Nature and Science of Sleep

Elevate Series

Open Access Full Text Article

REVIEW

# What Links Sleep and Neuropathic Pain?: A Literature Review on the Neural Circuits for Sleep and Pain Control

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**Abstract:** Neuropathic pain (NP), arising from lesions or diseases of the sensory nervous system, significantly disrupts sleep, creating a feedback loop where pain and sleep disturbances exacerbate each other. Research suggests that sleep disruption may contribute to progressing from acute to chronic NP. The neural circuits involved in sleep-wake regulation and pain processing are intricately interconnected, making it difficult to pinpoint the specific regions responsible for each function. This review seeks to disentangle these complex relationships by providing a detailed overview of the anatomical pathways involved in NP, extending from the peripheral to the central nervous system. Additionally, it examines the neurocircuits that govern sleep-wake cycles and their interaction with pain pathways. By illuminating these connections, this review aims to deepen our understanding of how sleep influences NP, ultimately guiding the development of more effective strategies for managing NP and its associated sleep disturbances to improve the quality of life for those affected.

**Keywords:** neuropathic pain, sleep disturbances, pain pathways, neural circuit

## Introduction

NP is an often debilitating condition arising from damage or dysfunction of the sensory nervous system, affecting 7% to 10% of the general population.[1,2] Symptoms of neuropathy include numbness or tingling, electric shock-like pain, or shooting.[3] Sleep disturbances as a broad descriptive term indicate a group of conditions that disturb normal sleep patterns due to any conditions, including physical, medical, or psychological states.[4] Empirical evidence supports that NP frequently leads to difficulties initiating sleep, increased nocturnal awakenings, and reduced sleep quality.[5,6] These sleep disturbances, in turn, amplify pain perception and lower pain thresholds,[7,8] later creating a cyclical relationship. However, the mechanism of the association between NP and sleep disturbances still has not been addressed. Hence, by finding the mechanism and focusing therapeutic interventions on breaking the cyclical relationship, clinicians may achieve a dual benefit of pain relief and improved sleep continuity, ultimately improving overall well-being.

Our previous research aimed at validating NP models as tools for evaluating the sleep-pain association showed a reduction of sleep from the 1st to the 5th day following nerve injury.[9] By the 10th day following the nerve injury, sleep had returned to levels comparable to those before the surgery. However, the paw withdrawal threshold still declined until the 15th post-surgery day,[9] suggesting that sleep disturbance-induced damaged nerve might lead to the change in pain modulation and progression of chronic NP. Nevertheless, it remains unknown whether sleep influences the progression of acute to chronic pain, and the underlying mechanisms of this potential involvement are yet to be determined. The neural circuits governing sleep-wake cycles and pain pathways are complex and extensive, making it challenging to discern which areas influence both processes. Due to the overlapping nature of the brain areas responsible for sleep and NP, identifying the specific regions and neurons responsible for each function is crucial. This review aims to elucidate these distinctions and provide an up-to-date summary of the anatomical pathways of NP and the neurocircuits involved in regulating sleep-wake cycles and their interplay with NP. By doing so, it seeks to enhance our comprehension of how

Received: 28 November 2024
Accepted: 7 April 2025
Published: 5 May 2025

sleep and NP are related, aiding in identifying mechanisms, therapeutic approaches, and considerations for treating chronic NP alongside sleep disorders. This review focuses specifically on NP.

## Literature Search Methods

This narrative review aimed to examine studies addressing the interaction between neuropathic pain and sleep disorders, specifically focusing on how neuropathic pain contributes to various sleep disturbances and neural pathways involved in this interaction. Original articles were identified through a systematic search strategy. We searched MEDLINE (PubMed) and Google Scholar for both human and animal studies, with no restrictions on the publication period, and included only English-language publications. The review encompasses a broad range of topics, with key search terms including "sleep disturbances", "sleep disorders", "sleep quality", "neuropathic pain", "trigeminal neuralgia", "orofacial pain", "peripheral nerve injury", "spinal cord injury", "polyneuropathy", "postherpetic neuralgia", "traumatic brain injury", "post-stroke neuropathic pain", "multiple sclerosis", "pain pathways", "sleep-wake neurocircuit", "circadian rhythm", "therapeutic interventions", and "sex differences". After removing duplicate articles, studies were screened by title and abstract for their potential to address the research questions. The selected studies were then thoroughly reviewed to ensure their relevance to the objectives of this review. Articles were excluded if they involved an ineligible population (eg, adolescents), did not specifically address neuropathic pain, lacked sleep assessments, or had inaccessible full texts. In Table 1, to evaluate the quality of the study, SYRCLE's Risk of Bias Tool[10] and Newcastle-Ottawa Scale[11] was used for animal studies and human studies, respectively. Low, moderate, and high risk of bias were used as the score for evaluation.

## Neuroanatomy of Pain Pathways

Pain is a vital sensory and emotional experience that serves as the body's alarm system, signaling potential harm. Pain signals travel through the ascending and descending pathways, shaping our pain perception. The ascending pathway begins at nociceptors, which detect harmful stimuli and send signals to the spinal dorsal horn (SDH). These signals then ascend via the spinothalamic tract to the thalamus, which relays them to the somatosensory cortex to interpret the pain's location, intensity, and quality. Conversely, the descending pathway modulates pain by dampening or amplifying signals. Originating in regions of the brainstem such as the periaqueductal gray (PAG), it sends inhibitory or excitatory signals to the rostroventral medulla (RVM) and SDH. We describe the pain pathways in more detail below, summarized in Figure 1.

### Ascending Pain Pathway: Spinothalamic Tract

Pain (and temperature) sensory information is processed through the activation of nociceptors by a variety of stimuli transmitted through myelinated Aδ (touch, temperature) and unmyelinated C fibers (pain). The primary afferent fibers, which transfer sensory information from the trunk and limbs, penetrate the spinal cord through the dorsal roots. These primary afferent neurons (also called first-order sensory neurons) enter the SDH and synapse with neurons in the SDH (laminae I and outer zone of laminae II), utilizing glutamate as their principal excitatory neurotransmitter for rapid signal transmission.[40] Besides, they send the collateral projections to deep laminae V's wide dynamic range neurons. Axons from laminae I and II (second-order sensory neurons) decussate in the spinal cord, forming the spinothalamic tract within the anterior white column. These fibers cross via the anterior white commissure, gather contralaterally, and form the lateral spinothalamic tracts. The lateral spinothalamic tract is clinically significant as it primarily transmits pain and temperature sensations.[41] At the brainstem level, this lateral spinothalamic tract sends small branches to the nuclei of the reticular formation, ventrolateral periaqueductal gray (vlPAG). In contrast, the main tract reaches directly to the ventral posterior nucleus (VPL) and the central nucleus of the thalamus. This tract terminates in VPL and then sends a branch into the posterior part of the ventral medial nucleus (VMPO). In particular, the VPL projects to the primary somatosensory cortex (SI). At the cortical level, nociceptive signals that transmit to SI are organized somatotopically according to Penfield's homuncular pattern.[42] VPL nuclei project directly into the SI. Depending on the intensity of noxious stimuli, these neurons in SI respond in a graded manner.[43] Thus, the SI may be involved in pain discrimination. In addition, VMPO projects into the insular cortex (contributing to autonomic and motivational responses). Imaging experiments supported the evidence that the insular cortex (IC) contributes to pain processing, and noxious stimulation causes the

