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IL-1b and TNF-a-driven sleep alterations: Neuroimmune mechanisms and behavioral implications

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ABSTRACT

Sleep is a fundamental physiological state essential for immune function, metabolic regulation, and recovery from illness. During infection, sleep patterns are altered in a stereotyped fashion-characterized by increased non-rapid eye movement (NREM) sleep and reduced rapid eye movement (REM) sleep. These sleep changes are not incidental consequences of illness but reflect an evolutionarily conserved neuroimmune adaptation driven by proinflammatory cytokines. In particular, interleukin 1b (IL-1b) and tumor necrosis factor-a (TNFa) modulate sleep by acting directly on central nervous system circuits, including the serotonergic system and homeostatic sleep regulation. In this review, we synthesize current knowledge on how IL-1b and TNFa interact with sleep-regulating networks to alter behavioral state transitions during immune challenge. We also explore the broader clinical relevance of cytokine-driven sleep changes across infectious, psychiatric, and neurodegenerative disorders, and highlight emerging therapeutic opportunities targeting neuroimmune pathways to restore sleep homeostasis. Understanding these interactions is essential for advancing mechanistic insight into sleep regulation and for improving clinical management of inflammation-related sleep disturbances.

1. Introduction

Sleep is a fundamental physiological process that supports diverse aspects of physical and cognitive health. Modern sleep research began in 1953, characterized by the realization that sleep is an active process composed of two distinct phases: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep (Imeri and Opp, 2009). Despite decades of research, the biological purpose of sleep remains incompletely understood. Notably, growing evidence suggests that sleep is not only governed by neural circuits and circadian rhythms, but is also intimately linked with immune signaling pathways (Singh et al., 2024).

The immune system and sleep are tightly interwoven in a bidirectional relationship. Sleep disturbances modulate immune defense in complex and context-dependent ways-often leading to impaired host protection but, in some cases, eliciting immune activation that adaptively alters sleep architecture as part of a coordinated homeostatic response. Among immune mediators, proinflammatory cytokines, such as interleukin 1β (IL-1β) and tumor necrosis factor-a (TNFa), are key modulators of sleep, especially NREM sleep (Imeri and Opp, 2009; Singh et al., 2024; Zielinski and Gibbons, 2022; Zhang et al., 2017). These immune molecules are expressed endogenously in the central nervous system (CNS), and their levels fluctuate in a circadian fashion, aligning with changes in sleep propensity (Zielinski and Gibbons, 2022; Krueger et al., 1998; Early et al., 2018; Xu et al., 2023).

Sleep alterations during illness-typically involving fatigue, increased NREM sleep, and fragmented sleep-are broadly conserved features of the sickness behavior response, although their expression can vary with the dose and type of immune stimulation (Ibarra-Coronado et al., 2015; Davis and Raizen, 2017; Zielinski et al., 2019; Gool et al., 2024). While increased NREM and reduced REM sleep are generally regarded as restorative adaptations that promote immune recovery, mild fragmentation during acute infection may also serve adaptive purposes. These sickness-associated alterations in sleep are not incidental. Rather, they appear to be adaptive strategies that support immune recovery, thermoregulation, and energy conservation (Imeri and Opp, 2009; Parmeggiani, 2003). However, when fragmentation becomes excessive or

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chronic, as in prolonged inflammation, it may shift from adaptive to maladaptive, impairing recovery and immune efficiency (Ringgold et al., 2013). Inflammatory cytokines alter both neural activity and neuromodulator systems, particularly serotonin (5-hydroxytryptamine; 5-HT), to reshape sleep architecture (Manfridi et al., 2003; Alam et al., 2004). Yet, the mechanisms through which these immune signals interact with canonical sleep-regulating pathways remain incompletely defined.

This review synthesizes current knowledge on the interplay between the immune system and sleep, with a particular focus on cytokine-neurotransmitter interactions. By examining how proinflammatory signals such as IL-1b and TNFa influence serotonergic circuits and modulate sleep stages, we aim to clarify how infection alters sleep and why such changes may be beneficial to the host. In doing so, we also highlight knowledge gaps and emerging directions in neuroimmune-sleep research, aiming to inform both mechanistic insight and therapeutic strategies for inflammation-related sleep disturbances.

2. Fundamentals of sleep regulation: neural and chronobiological frameworks

In mammals, the drive to sleep arises from the coordinated influence of two interdependent biological processes: the homeostatic and circadian mechanisms, together known as the two-process model of sleep regulation (Borbély, 2022; Abhilash and Shafer, 2024). These systems interact to determine not only when we sleep, but also the depth, duration, and quality of sleep (Fig. 1).

The homeostatic process reflects "sleep pressure," which builds with increasing wakefulness and is alleviated by sleep. This pressure is thought to be mediated in part by neuromodulators such as adenosine, which accumulates in the basal forebrain during prolonged wakefulness. This system ensures that the body receives sufficient rest based on its recent activity and metabolic demands (Huang et al., 2024). In contrast, the circadian process is driven by the suprachiasmatic nucleus (SCN) of the hypothalamus, the body's master clock (Van Drunen and Eckel-Mahan, 2021; Scammell et al., 2017). The SCN synchronizes internal physiological rhythms-including sleep-wake cycles, core body temperature, hormone secretion, and immune function-to the external light-dark cycle. SCN neurons generate near-24-h oscillations in gene expression and electrical activity, entrained by photic signals received via melanopsin-expressing retinal ganglion cells that project to the SCN through the retinohypothalamic tract. Circadian outputs from the SCN influence a distributed network of arousal- and sleep-promoting regions to coordinate daily rhythms in vigilance and rest. The SCN through both direct neural projections and indirect multisynaptic pathways,

