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The complexities of the sleep-pain relationship in adolescents: A critical review

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Summary

Chronic pain is a common and disabling condition in adolescents. Disturbed sleep is associated with many detrimental effects in adolescents with acute and chronic pain. While sleep and pain are known to share a reciprocal relationship, the sleep-pain relationship in adolescence warrants further contextualization within normally occurring maturation of several biopsychological processes. Since sleep and pain disorders begin to emerge in early adolescence and are often comorbid, there is a need for a comprehensive picture of their interrelation especially related to temporal relationships and mechanistic drivers. While existing reviews provide a solid foundation for the interaction between disturbed sleep and pain in youth, we will extend this review by highlighting current methodological challenges for both sleep and pain assessments, exploring the recent evidence for directionality in the sleep-pain relationship, reviewing potential mechanisms and factors underlying the relationship, and providing direction for future investigations. We will also highlight the potential role of digital technologies in advancing the understanding of the sleep and pain relationship. Ultimately, we anticipate this information will facilitate further research and inform the management of pain and poor sleep, which will ultimately improve the quality of life in adolescents and reduce the risk of pain persisting into adulthood.

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Keywords

pain processing; chronic pain; sleep; insomnia; adolescence; polysomnography; circadian

1. Introduction

1.1. Structure of the review

Chronic pain in children and adolescents is a leading cause of morbidity and should be recognized as a major health concern [1]; it is common and frequently originates during the vulnerable period of biobehavioral maturation during adolescence. The experience of pain can evolve over time, progressing from acute episodes to a chronic, frequent condition. Addressing pain can improve daily functioning and reduce the risk of chronic pain persisting into adulthood. One key modifiable risk factor implicated in the early onset and maintenance of chronic pain is sleep. To this end, several reviews have focused on pediatric sleep and pain, including key reviews by Valrie *et al.* [2] (2013) and Allen *et al.* [3] (2016) that described the presence and clinical impact of sleep disturbances across several chronic pain conditions. Overall, adolescents with chronic pain self-report poorer sleep, which is associated with greater functional disability, decreased emotional and social functioning, reduced well-being, increased depressive symptomatology, reduced quality of life, and impaired cognitive function [4-8].

In this current review, we wanted to advance these reviews [2, 3] by considering the biobehavioral maturation processes during adolescence (*see* Section 2), which may increase vulnerability to sleep disruptions and pain. Here, we discussed adolescent brain development, neurological changes in systems associated with pain, and maturation of adolescent sleep-wake biology by drawing from the current literature on adolescents and children. We also provided a context for the prevalence and impact of chronic pain across adolescence (*see* Section 3). We then extended the reviews [2, 3] by examining the current evidence regarding sleep disruptions in adolescents with chronic pain (*see* Section 4). We also discussed the directionality of the sleep-pain relationship (*see* Section 5) since sleep and pain can be mutually reinforcing, whereby uncontrolled pain can cause sleep disruptions, and in turn, disturbed sleep can enhance pain sensitivity [9]. Leveraging a recent review by Afolalu *et al.* (2018) [10], we also included epidemiological studies evaluating sleep and pain across community-based samples. Our review extended previous reviews [2, 3] by examining the emergence of co-occurrence of sleep and pain in the general community. As most of our understanding is based on cross-sectional association, these studies offer key insights, including the trajectory of sleep and pain over time and potential drivers of these trajectories. In addition, longer timeframes (*vs.* one week) in the general population would increase generalizability of these findings.

While previous reviews [2, 3] highlighted potential factors underpinning the sleep-pain relationship, these reviews have mainly focused on psychological mechanisms (e.g., cognition, anxiety, depression, and mood). Here, we have provided potential mechanisms and moderators of the relationship (*see* Section 6) while providing some additional context for a sleep and pain framework (*see* Section 7). We also built on the review by Christensen

et al. (2019) [11] by expanding on potential neurobiological underpinnings of the sleep and pain relationship (*see* Section 8).

While sleep has emerged as a major complaint in chronic pain sufferers across the lifespan, the literature search revealed significant gaps in knowledge about the sleep-pain relationship in adolescents. Therefore, the current review highlighted these gaps and suggested potential new directions to advance the study of the sleep-pain relationship in adolescents (*see* Section 9). These new directions include the need to evaluate the multidimensionality of sleep and pain processes and consider the role of digital technologies in advancing the understanding of the sleep-pain relationship. At the end of the review, we provided some clinical implications (*see* Section 10).

1.2. Review Criteria

A comprehensive literature search was conducted of epidemiological, clinical, and experimental studies about pain and sleep in adolescents published in English using the electronic databases: PubMed, Google Scholar, Web of Science, and PsycINFO. Studies involving mixed samples of children and adolescents were also included in the review. A combination of one of more of the following keywords were used as search terms: “acute pain,” “sickle cell disease,” “juvenile idiopathic arthritis, “chronic pain,” “migraine,” “headache,” “musculoskeletal pain,” “fibromyalgia,” “low back pain,” “musculoskeletal pain,” “abdominal pain,” “functional abdominal pain disorders,” “pain intensity,” “disability,” “pain interference,” “nociception,” “pain pathways,” “adolescence,” “children,” “pediatric,” “sleep,” “sleep pathways,” “sleep disruption,” “sleep deprivation,” “sleep restriction,” “sleep disorders,” “poor sleep, “sleep quality,” “insufficient sleep,” “actigraphy,” “polysomnography,” “insomnia”, “chronotype,” “circadian” and “circadian rhythm.” Article searches yielded 392 articles, from which 194 were eventually selected as being relevant. A single author initially read and flagged relevant articles. Then, at least two authors reviewed the flagged articles of interest. We looked for papers that included various sleep domains (subjective vs. objective) and pain conditions, and pain within the general community. Articles were excluded for ineligible population (e.g., adult participants; studies without acute or chronic pain) or outcomes (e.g., lack of pain and sleep assessment in the same participants).

2. Adolescence: A vulnerable life-stage of profound biopsychosocial changes

The sleep-pain relationship in adolescence needs to be contextualized within the multitude of biopsychosocial changes occurring during this developmental period. Adolescence is the transitional period between childhood and adulthood, characterized by dramatic changes in physical, social, and intellectual/emotional functioning, coinciding with neurobiological changes in the brain as well as reactivation of the hypothalamic-pituitary-adrenal axis (HPA) that controls pubertal maturation [12]. The significant changes to brain structure and function during adolescence make the adolescent brain vulnerable to a variety of perturbations from the environment and behaviors [13]. Sex-specific trajectories of biobehavioral maturation also need to be considered in light of the emergence of strong

female-specific vulnerability for sleep [14] and pain conditions [1, 15]. For example, a recent study by Tong *et al.* (2022) [15] suggested that adolescence can be characterized by a *"hyper-representation of acute pain,"* which was demonstrated by greater perceptual (e.g., sensitivity to painful pressure) and brain activity in healthy adolescent females compared to older females. Several brain areas (e.g., medial prefrontal cortex, amygdala), including areas associated with the default mode network, exhibit greater activation in adolescents and are involved in several key processes (e.g., affect, pain, cognition). Additional research is needed to confirm this finding and explore if these developmental changes in brain function during adolescence increase vulnerability in the development of chronic pain.

In concert with the reorganization of the central nervous system, there are changes in the autonomic nervous system (ANS) across adolescence, following a sex-specific trajectory [16]. Upregulation of the ANS system is more readily observed in older adolescent girls (e.g., elevated heart rate and rapid age-related drop in vagal functioning in girls compared to boys). With these major system-wide changes across development, regulation of sleep behavior and homeostatic and circadian sleep processes also change [17]. For example, there is a dramatic decline in the duration and activity of Slow-wave sleep (SWS; reduction in N3 sleep and drop in Electroencephalography (EEG) power within the 0.3 - 4 Hz frequency), with an earlier decline in girls that continues into early adulthood [12, 17]. The biological changes in sleep and circadian processes, along with the environmental and psychosocial pressures, also lead to delayed bedtimes and shorter sleep duration [12]. As such, chronic "sleep deprivation" and "social jetlag" (e.g., a pattern of sleep deprivation during the week, followed by weekend rebounds or "catching-up sleep") are among the consequences of the "normal" changes in sleep across adolescence, with older adolescents sleeping less than their younger counterparts despite similar or increased sleep needs [12]. Overall, more research is needed to evaluate the implication of biological maturation within the context of emerging chronic pain conditions, which emerge or accelerate following puberty, especially in girls [18], and to evaluate the relationship between normal and abnormal physiological sleep and sleep-related processes implicated in pain processing.

