

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

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 Tool¹⁰ and Newcastle-Ottawa Scale¹¹ 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 A δ (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 - Reduced %NREM of TST - Diminished %REM of TST - 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 - Reduced %NREM of TST		Low	Monassi et al 2003 ¹⁶

(Continued)



Table I (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				
		CS7BL/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 - Reduction in sleep efficiency - Increased the number of arousals		Low	Andersen et al 2003 ¹⁸



	Painful polyneuropathy	Prospective observational study	Human	427 participants	Causal		MOS-Sleep	- Increased sleep latency - 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 - Reduced sleeping time		Moderate	Zelman et al 2006 ²³
		CC	Human	30 participants	Causal	Polysomnography, AHI		- Decreased sleep latency - Decreased sleep efficiency - Reduced %REM of TST - Increase in sleep fragments - 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

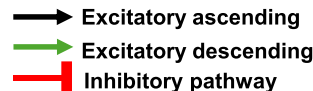
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Table 1 (Continued).

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 \square , body movement, nasal thermistor, plethysmography, SpO \square			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 - Daytime sleepiness		Moderate	Shafazand et al 2019 ³³
		Epidemiological review	Human	408 participants	Causal		NSQ	- difficulty in falling asleep - 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		Self-report	Disturbed sleep		High	Raffaelli 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, - Increased average duration of wakefulness - 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.



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, rostral ventral 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; viPAG, 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

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 A δ 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 (IPB) 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 IPB neuron input, induced vocalization, and behavioral hyperalgesia. Recently, it was found that excitation of glutamatergic or inhibition of GABAergic IPB 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 IPB 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, IPB 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 stimuli⁶⁶ and this effect might be due to the activation of ACC-vIPAG 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 VPL⁶⁸ but also have collateral axons that form synapses directly with IPB neurons. Mechanoreceptive fiber inputs activate the trigeminal spinal subnucleus caudalis (Vc)-IPB pathway, whereas C-fiber-mediated nociceptive inputs activate both pathways.⁶⁹ Interestingly, noxious facial stimulation activates the IPB more intensely than the hind paw. It has been demonstrated that excitation of the Vc-IPB 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 vIPAG in the midbrain, the rostroventral medulla (RVM) and nucleus raphe magnus (NRM) in the medulla, and locus coeruleus (LC) in pons.

The vIPAG contributes to the modulated pain process by projecting primarily to the RVM. Specifically, both glutamatergic and GABAergic neurons in the vIPAG 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 vIPAG-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 vIPAG glutamatergic neurons-RVM GABAergic-OFF neurons circuit or inhibiting vIPAG GABAergic neurons projecting to RVM GABAergic-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-HT₃ receptors. However, spinal excitatory interneurons only expressed 5-HT₃ 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} receptor⁷⁷ or activating at 5-HT₃ receptors in postsynaptic GABA interneurons may evoke later inhibit nociceptive transmission of primary afferent fibers.⁷⁸ Moreover, NRM receives many afferents projecting from vIPAG, 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 vIPAG-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 α 2-adrenoceptors in the DH and spVc or α 1 adrenoceptor of inhibitory interneurons⁸³ 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 α 1-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 α 1-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

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 interconnectivity 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 vPAG, 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 facilitatory 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 vPAG 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 vPAG-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 α 1- adrenergic receptors.¹³⁷ LC neurons project to GABAergic neurons in the spinal horn¹³⁸ and reduce pain via α 1- 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 α 1- 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 α 1- to α 2- 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-HT₃ 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-HT₃ receptors.¹⁴⁷ Pain condition somehow activates the 5-HT₃ 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 deprivation¹⁵² 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 7th 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-vIPAG^{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 responses¹⁹⁸ 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 IPB that project to SCN. Retrograde tracing experiments have shown that IPB 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

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 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) - 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 vIPAG - RVM pathways ¹³³	- Therapeutic strategies aimed at enhancing activity of vIPAG-RVM pathway function, such as neurostimulation therapy ^{176–178} targeted in vIPAG, may provide dual benefits in alleviating NP and improving sleep quality.
	Painful polyneuropathy	Insomnia	- thalamic ventral posterolateral (VPL) nucleus 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 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	<p>- Thalamus</p> <p>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.</p>	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	<p>- Thalamus³⁷</p>	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	<p>- Thalamus</p> <p>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.</p>	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.

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 $\alpha 2\delta$ 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; IPB, 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; vIPAG, 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.

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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.

References

1. Treede R-D, Jensen TS, Campbell J. Neuropathic pain: redefinition and a grading system for clinical and research purposes. *Neurology*. 2008;70(18):1630–1635. doi:10.1212/01.wnl.0000282763.29778.59
2. Shan L, Selvarajah D, Wang Z. Insights in neuropathic pain: 2022. *Front Pain Res*. 2023;4:1232025.
3. Dworkin RH. An overview of neuropathic pain: syndromes, symptoms, signs, and several mechanisms. *Clin J Pain*. 2002;18(6):343–349. doi:10.1097/00002508-200211000-00001
4. Karna B. *Sleep Disorder*. In: StatPearls Publishing; 2020.
5. Lampl C, Schweiger C, Haider B, Lechner A. Pregabalin as mono-or add-on therapy for patients with refractory chronic neuropathic pain: a post-marketing prescription-event monitoring study. *J Neurol*. 2010;257(8):1265–1273. doi:10.1007/s00415-010-5504-9
6. Almozino G, Benoliel R, Sharav Y, Haviv Y. Sleep disorders and chronic craniofacial pain: characteristics and management possibilities. *Sleep Med Rev*. 2017;33:39–50. doi:10.1016/j.smrv.2016.04.005
7. Onen SH, Alloui A, Eschallier A, Dubray C. Vocalization thresholds related to noxious paw pressure are decreased by paradoxical sleep deprivation and increased after sleep recovery in rat. *Neurosci Lett*. 2000;291(1):25–28. doi:10.1016/S0304-3940(00)01383-5
8. Nascimento DC, Andersen ML, Hipolide DC, Nobrega JN, Tufik S. Pain hypersensitivity induced by paradoxical sleep deprivation is not due to altered binding to brain mu-opioid receptors. *Behav Brain Res*. 2007;178(2):216–220. doi:10.1016/j.bbr.2006.12.016
9. Ho A, Lee S-J, Drew VJ. Sleep disturbance correlated with severity of neuropathic pain in sciatic nerve crush injury model. *J Sleep Res*. 2024;33(5):e14137. doi:10.1111/jsr.14137
10. Hooijmans CR, Rovers MM, De Vries RB, Leenaars M, Ritskes-Hoitinga M, Langendam MW. SYRCLE's risk of bias tool for animal studies. *BMC Med Res Method*. 2014;14:1–9. doi:10.1186/1471-2288-14-43
11. Wells GA, Shea B, O'Connell D. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. 2000.
12. Haviv Y ZA, Etzioni Y, Klitinich V, Dobriyan A, Sharav Y, Benoliel R. The impact of chronic orofacial pain on daily life: the vulnerable patient and disruptive pain. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2017;123(1):58–66. doi:10.1016/j.oooo.2016.08.016
13. Vazquez-Delgado E V-GM, Carlson C, Figueiredo R, Valmaseda-Castellon E, Valmaseda-Castellon E. Sleep quality and psychosocial characteristics of patients with painful post-traumatic trigeminal neuropathies. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2018;126(4):342–348. doi:10.1016/j.oooo.2018.05.051
14. Devor M, Wood I, Sharav Y, Zakrzewska JM. Trigeminal Neuralgia During Sleep. *Pain Pract*. 2008;8(4):263–268. doi:10.1111/j.1533-2500.2008.00214.x
15. Atar MÖ, Kamacı GK, Özcan F, Demir Y, Aydemir K. The effect of neuropathic pain on quality of life, depression levels, and sleep quality in patients with combat-related extremity injuries. *J Trauma Injury*. 2022;35(3):202–208. doi:10.20408/jti.2022.0019
16. Monassi CR, Bandler R, Keay KA. A subpopulation of rats show social and sleep-waking changes typical of chronic neuropathic pain following peripheral nerve injury. *Eur J Neurosci*. 2003;17(9):1907–1920. doi:10.1046/j.1460-9568.2003.02627.x
17. Alexandre C, Miracca G, Holanda VD. Nociceptor spontaneous activity is responsible for fragmenting non-rapid eye movement sleep in mouse models of neuropathic pain. *Sci Trans Med*. 2024;16(743):eadg3036. doi:10.1126/scitranslmed.adg3036
18. Andersen ML, Tufik S. Sleep patterns over 21-day period in rats with chronic constriction of sciatic nerve. *Brain Res*. 2003;984(1–2):84–92. doi:10.1016/S0006-8993(03)03095-6
19. Poliakov I, Toth C. The impact of pain in patients with polyneuropathy. *Eur J Pain*. 2011;15(10):1015–1022. doi:10.1016/j.ejpain.2011.04.013
20. D'Amato C, Morganti R, Di Gennaro F, Greco C, Marfia GA, Spallone V. A novel association between nondipping and painful diabetic polyneuropathy. *Diabetes Care*. 2014;37(9):2640–2642. doi:10.2337/dc14-0528
21. Sachau J, Kersebaum D, Hüllemann P. The association of self-reported symptoms of central sensitization and sleep disturbances in neuropathic pain. *Pain Rep*. 2023;8(5):e1098. doi:10.1097/PR9.0000000000001098
22. Abo-Elfetoh NM, Farag AI, Gabra RH. Impact of pain severity on functioning domains, sleep, and cognition in painful diabetic peripheral polyneuropathy patients. *Middle East Current Psychiatry*. 2022;29(1):83. doi:10.1186/s43045-022-00243-8
23. Zelman DC, Brandenburg NA, Gore M. Sleep impairment in patients with painful diabetic peripheral neuropathy. *Clin J Pain*. 2006;22(8):681–685. doi:10.1097/01.aip.0000210910.49923.09
24. Bahnasy WS, El-Heneedy YAE, El-Seidy EAS, Labib NAA, Ibrahim ISE. Sleep disturbances in diabetic peripheral neuropathy patients: a clinical and polysomnographic study. *Egyptian J Neurol Psychiatry Neurosurg*. 2018;54:1–7. doi:10.1186/s41983-018-0024-0
25. Drolet M, Brisson M, Schmader KE. The impact of herpes zoster and postherpetic neuralgia on health-related quality of life: a prospective study. *Can Med Assoc J*. 2010;182(16):1731. doi:10.1503/cmaj.091711
26. Lee DH, Park JE, Yoon DM, Yoon KB, Kim K, Kim SH. Factors associated with increased risk for clinical insomnia in patients with postherpetic neuralgia: a retrospective cross-sectional study. *Pain Med*. 2016;17(10):1917–1922. doi:10.1093/pm/pnw066
27. Shi T, Chen Z, Li W, Wang Z, Liu W. Prevalence of sleep disturbance in patients with cervical radiculopathy and an analysis of risk factors: a cross-sectional study. *Eur Spine J*. 2023;32(5):1624–1635. doi:10.1007/s00586-023-07655-y
28. Kocabicak E, Terzi M, Akpınar K, Paksoy K, Cebeci I, Iyigün O. Restless leg syndrome and sleep quality in lumbar radiculopathy patients. *Behav Neurol*. 2014;2014(1):245358. doi:10.1155/2014/245358
29. Mahn F, Hüllemann P, Gockel U. Sensory symptom profiles and co-morbidities in painful radiculopathy. *PLoS One*. 2011;6(5):e18018. doi:10.1371/journal.pone.0018018
30. Telles SC, Alves RC, Chadi G. Periodic limb movements during sleep and restless legs syndrome in patients with Asia A spinal cord injury. *J Neurol Sci*. 2011;303(1–2):119–123. doi:10.1016/j.jns.2010.12.019
31. Chiodo AE, Sitrin RG, Bauman KA. Sleep disordered breathing in spinal cord injury: a systematic review. *J Spinal Cord Med*. 2016;39(4):374–382. doi:10.1080/10790268.2015.1126449