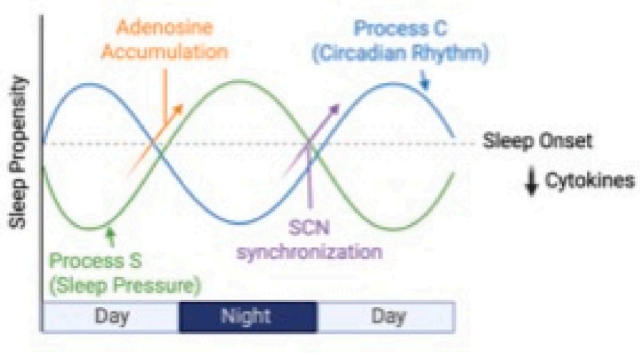

Fig. 1. Two-Process Model of Sleep Regulation. The homeostatic process (Process S) reflects sleep pressure that accumulates with wakefulness and dissipates with sleep, partly mediated by adenosine. The circadian process (Process C), governed by the SCN synchronization, entrains internal rhythms to the light-dark cycle. The interaction of these two processes determines sleep onset, depth, and duration. Cytokines can adjust the sleep onset threshold further.

communicates circadian timing information to other regions, including the locus coeruleus (LC), the dorsal raphe nuclei (DRN), and the tuberomammillary nucleus (TMN), which releases histamine (Van Drunen and Eckel-Mahan, 2021; Scammell et al., 2017). Within the arousal network, the LC release norepinephrine to promote wakefulness and cognitive alertness, while the DRN releases serotonin, contributing to transitions between wake and NREM sleep. The TMN provides histaminergic drive that sustains cortical activation during wakefulness. The ventrolateral preoptic area (VLPO), by contrast, exerts GABAergic inhibition on these arousal-promoting regions to initiate and maintain sleep (Gottesmann, 2002; Jones, 2020). Circadian SCN signaling to both the vLPO and LC-TMN-DRN axis ensures that sleep pressure is expressed at the biologically appropriate phase.

Modern lifestyles increasingly disrupt both circadian rhythm and homeostatic sleep drives. Societal factors such as shift work, extended screen time, and long commutes contribute to chronic sleep deprivation. And, epidemiological surveys show that the percentage of adults sleeping fewer than 6 h per night has reached unprecedented levels (Ford et al., 2015; Kang et al., 2020; Janssen et al., 2020; Restrepo et al., 2021). While early research on sleep deprivation focused mainly on alertness and cognitive performance, more recent evidence links short sleep duration to a range of physiological consequences, including metabolic, endocrine, immune, and cardiovascular effects (Faraut et al., 2012; Irwin et al., 2016). Notably, sleep deprivation impairs immune responses to vaccines, and is associated with elevated risk for obesity, insulin resistance, and cardiovascular disease (Zager et al., 2007; Sang et al., 2023; Chaput et al., 2023; Papatriantafyllou et al., 2022; Souza et al., 2024; Khan and Aouad, 2022). These associations may be mediated by hormonal changes-such as reduced leptin and elevated ghrelin-that increase appetite and impair glucose homeostasis. Critically, many of these chronic disease states are characterized by low-grade systemic inflammation–a state where there are high levels of inflammatory cytokines but no structural changes or loss of primary functions– suggesting a mechanistic link between sleep loss, immune dysregulation, and metabolic pathology (Irwin et al., 2016; León-Pedroza et al., 2015; Imeri and Opp, 2009). For example, individuals who sleep fewer than 5 h per night have a 2.5-fold increased risk of developing type 2 diabetes compared to those sleeping 7 h (Gottlieb et al., 2005). Likewise, the risk of myocardial infarction rises by 45 % in chronic short sleepers (Ayas et al., 2003). These findings reinforce the view that sleep is not merely a passive state but an active, regulated process with broad systemic consequences. Understanding how the nervous and immune systems interact to regulate sleep is essential for addressing both the physiological roles of sleep and the pathophysiology of its disruption.

3. Cytokines as sleep modulators: IL1b and TNFa at the neuroimmune interface

Sleep is tightly integrated with immune function, and proinflammatory cytokines play central roles in mediating this bidirectional relationship. Across 26 mammalian species, the amount of sleep was seen to be closely related to the number of white blood cell counts favoring better immune-competence (Preston et al., 2009). The decreased number and activity of phagocytes, natural killer cells, and the white blood cells in the REM-deprived animals suggest severely compromised or a weakened immune system (Opp, 2009). Among the most well-studied cytokines in the context of sleep regulation, IL-1b and TNFa-two cytokines known for their role in mediating inflammation and coordinating host defense (Krueger et al., 2001). Beyond their peripheral immune functions, both IL-1b and TNFa act directly within the CNS to modulate sleep architecture.

3.1. The source of cytokines

Sleep-regulatory cytokines such as IL-1b and TNFa, though initially

identified in the peripheral immune system, are now recognized to be produced by a diverse range of cell types both inside and outside the brain. These cytokines can influence sleep by acting within the CNS either through peripheral-to-central signaling, via humoral diffusion across leaky BBB and neural transmission through vagal afferents, or through local production by brain-resident immune and glial cells. Below, we break down the major sources contributing to CNS cytokine signaling.