3. Characterization and presence of chronic pain in adolescents

Figure 1 provides a graphical representation of the definitions and differentiation of chronic and acute pain. Figure 2 provides a graphical representation of the prevalence and impact of chronic pain, a common and disabling health condition affecting up to one-third of children and adolescents [1]. The prevalence of pain in late childhood and adolescence can vary depending on the criteria used to define the condition (headache: 8–83%; abdominal pain: 4–53%; back pain: 14–24%; Musculoskeletal (MSK) pain: 4–40%; multiple pains: 4–49% [1]). The negative impact of chronic pain on a child's or adolescent's health can be observed across several domains, including reductions in physical (e.g., greater functional disability [19]), psychological (e.g., greater internalizing and externalizing symptoms [20]), academic [21], and social (e.g., greater peer-and family stress [22]) functioning. If inadequately treated, a majority of youth with chronic pain will develop into adults with chronic pain [23]. Naturally, chronic pain persisting into adulthood results in reduced quality of life, socioeconomic burden [24], and risk for opioid misuse [25]. Some types of pain may greater persistence in adulthood. For example, in a cohort of pediatric patients with abdominal pain,

35% of patients reported recurrent symptoms when reassessed in adulthood during a 15-year follow up [26]. Similarly, in a study on adolescents with frequent headaches and widespread MSK pain, 19%, and 58.1% reported that they continued to experience weekly headaches (e.g., 14 years later [27]) and widespread MSK pain (e.g., 10 years later [28]) during a follow-up visit, respectively. The persistence of pain in adulthood also has important economic implications. It has been estimated that an average cost of ~$11.8 billion per year in total health care expenditures (e.g., office visits, medications, emergency room visits) in the United States for recurrent and chronic pediatric pain conditions [24], leading to burden on families (e.g., missed work for child's healthcare; out of pocket costs for healthcare) and healthcare systems (e.g., not enough providers leading to delayed treatment).

Current prevalence and incidence rates for chronic primary pain vary depending on age and biological sex. In general, late childhood and early adolescence coincide with the peak onset of several types of chronic primary pain [1], including headache (e.g., chronic migraine), abdominal pain (e.g., Functional abdominal pain disorders, FAPD), localized MSK pain (e.g., low back pain), and widespread MSK pain (e.g., Juvenile Fibromyalgia). An important factor related to the emergence and increase in chronic pain conditions is the onset of puberty [18], which is a critical period shown to alter pain sensitivity and influence psychosocial functioning via sex hormones (e.g., increases in estrogen and testosterone). In addition, evidence for a "sex by age" interaction in the development of chronic pain is emerging: Pain conditions are more prevalent in girls than in boys [1], particularly after the onset of puberty. For example, in third, sixth, and ninth graders (ages ~9, 12, and 15 years), it has been shown that almost twice as many girls (17%) than boys (8%) report headache at least once per week [29]. However, the nature of this sex difference in pain prevalence is not entirely clear.

4. Sleep studies in adolescents with chronic pain

Sleep disruption is a common complaint in adolescents with chronic pain conditions (*see* graphical representation in Figure 3). Most studies have used subjective measures to characterize these disturbances, including indices of perceived sleep quality (or satisfaction), sleep continuity (e.g., duration, night-time awakenings), and other reported behaviors such as insomnia symptoms, sleep breathing issues, morning sleepiness, and parasomnias. Few studies have used more objective indications of sleep, including Polysomnography (PSG; characterizes sleep macro- and micro-structure) and actigraphy (evaluates habitual wake/sleep patterns in free-living conditions) measures. While sleep disturbance is a major complaint in chronic pain patients, less is known about the role and implication of physiological sleep-specific (e.g., sleep stages, SWS activity), sleep-related (e.g., ANS function during sleep), and circadian features in altered pain processing [30-32]. This section reviews sleep in pediatric populations with chronic pain, considering studies that relied on self-reported assessments, actigraphy, and polysomnography.

4.1. Perceived sleep

Approximately half (54.2%) of pediatric pain patients report sleep disruption, compared to a 19.6% self-reported sleep disruption in pain-free adolescents [7]. Reported sleep difficulties

were collected by a variety of questionnaires (e.g., School Sleep Habits Questionnaire; Child Sleep Habits Questionnaire). Sleep difficulties ranged from several domains including poor sleep quality, insufficient sleep, daytime sleepiness, difficulty falling and staying asleep, and night awakenings. These sleep difficulties were consistently reported by youth with primary pain conditions such as headache [33-41], abdominal pain [42, 43], and MSK pain [44-46] relative to healthy peers.

Self-reported sleep difficulties (e.g., poor sleep quality, night awakenings, sleep anxiety) are also common in youth with secondary pain conditions, such as Juvenile idiopathic arthritis (JIA)[47-51] or Sickle cell disease (SCD)[52, 53]. Chronic pain patients and their parents also often self-report symptoms of sleep breathing disorders [52, 54]. Most of these findings are derived from cross-sectional studies, which were not designed to explore the question about directionality - Can poor sleep contribute to next day pain?

4.2. Actigraphy sleep

Actigraphy offers objective insight into sleep behaviors and sleep-wake habits in pediatric patients. Actigraphy enables the noninvasive measure of activity-based sleep/wake patterns over time [55] and can capture a more comprehensive understanding of sleep habits (such as bed- and wake-times) in free-living conditions, which are largely overlooked when using one-night measurements or cross-sectional questionnaires. Several studies on children and adolescents used actigraphy to investigate pain-sleep relationships; however, findings are inconclusive. Some authors report actigraphy-based sleep disruptions (later bed times, shorter sleep durations, lower sleep efficiency, and greater number of night-time awakenings) in groups of patients with mixed chronic pain conditions [4, 56, 57], patients with headaches [34, 58], cystic fibrosis (CF)[59] and pediatric oncology patients [60]. In contrast, others do not report significant differences in sleep measured using actigraphy in adolescent patients with abdominal pain compared with healthy controls [61], as well as between youth with headaches and matched controls [56, 62], despite the same children subjectively reporting sleep difficulties [56]. Based on the purely behavioral (movement vs. not movement) nature of actigraphy, a sole focus on actigraphy would seem to not fully reflect sleep processes in relation to pain (*see* Section 9).

4.3. Polysomnography sleep

PSG is considered the gold standard for sleep assessment, yet very few studies have used PSG to measure sleep in youth with chronic pain. This is largely driven by the high cost and demand of PSG assessments. From the few studies that have employed PSGs in adolescents, disrupted sleep (e.g., lower sleep efficiency, longer sleep onset latency, more wakefulness after sleep onset, higher EEG alpha/delta ratio), and the presence of more physiological sleep disorders (e.g., periodic limb movement disorder, sleep disordered breathing) are reported in youth with pain compared with healthy peers (*see* [2]).

For adolescent chronic pain patients, alterations in sleep architecture have also been reported. For example, children and adolescents with headache showed altered sleep continuity (e.g., a higher number of awakenings [35]). Others have reported differences in sleep architecture (e.g., reduction in time in bed, shorter sleep time, longer sleep latency,

shorter Rapid eye movement-REM, shorter SWS, and longer Non-rapid eye movement (NREM) 2) in children with headaches compared to healthy peers. Importantly, changes in sleep architecture were associated with increased severity of headaches [63, 64]. General PSG-based sleep alterations (e.g., more arousals and awakenings, less SWS, more alpha activity) have also been found in adolescents with JIA [65-67] and SCD (e.g., lower total sleep time and REM sleep percentage, higher REM sleep latency, a higher number of awakenings, movements and changes in sleep stage [68]). In addition, breathing disorders including snoring, episodic hypoxemia, and obstructive sleep apnea (OSA) are also common in adolescents with migraines [63], SCD [69-71], and JIA [72, 73]. These findings would seem in line with results in adults, showing that alterations of sleep continuity and architecture (i.e., increases in light sleep or decreases in SWS) are commonly reported in adult patients with chronic pain studies using PSG [74]. However, further research exploring PSG measures is needed to better understand the sleep and pain relationship in various pediatric pain populations. Despite many consistent results confirming the relationship between sleep PSG measure and pain, most research on sleep disturbances in adolescents with pain has been cross-sectional, leaving the question concerning the cause-effect relationship. That said, sleep problems are reported to be a strong predictor of chronic pain in adolescence [11].

5. Directionality of the sleep and pain relationship in adolescents

Pain and sleep disturbance can be mutually reinforcing, with pain disrupting sleep and disruptions in sleep increasing pain sensitivity. However, there is growing evidence that disturbed sleep may better predict changes in pain perception than pain predicts sleep disturbance in adult patients with chronic pain [9, 10]. For example, a recent systematic review and meta-analyses of sixteen epidemiological studies concluded that poor sleep quality and insufficient (or short) sleep duration were risk factors for developing chronic pain in the general adult population [10]. Importantly, this same pattern (i.e., poor sleep predicting future pain) has been demonstrated in adolescents as well [2, 3]. Given the high prevalence of co-occurrence between chronic pain and sleep disturbances in adolescents, exploring this relationship is imperative (*see* Figure 3).

In studies using micro-longitudinal study designs (e.g., one to two week observational periods), disturbed sleep is temporally associated with greater next-day pain related to acute surgery [75], acute MSK pain [76], mixed chronic pain conditions [56, 77], JIA [78], and SCD [79] in pediatric patients. These results are primarily from subjective diary assessments to capture daily pain and sleep across several days. The extent of subjective sleep disruption was associated with the intensity of symptoms; those reporting greater sleep disruption also report a greater decrease in physical, emotional, and social functioning compared with those reporting less sleep disruption [57]. However, the findings of studies using objective actigraphy, while sometimes mixed, mostly support that a relationship exists between several actigraphic sleep variables (e.g., sleep duration and efficiency; Wake after sleep onset, WASO) and next day pain [56, 76, 79].

Epidemiological studies have demonstrated that disturbed sleep in adolescents and young adults [80] is associated with the development of a pain condition (within 3 years).