32. Jensen MP, Hirsh AT, Molton IR, Bamer AM. Sleep problems in individuals with spinal cord injury: frequency and age effects. *Rehab Psychol.* 2009;54(3):323. doi:10.1037/a0016345
33. Shafazand S, Anderson Kim D, Nash Mark S. Sleep complaints and sleep quality in spinal cord injury: a web-based survey. *J Clin Sleep Med.* 2019;15(05):719–724. doi:10.5664/jcsm.7760
34. Biering-Sørensen F, Biering-Sørensen M. Sleep disturbances in the spinal cord injured: an epidemiological questionnaire investigation, including a normal population. *Spinal Cord.* 2001;39(10):505–513. doi:10.1038/sj.sc.3101197
35. Raffaelli W, Minella CE, Magnani F, Sarti D. Population-based study of central post-stroke pain in Rimini district, Italy. *J Pain Res.* 2013;6:705–711. doi:10.2147/JPR.S46553
36. Abdullah H, Jalil SZA, Noor NM, Amran ME. Sleep Apnea Prediction in the Post-Stroke Patient based on the Sleep, Pain and Depression Parameters. 2023 IEEE 2nd National Biomedical Engineering Conference (NBEC); IEEE; 2023.
37. Kaur T, Shih H-C, Huang ACW, Shyu B-C. Modulation of melatonin to the thalamic lesion-induced pain and comorbid sleep disturbance in the animal model of the central post-stroke hemorrhage. *Mol Pain.* 2022;18:17448069221127180. doi:10.1177/17448069221127180
38. Stanton BR, Barnes F, Silber E. Sleep and fatigue in multiple sclerosis. *Mult Scler J.* 2006;12(4):481–486. doi:10.1191/135248506ms1320oa
39. Scholz J, Finnerup NB, Attal N. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. *Pain.* 2019;160(1):53–59. doi:10.1097/j.pain.0000000000001365
40. Todd AJ, Wang F. Central nervous system pain pathways. In: *The Oxford Handbook of the Neurobiology of Pain.* Oxford, UK: Oxford University Press; 2018.
41. Carpenter MB, Sutin J. Human neuroanatomy. 1983.
42. Jones AKP, Kulkarni B, Derbyshire SWG. Pain mechanisms and their disorders. *Br Med Bul.* 2003;65:83–93. doi:10.1093/bmb/65.1.83
43. Lenz FA, Weiss N, Ohara S, Lawson C, Greenspan JD. The role of the thalamus in pain. In: Hallett M, Phillips LH, Schomer DL, Massey JM, editors. *Supplements to Clinical Neurophysiology.* Vol. 57. Elsevier; 2004:50–61.
44. Craig AD, Chen K, Bandy D, Reiman EM. Thermosensory activation of insular cortex. *Nat Neurosci.* 2000;3(2):184–190. doi:10.1038/72131
45. Coghill RC, Sang CN, Maisog JM, Iadarola MJ. Pain intensity processing within the human brain: a bilateral, distributed mechanism. *J Neurophysiol.* 1999;82(4):1934–1943. doi:10.1152/jn.1999.82.4.1934
46. Alkire MT, White NS, Hsieh R, Haier RJ. Dissociable brain activation responses to 5-Hz electrical pain stimulation: a high-field functional magnetic resonance imaging study. *J Am Soc Anesthesiologists.* 2004;100(4):939–946.
47. Ostrowsky K, Magnin M, Ryvlin P, Isnard J, Guenot M, Mauguière F. Representation of pain and somatic sensation in the human insula: a study of responses to direct electrical cortical stimulation. *Cereb Cortex.* 2002;12(4):376–385. doi:10.1093/cercor/12.4.376
48. Kortz MW, Lillehei KO. Insular cortex. 2021.
49. Lu C, Yang T, Zhao H. Insular cortex is critical for the perception, modulation, and chronification of pain. *Neurosci Bull.* 2016;32(2):191–201. doi:10.1007/s12264-016-0016-y
50. Labrakakis C. The role of the insular cortex in pain. *Int J Mol Sci.* 2023;24(6):5736. doi:10.3390/ijms24065736
51. Mazzola L, Isnard J, Mauguière F. Somatosensory and pain responses to stimulation of the second somatosensory area (SII) in humans. A comparison with SI and insular responses. *Cereb Cortex.* 2006;16(7):960–968. doi:10.1093/cercor/bhj038
52. Segerdahl AR, Mezue M, Okell TW, Farrar JT, Tracey I. The dorsal posterior insula subserves a fundamental role in human pain. *Nat Neurosci.* 2015;18(4):499–500. doi:10.1038/nn.3969
53. Stancak A, Fallon N. Emotional modulation of experimental pain: a source imaging study of laser evoked potentials. *Front Human Neurosci.* 2013;7:552. doi:10.3389/fnhum.2013.00552
54. Kong J, White NS, Kwong KK. Using fMRI to dissociate sensory encoding from cognitive evaluation of heat pain intensity. *Human Brain Mapp.* 2006;27(9):715–721. doi:10.1002/hbm.20213
55. Gu X, Gao Z, Wang X. Anterior insular cortex is necessary for empathetic pain perception. *Brain.* 2012;135(9):2726–2735. doi:10.1093/brain/aww199
56. Al-Khatir KM, Todd AJ. Collateral projections of neurons in laminae I, III, and IV of rat spinal cord to thalamus, periaqueductal gray matter, and lateral parabrachial area. *J Comp Neurol.* 2009;515(6):629–646. doi:10.1002/cne.22081
57. Geerling JC, Yokota S, Rukhadze I, Roe D, Chamberlin NL. Kölliker–Fuse GABAergic and glutamatergic neurons project to distinct targets. *J Comp Neurol.* 2017;525(8):1844–1860. doi:10.1002/cne.24164
58. Chiang MC, Bowen A, Schier LA, Tupone D, Uddin O, Heinricher MM. Parabrachial complex: a hub for pain and aversion. *J Neurosci.* 2019;39(42):8225–8230. doi:10.1523/JNEUROSCI.1162-19.2019
59. Han S, Soleiman MT, Soden ME, Zweifel LS, Palmiter RD. Elucidating an affective pain circuit that creates a threat memory. *Cell.* 2015;162(2):363–374. doi:10.1016/j.cell.2015.05.057
60. Sun L, Liu R, Guo F, et al. Parabrachial nucleus circuit governs neuropathic pain-like behavior. *Nat Commun.* 2020;11(1):5974. doi:10.1038/s41467-020-19767-w
61. Asano H, Arima Y, Yokota S, Fujitani M. New nociceptive circuits to the hypothalamic perifornical area from the spinal cord and spinal trigeminal nucleus via the parabrachial nucleus. *Biochem Biophys Res Commun.* 2019;512(4):705–711. doi:10.1016/j.bbrc.2019.02.153
62. Niu J-G, Yokota S, Tsumori T, Qin Y, Yasui Y. Glutamatergic lateral parabrachial neurons innervate orexin-containing hypothalamic neurons in the rat. *Brain Res.* 2010;1358:110–122. doi:10.1016/j.brainres.2010.08.056
63. Gauriau C, Bernard J-F. Pain pathways and parabrachial circuits in the rat. *Exp Physiol.* 2002;87(2):251–258. doi:10.1113/eph8702357
64. Dostrovsky JO. Role of thalamus in pain. In: *Progress in Brain Research.* Vol. 129. Elsevier; 2000:245–257.
65. LaGraize SC, Labuda CJ, Rutledge MA, Jackson RL, Fuchs PN. Differential effect of anterior cingulate cortex lesion on mechanical hypersensitivity and escape/avoidance behavior in an animal model of neuropathic pain. *Exp Neurol.* 2004;188(1):139–148. doi:10.1016/j.expneurol.2004.04.003
66. Mal J-H, Xiaol T-H, Changl C-W. Activation of anterior cingulate cortex produces inhibitory effects on noxious mechanical and electrical stimuli-evoked responses in rat spinal WDR neurons. *Eur J Pain.* 2011;15(9):895–899. doi:10.1016/j.ejpain.2011.04.003
67. LaBuda CJ, Fuchs PN. Attenuation of negative pain affect produced by unilateral spinal nerve injury in the rat following anterior cingulate cortex activation. *Neuroscience.* 2005;136(1):311–322. doi:10.1016/j.neuroscience.2005.07.010
68. Terrier L-M, Hadjikhani N, Destrieux C. The trigeminal pathways. *J Neurol.* 2022;269(7):3443–3460. doi:10.1007/s00415-022-11002-4



