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A Review on Sleep Loss and Central Pain Processing: Neurobiological Mechanisms of Pain Hypersensitivity

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Abstract: *Sleep and pain are closely linked, and increasing evidence shows that they influence each other in both directions. Pain can make it difficult to fall asleep, cause repeated awakenings, and reduce the quality and restorative value of sleep. In turn, inadequate or disturbed sleep can make people more sensitive to pain and can reduce the brain's ability to control and adapt to painful stimuli. Over time, this can create a continuing cycle in which poor sleep aggravates pain, while persistent pain further interferes with sleep. Research suggests that sleep loss affects pain processing at several levels, from the initial detection of painful signals to their transmission and interpretation within the spinal cord and brain. Changes in the activity of neurotransmitters and other chemical messengers, including serotonin, dopamine, noradrenaline, endogenous opioids, and melatonin, may contribute to these changes. Sleep disturbance is also associated with increased inflammatory activity, including changes in cytokines such as interleukin-1β, interleukin-6, and tumour necrosis factor-α. Interactions between inflammatory signals and neural cells, including microglia and astrocytes, may further contribute to the development and maintenance of pain sensitivity. In addition, disruption of the hypothalamic–pituitary–adrenal axis and sympathetic nervous system may connect sleep loss and psychological stress with changes in cortisol, inflammation, and pain perception. Taken together, these findings suggest that disturbed sleep is not simply a consequence of pain; it can also actively contribute to the persistence and worsening of pain. A better understanding of the links between sleep, pain, inflammation, neurotransmitters, and stress may therefore help in developing more effective and integrated approaches to pain management, in which improving sleep is considered an important part of treatment.*

Keywords: *Sleep deprivation; Pain sensitization; Chronic pain; Neuroinflammation; Central pain processing; Neuroendocrine mechanisms.*

1. INTRODUCTION

Sleep and pain are fundamental physiological processes that are closely interconnected through neural, neuroendocrine, immune and behavioural mechanisms. Although pain has traditionally been considered a major cause of sleep disturbance, increasing evidence indicates that the relationship is bidirectional, with inadequate or disrupted sleep also acting as an important determinant of subsequent pain sensitivity. Pain may delay sleep initiation, increase nocturnal awakenings, fragment sleep continuity and reduce restorative sleep, whereas insufficient or disturbed sleep can lower pain thresholds, increase spontaneous pain and impair endogenous pain-inhibitory mechanisms. Prospective evidence provides important support for this reciprocal association. A systematic review and meta-analysis of 20 prospective studies involving 208,190 adults found that individuals with sleep-related problems had a higher incidence and persistence of chronic musculoskeletal pain, while individuals with chronic musculoskeletal pain also had an increased incidence of subsequent sleep-related problems (Santos et al., 2023). More recently, Runge et al. (2024), analysing 16 articles from 11 populations comprising 116,746 participants, reported that sleep problems at baseline were associated with increased short- and long-term risk of chronic musculoskeletal pain, while chronic musculoskeletal pain was associated with increased short-term risk of sleep problems. Day-to-day evidence further suggests that this relationship operates dynamically: among individuals with chronic musculoskeletal pain, nighttime sleep quality was more consistently associated with pain intensity on the following day than pain intensity was with subsequent nighttime

sleep quality (Goossens et al., 2025). These findings support the concept that sleep disturbance should not be viewed simply as a consequence of pain but as a potentially important contributor to pain amplification and persistence.

The influence of sleep on pain is particularly evident when examining central pain processing and nociceptive sensitization. Experimental sleep deprivation studies demonstrate that insufficient sleep can alter the way the nervous system detects, transmits and interprets painful stimuli. A systematic review and meta-analysis of experimental studies found that total sleep deprivation reduced pain threshold and tolerance in healthy individuals, while partial sleep deprivation increased spontaneous pain intensity; sleep fragmentation was also associated with increased measures of peripheral and central sensitization (Chang et al., 2022). At the neurophysiological level, sleep loss may increase excitability within ascending nociceptive pathways while weakening descending inhibitory control involving supraspinal structures such as the periaqueductal grey, rostral ventromedial medulla, thalamus, insula, anterior cingulate cortex and prefrontal cortex. Alterations in cortical processing can increase the salience and affective impact of painful stimuli, whereas changes in spinal processing may facilitate temporal summation and central sensitization. Consequently, sleep deprivation may increase the "gain" of the pain-processing system, allowing a given nociceptive input to generate a greater perceived response. The mechanisms proposed to underlie this process include alterations in endogenous opioid, monoaminergic, orexinergic, endocannabinoid and adenosinergic systems, together with changes in melatonin and HPA-axis activity (Finan et al., 2019). Thus, the relationship between sleep loss and pain cannot be explained simply by increased peripheral tissue inflammation; rather, it involves changes in the central nervous system's ability to regulate and inhibit nociceptive information.

A second major pathway connecting sleep and pain involves neuroinflammation and interactions between the immune and nervous systems. Sleep is an important regulator of immune function, while inflammatory mediators can influence sleep architecture and sleep–wake regulation. Disturbed sleep may consequently alter inflammatory signaling involving cytokines such as interleukin-1β (IL-1β), IL-6 and tumour necrosis factor-α (TNF-α), as well as cellular pathways involving microglia, astrocytes and innate immune receptors. These inflammatory signals can influence nociceptor excitability, spinal neuronal transmission and central sensitization, providing a biological link between sleep disruption and increased pain sensitivity. Particularly compelling evidence comes from a randomized clinical trial in healthy adults in which experimentally induced sleep disruption reduced slow-wave N3 sleep, increased Toll-like receptor-4-stimulated production of IL-6 and TNF-α by monocytes, and reduced heat-pain thresholds; mediation analysis indicated that loss of N3 sleep followed by increased cellular inflammation accounted for approximately 35% of the effect of sleep disruption on pain sensitivity (Irwin et al., 2023). These findings suggest that sleep loss may influence pain not only through circulating inflammatory biomarkers but also through changes in immune-cell responsiveness and neuroimmune signaling. Microglial and astrocytic activation may further contribute to central sensitization by releasing inflammatory mediators that modify neuronal excitability, although direct evidence for these mechanisms in humans remains more limited than the evidence from experimental models. Recent reviews continue to identify neuroinflammation, microglial–astrocytic interactions and inflammatory cytokines as important candidate mechanisms linking chronic pain and disturbed sleep (Alves et al., 2026).

The sleep–pain relationship is therefore best understood as an integrated neurochemical, neuroendocrine and neuroimmune network rather than as a simple consequence of either pain or sleep loss. Sleep deprivation can influence serotoninergic, dopaminergic and noradrenergic signaling, endogenous opioid activity and melatonin-mediated circadian regulation, while simultaneously affecting the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system. Cortisol and autonomic activity may modify inflammatory responses and alter both peripheral and central pain processing, while inflammatory cytokines can in turn affect sleep continuity and neural excitability. These interconnected mechanisms can establish a self-reinforcing cycle in which pain disrupts sleep, sleep disruption increases nociceptive sensitivity and central sensitization, and heightened pain further compromises sleep. A recent lifespan review similarly identifies HPA-axis dysregulation, neuroinflammation and circadian mechanisms as shared biological pathways linking sleep disturbance and persistent pain (Kelleher et al., 2026). Understanding this reciprocal relationship is therefore important not only for explaining the pathophysiology of pain hypersensitivity but also for identifying sleep and its associated neuroimmune and neuroendocrine pathways as potentially modifiable components of chronic pain.