Similarly, several prospective longitudinal studies provide evidence that disturbed sleep increases the risk for the development of chronic pain following acute injury and for pain spreading from a localized disorder to a more widespread condition in adolescents [81]. A recent study by Arnison and colleagues [82] found a bidirectional relationship between insomnia symptoms and MSK pain in a community sample of adolescents (N = 2767). However, the effect of insomnia symptoms on pain was stronger than that of pain on insomnia symptoms. A recent study in China (N = 7072) reported bidirectional associations between sleep and pain (headache, stomachache, other nonspecific pain) in which insomnia symptoms and somatic complaints were associated with greater frequency of pain and insomnia symptoms, respectively. These associations were observed across all three pain complaints [83].

6. Factors contributing to the relationship between sleep and pain

Studies have reported several factors that are independently associated with poorer sleep quality and pain-related outcomes while also contributing to the sleep and pain relationship (i.e., via mediation). These factors include physiological (e.g., ANS, endocrine, hyperarousal), psychological (e.g., anxiety [77], depressive symptoms [77], negative affect/mood [84], internalizing symptoms [85]), and social factors (e.g., isolation) in addition to sociodemographic characteristics (e.g., biological sex or gender, age, medications[86]). In the following sections, we will highlight some of these factors. Most of our understanding in these factors is based on cross-sectional associations between pain and sleep. Hence, it is unclear whether the same associations continue to exist over time as pain symptoms change.

6.1. Sleep Hyperarousal

One of the potential physiological mechanisms linking poor sleep and pain is hyperarousal, which can be conceptualized as an abnormal state of upregulation across several psychophysiological domains. Sleep hyperarousal can negatively affect the ability to fall and stay asleep and lead to poorer sleep quality [87]. It is also elevated in adolescents with chronic pain [6, 7, 57, 88, 89]. For example, a recent study by Arnison and colleagues [90] leveraged data from a large epidemiological study in Sweden to examine the developmental trajectories (up to five years) of pain and insomnia symptoms in a community sample of adolescents (N = 2767). They identified four groups based on changes in pain grade (i.e., composite of pain intensity and interference across MSK pain, abdominal pain, and headache) and insomnia symptoms over the observational period. In addition to adolescents with consistently low (68.7%) and high (4.9%) levels of pain/insomnia symptoms across a 5-year period, two groups of adolescents exhibited either an increase (13.9%) or decrease (12.5%) in these symptom trajectories. More importantly, greater pre-sleep cognitive-emotional arousal (and a shift to later sleep timing) was associated with increasing pain/insomnia trajectory. In contrast, the opposite was observed for the decreasing symptom trajectory. Overall, heightened sleep hyperarousal at bedtime may play a critical role in the sleep-pain relationship since sleep hyperarousal can negatively affect an individual's ability to fall (e.g., altering the de-arousing processes occurring across the wake-to-sleep transition [87]) and stay (decreased sleep quality and continuity [7, 91, 92]) asleep.

6.2. Disturbances in circadian rhythms

Another plausible factor contributing to the sleep and pain relationship is disturbances in circadian rhythms. Support for circadian rhythms in pain is based on evidence that neurobiological systems involved in nociception and pain (as well as sleep-wake cycles) is under the control of a circadian clock [93]. For details on the role of the circadian clock in sleep, as well as the role of circadian clock rhythmicity and various painful conditions, we refer the reader to two previously published reviews (*see* [30, 93]). For example, Palada *et al.* (2020) [93] describe how the neurons in the suprachiasmatic nucleus of the hypothalamus respond to light stimuli from the retina and coordinate the clocks in peripheral tissues through the ANS and secretion of hormones and neurotransmitters (including melatonin, noradrenaline, dopamine, cortisol, and cytokines). These pathways are critically involved in the regulation of both the sleep-wake cycle and nociception. Bumgarner *et al.* (2021) [30] detail the evidence that individual structures in the pain system exhibit circadian rhythms in function. To name a few, the primary nociceptors of the dorsal root ganglia show daily rhythmic activity, the PAG exhibits circadian rhythms (although little is known about these rhythms in relation to circadian variations in pain modulation), and there is evidence that the locus coeruleus has clock gene loops. Diurnal rhythmicity in these neurobiological systems likely contributes to clinical pain, which often shows a circadian rhythm with pain peaking at certain time of the day (i.e., morning vs. afternoon vs. evening). It is important to note that this body of work is from adult populations.

Chronic pain is often associated with altered sleep-wake cycles, which could disrupt circadian rhythms and the underlying clock genes across a number of neurobiological and other physiological (i.e., immune, endocrine, endogenous opioid) systems underlying the perceptual experience of pain [30]. This effect is observed in patients with fibromyalgia, whose sleep-wake cycles and other rhythmic processes are related to frequent and intense pain. Disruption of circadian rhythms likely reduces pain thresholds [30] via changes in neurobiological, immune, and endocrine function [30]. Once initiated, this feedback loop likely results in states of chronically lowered pain thresholds and could contribute to prolonged periods of chronic pain (and sleep-wake cycles).

As far as we know, a specific role of circadian factors in the relationship between sleep and pain has not been explored explicitly in adolescents. However, as previously reviewed, compared with younger adolescents, older mature adolescents have delayed circadian rhythms in association with their later bedtimes (e.g., shift to later sleep-wake cycles [12]), and this delayed phase has been shown to predict increasing trajectories of greater pain and insomnia symptoms in adolescents over time [82]. Several factors could contribute to this phase delay (i.e., late chronotype) in adolescents, including changes in (a) the period of the biological clock, (b) sensitivity of the clock to light, (c) homeostatic sleep regulatory processes (i.e., building of sleep pressure), or even (d) interaction between these factors. Other external factors (e.g., early school start times; daytime physical activity; nighttime pain; daytime napping) may also influence the expression of the circadian system and contribute to a poorer sleep-wake cycle in adolescents.

Objective markers of circadian disruption in adolescents with chronic pain are lacking. However, adults with fibromyalgia showed altered 24-hour rest-activity patterns (i.e., altered

rest-activity rhythms or RAR), in whom pain, sleep, and other clinical features were associated with poorer RAR profiles [96]. These results are similar to those found in young adults with mood disorders, with greater symptoms being associated with later timing, lower rhythmicity and reduced overall activity [95]. Additional studies are needed to determine the clinical significance of disrupted 24 h rest–activity patterns as a marker of circadian disruption in adolescents with pain.

6.3. Biological Sex and Age

Although studies show significant sex (e.g., female predominance) and age (e.g., older age, puberty) differences in pain prevalence [1, 94], demographic factors have been largely overlooked in studying the relationship between sleep and pain. Interestingly, Zhang et al. [95] investigated the sex differences underlying the associations of sleep disturbances with pain and somatic symptoms in adolescents and middle-aged adults and found an interaction effect between insomnia and female sex on pain and somatic symptoms, suggesting that insomnia seems to modulate the sex differences in pain and somatic symptoms. These findings seem to support the possible role of sex as a moderator in the relationship between sleep and pain. Furthermore, the vast majority of non-human studies have only explored the neurobiological systems underlying sleep (e.g., circadian rhythms) and nociception (*see* Section 8) in males [30]. Thus, this limits our understanding about potential role of sex difference in sleep and pain. Considering the female predominance in chronic pain conditions, other designs (e.g., epidemiological; experimental manipulations like naturalistic sleep restriction [96]) or conditions (e.g., acute pain) might be needed to examine these associations to recruit a large sample of male participants.

6.4. Negative Mood

Negative mood (e.g., depressive/anxious symptoms) are commonly associated with poor sleep quality and short sleep duration. Several studies have provided evidence that negative mood is a key mediator of the temporal relationship between sleep and pain [77, 78, 84]. The increase in pain sensitivity resulting from sleep disturbance is likely based on shared regulatory pathways (*see* Section 8), many of which, incidentally, also overlap with the regulation of other behaviors. For example, the mesolimbic dopaminergic system underlies key cognitive functioning like attention, mood, and reward [97], in addition to sleep and pain. Therefore, multiple interactions are possible (e.g., sleep-mood-pain triad), and mood may mediate the sleep and pain relationship [2, 84]. Indeed, a recent longitudinal study in adolescents with MSK pain reported that depressed mood and anxious mood mediated the effect of insomnia symptoms on pain. Interestingly, the reverse effect of pain on insomnia symptoms was not found [82].

Considering that mood is a central mediator in the relationship between sleep and pain, the role of sleep should be placed in a larger context of emotion regulation (ER). ER reflects a set of cognitive/attentional, behavioral, and physiological processes underlying an individual’s ability to regulate their emotions during situations like pain (e.g., response-focused). Maladaptive ER can be impacted by sleep [98, 99] and pain [100] usually through negative affect and mood. Maladaptive ER is associated with greater pain and disability, particularly in adolescents with greater daily instability (or variability) in their negative

emotions (i.e., greater daily changes in the intensity of emotions from moment to moment) [101]. Overall, these studies suggest that poor sleep in adolescents impairs their ability to manage and cope with chronic pain [4], which may, in turn, set up a cycle of poor sleep and pain.

