in comparison with MDD, studies examining this relationship are relatively scarce (e.g., there are 8 studies from '99–2011 [119]).

Patients with a BPD diagnosis are often stigmatized by healthcare professionals as "difficult" (reviewed by [276]; see also [277–280]). In BPD, in comparison with other psychiatric disorders, symptoms may be seen as the responsibility or failing of the individual instead of part of the disorder: "perceived as purposefully misbehaving rather than experiencing an illness" [281]. There may be parallels in this stigmatization with chronic pain, particularly when chronic pain is not explained by injury, illness, or other physical or medical findings [282], with patients' symptoms (chronic pain) again reacted to as a personal failing – e.g., in studies of adolescents, pain believed to be more medically based (i.e., associated with clear physical signs or injury) was reacted to more positively by healthcare providers [283, 284]. In BPD, this stigmatization can directly negatively impact care, e.g., by affecting patients already heightened rejection sensitivity – clinicians may emotionally withdraw during psychotherapy, which can have devastating effects [277, 279]. The framing of BPD diagnosis and the manner of delivering diagnosis can also have significant effects on subsequent engagement by the patient with services and treatment [285]. Similarly, disbelief of chronic pain patients can cause significant distress and depression (reviewed by [286]; see also [287]). Types of psychotherapeutic interventions under the cognitive behavioral therapy umbrella, in particular dialectical behavioral therapy and acceptance and commitment therapy, aim to improve skills in coping with (physical) distress in the context of chronic pain, and being able to function or attempt to function regardless – this can be compared to the role these therapies play in BPD treatment with aim to increase coping with emotional distress and discomfort (reviewed by [288]).

Attention-Deficit Hyperactivity Disorder

Psychological Factors

Additionally, as implicated in a range of other psychiatric disorders including PTSD and BPD as mentioned above, emotional dysregulation has also been highlighted as a shared aspect in ADHD and fibromyalgia [289]. Executive function deficits are key features of ADHD [290–292] and may also affect attentional processes and so the extent to which positive coping strategies can be used for chronic pain, increasing risk of symptoms both feeling worse and having a greater negative impact on daily functioning [293].

Genetic Correlation

Recent large GWAS, in addition to past twin and family studies [294–296], highlights that ADHD is a complex trait with a genetic component [294]. ADHD is genetically correlated with multisite chronic pain at a value of 0.56 (see online suppl. Table 3) – this is comparable to genetic correlation values seen between chronic pain traits and MDD [149]. Genetic correlation of 0.26 between migraine and ADHD has also been described [297], and Lundberg et al. [298] also note a "positive" genetic correlation value between ADHD and chronic pain (Fig. 1).

Dopamine and ECS

Links between dopamine and ECSs could also be involved in comorbidity between chronic pain and ADHD [299]. The ECS consists of two receptor types, CB1 and CB2. ECS components act as neuromodulators of several neuron types (glutamatergic, GABAergic, serotonergic) aside from dopaminergic and have been linked to a range of psychiatric disorders beyond ADHD [300]. CB2 receptors of the ECS were originally thought to be found entirely peripherally (i.e., outside the CNS), interacting with the immune system to modulate the release of cytokines [301–303]. Later, they were also found in CNS in microglia, neurons, and astrocytes [304–307], whereas CB1 receptors are found primarily in the CNS [308]. The ECS also plays a role in nociceptive signaling and chronic pain [309–312], again involving dopamine transmission and reward circuitry in the brain [312, 313], in addition to being highlighted as a potential therapeutic target in ADHD [299, 314–316].