- Immune cells in the brain parenchyma: Within the brain parenchyma, microglia represent the principal immune cell population and a major source of IL-1b and TNFa, particularly under conditions of sleep deprivation, infection, or systemic inflammation (Mendiola and Cardona, 2018; Smith et al., 2012; Henning et al., 2023). Microglia dynamically respond to changes in SWS and immune status by altering their morphology, transcriptional profile, and secretory behavior. Upon activation, they release cytokines that can modulate neuronal excitability and synaptic transmission in sleep-regulatory regions of the brain. In addition to microglia, parenchymal macrophage, perivascular macrophages, and a small population of resident T and B lymphocytes have been identified within the brain parenchyma (Silvin et al., 2023; Pasciuto et al., 2020). These cells may become activated under certain conditions, such as infection, autoimmunity, or chronic inflammation, and contribute to the local immune milieu, and regulate sleep. Recent works showed that stress or aging can increase the number of T cells in the brain and induce production of TNFa and other proinflammatory cytokines (Medina-Rodriguez et al., 2023). Additionally, sleep deprivation increased B cells in the brain parenchyma, which may secrete cytokines including TNFa (Korin et al., 2020). In addition to the immune cell populations, astrocytes, a type of glial cell, also contribute to IL-1b production especially in the context of sleep loss and metabolic stress (del Zoppo et al., 2000). Together, these brain parenchyma-resident immune cells form an integrated network capable of producing sleep-modulatory cytokines in response to both sleep deprivation and metabolic stress.
- Immune cells at the brain borders: Beyond the parenchyma, cytokine-producing immune cells also reside in border compartments of the CNS, including the meninges, choroid plexus and cerebrospinal fluid (CSF). These regions host diverse immune populations such as macrophages, dendritic cells, and T cells, which are strategically positioned to act as immunological sentinels (Dani et al., 2021; Piehl et al., 2022). Upon detecting systemic immune challenges, these cells can produce IL-1b and TNFa and transmit inflammatory signals into the CNS (Wieseler-Frank et al., 2007; Garabedian et al., 2000). These border-associated immune cells provide a crucial interface between the body and brain and may modulate sleep both directly (via cytokine release into adjacent brain regions or CSF) and indirectly (by influencing goal cell activity). Importantly, the choroid plexus and meningeal spaces are increasingly appreciated as sites where peripheral immune signals are translated into CNS-specific immune response.
- Peripheral immune cells and systemic signaling: Peripheral immune activation, such as during infection, trauma, or systemic inflammation, increases circulating levels of proinflammatory cytokines including IL-1b and TNFa. These cytokines can signal the brain through several mechanisms. One mechanism involves passive diffusion across leaky or fenestrated regions of the blood-brain-barrier, while another entails activation of vagal afferents that relay cytokine signals to brainstem and hypothalamic nuclei (Jin et al., 2024). A second, and often faster, route operates via neural transmission along vagal afferents. Cytokines such as IL-1b and TNFa can activate vagal sensory fibers innervating visceral organs. These afferents project to the nucleus tractus colitarius (NTS) in the brainstem, which in turn communicates with the paraventricular nucleus (PVN), LC, and hypothalamic sleep-regulatory nuclei (Zielinski et al., 2022). Activation of these pathways triggers central cytokine release and modulates neurotransmitter systems involved in arousal and sleep architecture. Through these pathways, peripheral immune signals can rapidly modulate central cytokine production and neuronal activity within sleep-regulating regions, thereby influencing sleep architecture even in the absence of direct pathogen invasion into the CNS.

3.2. Cytokines on normal sleep and infection-induced sleep changes

The role of cytokines in sleep regulation was first recognized in 1984, when Krueger and colleagues reported that IL-1b enhances slow-wave sleep (SWS) in rabbits (Krueger et al., 1984). This discovery was prompted by findings that astrocytes produce IL-1, suggesting it may act as a sleep-regulatory substance. Follow-up studies demonstrated that: 1) IL-1 administration increased electroencephalogram (EEG) slow wave activity in the delta frequency band; 2) its effects on sleep were dose dependent; and 3) IL-1b induced SWS was independent of fever, as it persisted in animals pretreated with anisomycin to block febrile responses. These early findings laid the groundwork for broader exploration of IL-1b′s somnogenic effects across species-including rats, mice, cats, and monkeys-confirming its conserved role in promoting sleep (Shoham et al., 1987a; Walter et al., 1989). Parallel investigations extended this work to TNFa. TNFa was also shown to induce SWS in several species and to exhibit circadian oscillations in its mRNA and protein expression that coincide with sleep-wake cycle (Shoham et al., 1987b). Notably, exogenous administration of either IL-1b or TNFa reliably increases NREM sleep, though often in a fragmented fashion (Krueger et al., 2001). These effects are dose- and phase-dependent: In rodent models, IL-1b promotes NREM sleep more effectively when administered before the onset of the dark (active) phase, reflecting a circadian modulation of its somnogenic effects. However, excessively high doses can paradoxically suppress sleep (Opp et al., 1991; Lancel et al., 1996). Conversely, blocking IL-1b or TNFa signaling-either pharmacologically (with neutralizing antibodies or receptor antagonists) or genetically (via knockout mice)-reduces spontaneous NREM sleep and attenuates rebound sleep following deprivation (Imeri et al., 2006; Takahashi et al., 1996; Baracchi and Opp, 2008).

In contrast to their promotion of NREM sleep, IL-1b and TNFa consistently suppress REM sleep (Manfridi et al., 2003; Rockstrom et al., 2018; Lu et al., 2006). Experimental administration of their inhibitors/antagonists leads to an upsurge in REM duration and reduce NREM time, while administration of these cytokines reduces REM duration and REM bout number, especially during sickness (Manfridi et al., 2003; Rockstrom et al., 2018). The precise mechanisms by which IL-1b and TNFa inhibit REM sleep remain poorly understood but may involve modulation of cholinergic neurons in the pons, serotonergic gating, or inhibition of REM-promoting neurons in the sublaterodorsal tegmental nucleus (STN) (Lu et al., 2006).

These sleep changes are not coincidental to illness but rather reflect a coordinated physiological response to infection. Pathogen-associated molecular patterns (PAMPs) from bacteria, viruses, and parasites induce the release of proinflammatory cytokines, including IL-1b and TNFa, which then mediate hallmark sleep changes: increased NREM, reduced REM, and greater sleep fragmentation. These effects have been replicated experimentally by administering purified microbial components, such as lipopolysaccharide (LPS), and are abolished when cytokine signaling is pharmacologically blocked (Ibarra-Coronado et al., 2015; Zielinski and Krueger, 2011). Functionally, these sleep alterations may be adaptive. Enhanced NREM sleep conserves energy and supports immune signaling, while suppression of REM allows thermogenic responses such as shivering-which are otherwise disabled during REM-to generate fever, an established host-defense mechanism (Imeri and Opp, 2009). This model is supported by clinical and experimental studies across multiple types of infections. Streptococcal infections can result in encephalitis lethargica-like syndromes characterized by

profound sleep-wake disruption (Dale et al., 2004), while HIV-infected individuals show altered sleep architecture even before AIDS symptoms emerge (Norman et al., 1990). Infection by Trypanosoma brucei causes extreme sleep fragmentation and the loss of diurnal sleep-wake rhythms (Lundkvist et al., 2004). Even common infections, such as influenza or the common cold, are known to alter sleep patterns (Drake et al., 2000; Bettis et al., 2006). Together, these findings establish IL-1b and TNFa as critical immune-neuromodulators that reshape sleep architecture during sickness-not as side effects, but as components of a strategic physiological program that supports host defense, energy conservation, and thermoregulation.

