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PSYCHIATRIC DISORDERS AS DYSFUNCTIONS OF SLEEP–IMMUNE–BRAIN NETWORK DYNAMICS: A SYSTEMS-LEVEL NEUROCOGNITIVE FRAMEWORKABSTRACT

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ABSTRACT: **Background:**Sleep disturbances and neuroimmune activation are increasingly recognized as core processes in the pathophysiology of psychiatric disorders. However, these domains have largely been investigated in isolation, limiting the development of integrative mechanistic frameworks capable of explaining transdiagnostic symptom overlap, clinical heterogeneity, and treatment resistance.**Objective:** This integrative review proposes a systems-level neurocognitive framework in which psychiatric disorders are conceptualized as emergent phenomena arising from dysregulated interactions among sleep regulation, neuroimmune signaling, and large-scale brain network dynamics.**Methods:** We conducted a narrative integrative review synthesizing evidence from sleep science, psychoneuroimmunology, and network neuroscience across mood, anxiety, trauma-related, and psychotic disorders. Findings from experimental, clinical, and neuroimaging studies were examined to identify convergent mechanisms linking sleep disruption, inflammatory activation, and neural network instability.**Results:** Converging evidence indicates that circadian misalignment, stress-system dysregulation, microglial and astroglial activation, neurotransmitter imbalance, and kynurenine pathway metabolism interact through nonlinear feedback loops that destabilize cortico-limbic circuits and large-scale brain networks, including default mode, salience, and executive control systems. These interactions promote maladaptive attractor states characterized by impaired synaptic plasticity, altered network connectivity, and persistent hyperarousal. **Conclusions:**Conceptualizing psychiatric disorders as disorders of coupled sleep–immune–brain systems provides a unifying mechanistic framework that transcends traditional diagnostic boundaries. This systems-level perspective highlights sleep and neuroimmune processes as central regulators of neural network stability and identifies promising targets for biomarker development and mechanism-based, precision-oriented interventions.

Keywords: Sleep–immune–brain systems. Neuroinflammation. Network neuroscience. Transdiagnostic psychopathology. Circadian dysregulation. Microglial activation. Kynurenine pathway. Systems psychiatry. Neural network dynamics. Precision psychiatry.

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1. INTRODUCTION

Psychiatric disorders represent one of the leading causes of disability worldwide and constitute a major public health challenge. Despite decades of research, their underlying neurobiological mechanisms remain only partially understood. Traditional diagnostic systems have largely conceptualized mental disorders as discrete categorical entities defined by clusters of symptoms, an approach that has facilitated clinical communication but has proven limited in explaining biological heterogeneity, symptom overlap, and high rates of comorbidity across psychiatric conditions (Insel et al., 2010; Kotov et al., 2017).

Accumulating evidence from neuroscience, psychoneuroimmunology, and systems biology increasingly challenges reductionist models of psychopathology that emphasize isolated neurotransmitter dysfunctions or localized brain abnormalities. Instead, psychiatric disorders appear to reflect disturbances in distributed and interacting biological systems involved in sleep regulation, immune function, stress responsivity, and large-scale brain network dynamics (McEwen, 1998; Miller & Raison, 2016; Bassett & Sporns, 2017). This shift has motivated the emergence of transdiagnostic and dimensional approaches that seek to identify shared mechanisms underlying diverse psychiatric phenotypes rather than disorder-specific abnormalities.

Among the biological processes implicated in transdiagnostic psychopathology, sleep dysregulation has emerged as one of the most robust and pervasive features across diagnostic categories. Insomnia, circadian rhythm disruption, and sleep fragmentation are highly prevalent in mood, anxiety, trauma-related, and psychotic disorders, often preceding symptom onset and predicting illness recurrence, chronicity, and functional impairment (Harvey, 2001; Baglioni et al., 2011; Wulff et al., 2010). Experimental and longitudinal studies further demonstrate that sleep disruption exerts causal effects on emotional regulation, cognitive control, and stress responsivity, suggesting that sleep disturbances represent an upstream vulnerability factor rather than a secondary epiphenomenon (Walker, 2009; Goldstein-Piekarski et al., 2015).

Parallel lines of research highlight the central role of neuroimmune activation in the pathophysiology of psychiatric disorders. Elevated levels of pro-inflammatory cytokines and acute-phase proteins have been consistently reported across mood, anxiety, and psychotic disorders and are associated with symptom severity, cognitive impairment, treatment resistance, and adverse clinical outcomes (Dantzer et al., 2008; Miller et al., 2009; Osimo et al.,

2020). Contemporary models in immunopsychiatry propose that inflammatory signaling influences brain function through multiple pathways, including modulation of neurotransmitter systems, synaptic plasticity, and neural circuit dynamics (Wohleb et al., 2016; Khandaker et al., 2017).

Despite the growing recognition that both sleep disturbances and neuroimmune activation are core features of psychiatric disorders, these domains have largely been investigated in isolation. Sleep research has traditionally focused on behavioral, circadian, and neurophysiological mechanisms, whereas immunopsychiatric models have emphasized inflammatory signaling and stress-related immune pathways, often without integrating sleep-related processes. This fragmentation has limited the development of comprehensive mechanistic frameworks capable of explaining how sleep disruption and immune dysregulation interact to shape brain function and behavior.

Importantly, emerging evidence suggests that sleep and neuroimmune processes converge on large-scale brain networks that underlie cognition, emotion, and stress regulation. Functional neuroimaging studies indicate that both sleep deprivation and inflammatory activation disrupt the organization and connectivity of cortico-limbic circuits and large-scale networks, including the default mode, salience, and executive control networks (Menon, 2011; Buckner et al., 2008). Alterations in these networks have been implicated in transdiagnostic symptom dimensions such as emotional dysregulation, rumination, threat hypervigilance, and cognitive inflexibility, raising the possibility that psychiatric disorders may reflect instability within interconnected sleep–immune–brain systems rather than isolated dysfunctions within single biological domains.