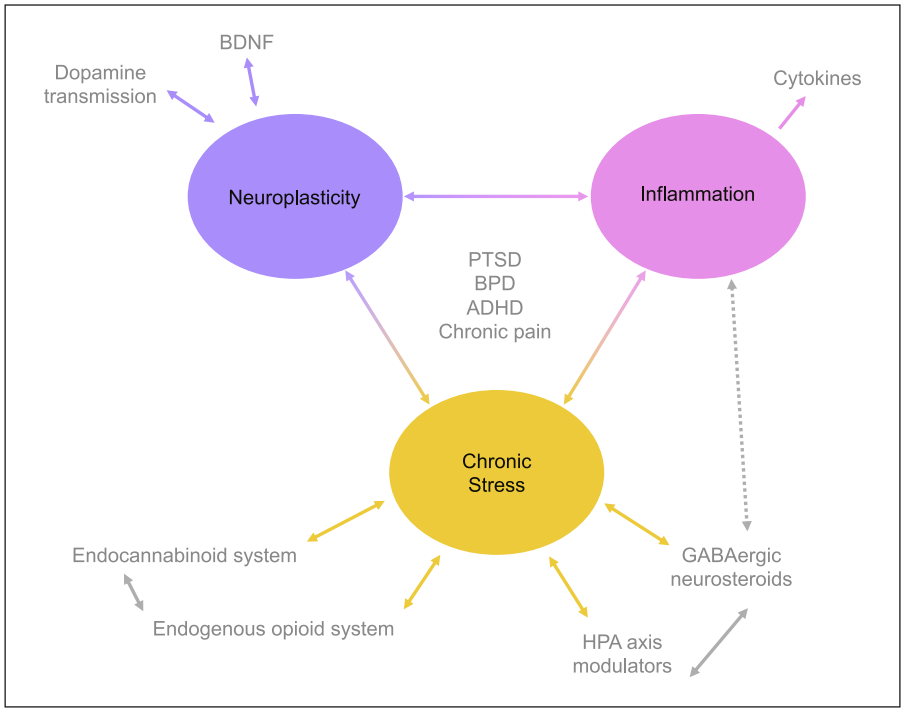

Fig. 1. Visual representation of possible systems and their interaction in relationships between chronic pain, ADHD, BPD, and PTSD.

Immune Factors

A potential shared mechanism driving ADHD and chronic pain comorbidity could be neuroinflammation. There is an existing body of literature on the importance of neuroinflammation (inflammatory responses in the brain and spinal cord) in chronic pain and chronic pain conditions [178], the role of the complement system in synaptic pruning [317–319], and crosstalk between the nervous system and immune system in chronic pain development [320, 321]. Neuroinflammation has also been implicated in the pathophysiology of ADHD [128, 322–324], based on the high comorbidity seen between ADHD and autoimmune and inflammatory disorders in children and adolescents [325–327], and association between family history of autoimmune and inflammatory disease and individual risk of developing ADHD [327–330]. Infection during the first few months of life, involving systemic inflammation, has also been associated with increased risk of later ADHD [322, 331–333].

Studies have also shown ADHD and increased levels of serum cytokines to be associated with one another [333–336], with the activity of these cytokines implicated in dopaminergic transmission dysfunction. Lower levels of serum cytokines have also been found in studies comparing pharmacologically treated and treatment-naive groups of people with ADHD, again implicating inflammation in ADHD pathology [337], although other studies showed higher levels of inflammatory markers in medicated versus unmedicated children and adults with ADHD [338].

HPA Axis Dysfunction

In ADHD, under-reactivity of the HPA axis as shown through low salivary cortisol levels has been linked to ADHD in adolescents [200, 339–341], with other studies showing cortisol-level improvements after completing an ADHD treatment program [342], and a relationship between level of executive dysfunction and lower cortisol levels [339].

BDNF

BDNF is a neurotrophic factor in the CNS and nervous system, involved in neural structure and plasticity, and its downregulation and polymorphisms at the gene have been associated with schizophrenia, mood disorders, Alzheimer's disease, and stress (reviewed by [343, 344]; see also [221]). BDNF can also stimulate proliferation of glial cells, involved in pain and chronic pain (reviewed by [345, 346]; see also [347, 348]), and interact with other immune cells in the regulation of pain response [221].

BDNF may play a role in ADHD pathogenesis, through its effects on neurogenesis, particularly development of

dopaminergic neurons (reviewed by [349–352]). Studies of BDNF levels in ADHD show mixed results: BDNF has been found at lower levels in saliva [340] and serum [353] in cohorts with ADHD, while other studies measuring plasma BDNF found higher levels [354, 355], or no difference in serum BDNF between those with ADHD and those without [356]; see also [357] for review. With regard to ADHD and fibromyalgia specifically, dopamine neurotransmission dysfunction (potentially involving BDNF) may contribute to comorbidity between the two conditions. In fibromyalgia, attention and cognitive problems are a common and debilitating issue [358], with dopaminergic transmission dysfunction implicated as a mechanism for these parallel experiences in both ADHD and fibromyalgia [128, 358, 359].

Note that a lot of research is on pain perception and acute pain, in both neuropathic and inflammatory cases, as opposed to chronic pain (reviewed by [360]; see also [361, 362]), and that results are mixed in terms of anti- and pro-nociceptive effects of BDNF. Other studies in rodents look at BDNF and chronic pain more specifically, and show BDNF as a regulator of atypical protein kinase Cs in initiating the transition from acute to chronic pain, and maintaining central sensitization [363], and that BDNF generally mediates acute to chronic pain transition [364, 365]. BDNF may also be involved in both opioid dependence and opioid-induced hyperalgesia as found in studies on rodents [366–369].