7. Pain and sleep interaction within the current conceptual frameworks

In adults and adolescents, there is a plethora of evidence supporting a reciprocal relationship between poor sleep and chronic pain (interrelated with other factors, e.g., mood). Both pain and poor sleep play a role in reinforcing one another and their respective comorbidities. Several conceptual models have been proposed to address the complexity of the relationship between pediatric pain and sleep. An earlier model by Lewin and Dahl [102] highlighted the complex, bidirectional relationship between pain and sleep, in which daytime pain can disrupt sleep quality and quantity (e.g., reduced sleep duration). In turn, insufficient sleep exacerbates pain the following day. An important aspect of their model was the impact on daytime physical and emotional functioning. For example, insufficient sleep could increase fatigue and decrease attentional control, which would independently amplify the perception of pain. Then, Valrie and colleagues [2] placed the model by Lewin and Dahl [102] within a larger biopsychosocial context, defined as the "*Pain and Sleep Associations in Pediatric Persistent Pain Populations*." In this model, pain, and sleep interact with several biological and psychosocial mediators in addition to developmental and sociodemographic moderators, including sex, race, and ethnicity. The factors have seldom been explored in the context of pain and sleep interactions. This model also incorporated the impact of the pain and sleep relationship on functional outcomes like disability and quality of life.

One of the main factors contributing to the relationship between sleep and pain in the model proposed by Valrie and colleagues [2] was negative affect. Empirical evidence supporting this model has been observed across several pediatric chronic pain populations [5, 57, 84]. Since then, additional psychological factors like low positive affect [103] and anxiety [77] have been considered in this model. As pointed out by Pavlova et al. [77], different psychological factors (e.g., mood vs. anxiety symptoms) may independently drive the pain and sleep interaction through various mechanisms like pre-sleep arousal [104] via anxiety and irritability via negative mood. These cognitive and affective mechanisms, in turn, can lead to further disruption of the quality and quantity of sleep [102].

Given the complexity of the sleep and pain relationship, there have been calls to develop a unified conceptual model [105] that integrates pain and sleep within a larger biopsychosocial and behavioral framework. While we are not formally proposing a new model, this review provides additional considerations for a future model. For example, existing conceptual models have not included factors underlying the amplification of pain perception by insufficient sleep, as suggested by Smith et al. [106] and Andreucci et al. [107]. Various biological mechanisms can influence how the nervous system processes and modulates pain, including low-grade inflammation, HPA, ANS, circadian rhythms, and neurotransmitter systems (e.g., serotonin). Furthermore, future models should focus on the temporal associations of sleep and pain to strengthen the evidence that sleep disturbances

are more significant predictors of pain (vs. opposite direction), capturing the biobehavioral maturation of adolescents.

Given the irregular patterns of clinical pain, future studies could evaluate these concepts in conditions where pain regularly occurs over short periods. For example, primary dysmenorrhea is a type of chronic pelvic pain, which is characterized by painful menstrual cramps. Emerging after menarche, the prevalence of dysmenorrhea is high in adolescence, with estimates of 2% - 29% of girls reporting severe menstrual pain [108] and adults (affecting 45-95% of women; 10-25% with severe pain; *see* review [109]). Dysmenorrhea, is a recurrent pain condition, which when severe, may adversely affect daily functioning and quality of life of adolescents, and may also be a risk factor for other chronic painful conditions later in life in women [108]. Dysmenorrhea presents features of both acute and chronic pain syndromes and is a recurring pain with a regular onset but short duration. Primary dysmenorrhea may lead to the development of central sensitivity to pain (e.g., abnormal augmentation of pain through mechanisms within the nervous system [109]). Women with primary dysmenorrhea report sleep disturbances associated with their pain but not at other times of the menstrual cycle [109]. Given dysmenorrhea's repetitive and predictable occurrence, it could be considered a biological model to study common mechanisms underlying sleep disturbance and chronic (recurrent) pain in young female populations and the directionality of their inter-relationship.

8. Anatomical substrate and neurobiological pathways underlying the sleep and pain relationship

8.1. Brief review of the shared neurocircuitry between sleep and pain

The shared neurocircuitry (including neuroanatomical structures, neurotransmitters, and homeostatic molecules) believed to be involved in both sleep and pain regulation include the brainstem monoamine nuclei, endogenous opioids, the periaqueductal gray matter (PAG), the orexinergic system, the immune system (including prostaglandins, PGs), the HPA, and homeostatic molecules including adenosine, melatonin, and nitric oxide. See Supplementary Table for a summary of the known effects of these shared systems on sleep pathways, pain pathways, the impact of sleep deprivation on these systems, and the implications of these findings, together with suggestions for future research. Sleep and pain are complex states, and their regulation remains incompletely understood. We refer the reader to detailed reviews of current knowledge of the complex individual neurocircuitry of sleep [110-112] and pain [113-115]. A recent review also details the proposed shared neurocircuitry between sleep and pain [86], bearing in mind that most of what is understood to-date is based on adult populations and animal studies.

8.2. Sleep deprivation as a model to understand the shared pain-sleep neurophysiological mechanisms in adolescents

As summarized in Section 2, typical sleep in adolescence is characterized by significant changes in sleep architecture, shorter sleep duration, and delayed bedtime [12]. Given that the somewhat *vague* term ‘sleep deprivation’ incorporates sleep quantity, quality and timing, adolescence (with all its embedded psychosocial and biological changes) can result

in a state of chronic sleep deprivation. Reduced sleep quality and/or quantity in children and adolescents is associated with an array of cognitive and behavioral deficits, including attentional deficits, poor executive functioning, reduced behavioral regulation, increased risk-taking behaviors, and inadequate impulse control [116]. This can also be observed with somatic symptoms in healthy adolescents. For example, partial experimental sleep restriction (6.5h in bed per night) for just five nights increased the occurrence and severity of pain-like symptoms compared with sufficient sleep (defined as 9.5h in bed)[96]. In addition, 'social jetlag' in adolescence is significantly correlated with significant neuroanatomical changes, including reduced grey matter volumes in the frontal cortex, Prefrontal cortex (PFC), precuneus cortex, and the Anterior cingulate cortex (ACC) [117].

As far as we are aware, studies investigating the effects of poor sleep in adolescents on brain structure and function, or neural processing, focus mainly on deficits in cognition, attention, reward, emotion regulation, executive function, and memory. There is a dearth of studies investigating the neurobiological mechanisms underlying both sleep and pain. Here, we will discuss only research on the effects of sleep deprivation in adolescents on anatomical sites/systems involved in *both* pain and sleep physiology. Considering what we know, we would argue that the state of chronic sleep deprivation occurring on the backdrop of the major neurodevelopmental changes in adolescents may also put them at risk of pain sensitization and susceptibility to chronic pain.

The natural structural changes that occur in the brains of this population further perpetuate the impact of sleep loss in this population. For example, social jetlag in adolescence is significantly correlated with reduced grey matter volumes in the frontal cortex, precuneus cortex, and the ACC [118]. Also, the PFC, involved in regulating cognitive function, appears to be particularly vulnerable to adolescents' sleep patterns. Maturation of the PFC begins during adolescence and continues into the 30's. However, early experiences (e.g., stress, hormone levels, disrupted sleep) can modify the basic neural circuitry which ultimately affect PFC trajectories and behavioral regulation [119]. In adolescents, social jetlag is inversely correlated with grey matter volumes in the medial PFC, whose functions include selective attention, cognitive, and ER. As such, these brain changes associated with social jetlag translate to impaired higher-order executive functions, including poor sleep performance [118]. Of note, the PFC in adults does not show the same vulnerability to sleep deprivation, as it does in adolescents. Studies using functional magnetic resonance imaging show that in adults, the PFC is able to modify activation patterns in response to cognitive demands following one night of sleep deprivation [120]. For example, a study investigating cerebral activation during verbal learning in healthy young adults (age range: 21 – 35 years) showed that the PFC was more responsive to cognitive demands after one night of sleep deprivation than after normal sleep, contrary to the authors' hypotheses. These results indicate that specific areas in the adult brain display dynamic, and possibly compensatory, changes in cerebral activation during learning after sleep deprivation [120]. This may not be the case in adolescents.

In terms of the pain experience, the cortical and subcortical brain areas commonly activated during acute pain stimuli include the primary and secondary somatosensory cortex, the insula, frontal cortex, amygdala, thalamus, and ACC [121]. Notably, given the effect of

inadequate sleep on the adolescent brain highlighted above, the ACC plays a role in the affective aspect of pain, including the perception of “pain unpleasantness,” and the PFC plays a role in memory and attentional networks that are activated during painful stimulation [122].

Together with the posterior parietal cortices, the ACC and PFC represent a significant portion of the “attentional matrix” involved in pain processing, and both the medial PFC and the ACC alter their activation patterns immediately preceding the onset of a noxious stimulation; suggesting that these regions play a role in anticipation of pain [122]. Interestingly, people living with various forms of chronic pain (including pain from rheumatoid arthritis, cluster headache, atypical facial pain, and dental pain) demonstrate abnormal (increased or decreased) activity in the ACC [122]. Diminished ACC response to acute pain is hypothesized to be an adaptive cortical mechanism [122].

The frontal cortex is involved in modulating the perception of pain by mediating the interactions between the key nociceptive processing regions (e.g., increased PFC activation decreases pain affect) seemingly through inhibiting the functional connection between the midbrain and the medial thalamus [123]. The PFC is likely critical for pain control as it is essential for the integration of information from all the sensory modalities as well as its connections to other higher-order brain regions. More specifically, and significantly in the context of chronic pain, the dorsolateral PFC is believed to be involved in blocking pain from entering the conscious thought [124]. The dorsolateral PFC is also involved in pain detection and modulation [125]. Indeed, the dorsolateral PFC is believed to serve as a relay station between higher-order cognitive processing and pain regulation [125]. Furthermore, individual differences in pain tolerance may be associated with distinct brain activation patterns. Individuals who report being highly sensitive to pain express stronger and more frequent activation of the ACC, primary somatosensory cortex, and PFC compared with individuals who report being less sensitive to pain [126]. Thus, the specific brain activation patterns and the integration of information between these structures produce the subjective perception of pain [123].