69. Katagiri A, Kato T. Multi-dimensional role of the parabrachial nucleus in regulating pain-related affective disturbances in trigeminal neuropathic pain. *J Oral Sci.* **2020**;62(2):160–164. doi:10.2334/josnusd.19-0432
70. Rodriguez E, Sakurai K, Xu J. A craniofacial-specific monosynaptic circuit enables heightened affective pain. *Nat Neurosci.* **2017**;20(12):1734–1743. doi:10.1038/s41593-017-0012-1
71. Tortorici V, Morgan MM. Comparison of morphine and kainic acid microinjections into identical PAG sites on the activity of RVM neurons. *J Neurophysiol.* **2002**;88(4):1707–1715. doi:10.1152/jn.2002.88.4.1707
72. Morgan MM, Whittier KL, Hegarty DM, Aicher SA. Periaqueductal gray neurons project to spinally projecting GABAergic neurons in the rostral ventromedial medulla. *Pain.* **2008**;140(2):376–386. doi:10.1016/j.pain.2008.09.009
73. Samineni VK, Grajales-Reyes JG, Copits BA. Divergent modulation of nociception by glutamatergic and GABAergic neuronal subpopulations in the periaqueductal gray. *eNeuro.* **2017**;4(2). doi:10.1523/ENEURO.0129-16.2017
74. Bardin L. The complex role of serotonin and 5-HT receptors in chronic pain. *Behav Pharmacol* **2011**;22(5 and 6):390–404. doi:10.1097/FBP.0b013e328349aae4
75. Li Y-Q, Takada M, Shinonaga Y, Mizuno N. Collateral projections of single neurons in the nucleus raphe magnus to both the sensory trigeminal nuclei and spinal cord in the rat. *Brain Res.* **1993**;602(2):331–335. doi:10.1016/0006-8993(93)90698-M
76. Fields HL, Basbaum AI, Clanton CH, Anderson SD. Nucleus raphe magnus inhibition of spinal cord dorsal horn neurons. *Brain Res.* **1977**;126(3):441–453. doi:10.1016/0006-8993(77)90596-0
77. Jeong HJ, Mitchell VA, Vaughan CW. Role of 5-HT1 receptor subtypes in the modulation of pain and synaptic transmission in rat spinal superficial dorsal horn. *Br J Pharmacol* **2012**;165(6):1956–1965. doi:10.1111/j.1476-5381.2011.01685.x
78. Alhaider AA, Lei SZ, Wilcox GL. Spinal 5-HT3 receptor-mediated antinociception: possible release of GABA. *J Neurosci.* **1991**;11(7):1881–1888. doi:10.1523/JNEUROSCI.11-07-01881.1991
79. Behbehani MM, Fields HL. Evidence that an excitatory connection between the periaqueductal gray and nucleus raphe magnus mediates stimulation produced analgesia. *Brain Res.* **1979**;170(1):85–93. doi:10.1016/0006-8993(79)90942-9
80. Panneton WM, Gan Q, Livergood RS. A trigeminoreticular pathway: implications in pain. *PLoS One.* **2011**;6(9):e24499. doi:10.1371/journal.pone.0024499
81. Westlund K, Craig A. Association of spinal lamina I projections with brainstem catecholamine neurons in the monkey. *Exp Brain Res.* **1996**;110:151–162. doi:10.1007/BF00228547
82. Hickey L, Li Y, Fyson SJ. Optoactivation of locus ceruleus neurons evokes bidirectional changes in thermal nociception in rats. *J Neurosci.* **2014**;34(12):4148–4160. doi:10.1523/JNEUROSCI.4835-13.2014
83. Suárez-Pereira I, Llorca-Torrallba M, Bravo L, Camarena-Delgado C, Soriano-Mas C, Berrocoso E. The role of the locus coeruleus in pain and associated stress-related disorders. *Biol Psychiatry.* **2022**;91(9):786–797. doi:10.1016/j.biopsych.2021.11.023
84. Jones SL. Descending noradrenergic influences on pain. In: Barnes CD, Pompeiano O, editors. *Progress in Brain Research.* Vol. 88. Elsevier; **1991**:381–394.
85. Brightwell JJ, Taylor BK. Noradrenergic neurons in the locus coeruleus contribute to neuropathic pain. *Neuroscience.* **2009**;160(1):174–185. doi:10.1016/j.neuroscience.2009.02.023
86. Taylor BK, Westlund KN. The noradrenergic locus coeruleus as a chronic pain generator. *J Neurosci Res.* **2017**;95(6):1336–1346. doi:10.1002/jnr.23956
87. Almeida A, Cobos A, Tavares I, Lima D. Brain afferents to the medullary dorsal reticular nucleus: a retrograde and anterograde tracing study in the rat. *Eur J Neurosci.* **2002**;16(1):81–95. doi:10.1046/j.1460-9568.2002.02058.x
88. Martins I, Carvalho P, de Vries MG. Increased noradrenergic neurotransmission to a pain facilitatory area of the brain is implicated in facilitation of chronic pain. *Anesthesiology.* **2015**;123(3):642–653. doi:10.1097/ALN.0000000000000749
89. Martins I, Costa-Araújo S, Fadel J, Wilson SP, Lima D, Tavares I. Reversal of neuropathic pain by HSV-1-mediated decrease of noradrenaline in a pain facilitatory area of the brain. *Pain.* **2010**;151(1):137–145. doi:10.1016/j.pain.2010.06.027
90. Kaushal R, Taylor BK, Jamal A. GABA-A receptor activity in the noradrenergic locus coeruleus drives trigeminal neuropathic pain in the rat; contribution of NMDA receptors in the medial prefrontal cortex. *Neuroscience.* **2016**;334:148–159. doi:10.1016/j.neuroscience.2016.08.005
91. Borbély AA. A two process model of sleep regulation. *Hum Neurobiol.* **1982**;1(3):195–204.
92. Borbély AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *J Sleep Res.* **2016**;25(2):131–143. doi:10.1111/jsr.12371
93. Borbély AA. Refining sleep homeostasis in the two-process model. *J Sleep Res.* **2009**;18(1):1–2. doi:10.1111/j.1365-2869.2009.00750.x
94. Dunwiddie TV, Masino SA. The role and regulation of adenosine in the central nervous system. *Annual Rev Neurosci.* **2001**;24(1):31–55. doi:10.1146/annurev.neuro.24.1.31
95. Latini S, Pedata F. Adenosine in the central nervous system: release mechanisms and extracellular concentrations. *J Neurochem.* **2001**;79(3):463–484.
96. Palmer T, Stiles G. Adenosine receptors. *Neuropharmacology.* **1995**;34(7):683–694. doi:10.1016/0028-3908(95)00044-7
97. Porkka-Heiskanen T, Alanko L, Kalinchuk A, Stenberg D. Adenosine and sleep. *Sleep Med Rev.* **2002**;6(4):321–332. doi:10.1053/smr.2001.0201
98. Malpaux B, Migaud M, Tricoire H, Chemineau P. Biology of mammalian photoperiodism and the critical role of the pineal gland and melatonin. *J Biol Rhythms.* **2001**;16(4):336–347. doi:10.1177/074873001129002051
99. Hildebrand GD, Fielder AR. Anatomy and physiology of the retina. *Pediatric Retina.* **2011**;2011:39–65.
100. Mure LS. Intrinsically photosensitive retinal ganglion cells of the human retina. *Front Neurol.* **2021**;12:636330. doi:10.3389/fneur.2021.636330
101. Meijer JH, Schwartz WJ. In search of the pathways for light-induced pacemaker resetting in the suprachiasmatic nucleus. *J Biol Rhythms.* **2003**;18(3):235–249. doi:10.1177/0748730403018003006
102. Chiou -Y-Y, Yang Y, Rashid N, Ye R, Selby CP, Sancar A. Mammalian period represses and de-represses transcription by displacing CLOCK–BMAL1 from promoters in a Cryptochrome-dependent manner. *Proc Natl Acad Sci.* **2016**;113(41):E6072–E6079. doi:10.1073/pnas.1612917113
103. Lande-Diner L, Boyault C, Kim JY, Weitz CJ. A positive feedback loop links circadian clock factor CLOCK-BMAL1 to the basic transcriptional machinery. *Proc Natl Acad Sci.* **2013**;110(40):16021–16026. doi:10.1073/pnas.1305980110