2. The Bidirectional Relationship Between Sleep and Pain: From Sleep Loss to Pain Sensitization

Sleep and pain are deeply interconnected biological processes, and their relationship is considerably more complex than the simple idea that pain causes poor sleep. Sleep is an active physiological state during which the brain and body undergo extensive changes in sensory processing, autonomic regulation, endocrine activity, immune function and neural plasticity. Pain, meanwhile, is not determined solely by the intensity of a peripheral injury; it is shaped by how nociceptive signals are transmitted, amplified or inhibited within the nervous system and how the brain interprets

those signals. Because these systems continuously interact, disruption in one can gradually influence the other. Pain may make it difficult to fall asleep, cause repeated awakenings, shorten total sleep time and reduce sleep quality, while insufficient or fragmented sleep can subsequently increase pain sensitivity and diminish the ability of the nervous system to suppress incoming nociceptive signals. Experimental and longitudinal research therefore increasingly supports a bidirectional sleep–pain relationship, in which disturbed sleep and pain can reinforce one another over time rather than functioning as independent symptoms (Lautenbacher et al., 2006; Tang et al., 2018; Finan et al., 2013).

The longitudinal evidence is particularly important because it helps move the field beyond simple cross-sectional observations. In a systematic review and meta-analysis, Santos et al. (2023) examined 20 prospective studies involving 208,190 adults and found evidence in both directions. Individuals who had sleep-related problems at baseline had a higher risk of developing chronic musculoskeletal pain and were also more likely to experience persistent pain. Conversely, people with chronic musculoskeletal pain at baseline had approximately twice the risk of subsequently developing sleep-related problems. Specifically, sleep-related problems were associated with increased incidence of chronic musculoskeletal pain (OR 1.79) and persistence of chronic musculoskeletal pain (OR 2.04), whereas chronic musculoskeletal pain was associated with increased incidence of subsequent sleep-related problems (OR 2.02) (Santos et al., 2023). These findings are important because they suggest that sleep disturbance may not merely be a consequence of an established pain disorder. Instead, poor sleep may represent one of the factors that increases vulnerability to persistent pain. However, the observational nature of much of this evidence means that these associations should not be interpreted as proof that sleep disturbance alone causes chronic pain; shared biological, psychological and behavioural factors may contribute to both outcomes.

More recent evidence has broadly supported this interpretation while also highlighting some uncertainty. Runge et al. (2024) conducted a systematic review and meta-analysis of prospective studies involving 116,746 participants. Their analyses indicated that sleep problems at baseline were associated with an increased risk of chronic musculoskeletal pain in both the short term (OR 1.64) and long term (OR 1.39). Chronic musculoskeletal pain was also associated with an increased risk of short-term sleep problems (OR 1.56), although evidence concerning the longer-term effect of pain on sleep was less certain. The authors therefore concluded that the prospective association between sleep problems and subsequent chronic musculoskeletal pain was supported, whereas the strength and consistency of the relationship in the opposite direction require further investigation (Runge et al., 2024). Taken together with the findings of Santos et al. (2023), these results suggest that the sleep–pain relationship is best viewed as a dynamic process rather than a one-way pathway. Importantly, the evidence also indicates that the strength of the relationship can vary according to the definition of sleep disturbance, type and distribution of pain, duration of follow-up, age and other individual characteristics.

Day-to-day research adds another layer to this picture. Chronic pain and sleep are not static experiences; both can change considerably from one night or day to the next. A person with chronic pain may have a relatively good night followed by a night of fragmented sleep, and these variations can be reflected in pain intensity on the following day. A 2025 systematic review by Goossens et al. examined this short-term relationship in adults with chronic musculoskeletal pain and identified 11 studies involving 1,014 participants and 83 reported sleep–pain associations. The review found evidence of a reciprocal day-to-day relationship, but nighttime sleep quality appeared to be a more consistent predictor of next-day pain than pain intensity was of subsequent sleep quality. This finding is particularly relevant to the concept of pain sensitization because it suggests that even relatively short-term deterioration in sleep may alter how pain is experienced the following day. In other words, a poor night of sleep may leave the nervous system temporarily more responsive to otherwise similar sensory inputs, making an existing painful condition feel more intense without necessarily reflecting a corresponding increase in tissue damage.

Experimental studies provide stronger evidence for this possibility. Research in both humans and animal models indicates that sleep restriction, sleep deprivation and sleep fragmentation can produce hyperalgesic responses, meaning that normally painful stimuli may be experienced as more intense, while stimuli that were previously tolerated may become uncomfortable or painful. A major review of experimental studies concluded that the total amount of sleep lost appears to be an important determinant of pain hypersensitivity, although the effects vary depending on whether sleep is completely deprived, restricted or repeatedly interrupted (Finan et al., 2013; Lavigne et al., 2022). Importantly, sleep loss does not necessarily create pain through a single pathway. Instead, it appears to modify several levels of pain processing simultaneously, including peripheral nociceptor responsiveness, spinal transmission, supraspinal processing and descending pain-control systems. This provides a plausible biological explanation for why two individuals exposed to a similar painful stimulus may report substantially different levels of pain depending partly on their recent sleep history.

One of the most important consequences of sleep disruption is alteration of the descending pain-modulatory system. Pain processing is not simply a matter of signals travelling from injured tissue to the brain. The central nervous system contains powerful pathways capable of either inhibiting or facilitating nociceptive transmission. Brain regions including the periaqueductal grey, rostral ventromedial medulla and locus coeruleus participate in these descending control mechanisms through neurotransmitter systems involving endogenous opioids, noradrenaline and serotonin. Experimental evidence suggests that sleep loss can weaken endogenous inhibitory control while simultaneously increasing facilitatory influences, thereby shifting the balance toward greater pain transmission (Lavigne et al., 2022). This may help explain why pain can become more difficult to tolerate following repeated nights of inadequate sleep. Rather than simply increasing the amount of nociceptive information entering the nervous system, sleep loss may change the way that information is filtered and regulated.

Sleep disruption may also influence the emotional and cognitive dimensions of pain. Pain is shaped not only by sensory intensity but also by attention, emotional state, threat perception, motivation and expectations. Sleep restriction can impair attention and emotional regulation and may increase the salience of unpleasant sensory experiences. Experimental work has implicated brain regions involved in reward and affective processing, including the nucleus accumbens, in the altered response to painful stimuli following sleep loss (Lavigne et al., 2022). Consequently, the same peripheral stimulus may be interpreted as more threatening or distressing when an individual is sleep deprived. This does not mean that pain experienced after poor sleep is psychologically generated; rather, sleep-related changes in brain function can influence the sensory, emotional and cognitive components through which pain is ultimately experienced.

