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Mini Review

Sleep Disorders and Immune Dysregulation: Implications for Neurological Autoimmune Disease

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INTRODUCTION

Sleep is a fundamental biological process essential for survival, cognition, and systemic homeostasis. Beyond its well-established role in memory consolidation and neural restoration, sleep has emerged as a central regulator of immune function and inflammatory balance. Over the past two decades, advances in psychoneuroimmunology have reshaped the traditional view of sleep as a passive state, demonstrating instead that sleep constitutes an active biological window during which immune processes are dynamically orchestrated.

The conceptual framework linking sleep and immune regulation was formalized by Besedovsky et al. [1], who demonstrated that sleep facilitates antigen presentation, promotes T-cell activation, and enhances immunological memory formation. During early nocturnal sleep, particularly Slow-Wave Sleep (SWS), neuroendocrine conditions favor adaptive immune responses through reduced sympathetic tone, decreased cortisol secretion, and increased release of growth hormone and prolactin. These hormonal and autonomic changes promote lymphocyte trafficking to secondary lymphoid organs, optimizing immune surveillance and memory consolidation.

Experimental and clinical studies have since confirmed that sleep loss disrupts both innate and adaptive immunity. Acute sleep deprivation reduces Natural Killer (NK) cell cytotoxic activity and alters leukocyte trafficking, while chronic sleep restriction induces a sustained low-grade inflammatory state characterized by elevated interleukin-6 (IL-6), Tumor Necrosis Factor-α (TNF-α), and C-reactive protein levels (Irwin et al. [2]; Garbarino et al. [3]. These immune alterations are clinically relevant, as insufficient sleep has been associated with impaired vaccine responses, increased susceptibility to infection, and amplification of inflammatory disease risk.

From a neurological perspective, the sleep–immune axis is of particular relevance. Many neurological disorders are now recognized as conditions of immune dysregulation and neuroinflammation, including Multiple Sclerosis (MS), Autoimmune Encephalitis (AE), neuromyelitis optica spectrum disorders (NMOSD/MOGAD), and Myasthenia Gravis (MG). Sleep disturbances are highly prevalent in these conditions and are often attributed to pain, fatigue, disability, or psychological distress. However, accumulating evidence suggests that sleep disruption may actively contribute to immune activation and disease propagation rather than merely reflecting disease burden.

Importantly, immune mediators involved in neuroinflammation also participate in sleep–wake regulation. Cytokines such as IL-1β and TNF-α act on hypothalamic and brainstem nuclei to modulate sleep architecture, while circadian immune signals influence both sleep timing and inflammatory responses. This

shared neurobiological substrate suggests that sleep and immune regulation are tightly coupled processes within the central nervous system.

This article is intended as a narrative review, aiming to provide an integrated, clinico-mechanistic synthesis of current evidence on sleep–immune interactions, with a specific focus on neurological autoimmune diseases. By bridging experimental mechanisms with clinical observations, this review highlights sleep as a modifiable determinant of immune homeostasis and a potential therapeutic target in autoimmune neurology.

METHODS

A narrative approach was chosen to integrate heterogeneous mechanistic and clinical data that cannot be adequately captured through quantitative sybthesis alone. This work was designed as a narrative, non-systematic review intended to integrate experimental, translational, and clinical evidence on the relationship between sleep and immune function, with particular emphasis on neuro-immunological mechanisms and neurological autoimmune disorders.

A comprehensive literature search was conducted using PubMed/MEDLINE, Scopus, and Web of Science databases up to April 2025. Search terms included “sleep,” “sleep deprivation,” “circadian rhythm,” “immune system,” “cytokines,” “neuroinflammation,” “multiple sclerosis,” “autoimmune encephalitis,” “myasthenia gravis,” and “NMOSD.” Reference lists of key reviews and landmark experimental studies were manually screened to identify additional relevant publications.

Priority was given to peer-reviewed human clinical studies, translational research, and pivotal animal studies elucidating mechanistic pathways. Recent publications (approximately 2015–2024) were emphasized, while earlier foundational studies were retained when necessary to establish core biological concepts. Given the heterogeneity of study designs and outcomes, findings were synthesized qualitatively rather than through meta-analysis.