From a systems neuroscience perspective, psychiatric disorders can therefore be conceptualized as emergent phenomena arising from nonlinear interactions among multiple regulatory systems. Sleep disruption promotes stress-system activation and inflammatory signaling, while immune mediators, in turn, alter sleep architecture, circadian rhythms, and neural excitability. These reciprocal interactions can generate self-reinforcing feedback loops that stabilize maladaptive physiological states over time, consistent with dynamical systems models of psychopathology that emphasize reduced flexibility and pathological attractor states (Friston, 2010; McEwen, 1998).

In this context, there is a clear need for integrative theoretical frameworks that explicitly link sleep regulation, neuroimmune signaling, and brain network dynamics within a

unified model of psychiatric pathophysiology. Addressing this gap is essential for advancing transdiagnostic approaches, refining psychiatric classification, and informing mechanism-based and precision-oriented interventions.

Accordingly, this integrative narrative review proposes a systems-level neurocognitive framework in which psychiatric disorders are conceptualized as dysfunctions of coupled sleep–immune–brain network dynamics. By synthesizing evidence across molecular, cellular, circuit, and network levels, we aim to (i) delineate the key mechanisms through which sleep disruption and neuroimmune activation interact, (ii) elucidate how these interactions destabilize large-scale brain networks, and (iii) highlight the implications of this framework for transdiagnostic understanding, biomarker development, and clinical intervention.

2. Conceptual and Theoretical Framework

2.1 From Reductionist Models to Systems-Level Psychiatry

Traditional neurobiological models of psychiatric disorders have predominantly relied on reductionist explanations centered on neurotransmitter imbalances or localized brain abnormalities. Although these approaches have contributed to important pharmacological advances, they have proven insufficient to account for the marked heterogeneity, symptom overlap, and high rates of comorbidity observed across psychiatric conditions (Insel et al., 2010; Kotov et al., 2017). Moreover, reductionist models struggle to explain why diverse disorders share common biological features and why treatment responses vary substantially among individuals with ostensibly similar diagnoses.

Advances in systems biology and network neuroscience have increasingly challenged these limitations by emphasizing that brain function emerges from dynamic interactions among distributed biological systems rather than from isolated components (Bassett & Sporns, 2017). Within this perspective, psychiatric disorders are understood as disturbances in multilevel regulatory systems involving sleep–wake regulation, stress responsivity, immune signaling, and large-scale neural network organization (McEwen, 1998; Menon, 2011). This conceptual shift provides a foundation for integrating sleep and neuroimmune processes into contemporary models of psychopathology.

2.2 The Sleep–Immune–Brain Systems Model (SIBSM)

Building on this systems-level perspective, we propose the Sleep–Immune–Brain Systems Model (SIBSM) as an integrative framework for conceptualizing psychiatric disorders. The SIBSM posits that sleep regulation, neuroimmune signaling, and large-scale brain network dynamics constitute interdependent subsystems operating within a shared regulatory architecture. Dysregulation within and between these subsystems gives rise to maladaptive system states that manifest clinically as psychiatric symptoms.

Within this model, sleep disturbances and neuroimmune activation are not treated as secondary or epiphenomenal features of psychiatric disorders. Instead, they are conceptualized as core drivers of neural network instability that shape emotional regulation, cognitive processing, and stress responsiveness. The SIBSM therefore reframes psychiatric disorders as emergent phenomena arising from dysfunctional interactions among coupled biological systems, rather than as discrete disease entities localized to specific neurotransmitters or brain regions.

2.3 Multilevel Architecture of Sleep–Immune–Brain Interactions

A central premise of the SIBSM is that sleep–immune–brain interactions operate across multiple levels of biological organization. At the molecular level, circadian clock genes, inflammatory signaling cascades, neurotransmitter metabolism, and stress-related molecular pathways regulate temporal coordination and homeostasis (Wulff et al., 2010; Musiek & Holtzman, 2016). Disruptions at this level alter the timing and magnitude of physiological processes essential for neural stability.

At the cellular level, neuroimmune interactions involving microglia and astrocytes play a critical role in synaptic remodeling, plasticity, and homeostatic regulation. Sleep loss promotes microglial priming and astrocytic dysregulation, amplifying inflammatory responses and altering synaptic structure and function (Lucassen et al., 2010; Wohleb et al., 2016). These cellular processes provide a mechanistic bridge between peripheral immune activation and central neural dysfunction.

At the circuit level, sleep and neuroimmune disturbances converge on cortico-limbic pathways involved in emotional regulation, memory processing, and stress reactivity. Altered prefrontal–limbic connectivity, hippocampal plasticity, and amygdala responsivity have been

observed in association with both sleep disruption and inflammatory activation (Walker, 2009; Goldstein-Piekarski et al., 2015).

Finally, at the network level, sleep and immune processes influence the organization and dynamics of large-scale brain networks, including the default mode, salience, and executive control networks. Dysregulation at this level alters the balance between network integration and segregation, impairing cognitive flexibility, emotional regulation, and adaptive behavior (Buckner et al., 2008; Menon, 2011).

2.4 Dynamic Interactions, Feedback Loops, and Attractor States

A defining feature of the SIBSM is the recognition that interactions among sleep regulation, immune signaling, and brain networks are governed by nonlinear dynamics and reciprocal feedback loops. Sleep disruption activates stress-related and inflammatory pathways, while neuroimmune mediators alter sleep architecture, circadian timing, and neuronal excitability. These bidirectional influences create self-reinforcing cycles that may stabilize maladaptive physiological states over time (Irwin, 2019; Miller & Raison, 2016).

From a dynamical systems perspective, psychiatric disorders can be conceptualized as pathological attractor states characterized by reduced system flexibility, impaired adaptive capacity, and persistent hyperarousal (Friston, 2010). Within such states, neural networks become less responsive to environmental inputs and more constrained by internally generated activity patterns, contributing to symptom persistence and treatment resistance.

2.5 Transdiagnostic Organization of Psychopathology

Within the SIBSM framework, traditional diagnostic categories are viewed as phenotypic expressions of shared underlying system-level dysregulation. Mood, anxiety, trauma-related, and psychotic disorders reflect different configurations and degrees of sleep–immune–brain instability rather than distinct disease entities with unique etiologies.