**Table 1** Summary of Sleep Disturbance and Sleep Disorder Induced by Different Types of Neuropathic Pain

| Classification of Neuropathic Pain | | ED | Study Subject | Sample (N) | Types of Relationship | Measurement | | Sleep Parameter | Relevant Sleep Disorders | Risk of Bias | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Object Assessments of Sleep: Polysomnography | Subject Assessments of Sleep: Sleep Diaries, Rating Scales, Questionnaires | | | | |
| Peripheral neuropathic pain | Trigeminal neuralgia | CS | Human | 200 patients with chronic orofacial pain, only 67 patients diagnosed with Trigeminal neuralgia | Causal | | Sleep quality rating score 0–10 | Poor sleep quality | Insomnia | Moderate | Haviv et al 2017[12] |
| | | CS | Human | 32 patients with a diagnosis of painful post-traumatic trigeminal neuropathy | Causal | | PSQI score | Poor sleep quality | | Moderate | Vazquez-Delgado et al 2018[13] |
| | | CS | Human | 74 participants | Causal | | Questionnaire | Wakefulness during sleep | | Moderate | Devor et al 2008[14] |
| | Neuropathic pain after peripheral nerve injury | CS | Human | 98 patients with combat-related extremity injuries, 52 with neuropathic pain and 46 without | Causal | | PSQI score | Poor sleep quality | Insomnia | Moderate | Atar et al 2022[15] |
| | | C57BL/6 mice underwent nerve injury, were randomly assigned to nerve injury (later divided into sciatic nerve crush injury and the common peroneal nerve ligation or sham-injury groups, and assessed for mechanical allodynia, EEG recording over 15 days with blinded outcome evaluation | Rodents | 7 mice per group | Causal | EEG analysis of sleep | | - Increased wakefulness<br>- Reduced %NREM of TST<br>- Diminished %REM of TST<br>- Sleep fragmentation | | Low | Ho et al 2024[9] |
| | | Before and after chronic constriction of the sciatic nerve, sleep-wake cycles, and mechanical and thermal allodynia/ hyperalgesia were quantified. | Rodents | 52 male Sprague-Dawley rats | Causal | EEG and EMG analysis of sleep | | - Increased wakefulness<br>- Reduced %NREM of TST | | Low | Monassi et al 2003[16] |

(*Continued*)

https://doi.org/10.2147/NSS.S509013

**Table 1** (Continued).

| Classification of Neuropathic Pain | | ED | Study Subject | Sample (N) | Types of Relationship | Measurement | | Sleep Parameter | Relevant Sleep Disorders | Risk of Bias | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Object Assessments of Sleep: Polysomnography | Subject Assessments of Sleep: Sleep Diaries, Rating Scales, Questionnaires | | | | |
| | | C57BL/6J mice (males and females) underwent nerve injury, were randomly assigned to nerve injury (later divided into spared nerve injury and chronic constriction injury or sham-injury groups, and assessed for EEG recording over 7 weeks with blinded outcome evaluation | Rodents | 7 mice per group | Causal | EEG and EMG analysis of sleep | | Sleep fragmentation | | Low | Alexandre et al 2024[17] |
| | | Wistar male rats underwent chronic constrictive injury and assessed for EEG recording over 21-day period | Rodents | 8 Wistar male rats for nerve injury group and 7 rats for the sham-injury group | Causal | EEG and EMG analysis of sleep | | - Reduced %NREM of TST<br>- Reduction in sleep efficiency<br>- Increased the number of arousals | | Low | Andersen et al 2003[18] |


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|---|---|---|---|---|---|---|---|---|---|---|---|
| | Painful polyneuropathy | Prospective observational study | Human | 427 participants | Causal | | MOS-Sleep | - Increased sleep latency<br>- Reduced sleeping time | Insomnia | Low | I. Poliakov, C. Toth 2011[19] |
| | | CS | Human | 113 participants | | | MOS-Sleep | - Reduced sleep quality | | Moderate | D'Amato et al 2014[20] |
| | | CS | Human | 3339 participants | Association | | MOS-Sleep | - Reduced sleep quality | | Moderate | Sachau et al 2023[21] |
| | | CS | Human | 100 participants | Causal | | PSQI | - Reduced sleep quality | | Moderate | Abo-Elfetoh et al 2022[22] |
| | | Survey-based CS observational study | Human | 255 participants | Causal | | MOS-Sleep | - Increased sleep latency<br>- Reduced sleeping time | | Moderate | Zelman et al 2006[23] |
| | | CC | Human | 30 participants | Causal | Polysomnography, AHI | | - Decreased sleep latency<br>- Decreased sleep efficiency<br>- Reduced %REM of TST<br>- Increase in sleep fragments<br>- high AHI score | SRBDs (Sleep Apnea) | Moderate | Bahnasy et al 2018[24] |
| | Post-herpetic neuralgia | Prospective study | Human | 261 participants | Causal | | DSIS | Interfere sleep | | Moderate | Drolet et al 2010[25] |
| | | Retrospective CS study | Human | 111 participants | Causal | | ISI | | Insomnia | Moderate | Lee et al, 2016[26] |
| | Painful radiculopathy | CS | Human | 186 participants | Causal | | PSQI, ISI | Disturbed sleep | Insomnia | Moderate | Shi et al 2023[27] |
| | | CC | Human | 66 participants | Causal | | PSQI | Disturbed sleep | | Moderate | Kocabicak et al 2014[28] |
| | | CS | Human | 450 participants | Causal | | MOS-Sleep | Disturbed sleep | | Moderate | Mahn et al 2011[29] |

(*Continued*)

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**Table 1** (Continued).

| Classification of Neuropathic Pain | | ED | Study Subject | Sample (N) | Types of Relationship | Measurement | | Sleep Parameter | Relevant Sleep Disorders | Risk of Bias | Reference |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Object Assessments of Sleep: Polysomnography | Subject Assessments of Sleep: Sleep Diaries, Rating Scales, Questionnaires | | | | |
| Central neuropathic pain | Central neuropathic pain associated with spinal cord injury | CC | Human | 24 participants | Causal | Polysomnography | ESS, IRLS Rating Scale | | SMD | Moderate | Telles et al 2011[30] |
| | | Systematic review | Human | 13 studies with total of 308 participants | Causal | Polysomnography, Hospital sleep lab: O□, body movement, nasal thermistor, plethysmography, SpO□ | | | SRBDs | Low | Chiodo et al 2016[31] |
| | | CS | Human | 620 participants | Causal | | MOS-sleep | - Shorter sleep duration | Insomina | Moderate | Jensen et al 2009[32] |
| | | Web-based survey | Human | 304 participants | Causal | | Self-report, ESS | - Shorter sleep duration<br>- Daytime sleepiness | | Moderate | Shafazand et al 2019[33] |
| | | Epidemiological review | Human | 408 participants | Causal | | NSQ | - difficulty in falling asleep<br>- More frequent awakenings | | High | Biering-Sørensen et al 2001[34] |
| | Central neuropathic pain associated with post-stroke pain | Retrospective, population-based study | Human | 660 participants | Causal | | Seft-report | Disturbed sleep | | High | Raffaeli et al 2013[35] |
| | | Observational study | Human | 50 participants | Association | AHI | | | SRBDs | Moderate | Abdullah et al, 2023[36] |
| | | All rats were divided into sham, thalamus lesion, and lesion+melatonin groups and then and assessed for mechanical hyperalgesia and EEG recording during 63 days. | Rodents | 24 male Sprague Dawley rats (approximately 8 weeks of age) | Association | Recording activity by camera | | - Reduced amount of sleep duration,<br>- Increased average duration of wakefulness<br>- disrupt circadian activities | Circadian Rhythm Sleep-Wake Disorders | Low | Kaur et al 2022[37] |
| | Central neuropathic pain associated with multiple sclerosis | CS | Human | 60 participants | Causal | | ESS | Excessive daytime sleepiness | Insomnia | Moderate | Stanton et al 2006[38] |

**Notes**: Neuropathic pain is classified following the classification of International Association for the Study of Pain (IASP).[39] Sleep Disorders was classified followed the AASM International Classification of Sleep Disorders – Third Edition, Text Revision (ICSD-3-TR).

**Abbreviations**: AHI, apnea-hypopnea index; CS, cross-sectional; CC, case-control; DSIS, daily sleep interference score; ED, experimental design; ESS, The Epworth Sleepiness Scale; ISI, Insomnia Severity Index; MOS-Sleep, Medical Outcomes Study Sleep measure; NSQ, Nordic Sleep Questionnaire; PSQI, Pittsburgh Sleep Quality Index; RBD, REM sleep behavior disorder; SMD, Sleep-related movement disorders; SRBDs, Sleep-related breathing disorders.