Given the intricate role that these brain areas (*also emphasized in* Supplementary Table) play in pain and how they are affected by sleep deprivation, it is possible that inadequate sleep in adolescence makes this population susceptible to chronic pain. Indeed, pediatric patients with complex regional pain syndrome display reduced grey matter in areas of the brain including the dorsolateral PFC [127, 128]. Such changes have been shown to correlate with both pain duration and intensity [129], and the reduction in dorsolateral PFC grey matter is believed to contribute to the development of a defective pain modulation system [128]. Further, the brain structure most affected varies according to pain condition, but they all commonly involve particular areas, including dorsolateral PFC, cingulate cortex, dorsal pons, and insula [127]. Importantly, abnormalities are partially reversed with pain resolution, and noninvasive stimulation of the dorsolateral PFC has been used as an effective treatment for specific chronic pain conditions in adults [125]. Therefore, it is suggested that the cortical transformations may be a consequence, not a cause, of the chronic pain condition. Here, also in light of the vulnerability of the neural circuitry of the PFC to early experiences [130], we argue that inadequate sleep could be a stressor or noxious stimulus that not only

contributes to these cortical changes, but over time, chronic exposure to inadequate sleep can result in poorer long-term outcomes, including clinical pain.

As far as we are aware, other shared underlying physiological mechanisms that link sleep and pain (Supplementary Table) have not yet been studied specifically in the context of adolescent sleep and pain. Also, the studies on sleep deprivation and pain commonly use some form of sleep restriction/partial sleep deprivation as an experimental model. However, more studies of delayed bedtimes/circadian timing shifts and "social jetlag" would be particularly insightful in understanding the pain-sleep interaction in adolescence. Since it is now shown that the suprachiasmatic nucleus indirectly projects to noradrenergic neurons in the locus coeruleus, as well as to the ventral tegmental area containing dopaminergic neurons [30, 93], studies using experimentally-imposed circadian misalignment in adolescents and experimental pain, as well as experimental modulation of pain, would be very valuable.

Furthermore, although there is evidence that the pain system exhibits circadian rhythms in function at all levels of hierarchical organization [30], the origins of these rhythms remain unclear. The current evidence does not allow us to unequivocally state that the circadian rhythmicity of pain thresholds arises exclusively from rhythms within the pain system alone. It is more likely that variations in pain thresholds are influenced by the integral relationships between the pain system and the circadian, endogenous opioid system, the immune and endocrine systems, and the ascending reticular activating system. These neurobiological interactions require further study in both adult and adolescent populations.

9. Methodological considerations for studying sleep and pain

As one considers aspects impacting the relationship between sleep and pain, several factors related to the presence and impact of pain should be considered when reviewing the literature and designing future studies. Whether the study looks at certain pain conditions or uses different pain assessment tools, these decisions could have considerable implications in interpreting the sleep-pain relationship. When considering the nature of the sleep-pain relationship, the complexity and multidimensionality of pain and sleep needs to be considered. The following section briefly reviews these factors.

9.1. Chronic pain conditions

One consideration for understanding the relationship between sleep and pain is the type of pain condition(s) studied. Studies have traditionally focused on patients with a single chronic pain condition, including headache [36, 63, 131], MSK-related pain [76, 132], abdominal pain [43, 133, 134], SCD [79, 103, 135], and JIA [51, 72, 136]. A smaller number of studies enrolled heterogeneous patient cohorts reflecting different pain conditions [6, 7, 57, 137], usually from tertiary care or specialty clinics. Collectively, these studies suggest that sleep is universally disrupted across different pediatric pain conditions, but no studies have empirically evaluated this. This raises a fundamental question: are certain aspects of disrupted sleep distinct (e.g., sleep-wake behaviors - increased daytime napping to manage headaches [33]) or shared (e.g., reduced sleep quality, insomnia symptoms)

across different pediatric pain conditions? Defining these aspects will likely have treatment implications as patients may benefit from specific sleep interventions.

9.2. Multisite pain

While these pain conditions are often localized at a single site, a significant proportion of youth (15-30% [138]) with chronic pain experience Multisite pain (MSP) [139]. Chronic MSP is commonly defined as pain in two or more anatomical sites, occurring concurrently or alternating with a certain time period. The occurrence of MSP also increases with age and can persist into adulthood [140]. The presence of chronic MSP has a pronounced negative impact, leading to poorer physical and psychosocial health, greater pain outcomes, and poorer quality of life (vs. youth with a single pain site) in patients with abdominal pain [141], SCD [142], and mixed presentation [139, 143, 144] in addition to large epidemiological studies in community samples [145-147]. The higher number of pain sites across the body, especially presenting as different pain conditions (e.g., headache + low back pain), is thought to reflect an alteration in how the CNS processes and modulates nociceptive information, which is often referred to as centralized pain [148]. A few studies have shown an association between a greater number of pain sites and poor sleep in adolescents. For example, MSP predicted poor sleep quality in a diverse community and clinical sample of adolescents [149], while pediatric patients with more than one pain site reported poorer sleep quality (7.54 ± 3.60) compared to patients with only one pain site. Finally, insufficient levels of sleep (e.g., sleeping 6 hours or less per day or experiencing other sleep-related symptoms) were more common in a community sample of adolescents with MSP [145]. Given the evidence that the risk of developing MSP is higher in adults with insomnia [150-152], sometimes showing a dose-response manner (e.g., a greater risk with more pain sites), future studies should consider the impact of MSP as a key patient-related factor in the relationship between sleep and pain.

9.3. Clinical pain outcomes

The presence and impact of clinical pain can be captured across several domains reflecting the experience (e.g., intensity, pain extent, occurrence) and impact (e.g., disability, interference) of pain. Given the multidimensional nature of pain, studies exploring the relationship between sleep and pain should consider how pain is assessed since other aspects may also be differentially sensitive to disruptions in sleep. In the following section, we review the most common pain assessments.

Pain Intensity.—One of the most common methods to characterize clinical pain is pain intensity. Using the NRS-11 [153, 154], previous cross-sectional and micro-longitudinal (daily) studies have reported associations between disrupted sleep and a patient's average (or usual) level of pain (e.g., week, month). Because these studies only used a single measure of pain, the extent to which these findings looking at sleep and pain relationships generalize to other pain-related domains, like pain unpleasantness (*see* Table 1), is unclear. However, pain intensity (somatosensory cortex, SI [155]) and unpleasantness (ACC and limbic areas [156]) can also exhibit differential responses to treatment. For example, in a recent study by Santucci et al. [134], ratings of pain unpleasantness decreased (vs. minimal changes in pain intensity) following percutaneous electrical nerve field stimulation in adolescents

with FAPD. Additional work is needed to evaluate if intensity and unpleasantness are differentially associated with sleep.

Functional Impairment.—Another important dimension, which has not been adequately assessed within the sleep and pain relationship, is the impairment of physical and psychosocial aspects of daily life [157]. Clinically, functional impairment is frequently used as a target for behavioral treatment (e.g., using coping strategies to improve daily functioning) and shows treatment-related changes before reductions in pain intensity [158]. Functional impairment is often assessed with two self-reported measures (*see* Table 1): Functional disability inventory (FDI [159]) and Patient-reported outcomes measurement information systems (PROMIS) Pediatric pain interference (PPI [160]). Few studies have examined the relationships between functional impairment and sleep. Murphy et al. [43] reported that sleep (based on the PROMIS Sleep Disturbance [161]) was associated with greater scores on the FDI in adolescents with abdominal pain. Similarly, Evans et al. [84] reported that both low positive and high negative affect mediated the relationship between poor sleep quality and greater disability, while the relationship between poor sleep quality and increased pain intensity was only mediated by negative affect. Pavlova et al. [77] also reported that psychological factors (e.g., greater depressive and anxiety symptoms) were mediators in the sleep-pain relationship. In a study by Larche et al. [162], poorer sleep quality was associated with greater physical impairment in a mixed sample of pediatric pain patients. Using a community-based sample, Solé et al. [163] provided evidence that poorer sleep (PROMIS Pediatric Sleep Disturbance) was associated with greater pain intensity (NRS-11) and pain-related interference (PPI); however, only pain interference, not pain intensity, was associated with poorer psychological functioning (e.g., depressive, anxiety, and anger symptoms), and a series of mediation modeling revealed poorer psychological functioning mediated with the relationship between poorer sleep and greater interference. Overall, these studies suggest that poor sleep may be a stronger driver of general (e.g., FDI) and pain-related (e.g., PPI) functional impairment in adolescents with chronic pain compared to pain intensity. However, additional research is needed to develop a daily or momentary measure of functional impairment.

9.4. Experimental pain sensitivity and pain modulation

Self-report measures of pain and other symptoms are used to diagnose patients and track clinical improvements following pain treatment. Still, this information often does not address pathophysiological mechanisms driving the pain experience. One common observation in pediatric and adult pain patients is alterations in how the nervous systems process and modulate nociceptive information. Specifically, patients exhibit widespread pain amplification due to increased facilitation (central sensitization) and/or reduced inhibition of nociceptive signaling [164].