Variability in the timing, intensity, and interaction of sleep disturbances, inflammatory processes, and network-level alterations gives rise to heterogeneous clinical presentations and trajectories. This transdiagnostic perspective provides a mechanistic explanation for symptom overlap and comorbidity and aligns with dimensional models of psychopathology such as the Research Domain Criteria (RDoC) and hierarchical taxonomies of mental disorders (Insel et al., 2010; Kotov et al., 2017).

2.6 Implications for Psychiatric Theory

By integrating sleep regulation, neuroimmune signaling, and brain network dynamics into a unified framework, the SIBSM challenges static and categorical conceptions of mental illness. Psychiatric disorders are reconceptualized as disorders of regulation within dynamic biological systems, shaped by feedback loops operating across molecular, cellular, circuit, and network levels.

This systems-level perspective provides a theoretical bridge between biological, psychological, and environmental factors and offers a foundation for advancing transdiagnostic research, biomarker discovery, and mechanism-based clinical interventions. Importantly, it situates sleep and neuroimmune processes as central regulators of neural network stability, thereby redefining their role in psychiatric theory and practice.

3. Epidemiology and Clinical Relevance of Sleep–Immune–Brain Dysregulation

Within the SIBSM framework, sleep dysregulation and neuroimmune activation are not independent pathological processes but tightly coupled components of a unified regulatory system. Disruptions in sleep–wake regulation propagate across neuroendocrine, autonomic, circadian, and immune pathways, generating cascading effects on neural circuits and large-scale brain network dynamics. Understanding these mechanisms requires an integrative, multilevel perspective that captures both linear effects and nonlinear feedback interactions.

3.1 Stress-System Dysregulation and HPA Axis Dynamics

One of the principal pathways linking sleep disturbance and neuroimmune activation involves dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Chronic sleep disruption is consistently associated with altered cortisol secretion patterns, including elevated nocturnal cortisol levels, flattened diurnal rhythms, and impaired negative feedback regulation (McEwen, 1998; Irwin, 2019). These alterations reflect sustained activation of stress-response systems and contribute to a physiological state of hyperarousal.

Persistent HPA axis activation exerts complex and time-dependent effects on immune function. While acute glucocorticoid signaling is typically anti-inflammatory, chronic stress exposure and prolonged cortisol release may induce glucocorticoid resistance, thereby facilitating pro-inflammatory immune states (Miller et al., 2009; Slavich & Irwin, 2014). This

paradoxical shift provides a mechanistic explanation for the co-occurrence of sleep disturbance, chronic stress, and low-grade inflammation observed across psychiatric disorders.

Within the SIBSM, HPA axis dysregulation functions as a critical coupling mechanism between sleep and immune subsystems, amplifying perturbations and contributing to the stabilization of maladaptive system states.

3.2 Autonomic Imbalance and Hyperarousal States

Autonomic nervous system dysregulation represents another core mechanism linking sleep disruption, inflammation, and psychopathology. Increased sympathetic activity and reduced parasympathetic tone have been documented in individuals with insomnia, mood disorders, and anxiety-related conditions (Goldstein-Piekarski et al., 2015). This autonomic imbalance sustains physiological hyperarousal, interfering with sleep initiation and maintenance and reinforcing stress-system activation.

Sympathetic signaling influences immune activity through adrenergic pathways that promote the production of pro-inflammatory cytokines, whereas parasympathetic activity exerts anti-inflammatory effects via the cholinergic anti-inflammatory pathway (Irwin, 2019). Dysregulation of autonomic balance therefore represents a key mechanism through which sleep disturbances and immune activation reciprocally reinforce one another.

From a systems perspective, sustained hyperarousal states reduce physiological flexibility and bias the system toward persistent activation, thereby destabilizing neural network dynamics and increasing vulnerability to psychiatric symptoms.

3.3 Circadian Disruption and Molecular Clock Mechanisms

Circadian rhythms coordinate physiological processes across neural, endocrine, metabolic, and immune systems. Disruption of circadian timing—whether due to behavioral factors, environmental misalignment, or genetic vulnerability—has profound consequences for sleep regulation and immune function (Wulff et al., 2010; Musiek & Holtzman, 2016).

Alterations in clock gene expression have been implicated in mood, psychotic, and stress-related disorders, supporting the view that circadian dysregulation constitutes a core transdiagnostic dimension of psychopathology. Experimental studies demonstrate that circadian misalignment shifts immune signaling toward pro-inflammatory states, alters cytokine rhythmicity, and disrupts immune cell trafficking (Irwin, 2019).

Within the SIBSM framework, circadian disruption acts as an upstream driver that simultaneously destabilizes sleep architecture, stress responsivity, and immune regulation, thereby exerting cascading effects on neural network organization.

3.4 Neuroimmune Signaling and Inflammatory Cascades

At the molecular and cellular levels, sleep disruption activates inflammatory signaling pathways, including nuclear factor kappa B (NF-κB) and inflammasome-related mechanisms that regulate the production of pro-inflammatory cytokines and chemokines (Dantzer et al., 2008; Miller & Raison, 2016). These immune mediators influence brain function through humoral, neural, and cellular routes, facilitating bidirectional communication between peripheral immune systems and the central nervous system.

Within the brain, cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α modulate neuronal excitability, synaptic transmission, and plasticity. Pro-inflammatory signaling alters glutamatergic and GABAergic balance within cortico-limbic circuits, contributing to emotional dysregulation, cognitive impairment, and heightened stress sensitivity (Wohleb et al., 2016).

Neuroimmune signaling thus represents a primary mechanism through which peripheral inflammation is translated into neural circuit and network-level dysfunction within the SIBSM.

3.5 Feedback Loops and System-Level Instability

A defining feature of sleep–immune–brain dysregulation is the presence of reciprocal feedback loops that promote system-level instability. Sleep loss activates stress and immune pathways, which in turn exacerbate sleep disturbances through effects on circadian regulation, autonomic tone, and neural excitability. Over time, these interactions give rise to stable but maladaptive physiological configurations characterized by persistent hyperarousal, inflammatory activation, and reduced adaptive capacity.