4. Cytokine-serotonin crosstalk in sleep regulation

Cytokine-mediated modulation of sleep does not occur in isolation but is deeply integrated with neuromodulatory systems that orchestrate arousal and sleep transitions. Among these, the serotonin system is one of the most extensively studied. Notably, IL-1band TNFa interact with serotonergic circuits, suggesting that these immune signals can reprogram brain state transitions by modulating the activity and output of 5-HT neurons (Fig. 2) (Murillo-Rodríguez et al., 2017; Monti and Jantos, 2008).

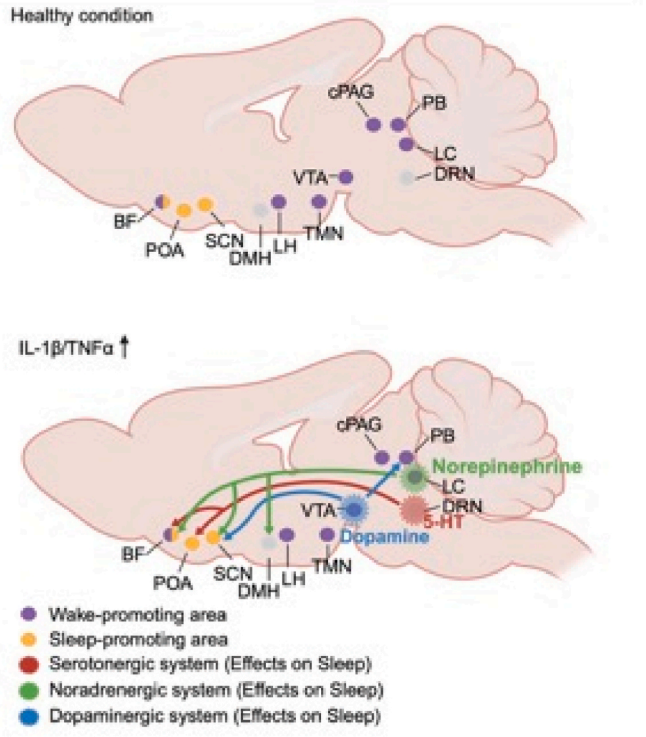

Fig. 2. Neurocircuitry underlying sleep regulation in healthy and immune activated conditions. The diagram highlights the interplay between immune activation and central neuromodulatory pathways in sleep regulation. Sagittal schematic of a mouse brain illustrating key brain regions and neurotransmitter pathways involved in sleep-wake regulation. In the healthy condition (top panel), wake-promoting nuclei (purple dots), including the locus coeruleus (LC), ventral tegmental area (VTA), tuberomammillary nucleus (TMN), parabrachial nucleus (PB), and others, maintain arousal. Sleep-promoting regions (yellow dots), such as the preoptic area (POA) and suprachiasmatic nucleus (SCN), balance this activity to regulate sleep initiation. In the immune activated condition (bottom panel), pro-inflammatory cytokines IL-1b and TNFa are elevated, leading to altered activity in neurotransmitter systems. This includes increased engagement of the serotonergic system (red projections from DRN), noradrenergic system (green projections from LC), and dopaminergic system (blue projections from VTA). Arrows indicate projections targeting both sleep- and wake-promoting areas, suggesting immune-mediated modulation of these circuits during sleep disturbance.

4.1. Dual role of serotonin in sleep and arousal

Serotonin's mechanistic role in sleep regulation remains incompletely understood. In the central nervous system, serotonin is synthesized in the raphe nuclei - a diffuse network of brainstem structures that project broadly throughout the brain (Berger et al., 2009). Early lesion studies found that ablation of the raphe nuclei caused profound insomnia, suggesting a sleep-promoting role for 5-HT (Jouvet, 1968). Similarly, intraperitoneal injection of para-chlorophenylalanine - an irreversible inhibitor of tryptophan hydroxylase, the rate-limiting enzyme in serotonin synthesis - led to reduced sleep (Weitzman et al., 1968). These findings, along with parallel studies on other monoamines, helped shape the monoaminergic theory of sleep, which posited serotonin as a key sleep-promoting neuromodulator (Jouvet, 1972). However, this view was later challenged. For example, cooling the dorsal raphe was found to induce sleep in cats, while raphe lesions in rats produced hyperactivity without significant effects on sleep (Cespuglio et al., 1976; Bouhuys and Van Den Hoofdakker, 1977). Electrophysiological studies and calcium imaging further complicated the picture, showing that serotonergic neurons in the dorsal raphe nucleus (DRN) are most active during wakefulness, reduce firing during NREM sleep, and are nearly silent during REM sleep (Trulson and Jacobs, 1979; McGinty and Harper, 1976; Oikonomou et al., 2019). Micro-dialysis studies mirrored these findings, showing that extracellular serotonin levels peak during wakefulness and fall progressively across NREM and REM sleep (Portas et al., 2000). These studies have provided contrasting evidence suggesting that serotonin may not simply promote sleep, but also promote wakefulness. More refined approaches - including in vivo recordings and optogenetic manipulations - have confirmed that DRN serotonergic neurons promote wakefulness through excitatory projections to arousal centers (Cespuglio et al., 1979; Venner et al., 2020). At the same time, serotonin appears to contribute indirectly to sleep homeostasis by facilitating the production or release of sleep-promoting molecules (Imeri and Opp, 2009). Taken together, these findings support a model in which serotonin acutely supports arousal but also plays a permissive role in regulating sleep pressure over time.

