Review

Discovery Medicine 2026; 38(207): 1027–1038
https://doi.org/10.24976/Discov.Med.202638207.82

Sleep Deprivation and Microglia-Dependent Synaptic Remodeling in Psychiatric Disorders

Yuyang Liu[1,†], Yingkun Sun[2,†], Ye Wang[1], Hong Yu[1], Lili Huang[1,*]

[1]School of Pharmacy, Heilongjiang University of Chinese Medicine, 150040 Harbin, Heilongjiang, China
[2]Department of Geriatrics, Heilongjiang Red Cross Sengong General Hospital, 150040 Harbin, Heilongjiang, China
*Correspondence: huanglili@hljucm.edu.cn (Lili Huang)
[†]These authors contributed equally.
Submitted: 9 January 2026 Revised: 6 February 2026 Accepted: 5 March 2026 Published: 20 April 2026

Sleep deprivation (SD) has been recognized as a pivotal factor exacerbating the risk of psychiatric disorders; however, the neurobiological mechanisms underlying SD-induced alterations in brain network structure cannot be fully explained by monoaminergic neurotransmitter imbalances alone. This review systematically elucidates the "sleep-microglia-synaptic remodeling" axis as a core pathological mechanism, proposing that SD disrupts central nervous system homeostasis and induces a phenotypic transition of microglia from physiological synaptic sentinels to pathological agents of excessive phagocytosis. At the molecular level, SD promotes the "over-pruning" of functional synapses by aberrantly reactivating developmental signaling pathways in the adult brain—specifically the complement component 3–complement receptor 3 (C3–CR3), adenosine triphosphate–P2Y12 receptor signaling (ATP–P2Y12), and astrocyte-microglia crosstalk. This process results in a reduced synaptic density and impaired structural plasticity. Such neuroimmune-mediated synaptic pathology constitutes a shared anatomical substrate for the cognitive and emotional deficits observed in major psychiatric conditions, including major depressive disorder, schizophrenia, and anxiety disorders. In summary, dissecting this mechanism not only offers a novel perspective on the comorbidity of sleep disturbances and psychiatric disorders but also highlights that targeting the blockade of pathological microglial phagocytic pathways serves as a promising therapeutic strategy for restoring synaptic homeostasis and treating psychiatric diseases.

Keywords: sleep deprivation; microglia; synaptic pruning; neuroimmunomodulation; depressive disorder; schizophrenia

Introduction

Sleep is a critical physiological process that maintains central nervous system (CNS) homeostasis, regulates the clearance of metabolic waste, and consolidates memory. However, with the accelerating pace of modern societal life, sleep deprivation (SD) has become a prevalent public health issue. Epidemiological surveys and clinical studies consistently indicate a significant bidirectional association between sleep disorders and various psychiatric illnesses, such as major depressive disorder, schizophrenia, and bipolar disorder [1,2]. Chronic sleep deprivation not only serves as a prodromal symptom of these conditions but also acts as an independent risk factor for disease exacerbation and cognitive impairment [3]. Although prior research has primarily focused on imbalances in monoaminergic neurotransmitter systems, this alone cannot fully elucidate the neurobiological basis for the increased susceptibility to psychiatric disorders induced by sleep loss, particularly alterations at the level of brain network structure [4].

Synaptic plasticity forms the neural foundation for the brain's adaptation to the environment, information processing, and emotional regulation. According to the Synaptic Homeostasis Hypothesis (SHY) proposed by Tononi and colleagues, wakefulness is accompanied by a net increase in synaptic weights, which consumes substantial energy and occupies limited cellular space; in contrast, the primary function of sleep is to restore energy balance and synaptic transmission efficiency through global downscaling (renormalization) of synaptic strengths, thereby maintaining synaptic homeostasis [5]. Notably, the core pathological features of psychiatric disorders often involve abnormalities in synaptic connections, manifested as reduced dendritic spine density in the prefrontal cortex (PFC) or hippocampus, as well as excessive synaptic pruning in specific brain regions [6–8]. This phenomenon suggests that sleep deprivation may disrupt the mechanisms maintaining synaptic homeostasis, thereby inducing or exacerbating the pathological processes of psychiatric disorders [9].