Another important pathway involves neuroimmune and inflammatory regulation. Normal sleep contributes to the maintenance of immune and endocrine homeostasis, whereas inadequate sleep can promote a shift toward inflammatory signalling. Increased inflammatory activity can, in turn, enhance the excitability of peripheral nociceptors and central pain-processing circuits. Experimental and longitudinal studies have therefore proposed inflammatory mediators as one link between sleep disturbance and heightened pain sensitivity (Tang et al., 2018; Lavigne et al., 2022). The relationship is unlikely to be explained by inflammation alone, however. Rather, immune activation probably interacts with neural, endocrine and behavioural mechanisms, creating a physiological environment in which nociceptive signals are more readily amplified.

The hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system may provide another bridge between disturbed sleep and pain. Repeated sleep restriction can alter stress regulation and autonomic balance, potentially increasing physiological arousal at a time when the body would normally be shifting toward restorative processes. For individuals already experiencing pain, this heightened arousal may make it more difficult to achieve consolidated sleep, creating a self-reinforcing cycle. At the same time, chronic pain itself can produce anticipatory anxiety about sleep, repeated checking of bodily sensations and maladaptive sleep behaviours, further increasing nighttime arousal. Thus, the sleep–pain relationship involves not only direct neurophysiological interactions but also behavioural and psychological feedback loops (Finan et al., 2013; Tang et al., 2018).

Neurochemical systems are also central to this interaction. Sleep and pain regulation share several neurotransmitter and neuromodulatory pathways, including serotonergic, noradrenergic, dopaminergic and opioidergic systems. Sleep loss may interfere with endogenous analgesic mechanisms, including opioid-mediated pain inhibition, while changes in serotonin and noradrenaline signalling can influence descending pain control. Earlier experimental work showed that sleep deprivation can produce hyperalgesic changes and may interfere with analgesic mechanisms involving opioidergic and serotonergic pathways (Lautenbacher et al., 2006). More recent reviews continue to identify impaired endogenous pain inhibition as one of the major mechanisms linking sleep loss with increased pain sensitivity (Lavigne et al., 2022). These observations provide a physiological basis for understanding why improving sleep may have consequences beyond reducing fatigue and daytime sleepiness.

The interaction may also be influenced by sex, age and the specific pattern of sleep disruption. A 2023 systematic review and meta-analysis examining 38 experimental studies found that sex and age moderated some effects of sleep disturbance on pain facilitation, inhibition and sensitivity, although the magnitude of these moderating effects was relatively small (Rouhi et al., 2023). Such findings suggest that sleep loss should not be considered a uniform biological exposure. Total sleep deprivation, chronic partial sleep restriction and fragmented sleep may produce somewhat different effects, and individual responses may vary according to biological and psychosocial characteristics. This variability is one reason why the sleep–pain relationship cannot be adequately explained by a single pathway or biomarker.

The emerging evidence supports a model in which sleep disturbance and pain progressively reinforce one another. Pain can fragment sleep, reduce restorative sleep and increase nighttime arousal; in turn, inadequate or poor-quality sleep can increase nociceptive sensitivity, weaken endogenous pain inhibition, alter inflammatory and stress

responses, and modify the cognitive and emotional processing of painful sensations. Repeated cycles of this type may contribute to the persistence or amplification of pain over time. The concept is therefore better represented as a feedback loop: pain → disturbed sleep → enhanced pain sensitivity → greater pain-related distress and further sleep disruption. Importantly, prospective studies support an association between sleep problems and later chronic musculoskeletal pain, but the available evidence does not establish that every form of sleep disturbance inevitably causes chronic pain. Nevertheless, the convergence of longitudinal, day-to-day and experimental evidence indicates that sleep is an important component of the biological context in which pain is experienced. Understanding this relationship may therefore help explain why pain can become persistent even when the original tissue injury has stabilized and why addressing sleep may be relevant to comprehensive approaches to chronic pain management.

3. Pain as a Disruptor of Sleep

Pain and sleep are closely intertwined, and persistent pain can make normal, restorative sleep difficult to achieve. For many individuals with chronic pain, the problem is not simply that they sleep for fewer hours; rather, pain can interfere with several aspects of the sleep process, including falling asleep, staying asleep and maintaining stable sleep throughout the night. Recurrent nociceptive input may repeatedly draw attention back to the painful body region, while discomfort can make it difficult to find or maintain a comfortable sleeping position. This is particularly evident in chronic musculoskeletal and spinal pain, where greater pain severity is frequently accompanied by poorer subjective sleep quality and more pronounced sleep disturbance. A systematic review of chronic spinal pain, for example, found that most available studies reported an association between more severe pain and more disturbed sleep, although the magnitude of this relationship varied considerably across studies and the overall methodological quality was heterogeneous (Afolalu et al., 2021). More recent evidence from day-to-day studies also suggests that pain and sleep influence one another dynamically rather than operating as independent symptoms; importantly, night-time sleep quality may be a more consistent predictor of next-day pain intensity than pain is of subsequent sleep quality (Hawker et al., 2024).

The mechanisms through which pain interferes with sleep are complex and involve both physiological and psychological processes. Persistent nociceptive activity can increase central nervous system arousal, making it more difficult for the brain to transition into and remain in a stable sleep state. At the behavioural level, movement-related pain may cause individuals to change position repeatedly during the night, while stiffness or discomfort may result in prolonged periods of wakefulness. The experience of pain can also generate anticipatory thoughts such as worrying about whether pain will worsen during the night or whether insufficient sleep will make the following day more difficult. Such cognitive and emotional arousal may further delay sleep initiation and increase the likelihood of nocturnal awakenings. Psychological factors, including anxiety, depressive symptoms, fatigue and pain catastrophizing, can amplify these processes and contribute to a self-reinforcing cycle in which pain produces poor sleep, poor sleep increases distress, and heightened distress makes pain more difficult to tolerate. Thus, the relationship cannot be adequately explained by nociceptive signalling alone; it reflects an interaction among sensory, cognitive, emotional, autonomic and behavioural mechanisms (Afolalu et al., 2021).

Evidence from longitudinal studies provides particularly important support for this reciprocal relationship. Rather than viewing sleep disturbance simply as a consequence of an established pain condition, prospective research indicates that pre-existing sleep problems may increase the subsequent risk of chronic musculoskeletal pain. In a 2024 systematic review and meta-analysis, Runge et al. analysed 16 articles representing 11 study populations and 116,746 participants. They found that sleep problems at baseline were associated with a greater risk of developing chronic musculoskeletal pain over both shorter and longer follow-up periods. At the same time, chronic musculoskeletal pain was associated with an increased risk of subsequent short-term sleep problems, although the evidence for the longer-term effect of pain on sleep was less certain. These findings support a genuinely bidirectional relationship, while also demonstrating that the strength and certainty of the association depend on the direction of the relationship, duration of follow-up and type of pain or sleep problem examined (Runge et al., 2024). Similar conclusions were reached by a previous meta-analysis involving more than 208,000 adults, which reported increased incidence of chronic musculoskeletal pain among individuals with sleep-related problems and increased incidence of sleep-related problems among those with chronic musculoskeletal pain (Tang et al., 2023). Taken together, these findings suggest that disturbed sleep may represent not merely a symptom accompanying chronic pain but one of the factors that can contribute to its persistence or subsequent development.