Treatment and Management Impacts of Comorbidity

Having neurodevelopmental disorder ASD and/or ADHD traits in addition to chronic pain makes both quality of life and pain interference worse, in comparison with cases of chronic pain only [293]. In addition, children with chronic pain, particularly girls, may be more at risk of having a comorbid neurodevelopmental disorder go undiagnosed [129] – this relationship between chronic pain and missed diagnoses was also seen across genders in adults [370]. Although ADHD is widely considered a disorder of childhood and adolescence, ADHD persists into adulthood in the majority of those diagnosed [371–373] – it may be the case that healthcare professionals, particularly those treating chronic pain, assume ADHD is not worth screening for in their adult patient populations. ADHD is also a significant risk factor for development of addiction and substance use issues [374–376], and this issue may be further compounded when comorbid chronic pain is present [358], again potentially impacting chronic pain treatment particularly in the case of opioid prescription. Similar to some treatments for co-occurring PTSD and chronic pain showing promise, successful treatment of ADHD with stimulant medications has been found to improve pain symptoms in general [130, 370, 377], in addition to improving cognitive symptoms associated with chronic pain disorders such as "fibrofog," cognitive impairments seen in fibromyalgia (reviewed by [359]).

Discussion

Chronic pain is commonly comorbid with most psychiatric disorders. Having comorbid chronic pain means effective treatment for either disorder is less likely, relative quality of life is reduced, and the impact that pain and psychiatric symptoms have on daily life is increased. Many psychiatric disorders, including ADHD, BPD, and PTSD as disorders of focus here, are more likely to be missed or misdiagnosed when comorbid chronic pain is present – conversely, where psychiatric diagnoses tend to be associated with more profound differences in or difficulties with communication (e.g., autism spectrum disorder, schizophrenia), chronic pain may be going underdiagnosed and undertreated. In addition, the overlap between chronic pain and many psychiatric disorders aside from MDD is understudied, despite, as shown here with ADHD, genetic overlap being comparable to that of chronic pain and MDD, and comorbidity being extremely common. Disorders such as ADHD and BPD are less likely to be screened for in chronic pain patients compared to MDD, which may be due to assumptions that these disorders are disorders only of childhood or are generally uncommon.

One over-arching theme in the overlap between chronic pain and PTSD, and chronic pain and BPD, is trauma, as discussed in previous sections. Despite ADHD appearing to fit less well into a trauma-related narrative compared to BPD and PTSD, this condition is also associated with trauma, with some studies showing children with ADHD more likely to have experienced a traumatic event [378, 379], longstanding observation that ADHD and "maltreatment" are related (reviewed by [379, 380]), and findings that accidents and injuries (potentially traumatic events) are more common in those with ADHD [381–385].

ADHD may also seem out of place as a neurodevelopmental disorder – however, studies in BPD suggest benefits to viewing BPD through neurodevelopmental lens [386, 387], in part due to the kind of contributing factors, such as traumatic events during developmental periods

(childhood), that are extremely common in BPD [388–390]. Additionally, as reviewed in previous sections and despite being classed as a neurodevelopmental disorder, ADHD often persists into adulthood and remains an important consideration in psychiatric condition – chronic pain overlap.

In addition to each disorder having a relationship with trauma and being an important factor to consider in psychiatric condition – chronic pain comorbidity, all three are also inter-related. ADHD has been noted as a risk factor in BPD diagnosis later in life, and 18–34% of adults with ADHD have been estimated to have comorbid BPD (reviewed by [391, 392]). BPD and PTSD are also commonly comorbid, with up to 70% of individuals with BPD having comorbid PTSD and up to 24% of individuals with PTSD also having BPD in some studies (reviewed by [393, 394]). Finally, higher rates of PTSD have also been observed in those with ADHD and vice versa in both child and adult populations [395].

Overall, and in addition to the points outlined above, we choose to highlight these three conditions as their relationship with chronic pain receives less attention that psychiatric disorders such as MDD, and reduced understanding and awareness of them in chronic pain overlap contribute to worse quality of life for individuals who have both conditions at once. A fuller understanding of the causes and consequences of comorbid psychiatric and chronic pain diagnoses could lead to more effective treatments for both disorders separately, and in cases where they are comorbid. Understanding what makes treatment of comorbid chronic pain and psychiatric disorder successful can lead to further understanding of the shared (and distinct) etiology of each disorder. Key areas that could explain mechanistic overlap in ADHD, BPD, PTSD, and chronic pain reviewed here include the endogenous opioid system, neurosteroids and the HPA axis, and neuro and systemic inflammation, and trauma is also highlighted as a key above-the-skin factor in the relationships between these psychiatric conditions and chronic pain. However, this list is nonexhaustive, and interaction between biological, psychological, and social/environmental factors remains important for chronic pain vulnerability and development, as well as for understanding the overlap between chronic pain and psychiatric conditions.

Conflict of Interest Statement

The authors declare no conflicts of interest.

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Author Contributions

Dr. Johnston and Dr. Huckins conceived and designed the study, and edited and revised the manuscript. Dr. Johnston performed literature searches and was responsible for the primary drafting of the manuscript.

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