In this process, the role of microglia has increasingly attracted attention. As resident immune cells in the CNS, microglia not only perform immune surveillance functions but also play a key role in synaptic remodeling during neural development and adulthood [10,11]. Under physiological conditions, microglia mediate the phagocytosis and pruning of excess or weaker synapses through the complement system (such as C1q and C3) and the Fractalkine signaling pathway, thereby optimizing neural circuits [12,13]. A re-

cent study has shown that microglial synaptic pruning function is highly activity-dependent and strictly regulated by the sleep-wake cycle [14]. Sleep deprivation can induce significant morphological changes and immune activation in microglia, leading to abnormally enhanced phagocytic function, which may erroneously eliminate healthy synaptic components and disrupt the integrity of neural circuits [15,16].

In summary, sleep deprivation-induced microglial overactivation and the resulting abnormal synaptic remodeling may serve as a key link between sleep disorders and the pathological changes in psychiatric diseases [17]. This article aims to review the latest research progress on how sleep deprivation regulates microglial function, with a focus on exploring the specific role of microglia-dependent synaptic remodeling in the pathogenesis of psychiatric disorders, and analyzing related molecular pathways, such as the complement cascade reaction and purinergic signaling, to provide a theoretical basis for clinical treatment strategies targeting neuroimmune modulation.

Microglia and Synaptic Homeostasis Under Physiological Conditions

Microglia, as highly dynamic sentinel cells in the CNS, are not in a quiescent state under physiological conditions but rather continuously perform immune surveillance of the brain parenchyma through their constantly extending and retracting processes [10,18]. Beyond classical immune defense functions, accumulating evidence supports that microglia are important regulators of synaptic structure and function, with their mediated synaptic pruning being essential for the refinement of neural circuits and the maintenance of synaptic plasticity in adulthood [12,19].

Mechanisms of Microglia-Mediated Synaptic Pruning

During critical periods of neural development, the brain generates excessive synaptic connections. Microglia specifically recognize and phagocytose redundant or functionally weaker pre- and postsynaptic components, such as axon terminals or dendritic spines, thereby retaining and strengthening effective neural connections [18]. This process, known as "synaptic pruning", extends into adulthood and plays a central role in learning, memory, and forgetting [18–20]. The process relies on a series of precise "find-me" and "eat-me" signaling mechanisms [19,21].

The complement system is one of the key pathways mediating microglial synaptic phagocytosis. Classical complement cascade molecules C1q and C3 act as "eat-me" signals tagging specific synapses, which are subsequently recognized by complement receptor 3 (CR3, composed of CD11b/CD18) on the microglial surface, triggering phagocytosis [19,22]. In addition, the CX3CL1-CX3CR1 signaling axis (Fractalkine pathway) plays an important role in neuron-microglia communication. Neuronally expressed CX3CL1 chemoattracts the CX3CR1 receptor, expressed exclusively on microglia, regulating microglial proximity to and pruning of synapses; deficiency in this pathway leads to insufficient synaptic pruning and abnormal neural network connectivity [23,24].

Purinergic signaling is equally indispensable in this process. Adenosine triphosphate (ATP) and adenosine diphosphate (ADP) released by neuronal activity activate P2Y12 receptors on the microglial surface, inducing rapid extension of microglial processes toward highly active synaptic sites, participating in the regulation of synaptic strength and the induction of long-term potentiation (LTP) or long-term depression (LTD) [25,26].

Physiological Regulation of Microglial Function by Sleep

Microglia exhibit significant circadian rhythmicity in their morphology and function, and are profoundly regulated by the sleep-wake cycle [27,28]. Transcriptomic studies have shown that a large number of genes in microglia related to immune surveillance and synaptic remodeling fluctuate in expression levels according to circadian rhythms, primarily controlled by intrinsic clock genes such as Bmal1 and Per1/2 [28,29]. During normal sleep, the contact area of cortical synapses typically decreases, which is consistent with the downscaling of synaptic strength proposed in the SHY [5].

Studies have revealed that sleep promotes structural remodeling of synapses by microglia. During non-rapid eye movement (NREM) sleep, microglial process activity increases, enabling more effective detection and clearance of accumulated metabolic waste and structurally unstable synaptic components [14,30]. Therefore, normal sleep architecture is essential for maintaining moderate microglial activation and synaptic homeostasis balance [11].

Impact of Sleep Deprivation on Microglia Morphology and Function

Sleep deprivation is recognized as a potent neurobiological stressor that significantly alters the brain's immune microenvironment. When the normal sleep-wake cycle is disrupted, microglia transition from a physiological surveillance state to a pathological activation state. This activation is characterized not only by pronounced morphological changes but also by increased release of immunoinflammatory mediators and alterations in metabolic signaling pathways, laying the groundwork for subsequent abnormal synaptic remodeling [31,32].