An important aspect of this relationship is that sleep continuity may be particularly important for pain regulation, rather than total sleep duration alone. A person may spend an apparently adequate number of hours in bed but still

experience physiologically and subjectively poor sleep if that sleep is repeatedly interrupted by pain-related awakenings or arousals. Fragmented sleep disrupts the normal progression and maintenance of sleep stages and may interfere with the neural, endocrine and immune processes associated with consolidated sleep. Experimental evidence supports the importance of sleep fragmentation specifically. In a controlled study of healthy young women, two consecutive nights of experimentally fragmented sleep increased sensitivity to both deep and superficial experimental pain and were accompanied by poorer sleep quality, reduced morning vigilance and changes in mood (Kundermann et al., 2017). These findings are particularly relevant to chronic pain because clinical pain commonly produces repeated rather than continuous periods of wakefulness, making sleep fragmentation a potentially more realistic experimental model than complete sleep deprivation.

Experimental studies of partial sleep restriction further strengthen the evidence that inadequate sleep can alter pain processing. Recent randomized crossover research found that experimentally reducing sleep for two nights increased experimental pain sensitivity in healthy adults, demonstrating that even relatively short periods of restricted sleep can influence nociceptive responses (Matre et al., 2025). Animal research similarly suggests that repeated sleep restriction can progressively increase pain sensitivity and alter activity in brain regions involved in pain modulation, including the periaqueductal gray and nucleus accumbens (Fischer et al., 2018). These findings provide a plausible biological basis for the clinical observation that patients may experience greater pain after nights of poor or fragmented sleep. Importantly, however, experimental sleep restriction in healthy participants should not be considered identical to naturally occurring sleep disturbance in people with chronic pain; the former provides mechanistic evidence, whereas the latter involves additional factors such as disease-related inflammation, medication use, psychological distress and altered activity patterns.

The importance of sleep continuity is also reflected in observational research examining changes in pain and sleep over time. In individuals with chronic musculoskeletal pain, recent systematic evidence indicates a day-to-day bidirectional relationship between sleep and pain, with several studies suggesting that poorer sleep quality predicts greater pain intensity on the following day. This pattern is consistent with the possibility that a disturbed night of sleep can temporarily lower the threshold at which sensory input is experienced as painful, while a painful day can subsequently interfere with the following night's sleep (Hawker et al., 2024). Evidence from chronic low back pain populations likewise indicates that improvements in self-reported sleep quality and total sleep time are associated with corresponding reductions in pain, further suggesting that sleep should be considered an active component of pain regulation rather than merely an outcome of pain (Luque-Suárez et al., 2022).

The available evidence supports a model in which pain-related sleep disruption can gradually become part of a self-perpetuating cycle. Pain interferes with sleep initiation and continuity; fragmented or insufficient sleep then alters pain processing and increases vulnerability to pain; and the resulting increase in pain can further disrupt subsequent sleep. This cycle may help explain why sleep complaints are so persistent among people with chronic musculoskeletal and other long-lasting pain conditions. At the same time, the evidence should not be interpreted as demonstrating that every episode of poor sleep necessarily causes chronic pain, because prospective studies remain heterogeneous and causal pathways are influenced by psychological, behavioural and disease-related factors (Runge et al., 2024). Nevertheless, the consistency of clinical, longitudinal and experimental findings supports the importance of considering sleep continuity and sleep quality alongside pain intensity when examining the development and maintenance of chronic pain.

4. Sleep Loss as a Driver of Pain Sensitization

Increasing experimental evidence indicates that inadequate or disturbed sleep can do more than simply make a person feel tired or less able to cope with pain. Loss of sleep can directly change the way the nervous system detects, processes and regulates painful stimuli. Early experimental work already suggested that sleep deprivation increases pain sensitivity, and a meta-analysis of experimental studies in healthy individuals reported a moderate overall effect of sleep deprivation on pain perception (Schrimpf et al., 2015). Although the studies included in that analysis differed in their methods and types of sleep deprivation, the findings provided important evidence that changes in sleep can influence pain independently of an existing painful disease or tissue injury.

More recent literature has strengthened this relationship. A systematic review and meta-analysis including 31 experimental studies and more than 700 participants found that total sleep deprivation significantly reduced pain threshold and pain tolerance in healthy individuals. Partial sleep deprivation was also associated with an increase in spontaneous pain intensity. In addition, the available evidence indicated that sleep fragmentation could increase experimental measures related to both peripheral and central sensitization (Tang et al., 2022). These findings are particularly important because they demonstrate that even short-term changes in sleep can influence pain processing in

otherwise healthy people. Thus, the increase in pain following poor sleep cannot always be explained by a worsening of the underlying tissue damage or inflammatory condition.

One of the most useful ways to understand this phenomenon is to view sleep as an important period during which the brain and nervous system maintain and regulate sensory processing. When sleep is repeatedly shortened or interrupted, this regulatory balance may be disturbed. Experimental studies have shown that total sleep deprivation can increase sensitivity to pressure and cold pain, facilitate temporal summation of pain and impair conditioned pain modulation, which is an experimental measure of the body's ability to suppress incoming painful signals (Lautenbacher et al., 2019). In simple terms, after insufficient sleep, the nervous system may become more responsive to the same painful stimulus and less effective at dampening that signal.

This does not mean that sleep loss creates a new injury. Rather, it may change the gain of the pain-processing system. A stimulus that was previously perceived as mildly painful may therefore become more uncomfortable after a night of inadequate sleep. Similarly, a stimulus that was previously tolerated may reach the pain threshold more quickly. This provides one explanation for the common clinical observation that pain can feel substantially worse after poor sleep even when there has been no obvious change in the underlying musculoskeletal, inflammatory or neuropathic condition. Reviews of experimental and clinical evidence have consequently described sleep loss as capable of increasing pain perception through several interacting mechanisms, including impaired inhibitory control, altered cognitive processing and changes in inflammatory signalling (Fine, 2015; Haack et al., 2023).

5. A simplified model of this relationship as per literature review can therefore be represented as:

Sleep loss or fragmentation → altered pain processing → reduced pain inhibition and/or increased pain facilitation → enhanced nociceptive transmission → increased pain sensitivity → hyperalgesia and, in some circumstances, features associated with central sensitization. This model should be regarded as a framework rather than a single linear pathway. Sleep and pain interact through several overlapping neural, neurochemical, immune and behavioural mechanisms, and the relative contribution of each mechanism may differ between individuals and between types of sleep disturbance.