The widespread pain amplification in pediatric patients can be probed safely and mechanistically with Quantitative sensory testing (QST, *see* Table 1 [165]), which encompasses an array of calibrated and psychophysically-based stimuli (thermal, mechanical) to characterize and quantify somatosensory functioning and how the CNS modulates nociceptive information [165]. Overall, pediatric patients with abdominal

[166, 167], MSK pain [168, 169], SCD [170], and migraine [171] exhibit widespread hypersensitivity to somatosensory stimuli as well as impaired pain modulating capacity, as reflected by poor pain modulatory profiles (increased facilitation and decreased inhibition; [172]). Significantly, these pain modulatory profiles can predict clinical trajectories in adolescents with headache [173] and FAPD [174], in which baseline CPM was associated with reductions in headache frequency (poorer CPM) and pain-related interference (better CPM) following psychological treatment, respectively. Differences between these two studies were likely due to methodological differences in patients (e.g., migraine patients less clinically severe vs. FAPD), CPM assessment, and clinical outcomes. Still, these preliminary studies support using CPM and other modulatory assessment methods to identify at-risk patients (e.g., identifying patients who will experience less pain reductions to a given treatment).

In terms of sleep, several studies in adults have shown that sleep disruption, either due to naturalistic causes (e.g., insomnia, night-shift work [175]) or experimentally (e.g., total/partial sleep deprivation, targeted sleep fragmentation), alters the perception of pain and its modulation. Adult patients with chronic pain and insomnia demonstrated an increased sensitivity to pain [106] and altered pain modulatory profiles, which are typically more facilitatory [176]. Experimental sleep disruption can also lead to increases in pain perception [177], reductions in pain inhibition (e.g., impaired descending pain mechanisms [178-181]), and increases in facilitation (e.g., facilitated peripheral and spinal excitability [181, 182]) in healthy adults, with evidence of a sex-related difference in these effects. However, several studies did not observe changes in pain perception or modulation following partial sleep restriction [183] or under naturalistic sleep [184], demonstrating that additional research is needed to understand how disrupted sleep impacts pain perception.

While QST can be used to probe the presence of augmented somatosensory processing and altered modulation in adolescents with pain, no studies that we are aware of have directly examined the association between experimental pain and sleep. Based on indirect evidence in healthy adolescents [96] that insufficient sleep can increase the frequency and magnitude of pain complaints, it is plausible that poor sleep would be associated with pain sensitivity and modulation in adolescents. It would be helpful to demonstrate which QST methods are differentially associated with sleep as pain sensitivity and modulatory profiles are conceptually distinct measures reflecting different pathophysiological mechanisms.

9.5. Multidimensionality of sleep

When considering the relationship between sleep and pain, there is a need to consider the multidimensionality of sleep at mechanistic (e.g., evaluating the specific sleep processes implicated in pain processing, development, and chronicity) and clinical (e.g., determining precise sleep targets for behavioral interventions) levels. Sleep questionnaires, widely used in pediatric pain research, address several sleep behaviors and dimensions (e.g., perceived sleep quality, sleep hygiene). Still, they only provide a “snapshot” of sleep, and the subjective sleep process measured by questionnaires is complex. For example, “sleep quality” may reflect several different sleep processes (e.g., duration, fragmentation,

restoration) that can vary between individuals and may or may not have a clear objective (e.g., actigraphy, PSG) correlates and specific links to distinct pain processes.

Considering that sleep is typically assessed either in isolation or across a few metrics (e.g., duration, quality), these approaches may not account for other aspects of sleep disrupted in adolescents with chronic pain. Given the lack of case-control differences in traditional actigraphy-based measures like duration and WASO, these other metrics may be differentially associated with pain-related outcomes. For example, recent interest in sleep health may provide insight into different aspects of sleep that contribute to pain. Sleep health, which can be defined as "*a multidimensional pattern of sleep-wakefulness, adapted to individual, social, and environmental demands, that promotes physical and mental well-being*" (*see* [185]), encompasses the dynamic and multidimensional aspects of sleep across several objectively (i.e., duration, efficiency, timing, regularity) and subjectively (i.e., daytime alertness, sleep satisfaction) assessed domains. Thus, good sleep health is characterized by "*subjective satisfaction, appropriate timing, adequate duration, high efficiency, and sustained alertness during waking hours*" [185] and regularity. It is likely that sleep health framework may identify certain dimensions like timing (e.g., later sleep-wake patterns [90]) or a cluster of dimensions that are differentially associated with pain, which can be targeted for intervention. However, research is needed to determine the precise definitions and quantification of "good *vs.* bad" across these domains.

9.6. Utilizing technologies to assess sleep

While still little used in the pediatric pain population due to its limited availability and high costs, PSG is necessary to expand our capability of differentiating and discriminating specific aspects of sleep and their association with pain processing and conditions. PSG has the advantage of providing both sleep macro-structure and micro-structure measures, allowing an in-depth characterization of the physiology of sleep. With PSG and associated measures, it is, therefore, possible to attain an integrated perspective of sleep [186] which can be applied to understand links between sleep disturbances beyond simple metrics, including impaired central and ANS coupling during sleep, elevated inflammatory markers, cortical and ANS hyperarousal, all of which may be implicated in altered pain processing.

Given the complexity of the sleep-pain relationship within the context of biobehavioral maturation and social changes (*see* Section 2), additional experimental and analytic methods might be needed to parse these associations. For example, available validated remote tools (i.e., sleep diaries and standard actigraphy) can capture an individual's "habitual sleep" and motion-based sleep/wake patterns in unsupervised free-living conditions over long periods of time (i.e., months). A big data approach may ultimately be required to analyze this time-series data to assess the directionality of the sleep-pain relationship. In addition, these approaches would also evaluate the mediating or moderating roles of various biopsychosocial and contextual factors affecting sleep and pain.

Learning from other fields, the use of Consumer sleep technology (CST) in chronic pain research, combined with ecological momentary assessments (e.g., mobile-based digital surveys), could also open new possibilities and directions to advance the understanding of the interaction between sleep and pain. While several limitations have been repeatedly

highlighted [187, 188], the advantage of CST is its cost-effectiveness and capability of passively tracking sleep, activity, and other physiological measures over time and on a large scale. Intuitive User experience (UX and interface (UI) designs, third-party integration, cloud-based research services (e.g., Fitabase, OURA cloud), and form-factor makes them suitable to wear 24/7. Among the possibilities, long-term tracking of sleep (i.e., months) during acute-to-chronic pain transitions may become feasible and ultimately allow the identification of sleep protective and risk factors for pain progression.

10. Clinical Implications

Adolescence is a critical time for the development of sleep and pain; consequently, addressing both conditions should be prioritized to reduce their long-term impact. Evidence suggests that sleep and pain should be screened for in clinical settings. This is especially important considering that poor sleep (a) is prevalent and co-occurs over time in adolescents with chronic pain, and more importantly, (b) it can negatively impact the efficacy of psychological treatments for pain. For example, shorter sleep duration [189], quality [190, 191], and insomnia symptoms [191] at baseline were associated with less improvement in disability following non-pharmacological treatments like cognitive-behavioral therapy (CBT). These studies suggest that adolescents with (or even at risk for) chronic pain would benefit from sleep screening and targeted interventions before beginning psychological treatment. These interventions could include CBT for insomnia (CBT-I), which is recommended as the first-line treatment for insomnia. Research into the effectiveness of CBT-I for adolescent pain is emerging with some promising work demonstrating its efficacy and feasibility [89, 192].

Evidence also suggests interventions targeting sleep timing (i.e., earlier chronotype) and reducing pre-sleep cognitive arousal might be particularly important to improving outcomes [90]. For example, patients undergoing interdisciplinary pain treatment show reductions in insomnia symptoms and daytime sleepiness, which were associated with improvements in disability but not pain [193]. Patients also had a dramatic change in their sleep timing (e.g., advancement of sleep onset by ~2 hours) [137]. These positive effects were likely due to the structured interventional activities and strict control over the sleep environment, which in turn, would stabilize the sleep/wake cycle. These two studies highlight the potential clinical benefits of targeting sleep phase. Furthermore, addressing pre-sleep arousal at bedtime should be considered, as heightened bedtime arousal can negatively affect an individual’s ability to fall and stay asleep [87]. Interventions like deep slow breathing with biofeedback [194] could improve sleep in adolescents with pain by downregulating psychophysiological arousal. Overall, as future research to optimize clinical interventions in the context of sleep and pain emerges, studies should consider the specific mechanisms underlying their treatment efficacy (i.e., moderators/mediators like negative affect, neurobiological changes, and the multidimensionality of sleep and pain) and potential subgroups that might respond differentially to treatment [90].

11. Summary

While the literature on sleep and pain relationships is more established in adults, there is a growing appreciation of this relationship in adolescence. We have highlighted several clinical- and community-based studies showing a high co-occurrence of sleep complaints and pain in adolescence. From these studies, there seems to be a stronger role of poor sleep (e.g., insomnia symptomatology, altered sleep structure) in the development and intensity of chronic pain. Overall, these studies highlight the clinical need to comprehensively assess and treat sleep-related complaints before or during pain treatment.