104. Trott AJ, Menet JS. Regulation of circadian clock transcriptional output by CLOCK: BMAL1. *PLoS Genetics*. 2018;14(1):e1007156. doi:10.1371/journal.pgen.1007156
105. Dubocovich ML, Benloucif S, Masana MI. Melatonin receptors in the mammalian suprachiasmatic nucleus. *Behav. Brain Res.* 1995;73(1–2):141–147. doi:10.1016/0166-4328(96)00086-1
106. Dubocovich ML. Melatonin receptors: role on sleep and circadian rhythm regulation. *Sleep Med.* 2007;8:34–42. doi:10.1016/j.sleep.2007.10.007
107. Glass JD, Lynch GR. Melatonin: identification of sites of antigonadal action in mouse brain. *Science*. 1981;214(4522):821–823. doi:10.1126/science.7292016
108. Vaněček J, Pavlik A, Illnerová H. Hypothalamic melatonin receptor sites revealed by autoradiography. *Brain Res.* 1987;435(1–2):359–362. doi:10.1016/0006-8993(87)91625-8
109. Drew VJ, Lee JM, Kim T. Optogenetics: solving the enigma of sleep. *Sleep Med Res.* 2018;9(1):1–10. doi:10.17241/smr.2018.00178
110. Fuller P, Sherman D, Pedersen NP, Saper CB, Lu J. Reassessment of the structural basis of the ascending arousal system. *J Comp Neurol.* 2011;519(5):933–956. doi:10.1002/cne.22559
111. Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature*. 2005;437(7063):1257–1263. doi:10.1038/nature04284
112. Gerashchenko D, Wisor JP, Burns D. Identification of a population of sleep-active cerebral cortex neurons. *Proc Natl Acad Sci.* 2008;105(29):10227–10232. doi:10.1073/pnas.0803125105
113. Morairty SR, Ditttrich L, Pasumarthi RK. A role for cortical nNOS/NK1 neurons in coupling homeostatic sleep drive to EEG slow wave activity. *Proc Natl Acad Sci.* 2013;110(50):20272–20277. doi:10.1073/pnas.1314762110
114. Van Dort CJ, Zachs DP, Kenny JD. Optogenetic activation of cholinergic neurons in the PPT or LDT induces REM sleep. *Proc Natl Acad Sci.* 2015;112(2):584–589. doi:10.1073/pnas.1423136112
115. Thakkar M, Portas C, McCarley RW. Chronic low-amplitude electrical stimulation of the laterodorsal tegmental nucleus of freely moving cats increases REM sleep. *Brain Res.* 1996;723(1–2):223–227. doi:10.1016/0006-8993(96)00256-9
116. Benarroch EE. Periaqueductal gray: an interface for behavioral control. *Neurology*. 2012;78(3):210–217. doi:10.1212/WNL.0b013e31823fcdde
117. Krause AJ, Prather AA, Wager TD, Lindquist MA, Walker MP. The pain of sleep loss: a brain characterization in humans. *J Neurosci.* 2019;39(12):2291–2300. doi:10.1523/JNEUROSCI.2408-18.2018
118. Foo H, Mason P. Brainstem modulation of pain during sleep and waking. *Sleep Med Rev.* 2003;7(2):145–154. doi:10.1053/smr.2002.0224
119. Becerra L, Chang P, Bishop J, Borsook D. CNS activation maps in awake rats exposed to thermal stimuli to the dorsum of the hindpaw. *Neuroimage*. 2011;54(2):1355–1366. doi:10.1016/j.neuroimage.2010.08.056
120. Millan MJ. Descending control of pain. *Progress Neurobiol.* 2002;66(6):355–474. doi:10.1016/s0301-0082(02)00009-6
121. Lu J, Jhou TC, Saper CB. Identification of wake-active dopaminergic neurons in the ventral periaqueductal gray matter. *J Neurosci.* 2006;26(1):193–202. doi:10.1523/JNEUROSCI.2244-05.2006
122. Weber F, Hoang Do JP, Chung S. Regulation of REM and non-REM sleep by periaqueductal GABAergic neurons. *Nat Commun.* 2018;9(1):354. doi:10.1038/s41467-017-02765-w
123. Kaur S, Thankachan S, Begum S, Liu M, Blanco-Centurion C, Shiromani PJ. Hypocretin-2 saporin lesions of the ventrolateral periaqueductal gray (vlPAG) increase REM sleep in hypocretin knockout mice. *PLoS One*. 2009;4(7):e6346. doi:10.1371/journal.pone.0006346
124. Tomim DH, Pontarolla FM, Bertolini JF. The pronociceptive effect of paradoxical sleep deprivation in rats: evidence for a role of descending pain modulation mechanisms. *Mol Neurobiol.* 2016;53:1706–1717. doi:10.1007/s12035-014-9059-0
125. Skinner GO, Damasceno F, Gomes A, de Almeida OM. Increased pain perception and attenuated opioid antinociception in paradoxical sleep-deprived rats are associated with reduced tyrosine hydroxylase staining in the periaqueductal gray matter and are reversed by L-DOPA. *Pharmacol Biochem Behav.* 2011;99(1):94–99. doi:10.1016/j.pbb.2011.04.009
126. Kim SH, Park JY, Shin HE. The influence of rapid eye movement sleep deprivation on nociceptive transmission and the duration of facial allodynia in rats: a behavioral and Fos immunohistochemical study. *J Headache Pain.* 2019;20(1):21. doi:10.1186/s10194-019-0977-0
127. Sardi NF, Lazzarini MK, Guilhen VA. Chronic sleep restriction increases pain sensitivity over time in a periaqueductal gray and nucleus accumbens dependent manner. *Neuropharmacology*. 2018;139:52–60. doi:10.1016/j.neuropharm.2018.06.022
128. Maret S, Dorsaz S, Gurcel L. Homer1a is a core brain molecular correlate of sleep loss. *Proc Natl Acad Sci.* 2007;104(50):20090–20095. doi:10.1073/pnas.0710131104
129. Zhu J, Hafycz J, Keenan BT, Guo X, Pack A, Naidoo N. Acute sleep loss upregulates the synaptic scaffolding protein, Homer1a, in non-canonical sleep/wake brain regions, claustrum, piriform and cingulate cortices. *Front Neurosci.* 2020;14:188. doi:10.3389/fnins.2020.00188
130. Diering GH, Nirujogi RS, Roth RH, Worley PF, Pandey A, Hugarir RL. Homer1a drives homeostatic scaling-down of excitatory synapses during sleep. *Science*. 2017;355(6324):511–515. doi:10.1126/science.aai8355
131. Ueta Y, Yamamoto R, Sugiura S, Inokuchi K, Homer KN. 1a suppresses neocortex long-term depression in a cortical layer-specific manner. *J Neurophysiol.* 2008;99(2):950–957. doi:10.1152/jn.01101.2007
132. Ronesi JA, Huber KM. Homer interactions are necessary for metabotropic glutamate receptor-induced long-term depression and translational activation. *J Neurosci.* 2008;28(2):543. doi:10.1523/JNEUROSCI.5019-07.2008
133. Chung G, Shim HG, Kim CY. Persistent activity of metabotropic glutamate receptor 5 in the periaqueductal gray constrains emergence of chronic neuropathic pain. *Curr Biol.* 2020;30(23):4631–4642. doi:10.1016/j.cub.2020.09.008
134. Breton-Provencher V, Sur M. Active control of arousal by a locus coeruleus GABAergic circuit. *Nat Neurosci.* 2019;22(2):218–228. doi:10.1038/s41593-018-0305-z
135. Gervasoni D, Darracq L, Fort P, Soulière F, Chouvet G, Luppi PH. Electrophysiological evidence that noradrenergic neurons of the rat locus coeruleus are tonically inhibited by GABA during sleep. *Eur J Neurosci.* 1998;10(3):964–970. doi:10.1046/j.1460-9568.1998.00106.x
136. Basheer R, Mager M, McCarley RW, Shiromani PJ. REM sleep deprivation increases the levels of tyrosine hydroxylase and norepinephrine transporter mRNA in the locus coeruleus. *Mol Brain Res.* 1998;57(2):235–240. doi:10.1016/S0169-328X(98)00088-6
137. Somarajan BI, Khanday MA, Mallick BN. Rapid eye movement sleep deprivation induces neuronal apoptosis by noradrenaline acting on Alpha1 adrenoceptor and by triggering mitochondrial intrinsic pathway. *Front Neurol.* 2016;7:25. doi:10.3389/fneur.2016.00025