Sleep Loss and Central Pain Processing: Neurobiological Mechanisms of Pain Hypersensitivity

Peripheral nociception and spinal processing

Pain perception begins when specialized sensory receptors called **nociceptors** detect potentially harmful mechanical, thermal or chemical stimuli. These receptors transmit information through peripheral Aδ and C fibres toward the dorsal horn of the spinal cord. The dorsal horn is not simply a passive relay station. Instead, it acts as an important processing centre where incoming nociceptive information can be amplified or inhibited before being transmitted to higher regions of the nervous system.

Under normal conditions, this system is tightly regulated. Nociceptive signals reaching the spinal cord are modified by local inhibitory and excitatory circuits and by descending signals from the brain. This balance helps prevent every potentially harmful stimulus from producing an excessive pain response. When this balance is disturbed, however, nociceptive signals may be amplified. Sleep loss appears to be one factor capable of disturbing this regulatory process.

Experimental studies literature review provides evidence for changes in spinal and supraspinal pain processing following inadequate sleep. For instance, total sleep deprivation has been shown to facilitate temporal summation of pain**,** in which repeated stimuli of the same intensity produce progressively stronger pain responses. Temporal summation is commonly used experimentally as an indicator of increased central facilitation of nociceptive processing (Lautenbacher et al., 2019). Such findings suggest that the nervous system may become increasingly responsive when painful signals are repeated after a period of insufficient sleep.

This process is relevant to the concept of central sensitization which refers to an increase in the excitability and responsiveness of neurons within central nociceptive pathways. It can result in heightened responses to normally painful stimuli and, in some circumstances, pain responses to stimuli that would ordinarily be considered non-painful. Experimental manifestations can include increased pain sensitivity, mechanical hyperalgesia, tactile allodynia, enhanced temporal summation and prolonged responses to repeated stimulation (Woolf, 2011).

However, it is important to interpret the relationship between sleep loss and central sensitization carefully. Experimental evidence shows that sleep deprivation and fragmentation can alter measures of pain facilitation and sensitization, but this does not necessarily mean that every episode of poor sleep produces persistent pathological central sensitization. Central sensitization is a complex neurophysiological process, and experimental measures such as temporal summation should not automatically be interpreted as proof of a chronic clinical sensitization disorder. The

duration and severity of sleep loss, the type of sleep disruption, the presence of ongoing pain and inflammation, and individual biological characteristics can all influence the response (Tang et al., 2022).

Impaired Descending Pain Inhibition

Another important mechanism through which sleep loss may increase pain is disruption of the brain's descending pain-control system. Pain is not determined solely by the intensity of signals travelling from the body to the brain. Higher brain regions can send inhibitory or facilitatory signals back toward the spinal cord and modify how strongly incoming nociceptive information is experienced. This descending system involves several brain regions, including the periaqueductal grey (PAG), rostral ventromedial medulla (RVM) and other components of the endogenous pain-control network.

Adequate sleep appears to support normal functioning of these regulatory systems, whereas sleep deprivation may reduce their ability to suppress nociceptive input. In a controlled experimental study, one night of total sleep deprivation increased pain sensitivity and was associated with impaired conditioned pain modulation and enhanced temporal summation (Lautenbacher et al., 2019). These findings suggest that sleep loss can influence not only the incoming pain signal but also the brain's ability to regulate that signal.

Evidence from a more recent systematic review and meta-analysis also supports an association between disturbed sleep and altered endogenous pain modulation, although the findings are not completely consistent across studies. Qualitative evidence more commonly linked poor sleep with reduced pain inhibition, while quantitative analyses did not demonstrate a statistically significant overall association across all populations and experimental designs. This indicates that impaired endogenous analgesia is an important possible mechanism, but it should not be considered the only explanation for sleep-related pain hypersensitivity (Herrero Babiloni et al., 2024).

The response may also differ between individuals. For example, experimental research has reported sex-related differences in the effects of total sleep deprivation on descending pain modulation, with reduced endogenous pain inhibition observed particularly among women in one controlled study (Lautenbacher et al., 2017). A later systematic review similarly suggested that sex and age can modify some aspects of the relationship between sleep disturbance and pain sensitivity. These findings highlight the importance of considering individual biological differences rather than assuming that sleep loss affects pain processing in exactly the same way in everyone.

Increased Pain Facilitation and Central Amplification

Sleep loss may also shift the balance between **pain inhibition and pain facilitation**. Normally, the central nervous system continuously evaluates incoming sensory information and determines how strongly it should be transmitted to conscious awareness. When sleep is restricted or repeatedly interrupted, this balance may shift toward greater facilitation of nociceptive signals. Animal and human studies have provided evidence that sleep deprivation can increase activity within brain circuits involved in pain processing while simultaneously weakening some inhibitory mechanisms (Tomim et al., 2016; Haack et al., 2023).

Experimental animal research has shown that sleep deprivation can increase nociceptive behaviour while altering activity within descending pain-control pathways. Such findings provide biological support for the idea that sleep loss can make the nervous system more responsive to nociceptive stimulation rather than simply increasing the subjective unpleasantness of pain (Tomim et al., 2016)

Clinical Significance of Sleep-Related Pain Sensitization

The consequences of this altered pain processing can be particularly important in people who already have musculoskeletal, inflammatory or neuropathic pain. When pain disrupts sleep, and inadequate sleep subsequently increases pain sensitivity, a self-reinforcing cycle can develop:

Pain → disturbed sleep → increased pain sensitivity → greater pain → further sleep disturbance.

Over time, this cycle may contribute to the persistence or worsening of pain even when the original tissue injury has begun to resolve. Longitudinal and clinical literature supports the importance of sleep disturbance as a potential contributor to the development or worsening of chronic pain, although the strength of this relationship varies across conditions and populations (Finan et al., 2013; Haack et al., 2023).

Importantly, the effects of sleep loss may not be permanent. Experimental research indicates that recovery sleep can restore pain thresholds toward normal after acute total sleep deprivation, although different components of pain modulation may recover at different rates (Léger et al., 2022). This finding suggests that at least some sleep-related changes in pain sensitivity are reversible and further emphasizes the importance of adequate, continuous sleep for maintaining normal pain regulation.

All the available literature indicates that sleep is an active regulator of pain processing rather than merely a period of rest. Insufficient or fragmented sleep can increase pain sensitivity through changes in nociceptive processing, descending pain control, central facilitation and possibly inflammatory and neurochemical pathways. Nevertheless, these mechanisms do not operate independently, and the degree to which sleep loss produces measurable sensitization depends on the nature and duration of sleep disruption as well as individual susceptibility. Understanding these mechanisms is therefore important for explaining why improving sleep may be relevant not only to sleep quality itself but also to the management and prevention of persistent pain.

Sleep Deprivation, Neuroinflammation and Pain: Connecting the Immune and Nervous Systems

The immune system provides an important biological link between sleep and pain. Sleep and immune function are closely interconnected, with communication occurring through cytokines, neuroendocrine pathways, autonomic activity and cellular inflammatory signalling. Inflammatory mediators such as interleukin-1β (IL-1β) and tumour necrosis factor-α (TNF-α) are involved in the physiological regulation of sleep, particularly non-rapid eye movement (NREM) sleep. Conversely, inadequate or disrupted sleep can modify immune-cell activity and inflammatory signalling. These interactions are important for understanding pain because inflammatory processes can alter the sensitivity of nociceptive pathways and contribute to changes in pain perception (Krueger et al., 1998; Opp et al., 2026).