As highlighted in our "Research Agenda," future investigations are needed to better understand the (a) directionality of the sleep and pain relationship and (b) physiological and psychosocial processes by which sleep impacts pain, as this may also include options for intervention. For example, what circadian factors (e.g., delayed sleep phase) or aspects of emotional regulation contribute to poor sleep and pain? How do individual differences in pre-sleep arousal, a common feature of insomnia, contribute to this relationship? How does biological sex affect this relationship? These studies should also consider research designs that consider the multidimensionality of sleep (e.g., perception, behaviors, duration, structure, quality, regularity) and pain (e.g., pain-related interference; multiple pain sites), and dynamics (e.g., time-course) of the relationship. Additionally, longitudinal assessments should be prioritized to evaluate the trajectories of sleep and pain, which can co-develop over time in a subgroup of adolescence. Overall, exploring how the sleep and pain relationship develops and persists is imperative given the high prevalence of co-occurrence between chronic pain and sleep disturbances in adolescents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ACC	Anterior cingulate cortex
ANS	Autonomic nervous system
CNS	Central nervous system
CBT	Cognitive behavioral therapy
CPM	Conditioned pain modulation
CST	Consumer sleep technology

EEG	Electroencephalography
ER	Emotion regulation
FAPD	Functional abdominal pain disorders
FDI	Functional disability inventory
GABA	Gamma-Aminobutyric acid
HPA	Hypothalamic–pituitary–adrenal axis
IL	Interleukin
JIA	Juvenile idiopathic arthritis
MSP	Multisite pain
MSK	Musculoskeletal
NO	Nitric Oxide
NREM	Non-rapid eye movement
NA	Noradrenaline
NRM	Nucleus raphe magnus
NRS-11	Numerical rating scale
OSA	Obstructive sleep apnea
PROMIS	Patient-reported outcomes measurement information system
PENFS	Percutaneous electrical nerve field stimulation
PAG	Periaqueductal gray
PSG	Polysomnography
PFC	Prefrontal cortex
PPI	PROMIS pain interference
PGS	Prostaglandins
QST	Quantitative sensory testing
REM	Rapid eye movement
RAR	Rest-activity rhythm
5-HT	Serotonin
SCD	Sickle cell disease
SWS	Slow-wave sleep

TS	Temporal summation
TNF	Tumor necrosis factor
UX	User experience
UI	User interface
VLPO	Ventrolateral preoptic nucleus
WASO	Wake after sleep onset

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Practical Points

- Sleep is a key factor implicated in chronic pain, with >50% of adolescents with chronic pain reporting sleep difficulties. While poor sleep perception has been widely reported across different pain conditions, evidence supporting objective sleep alterations is scarce and inconclusive.
- Chronic pain is a common and debilitating condition in adolescence, a critical developmental period associated with changes in biological systems underlying sleep and pain.
- Several methods are available to measure sleep in adolescents with chronic pain. While PSG is considered the gold standard for laboratory sleep assessment, it has rarely been used in pediatric pain research, limiting the understanding of the physiological processes implicated in chronic pain.
- Emerging evidence suggests that disrupted (or poorer) sleep is a stronger and more reliable predictor of next-day pain (*vs.* daily pain as a predictor of next-night sleep) in youth with chronic pain.
- The ability of the central nervous system to facilitate and inhibit pain processing, which is often altered in chronic pain, could be a critical neurobiological mechanism by which poor sleep increases pain perception.
- Most studies focus on pain intensity ratings with limited attention to outcomes like disability and pain-related interference.

Research Agenda

- There is a need for standardized, systematic, and precise definitions and quantification of the distinct sleep and pain processes (accounting for the multi dimensionality of both constructs) implicated in the sleep-pain relationship. For example, future studies should consider sleep in chronic pain patients within a 'sleep health' framework, which describes sleep in terms of their subjective perceptions of sleep (i.e., satisfaction/quality, alertness) and sleep-wake patterns (i.e., quantity, efficiency, timing, and regularity), which can be assessed with actigraphy or self-report. In agreement with a recent consensus statement for clinical trials for pediatric pain[195], future studies should consider pain-related domains (e.g., frequency/intensity of pain, interference in engagement in social, physical, and recreational activities). Other domains like overall well-being, general physical functioning, and emotional functioning (e.g., response-focused ER[99, 100]) should also be considered, given their role in sleep, pain, and overall health[10]. Appropriate psychometric development of these assessments will also need to be established.
- Compared to boys, adolescent girls report more sleep problems, more pain, stronger immune responses after the onset of puberty, stronger stress reactions due to sleep deficiency, more negative mood, more maladaptive emotion regulation strategies, and heightened pain sensitivity. However, few - if any - studies have explicitly examined sex differences in the sleep-pain relationship in adolescents. Future studies should address this gap in the literature. Furthermore, given potential differences between biological sex and gender identity, future studies should also consider if these concepts differentially impact the relationship between sleep and pain.
- The involvement of multiple factors in the sleep-pain relationship in adolescents needs to be further explored. While a few studies have examined potential mediators within the sleep-pain relationship, studies should consider multiple mediators (e.g., negative vs. positive affect) and assess them within a serial or parallel mediation model since these mechanisms are likely also related. In addition, moderators should also be considered. These factors have traditionally been used to control for contextual effects as covariates) in the sleep-pain relationship. For example, given the previously mentioned differences in biological sex, the pain-sleep relationship may be different in adolescent girls vs. boys.
- In light of the phase delayed and circadian rhythm changes observed in adolescents, together with lifestyle changes that likely routinely disrupt circadian rhythms (increased exposure to blue light at night; napping during the day), the integral relationships between the pain system and the circadian systems need to be further explored.

- In agreement with Andreucci et al. [107], there is a need for additional longitudinal studies to study the temporal relationship between sleep and pain in both clinical and non-clinical populations. These studies could provide information about the trajectories of poor sleep (e.g., insomnia symptoms) and pain in adolescent, as highlighted by a recent study [90], which showed sleep and pain can co-develop over time. This has clinical implications as interventions could be geared at targeting patients with established sleep (e.g., CBT) and pain issues or geared to prevent these issues in "at-risk" adolescents before sleep and pain issues develop.
- Beyond self-assessment of sleep quality measures, focusing on physiological sleep processes is deemed necessary to further expand our understanding of the physiology of the sleep-pain relationship. With the advent of ambulatory PSG devices, it is plausible to assess several physiological processes (e.g., EEG, ECG) in naturalistic environments.
- Consumer technology (e.g., passive tracking of sleep) combined with digital surveys (e.g., pain assessment within the EMA framework) may ultimately expand our understanding of the time-course of the sleep-pain relationship by allowing large-scale, remote patient monitoring of sleep and pain in unsupervised free-living conditions. The potential for large datasets would also consider demographic and other factors implicated in the pain-sleep relationship. Additional metrics like HR and GPS tracking may also provide insight into altered physiology and physical impairment observed in patients with pain. Additionally, novel statistical models, including Dynamic Structural Equation Modeling[196], should be considered to analyze complex time-series datasets.
- Additional research is needed to understand the shared neurobiological mechanisms between sleep and pain using QST methods and neuroimaging.
- While actigraphy and daily diaries have provided evidence regarding the relationship between poor sleep and pain, the timing of these assessments (particularly pain) at different times of day (e.g., morning, afternoon, and evening) is critical to understanding this bidirectional relationship. Furthermore, the ability of nocturnal pain, either spontaneous or evoked during the night, to interrupt sleep (e.g., waking up due to pain) should also be explored.
- The focus on "at-risk" samples (acute pain) may allow the investigation of the role of sleep disturbances in the development of chronic-pain conditions (acute > chronic).
- Mechanistic processes of sleep regulation (e.g., homeostatic, circadian) across physiological domains (e.g., cortical, ANS, endocrine) also need to be considered, especially in the context of the major changes that occur across adolescence.

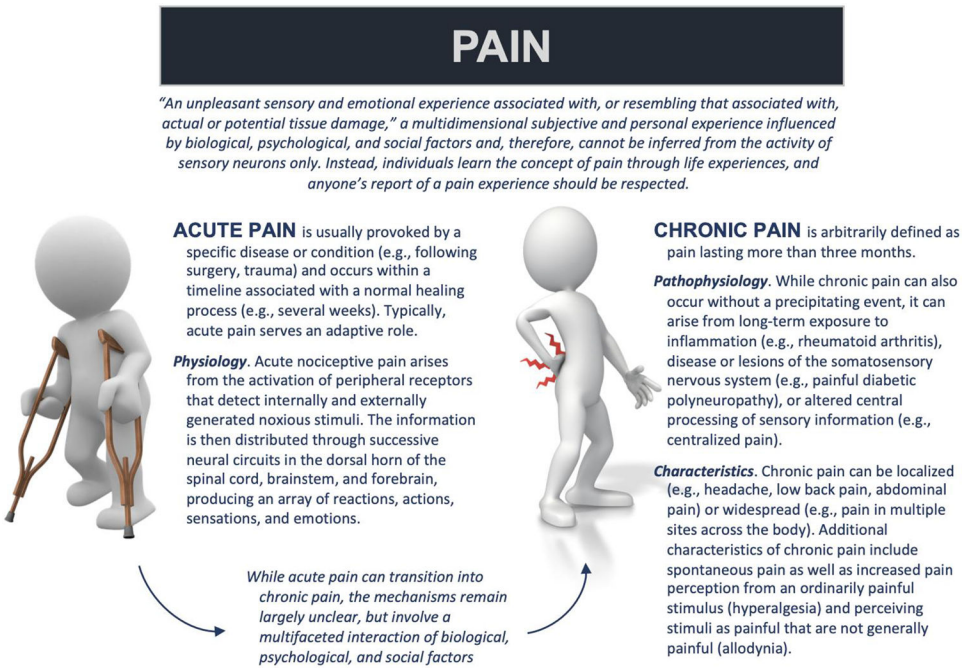

Figure 1.
Key Definitions for Pain, Acute Pain, and Chronic Pain.