From a dynamical systems perspective, psychiatric disorders can therefore be conceptualized as conditions of reduced flexibility in which the system becomes trapped in pathological attractor states (Friston, 2010). Within these states, neural networks exhibit constrained dynamics and diminished responsiveness to environmental input, providing a mechanistic substrate for symptom persistence, relapse, and treatment resistance.

Sleep dysregulation and neuroimmune activation emerge from complex and reciprocal interactions among neuroendocrine, autonomic, circadian, and inflammatory systems. Within the Sleep–Immune–Brain Systems Model (SIBSM), these processes are conceptualized as interdependent components of a unified regulatory architecture rather than as isolated abnormalities. Dysregulation within this architecture generates cascading effects across neural circuits and large-scale brain networks, ultimately giving rise to transdiagnostic psychiatric phenotypes (McEwen, 1998; Irwin, 2019; Miller & Raison, 2016).

4. Pathophysiological Mechanisms of Sleep–Immune–Brain Dysregulation

4.1 Stress-System Dysregulation and HPA Axis Dynamics

A central pathway linking sleep disturbances and neuroinflammation involves dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis. Chronic sleep disruption is consistently associated with altered cortisol secretion patterns, including elevated nocturnal cortisol levels, flattened diurnal rhythms, and impaired negative feedback regulation (McEwen, 1998; Irwin, 2019). These alterations reflect sustained activation of stress-response systems and contribute to persistent physiological hyperarousal.

Persistent HPA axis activation exerts complex and time-dependent effects on immune function. While acute glucocorticoid signaling typically suppresses inflammatory responses, chronic stress exposure and prolonged cortisol release may induce glucocorticoid resistance, thereby facilitating pro-inflammatory immune states (Miller et al., 2009; Slavich & Irwin, 2014). This paradoxical effect provides a mechanistic link between chronic stress, sleep disruption, and the low-grade inflammation observed across mood, anxiety, trauma-related, and psychotic disorders.

Within the SIBSM framework, HPA axis dysregulation functions as a critical coupling mechanism between sleep and immune subsystems, amplifying perturbations and contributing to the stabilization of maladaptive system states.

4.2 Autonomic Imbalance and Hyperarousal States

Autonomic nervous system dysregulation constitutes another core mechanism underlying sleep disturbances and psychiatric disorders. Increased sympathetic activity and reduced parasympathetic tone have been consistently documented in individuals with

insomnia, anxiety disorders, and mood disorders, reflecting a state of sustained physiological hyperarousal (Goldstein-Piekarski et al., 2015; Irwin, 2019). This autonomic imbalance interferes with sleep initiation and maintenance and perpetuates stress-system activation.

Sympathetic activation modulates immune function through adrenergic signaling pathways that promote the production of pro-inflammatory cytokines, whereas parasympathetic activity exerts anti-inflammatory effects via the cholinergic anti-inflammatory pathway (Irwin, 2019). Dysregulation of autonomic balance therefore represents a key mechanism through which sleep disturbances and inflammatory activation reciprocally reinforce one another.

From a systems-level perspective, autonomic imbalance contributes to the entrenchment of pathological attractor states by maintaining high-arousal physiological conditions that destabilize neural network dynamics and reduce adaptive flexibility.

4.3 Circadian Disruption and Molecular Clock Mechanisms

Circadian rhythms orchestrate physiological processes across neuroendocrine, metabolic, and immune systems. Disruption of circadian timing—whether due to behavioral, environmental, or genetic factors—has profound consequences for sleep regulation, immune function, and brain physiology (Wulff et al., 2010; Musiek & Holtzman, 2016).

Alterations in clock gene expression and circadian phase alignment have been implicated in mood, psychotic, and stress-related disorders, suggesting that circadian dysregulation represents a core transdiagnostic dimension of psychopathology. Experimental studies demonstrate that circadian misalignment alters cytokine rhythmicity, shifts immune signaling toward pro-inflammatory states, and disrupts immune cell trafficking (Irwin, 2019).

Within the SIBSM, circadian dysregulation acts as an upstream driver that simultaneously destabilizes sleep architecture and neuroimmune regulation, thereby exerting cascading effects on neural circuit function and large-scale brain network organization.

4.4 Neuroimmune Signaling and Inflammatory Cascades

At the molecular level, sleep disruption activates inflammatory signaling pathways, including nuclear factor kappa B (NF-κB) and inflammasome-related mechanisms that regulate the production of pro-inflammatory cytokines and chemokines (Dantzer et al., 2008; Miller & Raison, 2016). These immune mediators influence brain function through multiple

routes, including humoral, neural, and cellular pathways, facilitating bidirectional communication between peripheral immune systems and the central nervous system.

Within the central nervous system, neuroimmune signaling modulates neuronal excitability, synaptic transmission, and plasticity. Cytokines such as interleukin-1β, interleukin-6, and tumor necrosis factor-α alter glutamatergic and GABAergic transmission, thereby influencing excitatory–inhibitory balance within cortico-limbic circuits (Wohleb et al., 2016). These effects are central to emotional regulation, cognitive control, and stress responsiveness and provide a mechanistic substrate for psychiatric symptomatology.

Within the SIBSM framework, neuroimmune signaling represents a primary mechanism through which peripheral immune activation is translated into circuit- and network-level neural dysfunction.

4.5 Feedback Loops and System-Level Instability

A defining feature of sleep–immune–brain dysregulation is the presence of self-reinforcing feedback loops. Sleep disruption activates stress-related and immune pathways, which in turn exacerbate sleep disturbances through effects on circadian regulation, autonomic tone, and neural excitability. Over time, these reciprocal interactions give rise to stable but maladaptive physiological configurations characterized by persistent hyperarousal, inflammatory activation, and network-level dysregulation (Irwin, 2019; Miller & Raison, 2016).

From a dynamical systems perspective, psychiatric disorders can therefore be conceptualized as conditions of reduced physiological flexibility and impaired adaptive capacity. Within the SIBSM, these conditions correspond to pathological attractor states that constrain neural network dynamics and perpetuate transdiagnostic psychopathology (Friston, 2010).