4.2. IL-1b and TNFa modulate serotonergic tone

A growing body of evidence shows that IL-1b and TNFa can modulate the serotonergic system at both cellular and synaptic levels. For example, IL-1b suppresses serotonergic neuronal firing in the DRN, a key source of ascending 5-HT projections (Manfridi et al., 2003). At the same time, IL-1b enhances 5-HT release in downstream targets such as the POA and basal forebrain (BF)-regions implicated in sleep initiation and maintenance (Alam et al., 2004). These seemingly opposing effects, somatic inhibition and terminal facilitation, are thought to work together to dampen global arousal while enhancing local inhibition of arousal-promoting neurons, resulting in a net increase in NREM sleep (Krueger et al., 2008; Jewett and Krueger, 2012).

In addition to IL-1b, TNFa also appears to interact with serotonergic tone, although its effects are less well characterized. TNFa receptors are expressed in the raphe nuclei, and TNFa has been shown to alter 5-HT transporter expression and serotonin turnover in various brain regions, including the hippocampus and cortex (Dantzer et al., 2008). These changes may influence sleep indirectly by modifying serotonergic signaling plasticity in circuits that support arousal or emotional salience.

4.3. Functional consequences of cytokine-5-HT interaction

The interaction between cytokines and serotonin provides a mechanistic explanation for sickness-induced sleep changes, which was thought to increase NREM and suppress REM sleep (Murillo-Rodríguez et al., 2017; Monti and Jantos, 2008). More recently, it has been shown

that IL-1b's suppression of DRN activity would diminish serotonergic gating of REM-promoting neurons in the pons, thereby contributing to increased REM sleep (Kato et al., 2022). Conversely, increased 5-HT release in sleep-active regions such as the POA would favor transitions into and maintenance of NREM sleep. Interestingly, while 5-HT is canonically thought to promote wakefulness, optogenetic stimulation of the raphe nucleus is shown to promote NREM sleep (Oikonomou et al., 2019). Moreover, the timing and degree of 5-HT system activation appear to critically shape sleep outcomes in the presence of cytokine signaling. Studies in rodents have shown that exogenous IL-1b administration enhances NREM sleep primarily during the dark phase, when serotonergic activity is normally elevated (Imeri et al., 2000). This suggests that cytokines may act synergistically with circadian variations in neurotransmitter tone to reshape behavioral states during immune challenge. Interestingly, the interaction between 5-HT and cytokines is reciprocal. Serotonergic activation using 5-HTP can increase IL-1 mRNA transcription in the hypothalamus, but not the hippocampus or brainstem (Gemma and Opp, 2003). This cytokine-neurotransmitter loop may help explain the persistence of fatigue and hypersomnolence during prolonged immune activation, as seen in chronic infections or inflammatory diseases.

5. Beyond serotonin: cytokine interactions with additional sleep-wake neurotransmitters

While serotonin plays a role in cytokine-mediated sleep regulation, it is only one component of the broader neurochemical landscape that orchestrates arousal and sleep transitions. The sleep-wake cycle is governed by a distributed network of neurotransmitters, many of which are modulated directly or indirectly by proinflammatory cytokines such as IL-1b and TNFa. These interactions contribute to both the promotion of NREM sleep and the suppression of REM and wakefulness during immune activation (Fig. 2).

5.1. Norepinephrine and the locus coeruleus

Norepinephrine, produced by neurons in the locus coeruleus (LC) is a major driver of wakefulness and vigilance. Early electrophysiological studies on the activity of the LC-NE system across the sleep-wake cycle in rodents, cats, and monkeys, established that tonic LC activity progressively decreases when animals switch from engaged, behaviorally active states (~3Hz) to quieter, resting conditions (~1Hz), to slow wave sleep (<1Hz) (Chu and Bloom, 1973). In 2010, Carter et al. demonstrated that photoinhibition of LC-NE neurons during the active period caused a reduction in time spent in wakefulness as well as an increase in wake-to-sleep transitions. Conversely, photoactivation of LC-NE neurons during the inactive period produced immediate sleep-to-wake transitions (Carter et al., 2010).

Proinflammatory cytokines can modulate this arousal-promoting NE system. Both IL-1b and TNFa have been shown to reduce the firing rate of LC neurons and suppress NE release, particularly during infection or sleep deprivation (Mehta et al., 2022). For instance, IL-1b administration decreases NE tone in the cortex and hypothalamus, potentially through direct effects on LC neurons or by altering upstream hypothalamic regulation (Jagot et al., 2023; Tansey et al., 2024). The resulting decline in NE availability likely contributes to the increased NREM sleep and reduced arousal commonly observed during immune activation. (Darko et al., 1995). Moreover, chronic inflammation has been associated with dysregulated NE signaling in stress-related disorders (Rhie et al., 2020), which may underlie some of the fatigue, depression, anxiety, and cognitive slowing seen in chronic inflammatory states.

5.2. Dopamine and motivation-linked arousal

While dopamine (DA) is classically linked to reward and motivation, dopaminergic circuits-particularly those originating in the ventral tegmental area (VTA)-also contribute to arousal (Eban-Rothschild et al., 2016). Chemogenetic and optogenetic manipulations together with polysomnographic recordings demonstrated that VTA dopaminergic neurons are necessary for arousal and that their inhibition suppresses wakefulness, even in the face of ethologically relevant salient stimuli. Although DA has classically been associated with motivation and reward, substantial evidence also supports a role of DA in sleep-wake regulation (Monti and Monti, 2007). In particular, a number of pharmacological studies have shown that DA reuptake inhibitors, levodopa and D1, D2 & D3 receptor agonists all modify the amounts of SWS and paradoxical sleep without necessarily changing wakefulness (Galarraga et al., 1986; Mayers and Baldwin, 2005). In addition, Dopamine receptor type 2-expressing medium spiny neurons (D2-MSNs) in the medial portion of ventral striatum are shown to induce NREM sleep (Kato et al., 2022). Moreover, numerous clinical observations have described levodopa and DA-receptor agonists (pergolide, ropinirole, lisuride) as being responsible for excessive daytime sleepiness and 'sleep attacks' (Arnulf, 2005). In an animal model study, Dzirasa group demonstrated the role of DA in sleep-wake states by using hyperdopaminergic mice and acutely DA-depleted mice (Dzirasa et al., 2006). Taken together, these findings establish dopamine as a modulatory player in both arousal and sleep regulation. While the precise mechanisms remain incompletely understood, it is increasingly evident that dopaminergic tone influences transitions between behavioral states and contributes to the intensity and quality of sleep. Furthermore, proinflammatory cytokines such as IL-1b and TNFa can suppress dopaminergic signaling by reducing DA synthesis and release and altering receptor availability within mesolimbic and mesocortical circuits (Felger and Miller, 2012). Given this dual role, we hypothesize that IL-1b and TNFa may suppress the activity of dopaminergic neurons in the VTA, thereby contributing to the sleepiness and motivational blunting often observed during systemic inflammation.