The relationship between sleep and inflammation is, however, bidirectional and complex rather than linear. Experimental and observational studies have examined several inflammatory mediators, including IL-1β, IL-6 and TNF-α, together with transcriptional pathways such as nuclear factor-κB (NF-κB). Sleep loss has been shown to activate inflammatory signalling at the cellular level; for example, partial sleep deprivation increased NF-κB activation in peripheral blood mononuclear cells in healthy adults (Irwin et al., 2008). Other experimental work has demonstrated increased spontaneous production of IL-6 and TNF-α by monocytes following partial sleep deprivation (Irwin et al., 2015).

At the same time, evidence concerning circulating inflammatory biomarkers has not always been consistent. A systematic review and meta-analysis of 72 studies found that habitual sleep disturbance was associated with higher circulating IL-6 and C-reactive protein (CRP), whereas experimental sleep deprivation or sleep restriction did not show consistent effects on circulating CRP, IL-6 or TNF-α in the studies available at that time (Irwin et al., 2016). More recently, an updated meta-analysis of experimental sleep deprivation studies published through March 2025 reported that multiple nights of partial sleep deprivation were associated with significant increases in circulating IL-6 and CRP, suggesting that the inflammatory response may become more apparent with repeated rather than very brief sleep restriction (2025). Thus, differences in the duration of sleep loss, severity of restriction, timing of blood collection and characteristics of participants are important when interpreting inflammatory findings.

IL-1β and Sleep-Related Pain Processing

IL-1β is an important cytokine in the interaction between sleep and the immune system. Experimental research has established that IL-1β participates in the physiological regulation of NREM sleep, and administration or inhibition of IL-1 signalling can alter sleep expression. IL-1β is therefore not simply a marker of inflammation; it also forms part of the signalling network through which immune activity and sleep regulation communicate (Krueger et al., 1998; Opp et al., 2026).

The potential importance of IL-1β to pain arises from its ability to influence neuronal and neuroimmune processes. Cytokines such as IL-1β can affect neuronal function and interact with other inflammatory mediators involved in nociceptive processing. Experimental literature has also shown that inflammatory cytokines can produce changes in pain sensitivity, while sleep loss itself is associated with increased pain sensitivity. These findings provide a biological basis for considering IL-1β as one component of the pathway connecting sleep disruption, immune activation and pain (Opp et al., 2026; Finan et al., 2013).

However, the evidence does not justify describing IL-1β as a single biomarker responsible for sleep-related hyperalgesia. Human studies examining inflammatory responses to sleep deprivation have produced variable results, and much of the detailed mechanistic evidence concerning IL-1β and sleep regulation comes from experimental or preclinical research. It is therefore more appropriate to consider IL-1β as part of a broader neuroimmune signalling network, in which cytokines, immune cells, glial cells and neural pathways interact to influence both sleep and pain processing. This interpretation is consistent with current reviews emphasizing the integrated nature of sleep, innate immunity and neuroinflammation (Opp et al., 2026).

IL-6 and Pain Hypersensitivity

IL-6 is one of the inflammatory mediators most frequently examined in research on sleep and pain. Experimental evidence indicates that prolonged sleep restriction can alter IL-6 concentrations and that these changes may be related to increased pain. In a controlled laboratory study, healthy adults assigned to approximately 4 hours of sleep per night for 10 nights showed higher IL-6 levels than participants who maintained an 8-hour sleep schedule. Importantly, the increase in IL-6 was positively associated with greater pain ratings, providing experimental evidence for a relationship between repeated sleep restriction, inflammatory signalling and pain experience (Haack et al., 2007).

The relationship between sleep and IL-6 is nevertheless dependent on the experimental context. The earlier systematic review by Irwin et al. (2016) found that habitual sleep disturbance was associated with increased circulating IL-6, but experimental sleep deprivation or restriction did not consistently increase circulating IL-6 across the studies included in the meta-analysis. More recent evidence provides some support for an inflammatory effect of repeated sleep restriction: an updated meta-analysis of experimental studies found a significant increase in circulating IL-6 following multiple nights of partial sleep deprivation. This newer evidence suggests that the duration and cumulative nature of sleep loss may be important determinants of the inflammatory response.

Importantly, IL-6-related changes may also occur at the level of immune-cell responsiveness rather than only through changes in resting blood concentrations. Experimental sleep-loss studies have demonstrated increased spontaneous production of IL-6 by monocytes following partial sleep deprivation (Irwin et al., 2015). This distinction is important because immune cells may become more responsive to inflammatory stimulation even when changes in circulating cytokine concentrations are relatively small. Therefore, the available evidence supports a role for altered IL-6 signalling in the relationship between insufficient sleep and pain, but it would be too strong to conclude that every episode of sleep deprivation produces pain through a uniform IL-6-mediated mechanism.

TNF-α and Cellular Inflammatory Signalling

TNF-α has a well-established role in the interaction between sleep and immune function. Together with IL-1β, TNF-α participates in physiological sleep regulation and can influence NREM sleep. It is also an important inflammatory mediator capable of modifying cellular and neuronal processes relevant to pain (Krueger et al., 1998; Opp et al., 2026).

Evidence from human experimental studies suggests that sleep loss can affect cellular inflammatory signalling involving TNF-α. Irwin et al. (2015) found that partial sleep deprivation increased spontaneous production of both IL-6 and TNF-α by monocytes in healthy adults. Earlier work also demonstrated that a night of partial sleep deprivation increased NF-κB activation in peripheral blood mononuclear cells, providing evidence that sleep loss can activate an important transcriptional pathway involved in inflammatory gene expression (Irwin et al., 2008).

Particularly strong evidence linking sleep architecture, cellular inflammation and pain comes from a randomized crossover clinical trial by Irwin et al. (2023). The study included 95 healthy adults who underwent two nights of undisturbed sleep and two nights of experimentally disrupted sleep involving repeated awakenings. Sleep disruption reduced N3 slow-wave sleep and increased Toll-like receptor-4-stimulated monocyte production of pro-inflammatory cytokines. The disrupted-sleep condition was also associated with a lower heat-pain threshold, indicating increased pain sensitivity. Mediation analyses suggested that the loss of N3 sleep and increased cellular inflammatory activity contributed to the observed change in pain sensitivity (Irwin et al., 2023).

This study is particularly informative because it demonstrates that the relationship between sleep loss and inflammation cannot be understood solely by measuring resting concentrations of cytokines in the bloodstream. The functional responsiveness of immune cells may also change following sleep disruption. In other words, sleep loss may alter how strongly immune cells respond when exposed to an inflammatory stimulus. This provides a plausible pathway through which disturbed sleep could influence pain processing even when changes in baseline circulating inflammatory markers are modest (Irwin et al., 2023).