5. Neurobiological Mechanisms and Network Dynamics in the SIBSM Framework

Sleep dysregulation and neuroimmune activation converge across multiple levels of brain organization, from molecular signaling and cellular dynamics to circuit function and large-scale network architecture. Within the SIBSM framework, these processes are conceptualized as interacting forces that reshape synaptic plasticity, neurotransmitter systems, and network-level dynamics underlying cognition, emotion, and stress responsiveness (Lucassen et al., 2010; Wohleb et al., 2016; Bassett & Sporns, 2017). Psychiatric disorders thus

emerge not from isolated neural abnormalities but from distributed disruptions in neural organization driven by coupled sleep–immune processes.

5.1 Microglial Activation and Synaptic Remodeling

Microglia play a central role in translating immune signals into neural change. Under physiological conditions, microglia regulate synaptic pruning, plasticity, and homeostasis throughout development and adulthood. Chronic sleep disruption promotes microglial priming and activation, leading to exaggerated inflammatory responses and alterations in synaptic structure and function (Lucassen et al., 2010; Wohleb et al., 2016).

Activated microglia release pro-inflammatory cytokines, reactive oxygen species, and neuroactive mediators that influence neuronal excitability and synaptic transmission. These processes result in maladaptive synaptic remodeling, particularly within cortico-limbic circuits implicated in emotional regulation and memory processing. Experimental studies demonstrate that sleep deprivation alters dendritic spine density and synaptic efficacy in prefrontal and hippocampal regions, providing a neurobiological substrate for cognitive and affective disturbances observed across psychiatric disorders (Walker, 2009; Duman & Aghajanian, 2012).

Astrocytes further modulate neuroimmune signaling by regulating neurotransmitter uptake, metabolic support, and blood–brain barrier integrity. Dysregulation of astrocytic function amplifies synaptic instability and network-level dysfunction, highlighting the importance of glial–neuronal interactions within the SIBSM framework (Lucassen et al., 2010).

5.2 Neurotransmitter Systems and Immune Modulation

Sleep–immune interactions exert profound effects on neurotransmitter systems central to psychiatric disorders. Monoaminergic pathways—including serotonergic, dopaminergic, and noradrenergic systems—are highly sensitive to both sleep states and inflammatory signaling. Sleep disruption alters monoamine release, receptor sensitivity, and synaptic availability, while inflammatory mediators influence neurotransmitter metabolism and signaling efficiency (Miller et al., 2009; Wohleb et al., 2016).

A critical mechanism linking neuroinflammation and neurotransmission involves the kynurenine pathway of tryptophan metabolism. Pro-inflammatory cytokines activate indoleamine 2,3-dioxygenase (IDO), shifting tryptophan metabolism toward kynurenine derivatives that modulate glutamatergic and dopaminergic signaling. Neuroactive metabolites

such as quinolinic acid and kynurenic acid alter excitatory–inhibitory balance and synaptic plasticity, thereby contributing to cognitive dysfunction and affective symptoms (Dantzer et al., 2008; Miller & Raison, 2016).

Glutamatergic and GABAergic systems are particularly vulnerable to sleep loss and inflammatory activation. Pro-inflammatory cytokines enhance glutamatergic transmission while reducing GABAergic inhibition, resulting in increased cortical excitability and impaired network stability. Within the SIBSM, these neurotransmitter alterations represent key mechanisms linking immune activation and sleep disruption to large-scale network dysregulation (Duman & Aghajanian, 2012).

5.3 Cortico-Limbic Circuit Dysregulation

Cortico-limbic circuits constitute a critical interface between sleep–immune processes and psychiatric symptom expression. The prefrontal cortex, amygdala, hippocampus, and anterior cingulate cortex form interconnected networks supporting emotional regulation, threat detection, memory processing, and cognitive control (Buckner et al., 2008; Menon, 2011).

Sleep deprivation reduces prefrontal inhibitory control over limbic regions, resulting in heightened amygdala reactivity and impaired top-down emotional regulation. Neuroinflammatory processes further modulate cortico-limbic circuitry by altering neuronal excitability and synaptic connectivity within these regions. Functional neuroimaging studies demonstrate that inflammatory activation is associated with altered connectivity between prefrontal and limbic regions, supporting a central role for neuroimmune mechanisms in circuit-level dysregulation across psychiatric disorders (Goldstein-Piekarski et al., 2015; Wohleb et al., 2016).

Within the SIBSM, cortico-limbic dysregulation represents a primary pathway through which sleep and immune disturbances are translated into affective and cognitive symptomatology.

5.4 Large-Scale Brain Network Dynamics

Beyond localized circuits, sleep and neuroimmune processes exert powerful effects on large-scale brain networks underlying cognition and emotion. Functional neuroimaging studies indicate that both sleep deprivation and inflammatory activation disrupt the activity and

connectivity of the default mode network, salience network, and executive control network (Buckner et al., 2008; Menon, 2011).

The default mode network is implicated in self-referential processing and rumination, the salience network in threat detection and emotional relevance, and the executive control network in cognitive regulation and decision-making. Dysregulation of these networks alters the balance between internally and externally oriented processing and contributes to maladaptive information-processing patterns characteristic of psychiatric disorders.

From a network neuroscience perspective, psychiatric disorders can therefore be conceptualized as conditions of altered network dynamics rather than localized brain pathology. Sleep–immune interactions modulate the balance between integration and segregation within neural systems, influencing network flexibility, stability, and resilience. Persistent disruption of these dynamics represents a final common pathway linking sleep disturbances and neuroinflammation to transdiagnostic psychiatric phenotypes (Bassett & Sporns, 2017).

5.5 Developmental and Longitudinal Implications

Sleep and neuroimmune processes play a critical role in neurodevelopment. During sensitive developmental periods, sleep patterns and immune signaling shape synaptic pruning, circuit maturation, and large-scale network organization. Disruptions in sleep–immune interactions during childhood and adolescence may therefore confer long-term vulnerability to psychiatric disorders (McLaughlin et al., 2014; Entringer et al., 2015).