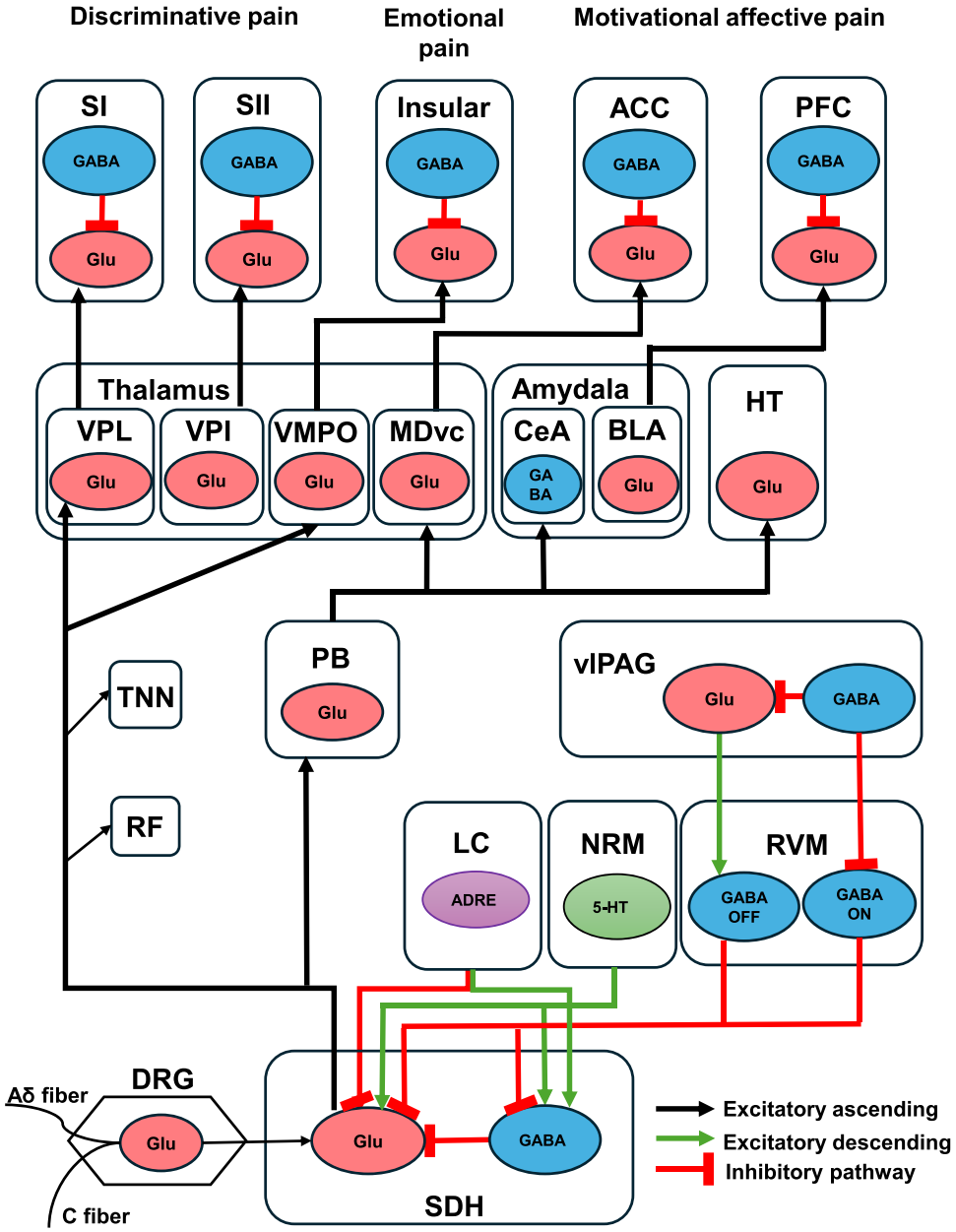


**Figure 1** Schematic presentation of pain pathways. Diagram showing the ascending and descending pain pathways.
**Abbreviations**: ACC, anterior cingulate cortex; BLA, basolateral amygdala; CeA, central nucleus of the amygdala; DRG, dorsal root ganglion; SDH, spinal dorsal horn; HT, hypothalamus; LC, locus coeruleus; MDvc, mediodorsal thalamus nucleus; NRM, nucleus raphe medulla; PB, parabrachial nucleus; PFC, prefrontal cortex; RF, reticular formation; RVM, rostroventral medulla; SI, primary somatosensory cortex; SII, secondary somatosensory cortex; TNN, Trigeminal Nociceptive Nucleus; VMPO, posterior part of the ventral medial nucleus; VPI, ventroposterior inferior nucleus; VPL, ventral posterior nucleus; vlPAG, ventrolateral periaqueductal gray; Glu, glutamatergic neurons; GABA, GABAergic neurons, Adre, noradrenergic neurons; 5-HT, serotonergic neurons.

activation of the IC.[44–47] IC is a distinct lobe of the cerebral cortex that forms the lateral sulcus (Sylvian fissure) on either side.[48] It is divided into anterior and posterior IC and plays a different role in pain.[49,50] Previous research proved that the posterior IC primarily coded pain intensity.[51,52] Research on IC lesions showed that the posterior IC is associated with higher pain intensity ratings; this is not the case for lesions in the anterior IC. The function of the anterior IC is related mainly to emotional processing,[53] cognitive evaluation,[54] and empathy for pain.[55]


https://doi.org/10.2147/NSS.S509013

## Ascending Pain Pathway: Spino-Parabrachial Pathway

The spino-parabrachial pathway is an extensive projection of spinal laminae I, III, and IV NK1-expressing neurons terminating into the lateral and external medial parabrachial (PB) nucleus.[56] Electrical stimulation indicated that PB neurons receive signals from Aδ and C-fibers, most of which are glutamatergic.[57] Furthermore, pain modulation-related peptides such as substance P, neurotensin, calcitonin gene-related peptide (CGRP), and dynorphin are colocalized inside these PB neurons.[58] At the forebrain level, PB neurons project to the central nucleus of the amygdala (CeA). An anterograde tracing experiment demonstrated that the nociceptive lateral PB (lPB) neurons, later identified as CGRP-expressing PB neurons,[59] projects to the CeA, mainly targeting the lateral capsular division (CeLC), to a lesser extent, in the lateral division (CeL). These projections increase the excitability of CeA neurons. In addition, the targeted administration of exogenous CGRP in CeA mimicked lPB neuron input, induced vocalization, and behavioral hyperalgesia. Recently, it was found that excitation of glutamatergic or inhibition of GABAergic lPB neurons caused NP-related behavior with aversive emotional responses in naïve mice, and the formation of chronic NP might be due to the imbalance of glutamatergic and GABAergic lPB neurons.[60] Moreover, PB-CeA circuits might transduce affective and motivational aspects of pain. Silencing CGRP neurons prevents pain reactions and memory development, while their optogenetic activation produces defense and threatening memory.[59]

Secondly, lPB neurons also send projections to glutamatergic neurons in the hypothalamic perifornical area (PeF). In particular, PeF-projecting lateral PB neurons induced c-Fos expression following formalin injection into the hind paw or face. Later, these PB neurons were confirmed to receive synapses from the SDH and were glutamatergic neurons.[61] Hypothalamic neurons attending to the SDH-PB-PeF pathway may contain orexin.[62] Another target of the spino-parabrachial pathway is the ventromedial hypothalamus, and this area also sends dense projection to dorsal PAG, which may involve the production of highly aversive behaviors.[63]

At the thalamus level, the spino-parabrachial tract sends projections to the mediodorsal thalamus nucleus and terminates in the anterior cingulate cortex (ACC).[64] The ACC is another region involved in processing the emotional and motivational dimensions of pain. One study confirmed that ACC lesions in the nerve ligation mouse model did not alter mechanical hyperalgesia; however, it significantly reduced aversive behavior.[65] Besides, electrical stimulation-induced ACC activity inhibited spinal wide-range neurons' mechanical stimuli[66] and this effect might be due to the activation of ACC-vlPAG circuit.[67]