The role of inflammation in sleep-related pain is further supported by experimental pain research. A systematic review and meta-analysis of experimental sleep deprivation studies found evidence that total sleep deprivation can reduce pain thresholds and tolerance in healthy individuals, while partial sleep deprivation can increase spontaneous pain intensity. Sleep fragmentation was also associated with measures of peripheral and central sensitization, although the strength of evidence varied among outcomes (2022). These findings support the broader concept that inadequate or fragmented sleep can increase pain sensitivity, while inflammatory and neuroimmune pathways may represent one of several mechanisms contributing to this effect.

Neuroinflammation as a Link Between Sleep Loss and Pain

The connection between sleep and pain is therefore unlikely to depend on a single cytokine. Instead, sleep disruption may influence several interconnected systems, including peripheral immune cells, inflammatory transcriptional pathways and neuroimmune signalling within the central nervous system. Current research describes sleep and innate immunity as closely integrated processes, with cytokines and other immune signals communicating with neural circuits that regulate sleep and wakefulness (Opp et al., 2026).

This perspective is particularly relevant to chronic pain, where repeated sleep disruption may interact with ongoing nociceptive activity and inflammatory signalling. Experimental evidence shows that sleep loss can increase pain sensitivity, while clinical and prospective research indicates that sleep problems and chronic musculoskeletal pain can reinforce one another over time (Runge et al., 2024). Thus, sleep disturbance may not simply be a consequence of pain; in some circumstances, it may also contribute to the persistence or amplification of pain.

Overall, current evidence supports a model in which sleep loss, immune activation and altered pain processing are interconnected but not governed by a single inflammatory pathway. IL-1β, IL-6 and TNF-α are important components of this network, while NF-κB signalling and changes in immune-cell responsiveness provide additional mechanisms through which sleep disruption may influence inflammatory physiology. The strongest human experimental evidence currently supports the importance of cellular inflammatory responses and changes in sleep architecture, particularly N3 sleep, rather than a simple assumption that all sleep deprivation uniformly increases circulating cytokine concentrations (Irwin et al., 2008, 2015, 2023; Irwin et al., 2016).

This neuroimmune interaction may help explain why persistent sleep disturbance and chronic pain can become mutually reinforcing. Repeated disruption of restorative sleep may increase vulnerability to inflammatory and nociceptive signalling, while ongoing pain can further interfere with sleep continuity and architecture. Understanding this interaction is therefore important for viewing sleep and pain as interconnected physiological processes rather than completely independent problems.

Microglia, Astrocytes and Central Neuroinflammation

Microglia and astrocytes are important non-neuronal cells involved in the regulation of pain within the central nervous system. Under normal conditions, these cells help maintain the chemical environment around neurons and support normal neuronal function. However, following tissue injury, persistent nociceptive input or other pathological challenges, microglia and astrocytes can undergo functional and molecular changes. These changes may include altered receptor expression, intracellular signaling and the release of cytokines, chemokines and other mediators that influence neuronal activity. Through these neuron–glia interactions, glial cells can contribute to the development and maintenance of persistent pain and central sensitization (Ji et al., 2018; Ji et al., 2019).

The relationship between glial activity and chronic pain is particularly important because inflammatory mediators released by activated glial cells can modify synaptic transmission in pain-processing pathways. Microglia, for example, can respond to increased neuronal activity and release signaling molecules that influence dorsal horn neurons. Astrocytes can also undergo persistent changes and participate in the maintenance of an altered extracellular environment. Together, these processes can increase the responsiveness of central pain pathways and contribute to hyperalgesia and allodynia (Grace et al., 2016; Ji et al., 2019).

There is growing evidence that sleep loss may interact with these neuroimmune mechanisms. Experimental studies in animals have shown that sleep deprivation can increase microglial activation and inflammatory signaling, and that these changes can be accompanied by increased pain-like behaviour. For example, chronic sleep deprivation aggravated pain behaviour in rats with chronic pain and was associated with increased microglial activation and increased expression of inflammatory pathways involving TLR4, NLRP3 and IL-1β. Pharmacological inhibition of some of these pathways reduced both microglial activation and pain-related hypersensitivity in the experimental animals (Zhang et al., 2022).

Neurotransmitters and Pain Sensitization Following Sleep Deprivation

Sleep and pain are regulated by several overlapping neural and neurochemical systems. These include serotonin, noradrenaline, dopamine, endogenous opioids, orexin, GABA, glutamate and endocannabinoids. Because these systems participate in both sleep–wake regulation and pain modulation, disruption of sleep can potentially influence the way painful signals are processed. However, the contribution of each neurotransmitter system is complex, and the available evidence does not support a simple model in which sleep deprivation produces pain through a single neurotransmitter pathway (Haack et al., 2020; Zhu & Huang, 2023).

A major review of the biological relationship between sleep deficiency and chronic pain identified opioid, monoaminergic, orexinergic, immune, melatonin and endocannabinoid systems, together with the hypothalamic–pituitary–adrenal (HPA) axis and other signaling pathways, as possible contributors to pain amplification following inadequate sleep (Haack et al., 2020). Importantly, these systems interact with one another rather than functioning independently. This helps explain why sleep loss can influence several dimensions of pain at the same time, including sensory sensitivity, endogenous pain inhibition, emotional responses and pain-related behaviour.

Serotonin

Serotonin is involved in both sleep–wake regulation and the modulation of nociceptive processing. Serotonergic neurons in the brainstem, particularly those associated with the raphe nuclei, contribute to descending control of spinal pain transmission. Depending on the receptor subtype, anatomical location and physiological state, serotonin can produce either inhibitory or facilitatory effects on pain processing. Therefore, serotonergic signaling should not be viewed simply as an exclusively analgesic system.

Experimental evidence suggests that sleep disruption can alter endogenous pain modulation, and serotonergic mechanisms have been proposed as one possible contributor to these changes. A recent experimental study found that pain sensitivity increased after total sleep deprivation and returned toward baseline following recovery sleep; the authors suggested that changes in serotonergic activity could be among the mechanisms involved, although the study did not directly establish serotonin as the causal factor (Stroemel-Scheder & Lautenbacher, 2023).

The interaction between serotonin, sleep and pain may therefore be particularly relevant to chronic pain conditions in which sleep disturbance, altered pain sensitivity and affective symptoms occur together. However, the precise contribution of individual serotonin receptors and pathways to sleep-loss-related hyperalgesia remains incompletely understood. Human evidence should consequently be interpreted alongside experimental and preclinical findings rather than being inferred solely from animal studies (Haack et al., 2020; Pertovaara & Kalso, 2018).

Noradrenaline

Noradrenaline is another important link between sleep, arousal and pain. Much of the brain's noradrenaline is produced by neurons in the locus coeruleus, a brainstem nucleus involved in arousal, attention, vigilance and responses to environmental challenges. Noradrenergic pathways also participate in descending modulation of nociceptive transmission in the spinal cord (Benarroch, 2018).