Longitudinal evidence suggests that chronic sleep disturbances and sustained inflammatory activation lead to progressive alterations in neural connectivity, cognitive functioning, and emotional regulation. Within the SIBSM framework, these findings support the hypothesis that sleep–immune dysregulation not only precipitates psychiatric symptoms but also contributes to their persistence, recurrence, and progression across the lifespan.

6. Pharmacological and Therapeutic Implications of the SIBSM Framework

The recognition of sleep dysregulation and neuroimmune activation as core mechanisms in psychiatric disorders necessitates a reconceptualization of therapeutic strategies. Traditional psychopharmacological models have primarily emphasized neurotransmitter modulation; however, accumulating evidence indicates that therapeutic

efficacy is also mediated by effects on sleep architecture, circadian regulation, immune signaling, and large-scale brain network dynamics (Krystal & Edinger, 2008; Irwin, 2019). Within the SIBSM framework, both pharmacological and non-pharmacological interventions can be conceptualized as modulators of system-level organization rather than as isolated symptom-targeting agents.

6.1 Antidepressants as Network-Modulating Agents

Monoaminergic antidepressants exert complex multilevel effects that extend beyond synaptic neurotransmission. In addition to modulating serotonergic and noradrenergic signaling, these agents influence sleep architecture, autonomic balance, stress responsivity, and inflammatory pathways (Harvey, 2001; Miller & Raison, 2016). Selective serotonin reuptake inhibitors and serotonin–noradrenaline reuptake inhibitors alter REM sleep regulation, hypothalamic–pituitary–adrenal axis activity, and autonomic tone, thereby modulating multiple components of the sleep–immune–brain system.

From a network neuroscience perspective, antidepressants may contribute to the stabilization of cortico-limbic circuits by partially restoring prefrontal inhibitory control over limbic regions. Reductions in pro-inflammatory cytokines observed in biologically stratified subsets of patients further suggest that part of their therapeutic effect may involve modulation of neuroimmune signaling (Miller et al., 2009; Osimo et al., 2020). These findings support a conceptualization of antidepressants as agents that recalibrate network dynamics through integrated effects on neurotransmission, sleep regulation, and immune function.

6.2 Sedative Antidepressants and Sleep–Plasticity Coupling

Sedative antidepressants exert pronounced effects on sleep continuity and slow-wave sleep, processes critical for synaptic homeostasis and memory consolidation (Palagini et al., 2013; Walker, 2009). Enhancement of deep sleep may facilitate adaptive synaptic remodeling within cortico-limbic circuits, thereby supporting emotional regulation and cognitive stability.

Mechanistically, these agents influence histaminergic, noradrenergic, and serotonergic systems that regulate arousal, circadian timing, and immune signaling. Their therapeutic effects may therefore reflect a coupling between normalization of sleep architecture and downstream modulation of neuroimmune processes, highlighting the clinical relevance of sleep-targeted pharmacological effects in psychiatric treatment.

6.3 Antipsychotics, Circadian Regulation, and Immunometabolic Interfaces

Antipsychotic medications exert multifaceted effects on dopaminergic, serotonergic, and histaminergic systems, with downstream consequences for sleep–wake regulation and circadian rhythms (Wulff et al., 2010). Second-generation antipsychotics frequently improve sleep continuity and reduce nocturnal hyperarousal, suggesting that circadian stabilization may represent an underrecognized mechanism contributing to therapeutic efficacy.

At the same time, antipsychotics exert significant effects on metabolic and inflammatory pathways. Weight gain, insulin resistance, and lipid dysregulation associated with long-term antipsychotic treatment contribute to systemic low-grade inflammation, creating complex interactions between neurobiological benefits and immunometabolic risks (Fernandes et al., 2017). Within the SIBSM framework, antipsychotics can therefore be conceptualized as agents that simultaneously stabilize neural circuits while reshaping immunometabolic processes, underscoring the importance of system-level perspectives when evaluating long-term outcomes.

6.4 Hypnotics and Modulation of Hyperarousal Networks

Hypnotic agents primarily reduce cortical excitability and autonomic activation, thereby facilitating sleep initiation and maintenance in states of hyperarousal. Mechanistically, these agents target excitatory–inhibitory imbalance within cortical and subcortical circuits involved in arousal regulation (Riemann & Voderholzer, 2003).

While short-term improvements in sleep may indirectly attenuate stress-related immune activation, hypnotics do not fundamentally modify neuroimmune signaling pathways or large-scale network dynamics. This distinction highlights a conceptual difference between symptomatic sleep induction and mechanism-based modulation of sleep–immune–brain interactions. Interventions combining hypnotic effects with treatments targeting inflammatory or network-level mechanisms may therefore be required for more durable clinical benefit.

6.5 Chronobiotics and Temporal Network Organization

Chronobiotic agents, including melatonin and melatonin receptor agonists, target circadian regulation and temporal synchronization of biological systems. Melatonin exerts pleiotropic effects on sleep–wake timing, circadian coherence, oxidative stress, and immune

modulation, positioning it at the intersection of sleep, circadian, and neuroimmune systems (Wulff et al., 2010; Irwin, 2019).

Circadian-based interventions such as light therapy and chronotherapy further demonstrate that temporal organization constitutes a modifiable therapeutic dimension. Within the SIBSM framework, chronobiotics can be conceptualized as agents that restore temporal coherence across neural and immune systems, thereby enhancing network stability and adaptive functioning.

6.6 Immunomodulatory Strategies and Neuroimmune Targeting

Emerging evidence supports the potential role of immunomodulatory interventions as adjunctive treatments in psychiatric disorders, particularly in biologically stratified subgroups characterized by elevated inflammatory markers (Miller & Raison, 2016; Khandaker et al., 2017). Anti-inflammatory agents, metabolic modulators, and cytokine-targeting therapies have demonstrated preliminary efficacy in selected populations, although results remain heterogeneous.