The trigeminal nociceptive sensory neurons innervating the face and head, which are transmitted through the trigeminal nerve to the trigeminal nuclei in the brainstem, later not only send project contralaterally to the VPL[68] but also have collateral axons that form synapses directly with lPB neurons. Mechanoreceptive fiber inputs activate the trigeminal spinal subnucleus caudalis (Vc)-lPB pathway, whereas C-fiber-mediated nociceptive inputs activate both pathways.[69] Interestingly, noxious facial stimulation activates the lPB more intensely than the hind paw. It has been demonstrated that excitation of the Vc-lPB circuit produces robust escape and avoidance behaviors, while inhibition specifically reduces facial nociception. Therefore, this neurocircuit is responsible for increased affective pain in the craniofacial region.[70]

## Other Pathways Contribute to Pain Processing

The spino-reticular and spino-mesencephalic pathways are part of the broader anterolateral system transmitting pain and temperature sensations. These pathways convey pain's slow, poorly localized, and affective aspects rather than the direct sensory-discriminative aspects. The ventroposterior inferior nucleus (VPI) of the thalamus receives projections from the spino-reticular tract. It transmits pain signals related to the emotional and arousal aspects of pain, sending projection to the reticular formation and then relaying to the thalamus, including the VPI. The spino-mesencephalic tract plays a role in pain modulation, projecting to regions like midbrain PAG before reaching thalamic nuclei, including the VPI. The VPI then sends projection to the secondary somatosensory cortex (SII), which is involved in pain-related learning.

The above evidence shows that the main spino-parabrachial and minor spino-reticular and spino-mesencephalic pathways contribute to motivational-emotional-affective pain. In contrast, spinothalamic pathways play a crucial role in discrimination and intensity of pain.

## Descending Pain Modulation Pathway

Descending pain modulation is the process in which the central nervous system regulates and modifies pain perception through descending circuits from the brain to the spinal cord. Key structures involved include vlPAG in the midbrain, the rostroventral medulla (RVM) and nucleus raphe magnus (NRM) in the medulla, and locus coeruleus (LC) in pons.

The vlPAG contributes to the modulated pain process by projecting primarily to the RVM. Specifically, both glutamatergic and GABAergic neurons in the vlPAG project to RVM ON, OFF, and Neutral neurons.[71,72] Later, it was found that both ON and OFF cells were GABAergic.[72] These RVM neurons then project to SDH. Within the DH, the projections from the RVM predominantly target interneurons and projection neurons located in the superficial laminae, especially laminae I and II, which are involved in processing nociceptive information. This vlPAG-RVM-DH pathway is integral to the descending modulation of pain, either inhibiting or facilitating nociceptive transmission depending on the specific neural circuits and neurotransmitters involved. Chemogenetic stimulation indicated that exciting vlPAG glutamatergic neurons-RVM GABAergic-OFF neurons circuit or inhibiting vlPAG GABAergic neurons projecting to RVM GABergic-ON neurons produce antinociceptive effects.[73]

NRM is a part of raphe nuclei groups in the caudal pons and medulla (near the RVM). Neurons in the NRM release serotonin (5-HT), which belongs to our brain's largest serotonin nuclei groups and plays a significant role in pain modulation. NRM sends projections bilaterally into the spinal cord and terminates in the spinal cord's laminae I, II, V, VI, and VII.[41] At the spinal cord level, spinothalamic neurons in superficial laminae and laminae X and spinal GABAergic interneurons expressed 5-$HT_{1A}$ and 5-$HT_3$ receptors. However, spinal excitatory interneurons only expressed 5-$HT_3$ receptors.[74] It is suggested that activation of the NRM causes analgesia due to the effects on the sensory trigeminal nuclei and spinal cord,[75] blocking their response to noxious stimuli.[76] Analgesic effects of NRM stimulation are partially mediated by activation of serotonin to spinal 5-$HT_{1A}$ receptor[77] or activating at 5-$HT_3$ receptors in postsynaptic GABA interneurons may evoke later inhibit nociceptive transmission of primary afferent fibers.[78] Moreover, NRM receives many afferents projecting from vlPAG, dorsal, and ventral parabrachial nuclei. Glutamate microinjection yielded an increase in PAG firing rates, which was linked to the firing rates of most NRM cells. Therefore, activation of vlPAG-NRM circuit can cause antinociception.[79]

The noradrenergic A5, A6, and A7 cell groups in LC received numerous projections from ascending spinothalamic tract neuron axons[80,81] and have been illustrated to modulate spinal nociceptive transmission through LC-spinal horn noradrenergic pathway. LC neurons are stimulated by noxious heat or chemicals in the absence of injury,[82] and stimulated LC neurons give rise to activation of postsynaptic α2-adrenoceptors in the DH and spVc or α1 adrenoceptor of inhibitory interneurons[83] as a result of antinociception.[84] However, LC attends facilities and maintains allodynia and hyperalgesia in NP conditions.[85] The locus coeruleus (LC) facilitates pain through various neural pathways.[86] One pathway involves the LC's noradrenergic projections to the dorsal reticular nucleus (DRt),[87] which enhances pain transmission in the spinal cord. Manipulations that alter noradrenaline levels in the DRt modulate pain sensitivity, with α1-adrenoreceptors playing a crucial role.[88,89] Another pathway is the LC's projection to the medial prefrontal cortex (mPFC), where noradrenaline release influences pain processing. Blocking α1-adrenoreceptors in the mPFC reduces NP, suggesting their involvement in pain facilitation.[90] The LC also affects pain through descending pathways to the spVc. Ablation of noradrenergic projections to the spVc reduces chronic pain,[90] highlighting the LC's role in maintaining pain through these descending pathways. The LC's interaction with the DRt, mPFC, and spVc modulates pain by shifting from inhibitory to facilitatory mechanisms.

# Neurocircuitry of Sleep-Wake Regulation

Two key processes regulate sleep: the sleep-dependent "Process S" and the sleep-independent circadian "Process C". The interaction between these processes, as elucidated by Alexander Borbély's 1982 model, is fundamental in understanding sleep dynamics.[91] Process S represents the accumulation of sleep debt, which elevates during the wake period and decreases during sleep.[92] The balance between Process S and Process C, known as sleep pressure, influences sleep propensity. Extended wakefulness heightens sleep propensity, leading to deeper sleep characterized by increased slow-wave activity (SWA) on EEG. Conversely, SWA diminishes as sleep propensity decreases, as seen after sleep


https://doi.org/10.2147/NSS.S509013

disturbances or recovery of sleep post-deprivation. Maintaining sleep propensity within a specific range introduces "sleep homeostasis".[93]

Sleep pressure regulation is closely linked to the accumulation of extracellular adenosine. As neurons metabolize ATP, adenosine accumulates and leaks into the extracellular space via nucleoside transporters.[94,95] Adenosine then binds to receptors on neuronal membranes, including A1, A2A, A2B, and A3 receptors.[96] Activating A1 receptors, primarily in wake-active neurons, induces sleepiness, while A2A receptors in sleep-active neurons enhance sleepiness.[94,97] This accumulation indicates high neuronal activity, signaling the need for rest by diminishing wake signals and reinforcing sleep signals. Sleep clears excess adenosine and replenishes ATP, reducing extracellular adenosine and facilitating wakefulness.

The circadian rhythm and the two-process model are significantly influenced by melatonin, a hormone product of the pineal gland.[98] Melatonin production is activated by darkness and inhibited by light, with retinal ganglion cells containing melanopsin responding to light to synchronize the body with the light-dark cycle.[99,100] Light inhibits melatonin secretion through signals from retinal ganglion cells to the pineal gland, while darkness reactivates it. Melatonin regulation involves the suprachiasmatic nucleus (SCN) in the hypothalamus, the master circadian pacemaker.[101] The SCN controls melatonin through a biological clock mechanism involving CLOCK and BMAL1 proteins, which promote PER and CRY proteins that suppress CLOCK and BMAL1, creating a feedback loop lasting about 24 hours.[102–104] Melatonin promotes sleep by interacting with receptors in the hypothalamus and SCN, inducing sleepiness and reducing alertness.[105–108] Melatonin levels peak at night, driving sleep onset and maintenance, and decrease at dawn, aiding in wakefulness. The interplay between adenosine and melatonin is central to regulating the two-process sleep model and circadian rhythm, reflecting the brain's responsiveness to environmental changes.