Sleep–Immune Mechanisms

Cytokine Regulation and Inflammatory Priming: Cytokines constitute a central molecular interface between sleep and immune function. Pro-inflammatory mediators such as IL-1β, TNF-α, and interferons are not only effectors of immune responses but also endogenous regulators of sleep. Krueger et al. [4] demonstrated that IL-1β and TNF-α promote NREM sleep when acutely elevated, whereas chronic elevation of these cytokines disrupts sleep continuity and architecture.

Sleep deprivation induces a shift toward a pro-inflammatory immune phenotype. Irwin et al. [2] showed that partial sleep loss activates nuclear factor κB (NF-κB)–dependent inflammatory pathways in circulating monocytes, resulting in increased production of IL-6 and TNF-α. This inflammatory priming persists beyond the period of sleep loss and accumulates with chronic restriction, creating a state of sustained low-grade inflammation.

From a neurological standpoint, this cytokine milieu has direct consequences. Peripheral inflammatory mediators can signal to the brain through humoral pathways, vagal afferents, and circumventricular organs, leading to microglial activation and astrocytic reactivity. In patients with underlying immune vulnerability, repeated sleep disruption may therefore lower the threshold for neuroinflammatory activation.

Circadian Rhythms and Immune Timing: Sleep is embedded within a circadian framework governed by the suprachiasmatic nucleus and peripheral molecular clocks. Nearly all immune cells express circadian clock genes that regulate their trafficking, differentiation, and effector functions. Scheiermann et al. [5] demonstrated that leukocyte migration follows circadian oscillations, with rhythmic expression of adhesion molecules and chemokines determining tissue homing.

Disruption of circadian rhythms—through shift work, jet lag, or irregular sleep schedules—desynchronizes immune timing and promotes inflammatory gene expression. Silver et al. [6] showed that antigen presentation and adaptive immune responses vary according to time of day, resulting in differential vaccine efficacy. In neurological autoimmune diseases, circadian misalignment may interact with disease-related fatigue, corticosteroid exposure, and autonomic dysfunction, further destabilizing immune homeostasis

Glymphatic Clearance and Neuroimmune Homeostasis: The glymphatic system plays a critical role in clearing metabolic waste, inflammatory mediators, and neurotoxic proteins from the brain, particularly during SWS. Xie et al. [7] demonstrated that deep sleep enhances cerebrospinal fluid–interstitial fluid exchange, facilitating efficient clearance of inflammatory by-products.

Impaired sleep continuity and reduced SWS may therefore contribute to accumulation of inflammatory metabolites within the central nervous system. In the

context of autoimmune neurology, this impaired clearance may prolong exposure of neural tissue to inflammatory signals, sustaining microglial activation and synaptic dysfunction.

Blood–Brain Barrier Integrity: Experimental evidence suggests that sleep restriction compromises blood–brain barrier (BBB) integrity. He et al. [8] reported that chronic sleep deprivation alters tight junction protein expression and increases BBB permeability in animal models. Although human data remain limited, these findings provide a plausible biological mechanism by which peripheral immune activation may more readily access the central nervous system under conditions of poor sleep [9]. BBB vulnerability is particularly relevant in autoimmune neurological diseases, where peripheral immune cell infiltration and antibody-mediated injury contribute to disease pathogenesis [10].

Disease-Specific Implications of Sleep Disorders in Neurological Autoimmune Diseases

Sleep and Immune Dysregulation in Multiple Sclerosis: Building on the general sleep immune mechanisms described above, multiple sclerosis represents a paradigmatic model in which these interactions become clinically manifest, insomnia, restless legs syndrome, periodic limb movements, circadian rhythm disruption, and sleep-disordered breathing are reported in more than half of MS patients and frequently coexist within the same individual. While traditionally interpreted as secondary to pain, fatigue, depression, or disability, accumulating evidence indicates that sleep disturbances in MS may actively modulate inflammatory activity and disease burden [11,12].