6. Clinical implications-infectious disease, depression, and neurodegenerative diseases

Mounting evidence from both experimental and clinical studies highlights the central role of cytokine-mediated sleep modulation in the pathophysiology of diverse diseases. Sleep is not only a behavioral output altered during illness but also a functional regulator of immune and neural homeostasis. The bidirectional relationship between inflammation and sleep disruption contributes to symptom burden, impairs recovery, and may even exacerbate underlying disease processes.

6.1. Infectious disease

Sleep alterations during infection are among the earliest and most conserved features of the acute-phase response. Infections ranging from mild respiratory viruses to life-threatening sepsis are associated with characteristic changes in sleep architecture, including increased NREM sleep, reduced REM sleep, and greater fragmentation. In animal studies, bacterial or viral infections increase total sleep duration and the amount of NREM sleep, while reducing the time spent in REM sleep (Opp and Krueger, 2015). It has been hypothesized that these alterations support recovery and represent adaptive responses to infection. Given that cytokine-induced behavioral changes during sickness are known to promote host defense, it is likely that the infection-induced changes in sleep also serve immune-benefit functions (Imeri and Opp, 2009; Dantzer, 2001). Supporting this, animal models show that reduced sleep correlates with lower survival rates, whereas increased sleep enhances survival following infectious challenges (Krueger and Majde, 1994; Kuo and Williams, 2014). For example, the administration of lipopolysaccharide (LPS), a bacterial cell wall components, induces strong immune response, including upregulation of IL-1b and TNFa, and leads to increased NREM sleep along with suppression of REM sleep and sleep

fragmentation (Krueger and Majde, 1994; Kuo and Williams, 2014).

Similar patterns are observed in humans, though the effects of immune activation on sleep are dose-dependent. Experimental administration of low to moderate doses of bacterial endotoxin (lipopolysaccharide, LPS) tends to increase NREM sleep and suppresses REM sleep, consistent with an adaptive, infection-induced sleep response (Mullington et al., 2000). In contrast, higher LPS doses or more prolonged inflammatory states are associated with sleep fragmentation, reduced total sleep time, and diminished sleep quality (Bryant et al., 2004; Irwin et al., 2016). Likewise, a study examining sleep following rhinovirus exposure found that symptomatic individuals had shorter total sleep time but no clear changes in NREM or REM sleep amounts (Drake et al., 2000). More recent research on the effects of naturally occurring respiratory infections (RIs) showed that illness alters both objective and subjective sleep (Lasselin et al., 2019). During symptomatic periods, individuals spent more time in bed and had longer sleep durations, but experienced more awakenings, particularly in the first days of illness. Participants also reported worse sleep quality, increased difficulty falling asleep, more restless and fragmented sleep, and reduced perceived depth of sleep (Lasselin et al., 2019). These findings suggest that while mild immune activation can promote sleep as part of a host-defense response, more intense or sustained inflammation may become disruptive to sleep continuity and quality.

Sleep disruption also plays a substantial role in chronic infectious disease such as HIV. Fatigue in HIV infection contributes significantly to disease-related disability and may be driven in part by elevated levels of TNFa. In HIV-infected patients with preserved CD4 T cell counts, nocturnal fluctuations in plasma TNFa levels were found to be temporally coupled to EEG delta amplitude during sleep, linking cytokine dynamics to NREM sleep regulation (Darko et al., 1995). Furthermore, youth with perinatally acquired HIV frequently exhibit sleep disturbances, neurocognitive deficits, and abnormal psychosocial function, which have been associated with elevated levels of inflammatory cytokines inducing TNFa (Foster et al., 2012).

6.2. Depression and neuropsychiatric disorders

In individuals with psychiatric disorders, sleep disturbances and altered cytokine levels are closely intertwined, although the literature reflects considerable heterogeneity and context dependence. Sleep deprivation, a common feature in conditions such as major depressive disorder (MDD) and schizophrenia, can elevate circulating pro-inflammatory cytokines, including IL-1b, IL-6, and TNFa. Conversely, increased levels of these cytokines can disrupt sleep continuity and architecture, suggesting a bidirectional and dose-dependent relationship between inflammation and sleep disruption in psychiatric illness (Irwin et al., 2016; Lasselin et al., 2019).

Experimental human studies using LPS have demonstrated that low to moderate doses can transiently increase NREM sleep and suppress REM sleep, whereas higher doses or prolonged exposure often lead to increased awakenings (Mullington et al., 2000; Bryant et al., 2004; Irwin et al., 2016). Moreover, while early work (Yirmiya et al., 2000) reported robust correlations between circulating cytokines and behavioral changes including depressive symptoms, anxiety, memory impairment, and sleep disruption, subsequent studies have found more variable effects. Later investigations show that induced cytokines by typhoid vaccination or endotoxin in mood are generally reproducible (Harrison et al., 2009; Eisenberger et al., 2010), but cognitive effects are inconsistent or modest, depending on dose, timing, and task sensitivity (Holden et al., 2008). Together, these findings indicate that immune-induced behavioral and sleep responses are not uniformly sleep-promoting, but instead reflect a spectrum of adaptive and maladaptive outcomes contingent on inflammatory load and neural sensitivity.