138. Willis WD, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol.* 1997;14(1):2–31. doi:10.1097/00004691-199701000-00002
139. Li J, Wei Y, Zhou J. Activation of locus coeruleus-spinal cord noradrenergic neurons alleviates neuropathic pain in mice via reducing neuroinflammation from astrocytes and microglia in spinal dorsal horn. *J Neuroinflammation.* 2022;19(1):123. doi:10.1186/s12974-022-02489-9
140. Kimura M, Suto T, Morado-Urbina CE, Peters CM, Eisenach JC, Hayashida K. Impaired pain-evoked analgesia after nerve injury in rats reflects altered glutamate regulation in the locus coeruleus. *Anesthesiology.* 2015;123(4):899–908. doi:10.1097/ALN.0000000000000796
141. Meisner JG, Marsh AD, Marsh DR. Loss of GABAergic interneurons in laminae I–III of the spinal cord dorsal horn contributes to reduced GABAergic tone and neuropathic pain after spinal cord injury. *J Neurotrauma.* 2010;27(4):729–737. doi:10.1089/neu.2009.1166
142. Modirrousta M, Mainville L, Jones BE. Orexin and MCH neurons express c-Fos differently after sleep deprivation vs. recovery and bear different adrenergic receptors. *Eur J Neurosci.* 2005;21(10):2807–2816. doi:10.1111/j.1460-9568.2005.04104.x
143. Aby F. Serotonergic neurons of the nucleus raphe Magnus in the control of nociceptive transmission in the dorsal horn of the spinal cord: an optogenetic study in different pathophysiological contexts [dissertation]. Accra: Université de Bordeaux; 2019.
144. Bardoni R. Serotonergic modulation of nociceptive circuits in spinal cord dorsal horn. *Curr Neuropharmacol.* 2019;17(12):1133–1145. doi:10.2174/1570159X17666191001123900
145. Millan MJ. Serotonin and pain: evidence that activation of 5-HT_{1A} receptors does not elicit antinociception against noxious thermal, mechanical and chemical stimuli in mice. *Pain.* 1994;58(1):45–61. doi:10.1016/0304-3959(94)90184-8
146. Kuner R. Central mechanisms of pathological pain. *Nature Med.* 2010;16(11):1258–1266. doi:10.1038/nm.2231
147. Rahman W, Suzuki R, Rygh LJ, Dickenson AH. Descending serotonergic facilitation mediated through rat spinal 5HT₃ receptors is unaltered following carrageenan inflammation. *Neurosci Lett.* 2004;361(1):229–231. doi:10.1016/j.neulet.2003.12.069
148. Cortes-Altamirano JL, Olmos-Hernandez A, Jaime HB. 5-HT₁, 5-HT₂, 5-HT₃ and 5-HT₇ receptors and their role in the modulation of pain response in the central nervous system. *Curr Neuropharmacol.* 2018;16(2):210–221. doi:10.2174/1570159X15666170911121027
149. Wu W-P, Hao J-X, Xu X-J, Wiesenfeld-Hallin Z, Koek W, Colpaert FC. The very-high-efficacy 5-HT_{1A} receptor agonist, F 13640, preempts the development of allodynia-like behaviors in rats with spinal cord injury. *Eur J Pharmacol.* 2003;478(2–3):131–137. doi:10.1016/j.ejphar.2003.08.047
150. Sprouse JS, Aghajanian GK. Electrophysiological responses of serotonergic dorsal raphe neurons to 5-HT_{1A} and 5-HT_{1B} agonists. *Synapse.* 1987;1(1):3–9. doi:10.1002/syn.890010103
151. Wei H, Pertovaara A. 5-HT_{1A} receptors in endogenous regulation of neuropathic hypersensitivity in the rat. *Eur J Pharmacol.* 2006;535(1–3):157–165. doi:10.1016/j.ejphar.2006.02.019
152. Blanco-Centurion CA, Salin-Pascual RJ. Extracellular serotonin levels in the medullary reticular formation during normal sleep and after REM sleep deprivation. *Brain Res.* 2001;923(1–2):128–136. doi:10.1016/S0006-8993(01)03209-7
153. Roman V, Walstra I, Luiten PG, Meerlo P. Too little sleep gradually desensitizes the serotonin 1A receptor system. *Sleep.* 2005;28(12):1505–1510.
154. Román V, Hagevoud R, Luiten PG, Meerlo P. Differential effects of chronic partial sleep deprivation and stress on serotonin-1A and muscarinic acetylcholine receptor sensitivity. *J Sleep Res.* 2006;15(4):386–394. doi:10.1111/j.1365-2869.2006.00555.x
155. Gear RW, Levine JD. Nucleus accumbens facilitates nociception. *Exp Neurol.* 2011;229(2):502–506. doi:10.1016/j.expneurol.2011.03.021
156. Tobaldini G, Aisengart B, Lima MM, Tambeli CH, Fischer L. Ascending nociceptive control contributes to the antinociceptive effect of acupuncture in a rat model of acute pain. *J Pain.* 2014;15(4):422–434. doi:10.1016/j.jpain.2013.12.008
157. Oishi Y, Lazarus M. The control of sleep and wakefulness by mesolimbic dopamine systems. *Neurosci Res.* 2017;118:66–73. doi:10.1016/j.neures.2017.04.008
158. Valencia Garcia S, Fort P. Nucleus Accumbens, a new sleep-regulating area through the integration of motivational stimuli. *Acta Pharmacol Sin.* 2018;39(2):165–166. doi:10.1038/aps.2017.168
159. Wang Y, Liu Z, Cai L, Guo R, Dong Y, Huang YH. A critical role of basolateral amygdala-to-nucleus accumbens projection in sleep regulation of reward seeking. *Biol Psychiatry.* 2020;87(11):954–966. doi:10.1016/j.biopsych.2019.10.027
160. Liu Z, Wang Y, Cai L, et al. Prefrontal cortex to accumbens projections in sleep regulation of reward. *J Neurosci.* 2016;36(30):7897. doi:10.1523/JNEUROSCI.0347-16.2016
161. Lazarus M, Chen J-F, Urade Y, Huang Z-L. Role of the basal ganglia in the control of sleep and wakefulness. *Curr Opin Neurobiol.* 2013;23(5):780–785. doi:10.1016/j.conb.2013.02.001
162. Blom SM, Pfister J-P, Santello M, Senn W, Nevian T. Nerve injury-induced neuropathic pain causes disinhibition of the anterior cingulate cortex. *J Neurosci.* 2014;34(17):5754. doi:10.1523/JNEUROSCI.3667-13.2014
163. Chen T, Koga K, Descalzi G. Postsynaptic potentiation of corticospinal projecting neurons in the anterior cingulate cortex after nerve injury. *Mol Pain.* 2014;10:1744–8069. doi:10.1186/1744-8069-10-33
164. Zhao R, Zhou H, Huang L. Neuropathic pain causes pyramidal neuronal hyperactivity in the anterior cingulate cortex. *Front Cell Neurosci.* 2018;12:107. doi:10.3389/fncel.2018.00107
165. Narita M, Niikura K, Nanjo-Niikura K. Sleep disturbances in a neuropathic pain-like condition in the mouse are associated with altered GABAergic transmission in the cingulate cortex. *Pain.* 2011;152(6):1358–1372. doi:10.1016/j.pain.2011.02.016
166. Park S, Kang I, Edden RAE, Namgung E, Kim J, Kim J. Shorter sleep duration is associated with lower GABA levels in the anterior cingulate cortex. *Sleep Med.* 2020;71:1–7. doi:10.1016/j.sleep.2020.02.018
167. Ma C, Zhong P, Liu D. Sleep regulation by neurotensinergic neurons in a thalamo-amygdala circuit. *Neuron.* 2019;103(2):323–334. doi:10.1016/j.neuron.2019.05.015
168. Hoda P, Mahdih F, Alireza I. Acute sleep deprivation decreases anxiety behavior via γ -aminobutyric acid-A receptor activation in central nucleus of amygdala. *J Sleep Sci.* 2017;1(4):139–142.
169. Liang S-H, Zhao W-J, Yin J-B. A neural circuit from thalamic paraventricular nucleus to central amygdala for the facilitation of neuropathic pain. *J Neurosci.* 2020;40(41):7837–7854. doi:10.1523/JNEUROSCI.2487-19.2020
170. Pacheco SR, Miranda AM, Coelho R, Monteiro AC, Bragança G, Loureiro HC. Overweight in youth and sleep quality: is there a link? *Arch Endocrinol Metabol.* 2017;61:367–373. doi:10.1590/2359-3997000000265