From a mechanistic perspective, MS is characterized by peripheral immune activation, blood–brain barrier disruption, and central microglial priming. Sleep deprivation amplifies these processes through sustained elevation of IL-6 and TNF-α, cytokines known to correlate with MS disease activity and fatigue severity. Irwin et al. [2] demonstrated that chronic sleep loss induces a persistent pro-inflammatory transcriptional profile in circulating immune cells, a phenomenon that may facilitate autoreactive T-cell trafficking into the central nervous system [13].

Clinically, poor sleep quality in MS correlates with increased fatigue, cognitive dysfunction, and reduced quality of life. Braley and Chervin [9] reported that sleep disorders independently predict fatigue severity, even after adjustment for depression and disability. Importantly, emerging data suggest that sleep disruption may influence relapse dynamics. Elevated inflammatory markers associated with insomnia and sleep fragmentation may lower the threshold for clinical exacerbations, particularly in patients with active disease or suboptimal disease-modifying therapy response.

Sleep-disordered breathing deserves special attention in MS. Intermittent nocturnal hypoxia induces oxidative stress and systemic inflammation, which may further compromise BBB integrity and exacerbate neuroinflammation. Recognition and treatment of obstructive sleep apnea in MS patients may therefore provide dual benefits: symptomatic improvement and potential attenuation of inflammatory burden [14].

Sleep Disturbances in Autoimmune Encephalitis: Autoimmune Encephalitis (AE) provides a unique model of direct immune-mediated disruption of sleep–wake regulatory networks. Profound sleep disturbances are frequently observed at disease onset and may persist well beyond the acute inflammatory phase. Clinical phenotypes include severe insomnia, hypersomnolence, circadian rhythm disorganization, and REM sleep behavior disorder [15].

Mechanistically, AE often involves antibodies targeting neuronal surface antigens expressed in limbic, hypothalamic, and brainstem structures critical for sleep regulation. Muñoz-Lopetegi et al. [7] demonstrated that sleep disturbances are not merely epiphenomena but reflect direct immune injury to sleep-regulating circuits. In anti-NMDA receptor encephalitis, for example, fragmentation of circadian rhythms and loss of normal sleep–wake cycling are frequently observed, reflecting hypothalamic and brainstem dysfunction.

Sleep disruption in AE may further perpetuate immune activation through sustained stress-axis engagement and cytokine release. Persistent insomnia or sleep fragmentation maintains elevated sympathetic tone and cortisol dysregulation, potentially delaying immune resolution and neurological recovery. Clinically, unrecognized sleep disorders may contribute to prolonged cognitive impairment, behavioral disturbances, and delayed functional improvement, even after immunological control of the disease [16].

Systematic sleep assessment in AE patients is therefore essential, both during the acute phase and in long-term follow-up. Recognition of sleep abnormalities may help differentiate ongoing immune activity from residual network dysfunction and guide rehabilitation strategies.

Sleep-Related Breathing Disorders in Myasthenia

Gravis: Myasthenia Gravis (MG) exemplifies the complex interplay between neuromuscular weakness, sleep physiology, and immune dysregulation. Sleep disturbances in MG are frequently underdiagnosed and include fragmented sleep, nocturnal hypoventilation, and obstructive sleep apnea. These abnormalities arise from respiratory muscle weakness, bulbar involvement, and reduced ventilatory reserve during sleep.

Prudlo et al. [10] demonstrated that sleep-disordered breathing is highly prevalent in clinically stable MG patients, emphasizing that respiratory sleep disorders may occur independently of overt daytime respiratory symptoms. From an immunological standpoint, intermittent hypoxia and sleep fragmentation induce systemic inflammation, oxidative stress, and sympathetic overactivation, potentially aggravating immune dysregulation.

Clinically, sleep-related breathing disorders in MG pose a significant diagnostic challenge. Nocturnal hypoventilation may mimic disease exacerbation, leading to inappropriate escalation of immunosuppressive therapy. Conversely, untreated sleep-disordered breathing may contribute to fatigue, morning weakness, and impaired quality of life, falsely attributed to myasthenic activity.