At the neurobiological level, immunomodulatory agents influence synaptic plasticity, neurotransmitter systems, and network dynamics by altering cytokine signaling, microglial activation, and kynurenine pathway metabolism. These mechanisms provide a rationale for targeting upstream neuroimmune processes as a strategy for modifying downstream neural dysfunction within a precision-oriented framework.

6.7 Toward Mechanism-Based and Precision-Oriented Psychiatry

Collectively, these findings support a shift from symptom-based psychopharmacology toward mechanism-based and precision-oriented treatment paradigms. Within the SIBSM framework, treatment selection may increasingly be informed by sleep phenotypes, circadian profiles, inflammatory markers, and network-level biomarkers rather than categorical diagnoses alone (Insel et al., 2010; Williams, 2016).

Integrating psychopharmacological, sleep-focused, chronobiological, and immunomodulatory interventions may yield synergistic effects by targeting multiple levels of system dysregulation simultaneously. This integrative strategy aligns with contemporary models of precision psychiatry and highlights the translational potential of systems-level frameworks for advancing psychiatric treatment.

7. Transdiagnostic and Clinical Implications of the SIBSM Framework

The integration of sleep dysregulation and neuroimmune activation into a unified systems-level framework has important implications for understanding psychiatric disorders beyond traditional diagnostic boundaries. Rather than being confined to discrete nosological categories, sleep–immune–brain interactions appear to constitute shared biological mechanisms underlying diverse psychiatric phenotypes. Within the SIBSM framework, psychopathology is reconceptualized as a continuum of system states emerging from variations in coupled sleep–immune–neural dynamics, consistent with contemporary transdiagnostic models of mental illness (Insel et al., 2010; Kotov et al., 2017).

7.1 Sleep–Immune Dysregulation as a Core Transdiagnostic Dimension

Accumulating evidence indicates that sleep disturbances and inflammatory processes cut across conventional diagnostic categories. Insomnia, circadian disruption, and physiological hyperarousal are consistently observed across mood, anxiety, trauma-related, and psychotic disorders, while inflammatory markers are associated with symptom severity, cognitive impairment, functional outcomes, and treatment resistance across these conditions (Baglioni et al., 2011; Irwin, 2019; Osimo et al., 2020).

Within the SIBSM framework, sleep–immune dysregulation is conceptualized not merely as an associated feature but as a core transdiagnostic biological dimension of psychopathology. Variability in the magnitude, timing, and interaction of sleep disturbances and immune activation contributes to heterogeneity in clinical presentation, illness trajectories, and treatment response across diagnostic categories.

7.2 Implications for Psychiatric Classification and Dimensional Models

The SIBSM challenges traditional categorical models of psychiatric classification by proposing that mental disorders are more accurately understood in terms of dynamic system states rather than static diagnostic entities. This perspective aligns with dimensional and mechanism-oriented frameworks such as the Research Domain Criteria (RDoC) and hierarchical taxonomies of psychopathology, which emphasize the integration of neurobiological processes across symptom domains (Insel et al., 2010; Kotov et al., 2017).

By framing sleep regulation and immune activity as fundamental biological dimensions, the SIBSM provides a conceptual foundation for refining psychiatric classification systems.

Incorporating sleep-related measures and inflammatory markers into dimensional models may facilitate the identification of biologically meaningful subtypes within and across diagnostic categories, thereby enhancing the clinical utility of transdiagnostic approaches.

7.3 Comorbidity as an Expression of Shared System-Level Dysregulation

Comorbidity represents a defining feature of psychiatric disorders and a major challenge for clinical practice. The SIBSM offers a mechanistic explanation for the high rates of comorbidity observed across diagnostic categories by emphasizing shared dysregulation within sleep–immune–brain systems.

From a systems perspective, comorbidity reflects convergence of multiple clinical syndromes on common biological pathways rather than the coexistence of independent disease processes. Shared disturbances in sleep regulation, inflammatory signaling, and network dynamics give rise to overlapping symptom profiles, thereby blurring traditional diagnostic boundaries. Conceptualizing comorbidity as an expression of shared system-level instability may inform the development of interventions capable of targeting multiple symptom dimensions simultaneously.

7.4 Clinical Stratification and Biomarker-Informed Approaches

The transdiagnostic perspective articulated by the SIBSM has direct implications for clinical assessment and patient stratification. Systematic evaluation of sleep patterns, circadian rhythms, and inflammatory markers may enhance the identification of biologically meaningful subgroups of patients. Objective sleep measures, including actigraphy and polysomnography, complemented by validated self-report instruments, can provide insight into underlying neurobiological vulnerabilities (Krystal & Edinger, 2008).

Although inflammatory biomarkers are not yet routinely implemented in psychiatric practice, accumulating evidence suggests that they may hold value for stratifying patients according to biological risk profiles and treatment responsiveness (Miller & Raison, 2016; Khandaker et al., 2017). Patients characterized by prominent sleep disruption and elevated inflammatory markers may represent a distinct biological phenotype associated with specific clinical trajectories. This biomarker-informed stratification paradigm reflects a broader shift toward precision psychiatry.

7.5 Implications for Treatment Selection and Clinical Decision-Making

The SIBSM also informs therapeutic decision-making by encouraging clinicians to move beyond diagnosis-centered treatment selection. Rather than relying exclusively on categorical diagnoses, treatment planning may increasingly consider sleep phenotypes, circadian profiles, immune status, and network-level markers of dysfunction.

Patients with severe insomnia and hyperarousal may benefit from interventions prioritizing sleep stabilization and circadian alignment, whereas individuals with elevated inflammatory markers may respond more favorably to adjunctive immunomodulatory strategies. Within the SIBSM framework, pharmacological and non-pharmacological interventions can be conceptualized as modulators of network dynamics. Psychopharmacological treatments, psychotherapeutic approaches, and chronobiological interventions may exert synergistic effects by targeting complementary levels of system dysregulation.

7.6 Toward a Network-Informed Model of Clinical Psychiatry

Integrating sleep and neuroimmune processes into psychiatric models supports a broader paradigm shift toward network-informed approaches to mental illness. In this paradigm, psychiatric disorders are understood as disturbances in dynamic interactions among interconnected biological systems rather than as static abnormalities localized to specific brain regions or neurotransmitter systems (Bassett & Sporns, 2017).