171. Couto LB, Moroni CR, Dos Reis Ferreira CM. Descriptive and functional neuroanatomy of locus coeruleus-noradrenaline-containing neurons involvement in bradykinin-induced antinociception on principal sensory trigeminal nucleus. *J Chem Neuroanatomy*. 2006;32(1):28–45. doi:10.1016/j.jchemneu.2006.03.003
172. Alba-Delgado C, Mico JA, Berrocoso E. Neuropathic pain increases spontaneous and noxious-evoked activity of locus coeruleus neurons. *Prog Neuro Psychopharmacol Biol Psychiatry*. 2021;105:110121. doi:10.1016/j.pnpbp.2020.110121
173. Viisanen H, Pertovaara A. Influence of peripheral nerve injury on response properties of locus coeruleus neurons and coeruleospinal antinociception in the rat. *Neuroscience*. 2007;146(4):1785–1794. doi:10.1016/j.neuroscience.2007.03.016
174. Krohn F, Lancini E, Ludwig M. Noradrenergic neuromodulation in ageing and disease. *Neurosci Biobehav Rev*. 2023;152:105311.
175. Chamberlain SR, Robbins TW. Noradrenergic modulation of cognition: therapeutic implications. *J Psychopharmacol*. 2013;27(8):694–718. doi:10.1177/0269881113480988
176. Cruccu G, Aziz T, Garcia-Larrea L. EFNS guidelines on neurostimulation therapy for neuropathic pain. *Eur J Neurol*. 2007;14(9):952–970. doi:10.1111/j.1468-1331.2007.01916.x
177. Cruccu G, Garcia-Larrea L, Hansson P. EAN guidelines on central neurostimulation therapy in chronic pain conditions. *Eur J Neurol*. 2016;23(10):1489–1499. doi:10.1111/ene.13103
178. Edwards CA, Kouzani A, Lee KH, Ross EK. Neurostimulation devices for the treatment of neurologic disorders. *Mayo Clin Proc*. 2017;92:1427–1444. doi:10.1016/j.mayocp.2017.05.005
179. Fischer TZ, Tan AM, Waxman SG. Thalamic neuron hyperexcitability and enlarged receptive fields in the STZ model of diabetic pain. *Brain Res*. 2009;1268:154–161. doi:10.1016/j.brainres.2009.02.063
180. Freeman OJ, Evans MH, Cooper GJ, Petersen RS, Gardiner NJ. Thalamic amplification of sensory input in experimental diabetes. *Eur J Neurosci*. 2016;44(1):1779–1786. doi:10.1111/ejn.13267
181. Han J, Xie Q, Wu X. The neural correlates of arousal: ventral posterolateral nucleus-global transient co-activation. *Cell Rep*. 2024;43(1):113633. doi:10.1016/j.celrep.2023.113633
182. Benarroch EE. Parabrachial nuclear complex: multiple functions and potential clinical implications. *Neurology*. 2016;86(7):676–683. doi:10.1212/WNL.0000000000002393
183. Kaur S, Pedersen NP, Yokota S. Glutamatergic signaling from the parabrachial nucleus plays a critical role in hypercapnic arousal. *J Neurosci*. 2013;33(18):7627–7640. doi:10.1523/JNEUROSCI.0173-13.2013
184. Yokota S, Kaur S, VanderHorst VG, Saper CB, Chamberlin NL. Respiratory-related outputs of glutamatergic, hypercapnia-responsive parabrachial neurons in mice. *J Comp Neurol*. 2015;523(6):907–920. doi:10.1002/cne.23720
185. Park A, Uddin O, Li Y, Masri R, Keller A. Pain after spinal cord injury is associated with abnormal presynaptic inhibition in the posterior nucleus of the thalamus. *J Pain*. 2018;19(7):727.e1. doi:10.1016/j.jpain.2018.02.002
186. Gerke MB, Duggan AW, Xu L, Siddall PJ. Thalamic neuronal activity in rats with mechanical allodynia following contusive spinal cord injury. *Neuroscience*. 2003;117(3):715–722. doi:10.1016/S0306-4522(02)00961-2
187. Gustin SM, Wrigley PJ, Youssef AM. Thalamic activity and biochemical changes in individuals with neuropathic pain after spinal cord injury. *Pain*. 2014;155(5):1027–1036. doi:10.1016/j.pain.2014.02.008
188. Jan JE, Reiter RJ, Wasdell MB, Bax M. The role of the thalamus in sleep, pineal melatonin production, and circadian rhythm sleep disorders. *J Pineal Res*. 2009;46(1):1–7. doi:10.1111/j.1600-079X.2008.00628.x
189. Gent TC, Bassetti CL, Adamantidis AR. Sleep-wake control and the thalamus. *Curr Opin Neurobiol*. 2018;52:188–197. doi:10.1016/j.conb.2018.08.002
190. Truini A, Barbanti P, Pozzilli C, Cruccu G. A mechanism-based classification of pain in multiple sclerosis. *J Neurol*. 2013;260:351–367. doi:10.1007/s00415-012-6579-2
191. McBenedict B, Goh KS, Yau RCC. Neuropathic pain secondary to multiple sclerosis: a narrative review. *Cureus*. 2024;16(6):e61587. doi:10.7759/cureus.61587
192. Beersma DG, Gordijn MC. Circadian control of the sleep–wake cycle. *Physiol Behav*. 2007;90(2–3):190–195. doi:10.1016/j.physbeh.2006.09.010
193. Sen A, Hoffmann HM. Role of core circadian clock genes in hormone release and target tissue sensitivity in the reproductive axis. *Mol Cell Endocrinol*. 2020;501:110655. doi:10.1016/j.mce.2019.110655
194. Kräuchi K. How is the circadian rhythm of core body temperature regulated? *Clin Auton Res*. 2002;12(3):147–149. doi:10.1007/s10286-002-0043-9
195. Scheiermann C, Kunisaki Y, Frenette PS. Circadian control of the immune system. *Nat Rev Immunol*. 2013;13(3):190–198. doi:10.1038/nri3386
196. Daguette I, Raverot V, Bouhassira D, Gronfier C. Circadian rhythmicity of pain sensitivity in humans. *Brain*. 2022;145(9):3225–3235. doi:10.1093/brain/awac147
197. Hagenauer MH, Crodelle JA, Piltz SH, Toporikova N, Ferguson P, Booth V. The modulation of pain by circadian and sleep-dependent processes: a review of the experimental evidence. In: *Women in Mathematical Biology: Research Collaboration Workshop*. NIMBioS, Knoxville: Springer International Publishing; 2017.
198. Segal JP, Tresidder KA, Bhatt C, Gilron I, Ghasemlou N. Circadian control of pain and neuroinflammation. *J Neurosci Res*. 2018;96(6):1002–1020. doi:10.1002/jnr.24150
199. Asai MM, Mayagoitia LL, Garcia DD, Matamoros-Trejo G-TG, Valdés-Tovar M-TM, Leff PP. Rat brain opioid peptides-circadian rhythm is under control of melatonin. *Neuropeptides*. 2007;41(6):389–397. doi:10.1016/j.npep.2007.09.001
200. Asai M, Valdés-Tovar M, Matamoros-Trejo G, García D. Melatonin induces enkephalins synthesis and release in the rat brain. *Salud Mental*. 2010;33(2):123–131.
201. Morioka N, Sugimoto T, Tokuhara M. Spinal astrocytes contribute to the circadian oscillation of glutamine synthase, cyclooxygenase-1 and clock genes in the lumbar spinal cord of mice. *Neurochem Int*. 2012;60(8):817–826. doi:10.1016/j.neuint.2012.03.005
202. Landgraf D, Long JE, Welsh DK. Depression-like behaviour in mice is associated with disrupted circadian rhythms in nucleus accumbens and periaqueductal grey. *Eur J Neurosci*. 2016;43(10):1309–1320. doi:10.1111/ejn.13085
203. Takada T, Yamashita A, Date A. Changes in the circadian rhythm of mRNA expression for μ -opioid receptors in the periaqueductal gray under a neuropathic pain-like state. *Synapse*. 2013;67(5):216–223. doi:10.1002/syn.21633