Objective sleep evaluation, including polysomnography or nocturnal capnography, should therefore be considered in MG patients presenting with disproportionate fatigue or morning weakness. Treatment of sleep-related breathing disorders with non-invasive ventilation may significantly improve symptoms and reduce diagnostic uncertainty.

Hypothalamic Involvement and Sleep Disruption in NMOSD and MOGAD: Neuromyelitis optica spectrum disorders (NMOSD) and myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) frequently involve the hypothalamus and brainstem, regions essential for sleep–wake regulation. Sleep disturbances in these disorders include hypersomnolence, circadian rhythm disruption, and, in rare cases, narcolepsy-like syndromes. Palma et al. [11] highlighted the role of orexin dysfunction in autoimmune neurological disease, linking hypothalamic inflammation to excessive daytime sleepiness and altered circadian regulation. In NMOSD, aquaporin-4 antibody–mediated astrocytopathy within hypothalamic nuclei may directly disrupt sleep–wake circuits, providing a mechanistic explanation for observed sleep phenotypes [17].

Clinically, hypersomnolence in NMOSD and MOGAD may serve as a marker of central inflammatory involvement and should prompt careful neuroimaging and immunological evaluation. Recognition of sleep abnormalities may therefore aid in early diagnosis and disease monitoring, particularly in patients with atypical presentations.

Integrative Perspective across Neurological Autoimmune Diseases: Across neurological autoimmune diseases, several convergent themes emerge. Sleep disturbances amplify immune dysregulation through cytokine signaling, circadian misalignment, microglial activation, and BBB vulnerability. Conversely, immune-mediated injury to sleep-regulating circuits further disrupts sleep architecture, creating a self-perpetuating cycle of neuroinflammation.

These observations challenge the traditional view of sleep disturbances as secondary symptoms and support their recognition as active modulators of disease trajectory. Incorporating sleep assessment into routine neuroimmunological care may therefore enhance diagnostic accuracy, improve symptom management, and potentially influence long-term outcome.

Linical Translation: Implications for Neurological Practice

The recognition of sleep as an active modulator of immune function carries important implications for clinical neurology, particularly in the management of immune-mediated and neuroinflammatory disorders. In routine practice, sleep disturbances are frequently underreported by patients and under-recognized by clinicians, often overshadowed by more overt neurological symptoms such as motor deficits, seizures, or cognitive impairment. However, the evidence reviewed here suggests that sleep disturbances may significantly influence inflammatory burden, symptom severity, and disease trajectory.

From a practical standpoint, neurologists should maintain a high index of suspicion for sleep disorders in patients presenting with disproportionate fatigue, fluctuating neurological symptoms, cognitive slowing, mood disturbances, or unexplained disease activity. Simple screening tools, including insomnia questionnaires, Epworth Sleepiness Scale, and targeted sleep history, may provide valuable initial insight. In selected cases, objective assessment with polysomnography, respiratory polygraphy, or actigraphy is warranted to characterize sleep architecture, identify sleep-disordered breathing, or detect circadian rhythm disruption [18].

Importantly, sleep evaluation may aid in differential diagnosis. In myasthenia gravis, nocturnal hypoventilation and obstructive sleep apnea may mimic disease exacerbation, leading to unnecessary escalation of immunosuppressive therapy. In multiple sclerosis, fatigue

Table 1: Sleep disorders, immune mechanisms, and clinical implications in neurological autoimmune diseases.