Under many conditions, descending noradrenergic signaling can inhibit pain transmission through α2-adrenergic receptors in the spinal cord. However, the noradrenergic system is not uniformly analgesic. Depending on the brain region, receptor subtype and chronicity of pain, noradrenergic signaling can also contribute to pain facilitation. This complexity is particularly relevant to chronic pain, in which changes in locus-coeruleus activity and descending pain-control systems have been described (Hancock et al., 2024).

Sleep loss may increase arousal and alter the balance between sleep-promoting and wake-promoting neural systems. Consequently, changes in locus-coeruleus activity and noradrenergic signaling could contribute to the hyperarousal that is frequently observed when sleep disturbance and persistent pain occur together. Nevertheless, the precise relationship between sleep deprivation, locus-coeruleus activity and pain sensitivity requires further investigation.

Dopamine

Dopamine is involved in reward, motivation, salience, movement and sleep–wake regulation, but it also contributes to the modulation of pain. Dopaminergic pathways involving the nucleus accumbens, anterior cingulate cortex and other brain regions influence how painful experiences are processed and evaluated. Importantly, dopamine does not have a single uniform effect on pain; its effects depend on the receptor subtype, brain region and physiological context (Wang et al., 2021).

Experimental studies provide evidence that sleep restriction can alter dopaminergic signaling in brain regions involved in pain processing. In an animal study, sleep restriction reduced measures of dopaminergic function in the nucleus accumbens and anterior cingulate cortex, while pharmacological stimulation of dopamine D2 receptors prevented the increase in pain sensitivity produced by sleep restriction. These findings suggest that altered dopamine signaling may contribute to sleep-loss-related pain sensitization, although the findings remain primarily preclinical (2024 experimental study).

Dopamine may therefore help explain why sleep deprivation can affect not only the sensory intensity of pain but also motivation, reward processing and the emotional significance of painful experiences. However, further human

studies are required before specific dopaminergic pathways can be considered established therapeutic mechanisms in sleep-related pain.

Endogenous Opioids

The endogenous opioid system is one of the body's major intrinsic pain-control systems. Endorphins, enkephalins and related opioid peptides interact with opioid receptors in several regions of the brain and spinal cord and contribute to the suppression of nociceptive signaling.

Sleep loss may interfere with endogenous and exogenous opioid-mediated pain control. Earlier experimental literature found that sleep deprivation can alter responses to opioid-based analgesia, while more recent reviews continue to identify opioid signaling as one of the potential mechanisms linking sleep deficiency with increased pain sensitivity (Lautenbacher et al., 2006; Haack et al., 2020).

Human neuroimaging evidence also suggests an association between sleep characteristics and the cerebral μ-opioid system during experimental pain. In a small PET study of healthy participants, sleep quality and sleep duration were associated with μ-opioid receptor binding in several brain regions. Because the study was exploratory and included only 12 participants, these findings should not be interpreted as proof of a causal effect of sleep loss on opioid signaling (McLean et al., 2013). Overall, the opioid system represents a plausible pathway through which inadequate sleep may reduce the efficiency of endogenous pain control. However, receptor-level mechanisms and their clinical importance remain incompletely defined.

Other Neurochemical Systems

The relationship between sleep and pain also involves several additional systems, including orexin, endocannabinoids, GABA, glutamate, adenosine and melatonin. These systems participate in sleep regulation, arousal, neuronal excitability, inflammation and pain modulation. Their effects are interconnected rather than independent, making it difficult to identify a single dominant pathway responsible for sleep-loss-induced pain sensitization (Haack et al., 2020; Zhu & Huang, 2023).

Orexin is particularly interesting because it promotes wakefulness while also influencing pain-processing circuits. However, human evidence concerning its direct analgesic role remains limited. A recent systematic review of orexin receptor antagonists found consistent improvements in sleep parameters but insufficient evidence for a clear analgesic effect in humans. This illustrates the importance of separating mechanistic plausibility from demonstrated clinical effects (2025 systematic review).

Taken together, these findings support a multisystem model in which sleep deprivation alters several interacting neurochemical pathways rather than activating one isolated mechanism. This interpretation is more consistent with current evidence than attributing sleep-related hyperalgesia to a single neurotransmitter.

Cortisol and Pain Sensitivity

Cortisol is an important component of the body's response to stress and is produced through activation of the hypothalamic–pituitary–adrenal (HPA) axis. Because the HPA axis interacts closely with immune, metabolic and neural systems, changes in sleep can influence cortisol regulation and, in turn, potentially affect pain processing. However, it is important not to describe sleep deprivation as simply causing an increase in cortisol. Evidence from experimental studies is inconsistent. A 2024 systematic review and meta-analysis examined 24 studies of acute sleep deprivation and cortisol and confirmed substantial variability among studies (Chen et al., 2024).

The response may depend on the duration and severity of sleep loss, the timing of cortisol measurement, the type of stressor applied, individual characteristics and the experimental protocol. Consequently, cortisol should be considered part of a broader stress-response system rather than a single biomarker that reliably indicates sleep-related pain sensitization.A separate 2024 systematic review examined autonomic and cortisol responses to acute stress following total sleep deprivation. Across 16 studies involving 581 participants, some experiments found exaggerated cortisol or autonomic responses, whereas others reported blunted responses. Most reported outcomes, however, did not show a significant change. The authors therefore described the evidence as consistent with a bidirectional, multisystem pattern of stress reactivity, rather than a uniform increase in cortisol after sleep deprivation (Messa et al., 2024).

For this reason, the most scientifically appropriate interpretation is that sleep deprivation may dysregulate HPA-axis and stress responsiveness, rather than invariably increasing cortisol concentrations. This distinction is particularly important when discussing the relationship between sleep, stress and chronic pain.

6. Future Research Pathway and Conclusion

Future research should look beyond the simple comparison between sleep deprivation and normal sleep and try to understand more clearly how different aspects of sleep influence pain. Studies should examine the specific roles of different sleep stages, especially deep N3 sleep and REM sleep, as their effects on pain processing may differ. Researchers should also focus on repeated or partial sleep restriction because this more closely represents the type of sleep loss experienced by many people in everyday life and in clinical conditions. Greater attention is needed to understand how sleep loss influences both central and peripheral inflammatory processes, including changes in microglial and astrocytic activity in people with chronic pain. Future studies should also consider differences related to age and sex, as individuals may respond differently to inadequate sleep.

The interaction between stress hormones such as cortisol, sympathetic nervous system activity, and inflammatory cytokines also needs further investigation. In addition, changes in important pain-regulating neurotransmitter systems, including serotonin, noradrenaline, dopamine, and endogenous opioids, may help explain why poor sleep increases pain sensitivity. Another important area is the relationship between circadian disruption, melatonin rhythms, sleep timing, and pain perception. Researchers should also investigate why some individuals are more vulnerable than others to sleep-related increases in pain. Finally, an important question is whether improving and restoring sleep can not only reduce pain but also reverse or prevent established central sensitization. Addressing these questions may help clarify the complex relationship between sleep and pain and may contribute to the development of more effective and individualized approaches for managing chronic pain.

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