Sleep abnormalities are particularly prominent in MDD, where patients frequently exhibit shortened REM latency, increased REM density, and reduced SWS. These alterations are not only clinical markers but may have mechanistic relevance. Although IL-1b and TNFa generally promote SWS under physiological conditions, their chronic elevation in MDD may instead contribute to sleep disruption (Fernandez-Mendoza et al., 2017). Prolonged or dysregulated cytokine signaling can impair normal sleep-promoting pathways by altering monoaminergic transmission, inducing glucocorticoid resistance, and desensitizing cytokine receptors within sleep-regulatory regions (Irwin and Opp, 2017). Thus, elevated cytokine levels in MDD may reflect a maladaptive or blunted neuroimmune response rather than an effective SWS-promoting signal. In adolescents with first-episode MDD, insomnia symptoms are associated with elevated peripheral levels of IL-1b, IL-6, and TNFa, suggesting a potential role for cytokine activity in early disease processes (Fernandez-Mendoza et al., 2017). Genetic factors further modulate inflammation-sleep-mood interactions. Functional polymorphisms in genes encoding IL-1b and TNFa have been associated with both increased risk of depression and poorer response to antidepressant treatment (Yu et al., 2003; Jun et al., 2003). Nonetheless, evidence for directionality remains mixed-whether inflammation drives sleep disturbance or disrupted sleep amplifies inflammation is still under investigation.

In schizophrenia, sleep and inflammation are also tightly interwoven. The disorder affects nearly 1 % of the population and involves genetic, immune, and environmental contributors. Cytokine concentrations, especially serum IL-6, TNFa, IL-12, and IL-1b, are enhanced in Schizophrenia (Zhu et al., 2014, 2018). Alterations in these cytokines lead to insomnia which is a greatest hallmark of Schizophrenic patients. In parallel, in human study, the schizophrenia group had longer sleep duration, worse sleep quality, and also showed increased levels of hs-CRP, IL-1b, IL6, and TNFa compared to non-psychiatric comparison participants (Lee et al., 2019). However, these associations vary in strength and significance across studies and disease stages, underscoring the importance of distinguishing correlation from causation.

Across psychiatric populations, depression-related symptoms such as fatigue, insomnia, and hostility, have been associated with increased levels of inflammatory markers in otherwise healthy adults (Suarez et al., 2002; Irwin et al., 2004). Yet the relationship is likely bidirectional and dynamic rather than linear-mild immune activation may initially promote sleep as part of an adaptive host-defense response, whereas chronic or exaggerated inflammation can disrupt sleep continuity and cognitive function, thereby perpetuating affective dysregulation. Understanding these feedback loops will be crucial for developing targeted interventions that address both inflammatory and sleep pathways in mental health.

6.3. Alzheimer's disease and neurodegenerative disorders

Sleep disturbances are extremely common in Alzheimer's disease (AD) and other neurodegenerative disorders, and mounting evidence suggests that cytokine-mediated inflammation plays a key role in this bidirectional relationship (Havekes et al., 2019). Individuals with AD frequently exhibit fragmented sleep, reduced SWS, increased nocturnal awakenings, and altered REM sleep architecture, changes that correlate with both cognitive decline and disease progression. Importantly, sleep disruption is not merely a symptom of AD but may also contribute to amyloid-beta (Ab) accumulation and tau pathology, exacerbating neurodegeneration. For example, amyloid plaques and tau tangles are also commonly found in brain regions critical for the regulation and modulation of the sleep-wake cycle, including locus coeruleus, hypothalamus, and the cortical layers (Rudelli et al., 1984). Importantly, the connection between AD pathogenesis at the level of Ab and the disruption of the sleep-wake cycle is thought to be reciprocal. Indeed, even a single night of sleep deprivation elevates Ab levels in the human brain (Shokri-Kojori et al., 2018). This clinical evidence is confirmed by rodent studies showing that chronic and acute sleep restriction in AD mouse models leads to elevated Ab levels in interstitial fluid (ISF), whereas chronic

sleep deprivation leads to Ab accumulation (Wang and Holtzman, 2020; Kang et al., 2020). The amount of ISF Ab also significantly increased during orexin infusion but decreased with infusion of a dual orexin receptor antagonist (Kang et al., 2020). Orexin is a neuropeptide that stimulates wake-promoting neurons and inhibits REM sleep (Pizza et al., 2022). Neuroinflammation, characterized by elevated IL-1b, IL-6, TNFa, and microglia activation, is now recognized as a core component of AD pathogenesis (Atienza et al., 2018; Chen et al., 2012; Wang et al., 2023). Patients with mild or moderate stages of AD have increased levels of IL-1b and TNFa, and chronic sleep disturbance also increases the expression of inflammatory cytokines like IL-6 and TNFa in humans (Chen et al., 2012). Experimental studies in transgenic mouse models of AD demonstrate that chronic elevations in IL-1b or TNFa caused by infection can accelerate Ab plaque formation and cognitive impairment (Wang et al., 2023). Conversely, sleep deprivation increases Ab production and impairs glymphatic clearance, further linking poor sleep quality to amyloid accumulation (Voumvourakis et al., 2023).

Beyond AD, similar sleep-inflammation interactions are evident in other neurodegenerative diseases. Patients with Parkinson's disease (PD) frequently report insomnia, REM sleep behavior disorder, and excessive daytime sleepiness, all of which correlate with increased serum TNFa and IL-6 levels (Dzamko, 2023; Zhang et al., 2025). Similarly, patients with Lewy body dementia or frontotemporal dementia show profound sleep-wake disruption linked to elevated proinflammatory markers. Importantly, sleep disruption in these disorders may also contribute to neurodegenerative progression. Both clinical and preclinical studies show that fragmented sleep enhances neuroinflammation via sustained cytokine production, impaired clearance of toxic proteins, and increased blood-brain barrier permeability. Thus, sleep may serve not only as a marker of neurodegenerative disease burden but also as a modifiable risk factor and therapeutic target.