Despite an incomplete understanding of sleep mechanisms, research has identified several brain structures essential for generating, maintaining, and transitioning between wakefulness, NREM sleep, and REM sleep. Optogenetics, which employs opsins and light for precise neuronal control, has been instrumental in elucidating the roles of specific neuron populations in sleep and wakefulness. Wakefulness and arousal are regulated by several brain areas, involving the basal forebrain (BF), bed nucleus of the stria terminalis, lateral hypothalamus (LH), tuberomammillary nucleus (TMN), ventral tegmental area, dorsal raphe nucleus, and LC.[109] During arousal, the electroencephalogram (EEG) reflects synaptic inputs from pyramidal neurons in the neocortex and hippocampus, primarily influenced by the thalamocortical system, which is under the control of the ascending arousal system.[110] This system includes two branches originating from the rostral pons: one involving the laterodorsal tegmentum (LDT) and pedunculopontine tegmental nuclei (PPT), which activate thalamic relay neurons for cortical information transmission, and the other involving activating neurons in the LH and BF.[111] This pathway includes histaminergic, serotonergic, dopaminergic, and noradrenergic neurons.[109]

Sleep-related neurons are located in regions such as the secondary motor cortex, nucleus accumbens core, ventrolateral preoptic area (VLPO), medial septum, cortical neuronal nitric oxide synthase (nNOS) neurons, LH, thalamic reticular nucleus, parafacial zone, LDT, and PPT.[109] nNOS neurons, identified as GABAergic and nNOS-expressing cells in deep cortical layers, promote NREM sleep and maintain homeostatic sleep drive, as evidenced by studies with nNOS knockout mice.[112,113] The mechanism is believed to involve nitric oxide.[113] Galaninergic neurons in the VLPO are critical for promoting NREM sleep by projecting to and inhibiting wake-promoting neurons in the brainstem and hypothalamus through GABA and galanin release.[109] Damage to the VLPO is associated with insomnia.[111] The VLPO inhibits monoaminergic and orexin neurons during sleep, reducing sleep interruptions. In contrast, monoaminergic neurons inhibit the VLPO during wakefulness, disinhibiting orexin neurons and forming a "flip-flop" circuit that regulates sleep-wake transitions.[109] REM sleep regulation involves LDT and PPT cholinergic neurons. Optogenetic activation of these neurons induces REM sleep episodes during NREM sleep without affecting REM bout durations.[114] Electrical excitation of the LDT can also produce REM sleep, underscoring the role of cholinergic LDT and PPT neurons in modulating REM sleep.[115] These neurons project to the sublaterodorsal nucleus, which is involved in muscle atonia during REM sleep, highlighting their involvement in REM sleep promotion.[114]

## Neural Pathways Linking Pain and Sleep

Numerous brain regions are involved in sleep and pain pathways,[116,117] a logical overlap given that pain signals alert the body to external threats, necessitating immediate wakefulness and activating arousal pathways.[118,119] This interconnectedness often precipitates sleep disturbance and its associated detriments. For example, the descending pain modulation system, involving the PAG and RVM, can inhibit pain, but poor sleep impairs its function, increasing pain sensitivity. The LC and its noradrenaline release are crucial in pain facilitation and wakefulness. Pain can activate the ascending arousal system, including the LC, disrupting sleep. The amygdala and ACC process the emotional aspects of pain, with chronic pain leading to stress and anxiety that further disturb sleep. The thalamus also plays a role in sleep regulation, and disruptions in its activity can alter pain perception and sleep. Neurotransmitters and hormones like serotonin, dopamine, and cortisol are common regulators of both pain and sleep, with imbalances due to chronic pain leading to sleep disturbances. Thus, it is paramount to pinpoint the specific brain regions engaged in sleep and pain processes and understand how these dual influences modulate their activities. This knowledge is crucial for unraveling the mechanisms underpinning chronic pain, potentially revealing whether these changes are a root cause. Such insights pave the way for innovative approaches to chronic pain treatment, enhancing our ability to develop targeted therapeutic strategies.

### Periaqueductal Gray

The PAG is central to the well-documented PAG-RVM descending system, a critical mechanism for pain modulation. Various forebrain and cortex regions send signals to the vlPAG, which then projects to the RVM. Later, the RVM targets the SDH to modulate nociceptive transmission either by facilitating or inhibiting it.[120] Besides its critical role in pain modulation, the PAG regulates the sleep-wake cycle.[121–123] PAG dopaminergic neurons promote wakefulness,[121] whereas GABAergic neurons inhibit REM sleep and consolidate NREM sleep.[122] Previous research has evidenced that acute REM sleep deprivation exacerbates pain by activating the PAG-RVM descending facility pain pathway.[124–126] One study extends these findings by showing that chronic sleep restriction also induces pronociception, with local expression of c-Fos in PAG correlated with pain intensity.[127] Thus, a lack of sleep, whether chronic sleep restriction or acute REM sleep deprivation, disrupts the PAG's ability to modulate pain. Other research found that one-hour sleep deprivation triggered the expression of Homer1a,[128,129] a protein known to reduce dendritic spine size and density, contributing to long-term depression.[130–132] Concurrently, it was evident that the upregulation of Homer1a led to the inactivation of metabotropic glutamate receptor 5 in vlPAG neurons, contributing to chronic pain in neuropathic conditions.[133] Based on these findings, it is proposed that the increased Homer1a expression, which leads to decreased activity in vlPAG-RVM circuitry, might be due to sleep disturbances caused by NP rather than pain itself.

### Locus Coeruleus

LC, a small nucleus in the pons, comprises noradrenergic neurons that project efferents and afferents throughout the central nervous system. LC contributes to sleep-wake regulation, attention, and pain modulation.[134,135] Sleep deprivation might affect LC activity and switch the function of LC from inhibiting to facilitating pain. REM sleep deprivation (REMSD) elevated tyrosine hydroxylase and norepinephrine transporter mRNA expression in LC.[136] One study found that REMSD leads to neuronal apoptosis and loss, mediated by elevated noradrenaline (NA) in the brain acting through α1- adrenergic receptors.[137] LC neurons project to GABAergic neurons in the spinal horn[138] and reduce pain via α1-adrenergic receptor activation.[139] However, in conditions of nerve injury, the LC facilitates pain.[85,86,140] A possible mechanism is that REMSD elevates noradrenaline in the LC, causing the loss of spinal GABAergic neurons through α1-adrenergic receptor activation. This loss of GABAergic neurons results in reduced inhibition of spinal sensory neurons, ultimately leading to chronic pain.[141] Another potential mechanism is the switch from depolarizing to hyperpolarizing actions of noradrenaline due to the change of α1- to α2- adrenergic receptors.[142] and causes inhibition of spinal GABA neurons instead of excitation. However, these hypotheses should be confirmed in the future.