Network-informed psychiatry emphasizes the importance of temporal dynamics, feedback loops, and system-level interactions in shaping psychopathology. Within the SIBSM framework, sleep–immune–brain interactions emerge as central regulators of network stability and adaptability. Therapeutic strategies that enhance network flexibility and resilience may therefore yield more durable clinical outcomes than interventions targeting isolated symptoms.

8. Limitations and Future Directions

Despite growing evidence supporting the role of sleep dysregulation and neuroimmune activation in psychiatric disorders, several limitations of the current literature must be acknowledged. First, a substantial proportion of existing studies relies on cross-sectional and correlational designs, which restrict causal inference regarding the temporal dynamics and directionality of sleep–immune–brain interactions. Although experimental and translational

studies have provided important mechanistic insights, their generalizability to heterogeneous clinical populations remains limited.

Second, marked heterogeneity characterizes both sleep phenotypes and inflammatory profiles across psychiatric disorders. Variability in methodological approaches—including differences in sleep assessment techniques, biomarker selection, neuroimaging paradigms, and sample characteristics—complicates the integration of findings across studies. This heterogeneity constrains the precision with which mechanistic pathways can be delineated and likely contributes to inconsistencies in reported associations between sleep disturbances, inflammation, and psychiatric outcomes.

Third, much of the existing literature has examined sleep dysregulation and neuroinflammation in relative isolation rather than within integrative, multilevel frameworks. The relative scarcity of longitudinal and multimodal investigations incorporating molecular, cellular, circuit, and network-level measures limits our understanding of how sleep–immune–brain interactions evolve across developmental stages and illness trajectories. Moreover, the dynamic interplay between environmental stressors, genetic vulnerability, and biological regulatory systems remains insufficiently characterized.

Fourth, although emerging evidence supports the potential clinical relevance of sleep-related and inflammatory biomarkers, their routine implementation in psychiatric practice remains limited. Challenges related to cost, accessibility, standardization, and clinical interpretability currently hinder the translation of biomarker-informed approaches into everyday clinical settings, particularly outside specialized research contexts.

Future research should prioritize longitudinal and experimental designs capable of elucidating causal pathways linking sleep dysregulation, neuroimmune activation, and psychiatric symptomatology. Large-scale cohort studies integrating objective sleep measures, inflammatory biomarkers, and neuroimaging data will be essential for identifying biologically meaningful subtypes of psychiatric disorders and for mapping the temporal evolution of sleep–immune–brain interactions across the lifespan.

Advances in network neuroscience and computational psychiatry offer promising avenues for investigating how sleep and immune processes shape brain network dynamics. The application of machine learning approaches and systems-level modeling to multimodal datasets may facilitate the development of predictive frameworks linking biological markers to clinical outcomes, illness trajectories, and treatment response.

From a translational perspective, clinical trials targeting sleep and inflammatory pathways represent a critical frontier in psychiatric research. Stratifying participants based on sleep phenotypes, circadian profiles, and inflammatory markers may enhance treatment efficacy and support the development of mechanism-based interventions. Furthermore, integrating chronobiological, immunomodulatory, and psychopharmacological strategies may yield synergistic effects by addressing multiple levels of neurobiological dysregulation simultaneously.

Future work should also examine the developmental and environmental determinants of sleep–immune–brain interactions. Investigating the impact of early-life stress, trauma, social adversity, and lifestyle factors on sleep and immune regulation may provide important insights into the origins of vulnerability to psychiatric disorders and inform preventive and early-intervention strategies.

Ultimately, bridging the gap between mechanistic insights and clinical practice will require the development of standardized frameworks for integrating sleep- and immune-related markers into psychiatric assessment and treatment planning. Advancing this translational agenda represents a critical step toward realizing the broader goals of precision psychiatry.

9. CONCLUSION

This integrative review advances a systems-level neurocognitive perspective on psychiatric disorders by synthesizing converging evidence linking sleep dysregulation, neuroimmune activation, and large-scale brain network dynamics. Rather than conceptualizing sleep disturbances and inflammatory processes as secondary or peripheral features, the Sleep–Immune–Brain Systems Model (SIBSM) positions these mechanisms as central regulators of neural stability, cognitive–affective functioning, and vulnerability to psychopathology.

Across molecular, cellular, circuit, and network levels, evidence reviewed here indicates that disruptions in circadian regulation, stress-system dynamics, neuroimmune signaling, and synaptic plasticity interact through nonlinear feedback loops that destabilize cortico-limbic circuits and large-scale brain networks. These interactions give rise to maladaptive system states characterized by persistent hyperarousal, reduced network flexibility, and impaired adaptive capacity, providing a mechanistic substrate for transdiagnostic symptom overlap, comorbidity, and clinical heterogeneity.

By framing psychiatric disorders as disorders of regulation within coupled sleep–immune–brain systems, the SIBSM offers a unifying framework that transcends traditional diagnostic boundaries and aligns with contemporary dimensional and network-based models of mental illness. This perspective helps reconcile findings from sleep science, psychoneuroimmunology, and network neuroscience within a coherent explanatory architecture, thereby addressing long-standing fragmentation in the psychiatric literature.

From a translational standpoint, the SIBSM highlights sleep and neuroimmune processes as promising targets for biomarker development and mechanism-based intervention. Conceptualizing pharmacological, chronobiological, psychotherapeutic, and immunomodulatory strategies as modulators of network dynamics underscores the potential value of integrative and precision-oriented treatment approaches that address upstream regulatory mechanisms rather than downstream symptom manifestations alone.

In summary, understanding psychiatric disorders through the lens of coupled sleep–immune–brain systems provides a biologically grounded and clinically relevant framework for advancing research, refining psychiatric classification, and informing next-generation therapeutic strategies. By emphasizing system-level interactions and network dynamics, the SIBSM contributes to an evolving paradigm in psychiatry that prioritizes integration, mechanism, and precision in the study and treatment of mental illness.

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