204. Leung CG, Mason P. Physiological properties of raphe magnus neurons during sleep and waking. *J Neurophysiol.* **1999**;81(2):584–595. doi:10.1152/jn.1999.81.2.584
205. Aston-Jones G, Chen S, Zhu Y, Oshinsky ML. A neural circuit for circadian regulation of arousal. *Nat Neurosci.* **2001**;4(7):732–738. doi:10.1038/89522
206. Gaudet AD, Fonken LK, Ayala MT. Spinal cord injury in rats disrupts the circadian system. *eNeuro.* **2018**;5(6):ENEURO.0328–18.2018. doi:10.1523/ENEURO.0328-18.2018
207. Burish MJ, Chen Z, Yoo S-H. Emerging relevance of circadian rhythms in headaches and neuropathic pain. *Acta Physiol.* **2019**;225(1):e13161. doi:10.1111/apha.13161
208. Bumgarner JR, Walker WH, Nelson RJ. Circadian rhythms and pain. *Neurosci Biobehav Rev.* **2021**;129:296–306. doi:10.1016/j.neubiorev.2021.08.004
209. Deboer T, Détári L, Meijer JH. Long term effects of sleep deprivation on the mammalian circadian pacemaker. *Sleep.* **2007**;30(3):257–262. doi:10.1093/sleep/30.3.257
210. Yang D-F, Huang W-C, Wu CW, Huang C-Y, Y-CSH Y, Tung Y-T. Acute sleep deprivation exacerbates systemic inflammation and psychiatry disorders through gut microbiota dysbiosis and disruption of circadian rhythms. *Microbiol Res.* **2023**;268:127292. doi:10.1016/j.micres.2022.127292
211. Morioka N, Saeki M, Sugimoto T. Downregulation of the spinal dorsal horn clock gene *Per1* expression leads to mechanical hypersensitivity via c-jun N-terminal kinase and CCL2 production in mice. *Mol Cell Neurosci.* **2016**;72:72–83. doi:10.1016/j.mcn.2016.01.007
212. Warfield AE, Gupta P, Ruhmann MM. A brainstem to circadian system circuit links Tau pathology to sundowning-related disturbances in an Alzheimer's disease mouse model. *Nat Commun.* **2023**;14(1):5027. doi:10.1038/s41467-023-40546-w
213. Raver C, Uddin O, Ji Y. An amygdalo-parabrachial pathway regulates pain perception and chronic pain. *J Neurosci.* **2020**;40(17):3424–3442. doi:10.1523/JNEUROSCI.0075-20.2020
214. Kramer PR, Hornung RS, Umorin M, Benson MD, Kinchington PR. Neurexin 3 regulates synaptic connections between central amygdala neurons and excitable cells of the lateral parabrachial nucleus in rats with varicella zoster induced orofacial pain. *J Pain Res.* **2024**;17:2311–2324. doi:10.2147/JPR.S441706
215. Lee SE, Greenough EK, Oancea P, Scheinfeld AR, Douglas AM, Gaudet AD. Sex differences in pain: spinal cord injury in female and male mice elicits behaviors related to neuropathic pain. *J Neurotrauma.* **2023**;40(9–10):833–844. doi:10.1089/neu.2022.0482
216. Abraham A, Barnett C, Katzberg HD, Lovblom LE, Perkins BA, Bril V. Sex differences in neuropathic pain intensity in diabetes. *J Neurol Sci.* **2018**;388:103–106. doi:10.1016/j.jns.2018.03.008
217. Cardinez N, Lovblom LE, Bai J-W. Sex differences in neuropathic pain in longstanding diabetes: results from the Canadian study of longevity in type 1 diabetes. *J Diabet Complicat.* **2018**;32(7):660–664. doi:10.1016/j.jdiacomp.2018.05.001
218. Bouillon L, Finn DP, Llorente-Berzal Á. Sex differences in a rat model of peripheral neuropathic pain and associated levels of endogenous cannabinoid ligands. *Front Pain Res.* **2021**;2:673638. doi:10.3389/fpain.2021.673638
219. Rosen S, Ham B, Mogil JS. Sex differences in neuroimmunity and pain. *J Neurosci Res.* **2017**;95(1–2):500–508. doi:10.1002/jnr.23831
220. Gregus AM, Levine IS, Eddinger KA, Yaksh TL, Buczynski MW. Sex differences in neuroimmune and glial mechanisms of pain. *Pain.* **2021**;162(8):2186–2200. doi:10.1097/j.pain.0000000000002215
221. Ghazisaeidi S, Muley MM, Salter MW. Neuropathic pain: mechanisms, sex differences, and potential therapies for a global problem. *Annu Rev Pharmacol Toxicol.* **2023**;63:565–583. doi:10.1146/annurev-pharmtox-051421-112259
222. Craft RM, Mogil JS, Maria Aloisi A. Sex differences in pain and analgesia: the role of gonadal hormones. *Eur J Pain.* **2004**;8(5):397–411. doi:10.1016/j.ejpain.2004.01.003
223. Barcelon E, Chung S, Lee J, Lee SJ. Sexual dimorphism in the mechanism of pain central sensitization. *Cells.* **2023**;12(16):2028. doi:10.3390/cells12162028
224. Fauchon C, Kim JA, El-Sayed R. Exploring sex differences in alpha brain activity as a potential neuromarker associated with neuropathic pain. *Pain.* **2022**;163(7):1291–1302. doi:10.1097/j.pain.0000000000002491
225. Ray PR, Shiers S, Caruso JP. RNA profiling of human dorsal root ganglia reveals sex differences in mechanisms promoting neuropathic pain. *Brain.* **2023**;146(2):749–766. doi:10.1093/brain/awac266
226. Smith MT Jr, Remeniuk B, Finan PH. Sex differences in measures of central sensitization and pain sensitivity to experimental sleep disruption: implications for sex differences in chronic pain. *Sleep.* **2019**;42(2):zsy209. doi:10.1093/sleep/zsy209
227. Rouhi S, Topcu J, Egorova-Brumley N, Jordan AS. The impact of sleep disturbance on pain perception: a systematic review examining the moderating effect of sex and age. *Sleep Med Rev.* **2023**;71:101835. doi:10.1016/j.smrv.2023.101835
228. Melikoglu MA, Celik A. Does neuropathic pain affect the quality of sleep? *Eurasian J Med.* **2017**;49(1):40–43. doi:10.5152/eurasianjmed.2017.16261
229. Yezierski RP. The effects of age on pain sensitivity: preclinical studies. *Pain Med.* **2012**;13(Suppl 2):S27–S36. doi:10.1111/j.1526-4637.2011.01311.x
230. Gibson SJ, Helme RD. Age-related differences in pain perception and report. *Clin Geriatric Med.* **2001**;17(3):433–456. doi:10.1016/s0749-0690(05)70079-3
231. Lautenbacher S, Peters JH, Heesen M, Scheel J, Kunz M. Age changes in pain perception: a systematic-review and meta-analysis of age effects on pain and tolerance thresholds. *Neurosci Biobehav Re.* **2017**;75:104–113. doi:10.1016/j.neubiorev.2017.01.039
232. Espiritu JRD. Aging-related sleep changes. *Clin Geriatric Med.* **2008**;24(1):1–14. doi:10.1016/j.cger.2007.08.007
233. Redline S, Kirchner HL, Quan SF, Gottlieb DJ, Kapur V, Newman A. The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Internal Med.* **2004**;164(4):406–418. doi:10.1001/archinte.164.4.406
234. Moraes W, Piovezan R, Poyares D, Bittencourt LR, Santos-Silva R, Tufik S. Effects of aging on sleep structure throughout adulthood: a population-based study. *Sleep Med.* **2014**;15(4):401–409. doi:10.1016/j.sleep.2013.11.791
235. Dijk D-J, Duffy JF, Czeisler CA. Age-related increase in awakenings: impaired consolidation of NonREM sleep at all circadian phases. *Sleep.* **2001**;24(5):565–577. doi:10.1093/sleep/24.5.565
236. Kapustin D, Bhatia A, McParland A. Evaluating the impact of gabapentinoids on sleep health in patients with chronic neuropathic pain: a systematic review and meta-analysis. *Pain.* **2020**;161(3):476–490. doi:10.1097/j.pain.0000000000001743

237. Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. *Curr Med Res Opin.* **2010**;26(10):2411–2419. doi:10.1185/03007995.2010.516142
238. Backonja M, Beydoun A, Edwards KR. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA.* **1998**;280(21):1831–1836. doi:10.1001/jama.280.21.1831
239. Sabatowski R, Gálvez R, Cherry DA. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomised, placebo-controlled clinical trial. *Pain.* **2004**;109(1–2):26–35. doi:10.1016/j.pain.2004.01.001
240. Fink K, Dooley DJ, Meder WP. Inhibition of neuronal Ca²⁺ influx by gabapentin and pregabalin in the human neocortex. *Neuropharmacology.* **2002**;42(2):229–236. doi:10.1016/S0028-3908(01)00172-1
241. Boyle J, Eriksson ME, Gribble L. Randomized, placebo-controlled comparison of amitriptyline, duloxetine, and pregabalin in patients with chronic diabetic peripheral neuropathic pain: impact on pain, polysomnographic sleep, daytime functioning, and quality of life. *Diabetes Care.* **2012**;35(12):2451–2458. doi:10.2337/dc12-0656
242. Ito H, Takemura Y, Aoki Y, Hattori M, Horikawa H, Yamazaki M. Analysis of the effects of a tricyclic antidepressant on secondary sleep disturbance induced by chronic pain in a preclinical model. *PLoS One.* **2020**;15(12):e0243325. doi:10.1371/journal.pone.0243325
243. Sindrup SH, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain.* **1999**;83(3):389–400. doi:10.1016/S0304-3959(99)00154-2
244. Argoff CE. The coexistence of neuropathic pain, sleep, and psychiatric disorders: a novel treatment approach. *Clin J Pain.* **2007**;23(1):15–22. doi:10.1097/01.aip.0000210945.27052.b3
245. Huzmeli ED, Urfali S, Gokcek O. Neuropathic pain and sleep quality. In: *Neurological Modulation of Sleep.* Elsevier; **2020**:169–174.
246. Higgins DM, Heapy AA, Buta E. A randomized controlled trial of cognitive behavioral therapy compared with diabetes education for diabetic peripheral neuropathic pain. *J Health Psychol.* **2022**;27(3):649–662. doi:10.1177/1359105320962262
247. Budh CN, Kowalski J, Lundeberg T. A comprehensive pain management programme comprising educational, cognitive and behavioural interventions for neuropathic pain following spinal cord injury. *J Rehabil Med.* **2006**;38(3):172–180. doi:10.1080/16501970500476258
248. Cardinali DP, Brown GM, Pandi-Perumal SR. Chronotherapy. In: Swaab DF, Kreier F, Lucassen PJ, Salehi A, Buijs RM, editors. *Handbook of Clinical Neurology.* Vol. 179. Elsevier; **2021**:357–370.
249. Yang B, Wei W, Fang J, Xue Y, Wei J. Diabetic neuropathic pain and circadian rhythm: a future direction worthy of study. *J Pain Res.* **2024**;17:3005–3020. doi:10.2147/JPR.S467249
250. Gilron I. Impact of chronobiology on neuropathic pain treatment. *Pain Management.* **2016**;6(3):241–247. doi:10.2217/pmt-2015-0007
251. Burgess HJ, Park M, Ong JC, Shakoor N, Williams DA, Burns J. Morning versus evening bright light treatment at home to improve function and pain sensitivity for women with fibromyalgia: a pilot study. *Pain Med.* **2017**;18(1):116–123. doi:10.1093/pm/pnw160
252. Burgess HJ, Rizvydeen M, Kimura M. An open trial of morning bright light treatment among US military veterans with chronic low back pain: a pilot study. *Pain Med.* **2019**;20(4):770–778. doi:10.1093/pm/pny174
253. Burns JW, Gerhart J, Rizvydeen M, Kimura M, Burgess HJ. Morning bright light treatment for chronic low back pain: potential impact on the volatility of pain, mood, function, and sleep. *Pain Med.* **2020**;21(6):1153–1161. doi:10.1093/pm/pnz235
254. Elliott JE, McBride AA, Balba NM. Feasibility and preliminary efficacy for morning bright light therapy to improve sleep and plasma biomarkers in US veterans with TBI. A prospective, open-label, single-arm trial. *PLoS One.* **2022**;17(4):e0262955. doi:10.1371/journal.pone.0262955
255. Oggiam DS, Jorgetto JV, Chinini GL, Gamba MA, Kusahara DM. Effects of monochromatic infrared light on painful diabetic polyneuropathy: randomized controlled trial. *Pain Manage Nurs.* **2025**;26(1):45–54. doi:10.1016/j.pmn.2024.08.012
256. Boon M, van Dorp E, Broens S, Overdyk F. Combining opioids and benzodiazepines: effects on mortality and severe adverse respiratory events. *Annals Palliative Med.* **2020**;9(2):54257–54557. doi:10.21037/apm.2019.12.09
257. Fan H, Yu W, Zhang Q. Efficacy and safety of gabapentin 1800 mg treatment for post-herpetic neuralgia: a meta-analysis of randomized controlled trials. *J Clin Pharm Therapeut.* **2014**;39(4):334–342. doi:10.1111/jcpt.12167
258. Hahn J, Jo Y, Yoo SH, Shin J, Yu YM, Ah Y-M. Risk of major adverse events associated with gabapentinoid and opioid combination therapy: a systematic review and meta-analysis. *Front Pharmacol.* **2022**;13:1009950. doi:10.3389/fphar.2022.1009950
259. Gilron I, Bailey JM, Tu D, Holden RR, Weaver DF, Houlden RL. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med.* **2005**;352(13):1324–1334. doi:10.1056/NEJMoa042580
260. Gnanadesigan N, Espinoza RT, Smith R, Israel M, Reuben DB. Interaction of serotonergic antidepressants and opioid analgesics: is serotonin syndrome going undetected? *J Am Med Directors Assoc.* **2005**;6(4):265–269. doi:10.1016/j.jamda.2005.04.012
261. Ansari H, Kouti L. Drug interaction and serotonin toxicity with opioid use: another reason to avoid opioids in headache and migraine treatment. *Current Pain Headache Rep.* **2016**;20:1–7. doi:10.1007/s11916-016-0579-3
262. Beery AK, Zucker I. Sex bias in neuroscience and biomedical research. *Neurosci Biobehav Rev.* **2011**;35(3):565–572. doi:10.1016/j.neubiorev.2010.07.002

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