## Nucleus Raphe Medulla

It is well known that NRM contributes to the analgetic effect by excitation of spinal GABAergic neurons through the 5-$HT_3$ receptor or inhibition of spinothalamic neurons through the 5-$HT_{1A}$ receptor.[143,144] However, other studies consistently observed that the descending serotonergic pathway might contribute to facility pain perception depending on the stage of pain and cause hypersensitivity in a pain mouse model.[145,146] Especially it was demonstrated that nerve injuries increase the facility pain effect of the descending serotonergic pathway, inducing mechanosensitivity through the activation of spinal 5-$HT_3$ receptors.[147] Pain condition somehow activates the 5-$HT_3$ receptor in the spinal horn's excitatory interneurons and leads to spinothalamic neuron activation.[148] Activation of the 5-$HT_{1A}$ receptor was also reported to induce pain.[149] It was suggested due to activation of the 5-$HT_{1A}$ receptor in spinal GABAergic neurons.[74] Besides, neuropathic hypersensitivity formed due to the elevated 5-$HT_{1A}$ autoreceptors in raphe nuclei leads to a decreased release of serotonin into the spinal horn and later reduced function of the serotonergic inhibition pathway.[150,151] The above evidence shows that there are both descending serotonergic facility and inhibitory pain pathways, and somehow, neuroplasticity switches their function from antinociception to pronociceptive in chronic pain conditions. Serotonergic neurons in dorsal raphe also contribute to facility wakefulness, and their activities are inhibited during REM sleep. Several studies showed that extracellular serotonin levels induced in total sleep deprivation[152] and 5-$HT_{1A}$ receptors were only desensitized after eight days of sleep deprivation.[153,154] Therefore, one possibility is that NP-induced sleep disturbance might elevate the high serotonin levels, deactivate the 5-$HT_{1A}$ receptors in spinal GABAergic neurons, and, finally, chronic pain.

## Nucleus Accumbens

The nucleus accumbens (NAc), located in the ventral striatum, is an essential portion of the mesolimbic dopaminergic system, playing a significant role in modulating pain,[155,156] and the sleep-wake cycle.[157–160] It is hypothesized that sleep pressure increases NAc efferent activity to block brainstem wake-promoting nuclei and hypothalamus.[161] Recent study found that increased NAc activity, with elevated c-Fos expression levels, modulates the acute selective REM sleep deprivation's pronociceptive impact, and lesions of NAc prevented the sleep deprivation-induced hypersensitivity.[127] Therefore, emerging evidence suggests that sleep deprivation could change the NAc activity in pain modulation.

## Anterior Cingulate Cortex (ACC)

ACC is involved in various functions, including emotion regulation, decision-making, and response to pain. Several studies show that the alternation of AAC neural activities is due to nerve injury and sleep disturbance. Strong evidence supports that peripheral nerve damage caused the elevation of AAC pyramidal neurons[162–164] and a decrease in GABA levels released extracellularly in the mouse cingulate cortex on the 7$^{th}$ postoperative day.[165] Besides, imaging research indicated shorter sleep durations had lower GABA levels in the ACC/mPFC than longer sleep durations.[166] As we know, nerve damage induced sleep disturbances in the NP mice model, which might be the reason for the reduction in GABA levels (Narita's study showed that the level of GABA transporter only reduced after seven days of nerve injury).[165] Later, the imbalance of excitatory and inhibitory activities in ACC leads to a chronic pain state.

## Amygdala

Central nuclei of the amygdala (CeA), a subnucleus of the amygdala, recently was found to contribute to promoting NREM sleep. NTS-expressing CeA GABAergic neurons activated and inactivated by optogenetic stimulation promoted and suppressed non-REM sleep, respectively.[167] Acute sleep deprivation activates the $GABA_A$ receptor in the central nucleus of the amygdala.[168] Moreover, GABAergic neurons in CeA attend to facilitate pain through the CeA-vlPAG$^{Glu+}$ circuit.[169]

# Neuropathic Pain and Sleep Disorders

NP, arising from nerve damage or dysfunction, often interlinks with sleep disturbances, forming a feedback loop that exacerbates patient distress. Research shows that a significant portion of those with NP experience disrupted sleep, which

subsequently increases their pain sensitivity. These sleep disturbances manifest through various symptoms, including difficulty initiating and maintaining sleep, frequent nocturnal awakenings, poor sleep quality, and excessive daytime sleepiness.[170] Additionally, NP shows high comorbidity with insomnia, sleep-related breathing disorders, and sleep-related movement disorders. Both human and animal studies provide substantial evidence of sleep disruptions and disorders triggered by various types of NP, as summarized in Tables 1 and 2.

## Circadian Rhythms Disruptions and Their Role in Neuropathic Pain and Sleep Interaction

The circadian system, orchestrated by SCN in the hypothalamus, regulates various physiological processes, including sleep-wake cycles,[192] hormone secretion,[193] body temperature,[194] immune function,[195] and pain perception.[196] Emerging research suggests that pain sensitivity is influenced by circadian rhythms, exhibiting fluctuations that align with the body's internal clock.[196,197] This variability is driven by multiple factors: key brain regions involved in pain modulation express circadian clock genes, while the circadian system also interacts with immune responses[198] and endogenous analgesic mechanisms.[199,200] For instance, brain regions associated with neural pathways for modulation of NP, such as the SDH,[201] PAG,[202] also expressed circadian clock genes. NP-related neuronal activity in the PAG, RVM, and LC exhibits circadian rhythmicity, contributing to temporal variations in pain modulation. The PAG demonstrates fluctuations in opioid receptor expression,[203] the RVM's on/off pain neurons display activity patterns aligned with the sleep-wake cycle,[204] and the noradrenergic output of LC, regulated by the SCN, mediates circadian-dependent changes in pain sensitivity.[205] These dynamic regulatory processes contribute to the temporal patterning of pain perception, highlighting the intricate relationship between the body's biological clock and pain processing.

NP and circadian rhythms have shown a bidirectional relationship in which NP can alter circadian patterns,[206] while disrupted circadian rhythms can exacerbate pain sensitivity.[207,208] One potential mechanism for NP disrupting circadian rhythm might be NP-induced sleep disturbances. As mentioned above, NP could significantly disrupt sleep by altering sleep-wake cycles, leading to fragmented or poor-quality sleep. Persistent pain signals interfere with normal sleep architecture, reducing deep sleep stages and increasing nighttime awakenings. These sleep disturbances, in turn, impair the body's ability to reset its circadian rhythms, leading to a desynchronized biological clock.[209,210] On the other hand, a dysregulated circadian rhythm may exacerbate pain perception and contribute to the transition from acute to chronic NP by altering neuroinflammation and circadian clock genes in NP-modulated brain regions.[211] Another possible way NP may alter the circadian rhythm is through the involvement of dynorphin-positive cells in the lPB that project to SCN. Retrograde tracing experiments have shown that lPB neurons are projected to the SCN and colocalized with dynorphin.[212] Moreover, NP conditions increase spontaneous and evoked activity in PB neurons, including dynorphin-positive cells, leading to a significant rise in after-discharges.[213,214] Consequently, the lateral PB-SCN projection may contribute to circadian rhythm disruption. However, the precise mechanisms by which this projection affects circadian rhythm require further investigation.

## Age and Sex Differences in Neuropathic Pain and Sleep Disorders Association

The existence of sex differences in NP has been focusing recently. Several human and animal studies indicated that females generally reported higher pain sensitivity and showed more frequent pain compared to males.[215–218] Recent research highlights multiple mechanisms underlying sex differences in NP, including neuro-immune signaling,[219–221] gene expression, hormonal influences,[222] neuroplasticity,[223] and brain activity.[224] For instance, in males, NP is associated with activating cytokines such as OSM, LIF, and SOCS11, whereas in females, pathways involving CCL1, CCL19, and CCL21 play a more prominent role.[225] Besides, hormones also play a role, as estrogen can both suppress and amplify pain, testosterone reduces pain, and progesterone generally amplifies it except during pregnancy.[222] Sex differences also play a critical role in the sleep-deprivation-related alteration of pain perception and intensity.[226] In fact, one meta-analysis evidenced that sleep disturbances enhance pain facilitation and reduce inhibition in females, whereas they have the opposite effect in males.[227] Combining the above evidence, we might see the contribution of sex differences in both