7. Discussion

Sleep is an evolutionarily conserved, physiologically essential process that is deeply interconnected with immune function. This review highlights the complex, bidirectional interactions between the immune system and sleep, with a particular focus on the role of proinflammatory cytokines IL-1b and TNFa in modulating sleep architecture through neurotransmitter system such as serotonin, norepinephrine, and dopamine. The evidence demonstrates that immune signals are not passive byproducts of illness but are active modulators of sleep-wake regulation, capable of reshaping neural circuits to support adaptive physiological responses (Imeri and Opp, 2009; Alam et al., 2004; Krueger et al., 2001; Murillo-Rodríguez et al., 2017; Monti and Jantos, 2008).

The sleep alterations that accompany infection, characterized by increased NREM sleep, suppressed REM sleep, and heightened sleep fragmentation, are increasingly recognized as part of a coordinated sickness behavior response (Ibarra-Coronado, 2015; Davis and Raizen, 2017; Zielinski et al., 2019). By promoting NREM sleep and reducing REM sleep, cytokine-mediated changes may conserve energy, optimize thermoregulation, and enhance immune efficiency during periods of host defense (Imeri and Opp, 2009; Parmeggiani, 2003). This adaptive perspective is supported by experimental data showing that animals with increased sleep during infection exhibit better survival outcomes, while those with impaired sleep display reduced immune competence (Opp, 2009). Moreover, administration of LPS induces strong immune responses, increases NREM sleep, suppresses REM sleep, and fragments sleep architecture, effects that can be abolished by blocking cytokine signaling (Zielinski and Krueger, 2011; Krueger and Majde, 1994; Kuo and Williams, 2014). These findings reinforce the view that immune-driven sleep changes are not incidental but play active roles in host defense.

At the molecular level, cytokines such as IL-1b and TNFa act both directly and indirectly on sleep-regulatory brain regions (Mendiola and Cardona, 2018; Smith et al., 2012; Henning et al., 2023). Within the CNS, glial cells (del Zoppo et al., 2000) and brain-resident immune populations, such as microglia, perivascular macrophage, and T and B lymphocytes, are key sources of these cytokines during sleep deprivation, infection, or systemic inflammation. Furthermore, peripheral immune activation can relay cytokine signals to the brain through humoral and neural routes, possibly including vagal afferent pathways (Jin et al., 2024). Importantly, the actions of IL-1b and TNFa are not limited to sleep promoting effects. They also modulate key neurotransmitter systems, particularly serotonergic, noradrenergic, and dopaminergic circuits, resulting in the complex and sometimes paradoxical sleep outcomes observed across different contexts (Murillo-Rodríguez et al., 2017; Monti and Jantos, 2008; Dantzer et al., 2008; Mehta et al., 2022).

Clinical implications of this neuroimmune-sleep crosstalk extend beyond infectious disease. In chronic conditions such as depression, schizophrenia, and neurodegenerative disorders (including Alzheimer's and Parkinson's diseases), elevations in inflammatory cytokines are frequently, but not uniformly, associated with sleep disturbances (Fernandez-Mendoza et al., 2017; Yirmiya et al., 2000; Zhu et al., 2014, 2018; Havekes et al., 2019; Atienza et al., 2018; Dzamko, 2023). Across studies, effect sizes are often small to moderate, and findings vary depending on sample characteristics, assay type and timing, mediation exposure, and disease stage. Nonetheless, the overall pattern supports a bidirectional relationship, wherein sleep disruption can amplify inflammatory signaling, while chronic inflammation can alter sleep architecture and quality-creating a self-reinforcing cycle that worsens disease outcomes (Shokri-Kojori et al., 2018; Voumvourakis et al., 2023). For example, in Alzheimer's disease, sleep fragmentation is associated with increased amyloid accumulation, microglial activation, and neuroinflammation, suggesting a mechanistic link between disrupted sleep and disease progression. In depression, insomnia is associated with elevated IL-1b and TNFa, which may contribute to treatment resistance and persistent fatigue, though the direction of causality remains uncertain and likely varies across individuals. These findings underscore that while inflammation-sleep associations are well-documented, they are complex, context-dependent, and not uniformly strong across cohorts. Understanding the temporal dynamics and dose-response characteristics of cytokine-sleep interactions remains an important area for future research. Emerging evidence from human studies suggests translational opportunities for targeting inflammation to improve sleep quality in clinical populations. Anti-cytokine therapies (such as TNFa inhibitors) may represent promising avenues for ameliorating sleep disturbances in inflammatory disease (Taylor-Gjevre et al., 2011). Studies have found that suppression of TNFa decreases obstructive sleep apnea therapies (Walsh et al., 2012), and also improves sleep quality in patients with ankylosing spondylitis (AS) (Karatas et al., 2018). In patients with rheumatoid arthritis and other rheumatic conditions, biologic therapies that target TNFa have been associated with improved subjective sleep quality, reduced fatigue, and better overall quality of life (Wu et al., 2022). Although data on IL-1b blockade remain limited, experimental studies suggest that antagonism of IL-1 signaling can normalize sleep continuity and restore homeostatic sleep responses (Schmidt et al., 2015). However, such interventions must be approached cautiously, as sleep itself supports immune recovery, and excessive suppression of inflammatory signaling could impair host defense. The development of targeted approaches that modulate specific cytokine-neurotransmitter circuits without broadly suppressing immune function will be key.

In conclusion, sleep and immune function are intricately intertwined through cytokine-mediated pathways that influence neural circuits controlling sleep and arousal. Far from being coincidental to illness, immune-driven changes in sleep appear to serve adaptive roles in recovery and defense. Future research clarifying these interactions at molecular, circuit, and behavioral levels will be essential for developing new strategies to manage sleep disturbances in both acute and chronic disease. More broadly, deepening our understanding of the neuroimmune regulation of sleep may provide insights into fundamental

questions of why sleep evolved, how it is maintained, and how it can be harnessed to improve human health.

CRediT authorship contribution statement

Nathan Zhang: Writing – original draft. **Kyungsoo Park:** Writing – review & editing. **Shinjae Chung:** Funding acquisition, Writing – review & editing. **Yeong Shin Yim:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Yeong Shin Yim reports financial support was provided by University of Pennsylvania. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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