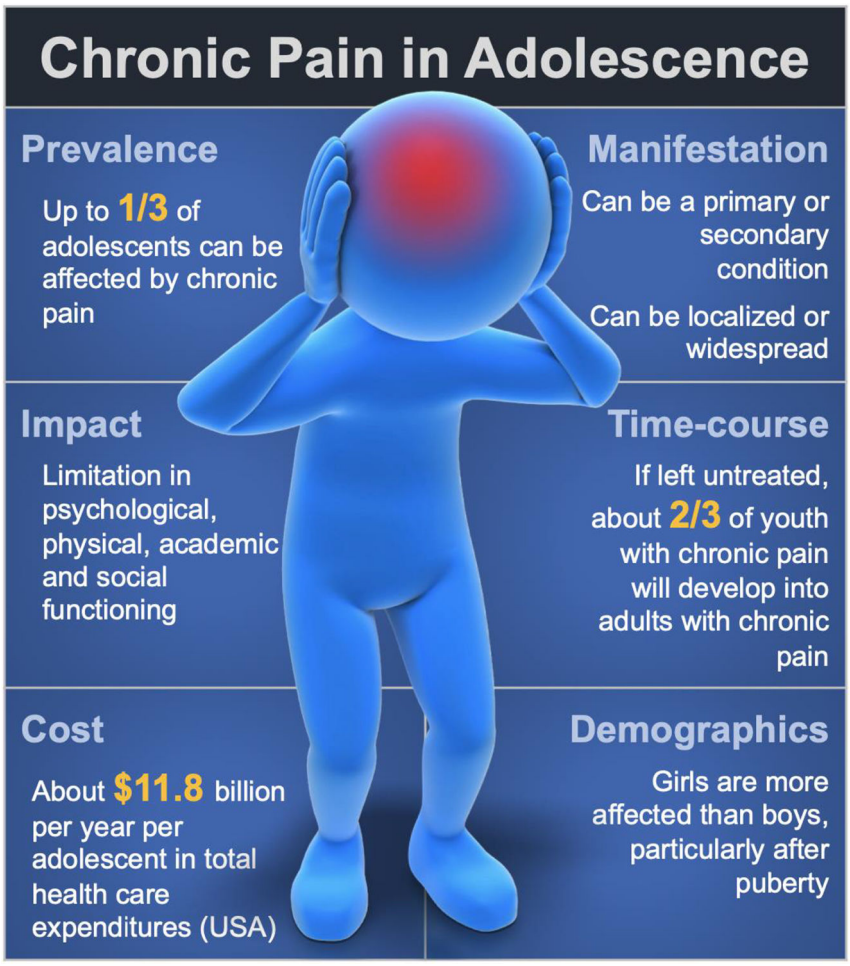

Figure 2.
Chronic pain in adolescence: Prevalence, manifestation, impact, time-course, cost, and demographics.

Figure 3.
Characteristics of Sleep in Adolescents with Chronic Pain.

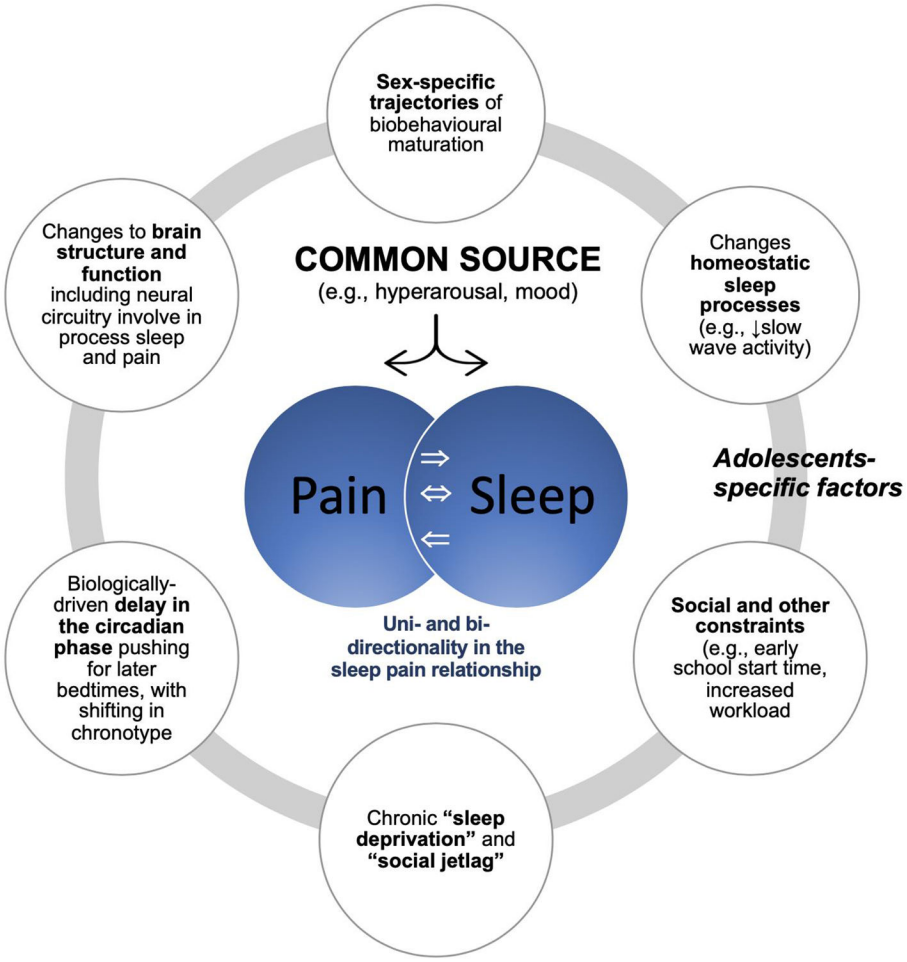

Figure 4.

Sleep and pain relationship in the context of adolescents biobehavioral maturation.

Table 1:

A summary of Clinical and Experimental Pain Outcomes

Outcome	Description of Assessment	Implications and future research recommendations
Clinical		
Pain Intensity	The sensation of pain can be described in terms of its magnitude or "how strong the pain feels." Pain intensity reflects the sensory dimension of pain. Pain intensity is commonly assessed with a numerical rating scale (NRS), which is an 11-point Likert scale ranging from 0 (No pain) to 10 (Worst Pain Possible/Imaginable [155, 156]).	Assessment of pain intensity and unpleasantness
Pain Unpleasantness	The sensation of pain can also be described as unpleasant, or "how disturbing the pain is" (Price et al., 1983). Pain unpleasantness reflects an affective dimension of pain, and while it can be associated with the sensory dimension of pain (e.g., pain intensity), it is often a distinct sensation.	
Disability & Pain-related Interference	The Functional Disability Inventory (FDI [161]) measures general physical and psychosocial functioning in adolescents with chronic pain. The Patient-Reported Outcomes Measurement Information Systems (PROMIS) Pediatric Pain Interference (PPI) measures pain-specific functional impairment over the past 7 days [162]. While these two self-report measures are correlated), the FDI (e.g., general interference in physical activities) and PPI (e.g., pain-related interference in psychological, social, and physical activity) capture different aspects of impairment.	Assessment of disability and/or Interference Development of daily measures of disability
Experimental		
Generalized Somatosensory Function	Specialized tools like thermal probes, hand-held algometers, and pinprick stimulators can assess sensitivity to heat/cold, pressure, and punctate pain as these methods can evaluate small-caliber A-delta & C-fibers, which are important for the transmission of nociceptive information. Sensitivity to these modalities can also capture different dimensions, including the first sensation of pain (e.g., threshold), time or temperate a participant can tolerate (e.g., tolerance), or suprathreshold ratings of pain intensity. These methods have been used in pediatric pain studies, including heat pain, cold immersion, and pressure pain thresholds.	Inclusion of pain assessments before nighttime and in the morning
Pain Modulation	Through bottom-up and top-down processes, noxious sensory information can be facilitated or inhibited within the spinal cord, brainstem, and cortex. Facilitation and inhibition are key features of the nervous system's ability to process nociceptive afferent information. Disruptions of this processing may contribute substantially to sensory features of chronic pain and may be relevant to the sleep-pain relationship. Several QST methods are available to probe disruptions in central modulation in patients, reflecting pain amplification in each dimension (e.g., increased facilitation and/or reduced inhibition). • Conditioned pain modulation (CPM) is characterized by the change in pain of a test stimulus (pressure) before and following a conditioning stimulus (cold water) at a contralateral site. Typically, CPM is defined by a reduction in pain sensitivity of the test stimulus. But, in youth with chronic pain, the inhibition is often smaller, or sensitivity is increased (e.g., facilitation). • Another QST method is Temporal Summation (TS), which is observed by increases in pain sensitivity to a repeated train of painful stimuli. Youth with chronic pain often report greater increases in pain. • Other QST methods like offset analgesia (defined as a disproportionate decrease in pain following a slight drop in stimulus intensity) and spatial summation (characterized by increased pain perception when applying two painful stimuli simultaneously *vs.* one stimulus alone) could also be used but has not been adequately evaluated in pediatric pain nor sleep.	