https://doi.org/10.2147/NSS.S509013



**Table 2** Comprehensive Summary of Neuropathic Pain, Sleep Disorders, Neural Pathways, and Clinical Implications

| Classification of Neuropathic Pain | | Relevant Sleep Disorders | Neuronal Pathways Involved Neuropathic Pain Disrupts Sleep | Clinical Implications |
|---|---|---|---|---|
| Peripheral neuropathic pain | Trigeminal neuralgia | Insomnia | LC - Trigeminal sensory nuclei pathway<br>Neuroanatomical studies reveal reciprocal connections between the locus coeruleus (LC) and trigeminal sensory nuclei.[171] The LC plays a key role in arousal, with its neurons exhibiting maximal activity during wakefulness and reduced firing during sleep. While no studies have directly examined the impact of trigeminal neuropathic pain on LC activity, evidence from other neuropathic pain models indicates LC hyperactivation.[172,173] Therefore, trigeminal neuralgia may similarly disrupt sleep through activation on LC neurons. | - Neuromelanin-sensitive MRI, PET tracers like MeNER, and EEG[174] can help assess LC integrity, activity, and noradrenergic dysfunction in Investigating the role of the locus coeruleus (LC) in sleep disorders and trigeminal neuralgia (TN)<br>- Given the LC's role in arousal and its potential hyperactivation in trigeminal neuralgia, targeted neuromodulation (eg, noradrenergic modulation[175]) may help manage both NP and sleep disruptions in affected patients. |
| | Neuropathic pain after peripheral nerve injury | Insomnia | - Decreased activation of vlPAG - RVM pathways[133] | - Therapeutic strategies aimed at enhancing activity of vlPAG-RVM pathway function, such as neurostimulation therapy[176–178] targeted in vlPAG, may provide dual benefits in alleviating NP and improving sleep quality. |
| | Painful polyneuropathy | Insomnia | - thalamic ventral posterolateral (VPL) nucleus<br>Recent studies suggest that central pain processing mechanisms play a crucial role in painful diabetic peripheral neuropathy. Aberrant neurons within the ventral posterolateral (VPL) thalamus exhibit hyperexcitability, amplifying pain perception in diabetic patients.[179,180] Notably, VPL activity is heightened during wakefulness and is more closely associated with arousal than conscious awareness. This region may also co-activate with the global cortex, particularly sensory-motor areas, to regulate arousal states.[181] Consequently, the dysregulated activation of the VPL in painful diabetic polyneuropathy may disrupt normal sleep architecture, contributing to sleep disturbances. | Treatments targeting thalamic hyperactivity, such as transcranial magnetic stimulation (TMS) or pharmacological interventions, may help alleviate both NP and sleep disturbances in patients with painful diabetic neuropathy. |
| | | SRBDs (Sleep Apnea) | - Parabrachial nucleus<br>Glutamatergic neurons in the parabrachial nucleus (PB) play a dual role in controlling both neuropathic pain and arousal.[182] Emerging evidence showed that PB glutamatergic signaling is critical for hypercapnic arousal, relaying sensory inputs to arousal-promoting regions like the hypothalamus and cortex.[183,184] Additionally, one report indicated that activation of glutamatergic LPBN neurons by optogenetics induces neuropathic pain-like behavior in naive mice.[60] Even though, no evidence support how PB neurons activated under painful diabetic neuropathy, PB might potential involve in painful diabetic neuropathy caused sleep apnea. | Considering PB's role in hypercapnic arousal and pain modulation, investigating its involvement in painful diabetic neuropathy-related sleep apnea could open new therapeutic avenues, including PB-targeted interventions for sleep-disordered breathing in neuropathic pain patients. |

| | | | | |
|---|---|---|---|---|
| Central neuropathic pain | Central neuropathic pain associated with spinal cord injury | SRBDs | - Thalamus<br>Emerging evidence indicates the altered activity of thalamus in spinal cord injury and contribute to central neuropathic pain associated with spinal cord injury.[185–187] Thalamus also plays in central role in sleep-wake regulation.[188,189] Therefore, abnormal thalamus activity might contribute to the association sleep disturbance and spinal cord injury-related neuropathic pain. | Interventions that modulate thalamic activity, such as neuromodulation or targeted pharmacotherapy, may improve both neuropathic pain and sleep disturbances in spinal cord injury patients. |
| | Central neuropathic pain associated with post-stroke pain | Circadian Rhythm Sleep-Wake Disorders | - Thalamus[37] | Melatonin treatment for circadian rhythm sleep disorders might help to resolve the sleep disorder and neuropathic pain comorbidity in post-stroke patients.[37] |
| | Central neuropathic pain associated with multiple sclerosis | Insomnia | - Thalamus<br>Damaged thalamus is hypothesized to central neuropathic pain in MS patients.[190,191] Moreover, thalamus plays a central role in sleep-wake regulation.[188,189] Therefore, abnormal thalamus activity might contribute to the association sleep disturbance and MS-related neuropathic pain. | Managing MS-related neuropathic pain with strategies that also address sleep dysfunction—such as neurostimulatory approaches or symptom-specific pharmacological treatments—may enhance patient outcomes. |


https://doi.org/10.2147/NSS.S509013

NP and sleep disorders. It is well-documented that sleep disturbance and NP have a bidirectional association. Therefore, a question is whether sex differences contribute to the association between NP and sleep disorders. Whether women are more prone to severe sleep disturbances due to their heightened pain sensitivity or if sleep disruptions further amplify NP symptoms in women. The question was confirmed with 80% of patients with NP (NP) experiencing poor quality of sleep, with female sex being a factor correlated with poor sleep.[228] This suggests that women with NP may be more susceptible to sleep disturbances than men. While research has demonstrated a link between poor sleep and increased pain perception, the specific mechanisms underlying sex differences in this relationship require further investigation.

Age-related changes in pain processing and sleep regulation also play a significant role in the interaction between NP and sleep disorders. Older adults experience alterations in nociceptive inhibition, leading to increased pain perception and prolonged recovery from painful stimuli.[229–231] At the same time, aging is associated with reduced sleep efficiency, increased sleep fragmentation, and a decline in slow-wave sleep,[232–235] all of which can contribute to heightened pain sensitivity. These changes create a cycle in which poor sleep exacerbates pain while persistent pain further disrupts sleep. A crucial question is whether age differences drive severe sleep disturbances in individuals with NP or whether aging exacerbates pain symptoms in those with pre-existing sleep disorders. Research suggests that older adults with NP experience more significant difficulties in maintaining restorative sleep, which may, in turn, worsen their pain experience. However, the extent to which these age-related changes influence the bidirectional relationship between NP and sleep disorders remains an area of ongoing study. In the future, research should be conducted to directly compare younger and older patients regarding the influence of NP on sleep quality.

Both age and sex differences are critical in understanding the interplay between NP and sleep disturbances. Recognizing these differences can help guide more targeted approaches to managing pain and improving sleep quality in affected individuals.

# Therapeutic Interventions

## Basic Mechanism of Pharmacological Treatments

Pharmacological treatments targeting pain and sleep disturbances in NP patients hold promise for improving overall patient outcomes. Medications such as gabapentin and pregabalin are commonly prescribed, as they have been shown to alleviate NP while also enhancing sleep quality by reducing sleep interruptions and improving sleep maintenance.[236–239] Gabapentin and pregabalin relieve pain by binding to the α2δ subunit of voltage-gated calcium channels in neurons, reducing calcium influx and subsequently decreasing the release of excitatory neurotransmitters like glutamate and substance P. This action dampens the overactivity of pain pathways in the central nervous system, helping to alleviate NP.[240]

Additionally, low-dose antidepressants like amitriptyline not only help with pain relief but also have sedative properties that aid in sleep.[241,242] Amitriptyline relieves pain primarily by inhibiting serotonin and norepinephrine reuptake, enhancing their role in suppressing pain signals in the central nervous system. It also blocks sodium channels and serves as an antagonist to NMDA receptors, reducing nerve excitability and pain signal amplification. Furthermore, the sedative effects of amitriptyline may indirectly aid in pain management by improving sleep and reducing anxiety.[243] These dual-action therapies are beneficial, as they address the intertwined nature of pain and sleep disturbances, potentially breaking the cycle of pain-induced insomnia and its exacerbating effects on NP.