Sleep Disorder	Immune / Neuroimmune Mechanisms	Neurological Autoimmune Disease	Clinical Implications
Insomnia	Increased IL-6 and TNF-α, HPA axis dysregulation, Th17/ Treg imbalance [1,2]	Multiple sclerosis	Fatigue, cognitive impairment, possible relapse amplification
Sleep fragmentation	Microglial priming, circadian immune desynchronization [3,4]	Autoimmune encephalitis	Persistent neuropsychiatric symptoms
Obstructive sleep apnea	Intermittent hypoxia, systemic inflammation, BBB vulnerability [5,6]	Myasthenia gravis	Mimics disease worsening, underdiagnosed respiratory burden
Hypersomnia	Hypothalamic inflammation, orexin dysfunction [7,8]	NMOSD, MOGAD	Marker of central inflammatory involvement
REM sleep behavior disorder	Brainstem immune-mediated injury [9]	Autoimmune encephalitis	Indicator of brainstem involvement
Poor sleep quality	Impaired glymphatic clearance, inflammatory metabolite accumulation [10]	Neuroinflammatory disorders	Sustained neuroinflammation

driven by sleep fragmentation may be misinterpreted as inflammatory disease activity. In autoimmune encephalitis, persistent sleep disturbances may reflect ongoing network dysfunction rather than active immune inflammation. Integrating sleep assessment into clinical reasoning therefore enhances diagnostic precision and therapeutic decision-making.

Beyond symptom management, addressing sleep disturbances may have broader immunological consequences. Improved sleep continuity is associated with reduced levels of pro-inflammatory cytokines such as IL-6 and TNF-α and restoration of circadian immune regulation. Although direct causal evidence in neurological autoimmune diseases remains limited, these findings support the concept that sleep represents a modifiable factor within the neuroimmune axis [19].

Therapeutic Implications and Future Directions

Targeting sleep disturbances in neurological autoimmune diseases represents a promising and underutilized therapeutic avenue. Non-pharmacological interventions, particularly cognitive behavioral therapy for insomnia (CBT-I), have demonstrated efficacy in improving sleep quality across a range of chronic medical conditions and may be safely applied in neuroimmunological populations.By reducing hyperarousal and restoring sleep continuity, CBT-I may indirectly attenuate inflammatory signaling and improve daytime functioning.

Treatment of sleep-disordered breathing is of particular importance. Continuous Positive Airway Pressure (CPAP) therapy in patients with obstructive sleep apnea reduces intermittent hypoxia, sympathetic activation, and systemic inflammation. In patients with multiple sclerosis or myasthenia gravis, addressing sleep-related breathing disorders may improve fatigue, cognitive performance, and overall quality of life, while potentially reducing inflammatory stress on the central nervous system.

Pharmacological approaches also merit consideration. Melatonin, beyond its role in circadian entrainment, exhibits immunomodulatory, antioxidant, and neuroprotective properties. Experimental studies suggest that melatonin may influence T-cell differentiation and cytokine production, although clinical data in autoimmune neurology remain limited. Chronotherapy—aligning immunomodulatory treatments with circadian rhythms—represents another emerging strategy, supported by evidence that immune responsiveness varies across the day.

From a research perspective, future studies should prioritize longitudinal designs integrating objective sleep measures, circadian biomarkers, immune profiling, and clinical outcomes. Identifying sleep-related immune signatures may enable the development of novel biomarkers reflecting disease activity, treatment response, or relapse risk. Such approaches may ultimately support more personalized and temporally optimized therapeutic strategies in autoimmune neurology.

INTEGRATION OF TABLE

To enhance clarity and clinical applicability, the main sleep disorders, underlying immune mechanisms, and disease-specific neurological implications discussed in this review are summarized in [Table 1].

CONCLUSION

Sleep is a central regulator of immune homeostasis and a critical interface between the nervous and immune systems. Far from representing a passive state, sleep constitutes a biologically active period during which immune surveillance, inflammatory balance, and neuroimmune communication are optimized. In neurological autoimmune diseases, sleep disturbances should not be regarded as secondary or incidental symptoms. Instead, they emerge as active modulators of immune dysregulation and disease expression. Recognizing and treating sleep disorders may therefore improve symptom control, refine diagnostic accuracy, and potentially influence long-term neurological

outcomes. In an era where neuroimmunology increasingly defines neurological disease mechanisms, integrating sleep assessment and management into routine clinical practice represents a rational, accessible, and potentially impactful strategy.

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