## Clinical Implications

Non-pharmacological approaches to managing both pain and sleep disturbances in NP patients include cognitive-behavioral therapy (CBT), physical therapy, and lifestyle modifications.[244,245] CBT for insomnia (CBT-I) is particularly effective, addressing maladaptive thoughts and behaviors related to sleep, thereby improving sleep quality and reducing pain perception.[246,247] Physical therapy, including exercises and manual therapy, can alleviate pain and promote better sleep by improving physical function and reducing discomfort. Mindfulness and relaxation techniques, such as meditation and progressive muscle relaxation, also play a crucial role in reducing stress and anxiety, which can exacerbate both

pain and sleep problems. Integrating these non-pharmacological strategies provides a holistic approach to interrupting the feedback loop of pain and poor sleep, leading to improved quality of life for patients.

Given the association between disrupted circadian rhythm and neuropathic pain, chronotherapy[248–250] and light therapy, as non-pharmacological approaches, might be beneficial for managing circadian dysrhythmia and neuropathic pain. Chronotherapy systematically adjusts sleep timing and exposure to external cues, while light therapy, particularly morning bright light exposure, modulates the suprachiasmatic nucleus (SCN) to regulate circadian rhythms. Clinical studies have demonstrated that light therapy improves sleep efficiency and reduces pain perception in patients with fibromyalgia and other chronic pain conditions.[251–254] A randomized controlled trial on diabetic neuropathy patients found that monochromatic infrared light exposure significantly reduced pain intensity and improved sleep quality.[255] By restoring circadian alignment, these interventions may attenuate central sensitization, improve sleep architecture, and reduce neuropathic pain severity. Further research is warranted to refine optimal light wavelengths, duration, and timing for individualized treatment strategies.

Managing NP and sleep disturbances necessitates a keen awareness of potential drug-drug interactions.[256] Medications such as gabapentin and pregabalin, pivotal for alleviating NP, may interact synergistically with central nervous system depressants like benzodiazepines or opioids, thereby amplifying risks of sedation, respiratory depression, and compromised motor coordination.[257–259] Furthermore, the concomitant use of antidepressants like amitriptyline with other sedatives or analgesics can exacerbate side effects, including dizziness, confusion, and gastrointestinal disturbances.[260,261] These interactions undermine therapeutic efficacy and increase the likelihood of adverse effects, emphasizing the necessity for meticulous medication management and vigilant monitoring by healthcare providers to safeguard patient safety and achieve optimal therapeutic outcomes.

## Limitations and Gaps in Current Research and Future Direction

It is known that nerve injury can cause sleep disruption, including decreased time spent in NREM and REM sleep in several NP mouse models. However, future studies should confirm whether the change in sleep-related brain region's activities caused by NP-induced sleep disturbance are similar to those resulting from sleep deprivation. Additionally, the sleep disturbances caused by NP leading to the progression of chronic pain remain incompletely understood. Therefore, future research should be conducted to discover how enhancing sleep might help prevent this progression.

As summarized in Table 1, most existing research relies on cross-sectional or short-term experimental designs, offering only a snapshot of the interaction between sleep and NP. Longitudinal studies that track the progression of sleep disturbances and chronic NP over time could provide deeper insights into their bidirectional relationship, revealing dynamic feedback mechanisms that may drive symptom persistence or exacerbation.

Research on sex differences in the bidirectional relationship between NP and sleep disruption remains limited. Most studies, whether in animal models or humans, predominantly use males to minimize variability,[262] as hormonal fluctuations in females—particularly those driven by estrogen and progesterone—are often considered confounding factors. However, this sex bias overlooks critical neurobiological and physiological differences that may influence pain perception and sleep regulation. Expanding research to include female subjects is essential for a more comprehensive understanding of these interactions and for developing more effective, sex-specific therapeutic strategies.

Given the bidirectional relationship between NP and circadian rhythm disruptions, therapeutic interventions targeting circadian restoration may offer significant benefits. Strategies such as light therapy, melatonin supplementation, structured sleep schedules, and cognitive-behavioral therapy for insomnia (CBT-I) have shown promise in improving circadian alignment and reducing NP symptoms. Addressing circadian dysregulation may help break the cycle of NP and sleep disruption, ultimately enhancing the quality of life for neuropathic pain patients. Understanding the circadian regulation of NP provides valuable insights into optimizing NP management, such as timing medications and therapies to align with the body's natural rhythms for improved efficacy.

## Conclusion

In conclusion, the intricate association between sleep and NP underscores the complexity of the neural circuits involved in both processes. This review highlights the critical need to dissect the specific brain regions and neuronal subtypes that

regulate sleep-wake cycles and pain pathways. For instance, PAG plays a central role in descending pain modulation, and sleep disturbances can disrupt its ability to inhibit pain via the RVM, exacerbating chronic pain. LC and its noradrenergic system facilitate wakefulness and pain perception, with REM sleep deprivation increasing noradrenaline levels, leading to spinal GABAergic neuron loss and heightened pain sensitivity. Similarly, NRM exhibits bidirectional serotonergic control over pain, where neuropathic conditions shift its function from antinociceptive to pronociceptive through altered 5-HT receptor activity. NAc, a key regulator of motivation and arousal, has been implicated in sleep deprivation-induced hyperalgesia. At the same time, ACC and amygdala contribute to pain's emotional and affective dimensions, with disrupted GABAergic signaling in these regions reinforcing chronic NP states. Our previous research indicates that sleep disturbances following nerve injury may contribute to changes in pain modulation and the progression of chronic pain.[9] Collectively, these findings suggest that neuropathic pain-induced sleep disturbances engage maladaptive neuroplastic changes in pain-processing circuits, further perpetuating chronic pain. Understanding these interactions will be essential for developing targeted interventions that alleviate pain and restore sleep homeostasis, offering a more comprehensive approach to neuropathic pain management.

By mapping the anatomical pathways from the peripheral to the central nervous system and examining the neurocircuits involved in sleep-wake regulation, we aim to shed light on the bidirectional relationship between sleep and NP. This enhanced understanding is crucial for identifying potential targets for intervention, which could enhance the quality of life for patients suffering from chronic NP and associated sleep disorders. Ultimately, this review seeks to pave the way for innovative therapeutic approaches that address pain management and sleep disorders, offering hope for better clinical outcomes.

## Abbreviations

5-HT, 5-hydroxytryptamin as serotonin; ACC, Anterior cingulate cortex; BF, Basal forebrain; CBT, Cognitive-behavioral therapy; CeA, Central nucleus of the amygdala; CGRP, Calcitonin gene-related peptide; DRt, Dorsal reticular nucleus; EEG, Electroencephalogram; IC, Insular cortex; LC, Locus coeruleus; LDT, Laterodorsal tegmentum; LH, Lateral hypothalamus; lPB, lateral Parabrachial; mPFC, Medial prefrontal cortex; NA, Noradrenaline; NAc, Nucleus accumbens; nNOS, Neuronal nitric oxide synthase; NP, Neuropathic pain; NREM, Non-rapid eye movement; NRM, Nucleus raphe magnus; PAG, Periaqueductal gray; PB, Parabrachial; PeF, Perifornical area; PPT, Pedunculopontine tegmental nuclei; REM, Rapid eye movement; REMSD, REM sleep deprivation; RVM, Rostroventral medulla; SCN, Suprachiasmatic nucleus; SDH, Spinal dorsal horn; spVc, Spinal trigeminal Subnucleus caudalis; spVc, Trigeminal spinal subnucleus caudalis; SWA, Slow-wave activity; TMN, Tuberomammillary nucleus; vlPAG, Ventrolateral periaqueductal gray; VLPO, Ventrolateral preoptic area; VMPO, Ventral medial nucleus; VPI, Ventroposterior inferior nucleus; VPL, Ventral posterior nucleus.

## Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## Acknowledgments

This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korea government (MSIT) (NRF-2022R1A2C3009749; RS-2023-00302281).

## Author Contributions

Anh Ho: Conceptualization, Methodology, Writing – Original draft preparation. Victor J Drew: Conceptualization, Writing - Original draft preparation. Tae Kim: Conceptualization, Writing – Reviewing and Editing. All authors agreed on the journal to which the article will be submitted; reviewed and agreed on all versions of the article before submission, during revision, the final version accepted for publication, and any significant changes introduced at the proofing stage; and agreed to take responsibility and be accountable for the contents of the article.

## Disclosure

The authors have no competing interests to declare.

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