Morphological Remodeling and Immune Phenotype Transformation

Morphological changes serve as the gold standard for assessing microglial activation status. Under physiologi-

cal conditions, resting microglia exhibit a ramified morphology, with small cell bodies and long, thin processes that facilitate monitoring of the synaptic microenvironment. However, multiple studies in rodent models have demonstrated that both acute and chronic sleep deprivation induce transformations in microglia within the cerebral cortex and hippocampus, including shifts toward ameboid or hyperramified forms. These changes manifest as cell body hypertrophy, process retraction and thickening, and alterations in cell surface area-to-volume ratio, typically indicating enhanced phagocytic activity [31,33,34].

These morphological shifts are accompanied by the upregulation of specific markers. Sleep deprivation significantly increased expression of ionized calcium-binding adapter molecule 1 (Iba1) and cluster of differentiation 68 (CD68) on the microglial surface, with the latter primarily localized to phagocytic lysosomes; elevated CD68 levels directly indicate heightened phagocytic capacity [31,32]. This activated state is not uniformly distributed but is predominantly concentrated in brain regions closely associated with cognition and emotional regulation, such as the PFC and hippocampus, suggesting that sleep deprivation exerts selective effects on specific neural circuits [16,34].

Release of Neuroinflammatory Factors

Sleep deprivation not only alters the structure of microglia but also promotes their polarization toward a proinflammatory phenotype (similar to M1-like) [35,36]. According to the "cytokine hypothesis" of sleep regulation, sleep loss leads to a secondary elevation in brain proinflammatory cytokine levels [37]. Studies have shown that following sleep deprivation (SD) exposure, mRNA transcription and protein release of interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6) in microglia are significantly increased [32,34,38]. These cytokines not only act as regulators of sleep homeostasis but, when excessive, serve as neurotoxic mediators, further disrupting blood-brain barrier permeability and establishing a positive feedback loop that sustains microglial activation [39,40]. This SD-induced "sterile neuroinflammation" environment alters neuron-glia communication signals, rendering synapses vulnerable to damage.

Metabolic Signaling and the Mediating Role of Purinergic Receptors

Prolonged wakefulness leads to the accumulation of metabolic byproducts in the brain interstitial fluid, which may serve as an initiating factor for microglial activation [15]. Among these, adenosine and adenosine triphosphate (ATP) play particularly critical roles [41]. As wakefulness duration extends, extracellular adenosine concentrations rise, acting on microglial surface adenosine A_{2A} receptors to induce morphological retraction and release of inflammatory mediators [42,43]. Simultaneously, ATP released from hyperactive or stressed neurons acts as damage-associated molecular patterns (DAMPs), activating the NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome pathway in microglia via P2X7 and P2Y12 receptors [37,44]. This indicates that sleep deprivation, by mimicking a state of metabolic stress, misleads microglia into initiating an immune response similar to that triggered by brain injury.

Mechanisms of SD-Induced Microglial-Dependent Synaptic Remodeling

Although synaptic pruning is a necessary process for refining neural circuits during development, its reactivation induced by sleep deprivation in adulthood is often destructive [45]. A study shows that sleep deprivation disrupts developmental signaling pathways, impairing microglia's ability to accurately distinguish functional synapses from redundant ones, thereby causing "over-pruning" [46]. The schematic representation of these microglial-dependent synaptic remodeling mechanisms under physiological and sleep-deprived conditions is illustrated in Fig. 1.

Abnormal Reactivation of the Complement Cascade

The complement system is the core mechanism mediating microglial synaptic elimination [47]. Bellesi *et al.* [15] found that sleep deprivation leads to significant upregulation of C3 mRNA and its protein levels in mouse cortical neurons. This deposition of C3 acts as an "eat me" signal, recognized by the high-affinity receptor CR3 on the microglial surface, thereby triggering the phagocytic cascade [18,45,48].

Under normal sleep conditions, complement levels remain low; whereas during sleep deprivation states, postsynaptic components, such as dendritic spines, are erroneously marked [49]. Electron microscopy and related imaging analyses have shown that sleep loss promotes glial engulfment of synaptic elements and is accompanied by increased microglial activation in the mouse cortex [15]. This indicates that sleep deprivation reactivates the developmental C3-CR3 axis, leading to pathological clearance of synapses that should be preserved in the adult brain, which may be the molecular basis for cognitive deficits and disruptions in network connectivity [18,48].

MerTK Pathway and Phosphatidylserine Externalization

In addition to the complement system, the Mer tyrosine kinase receptor (MerTK) is also a key receptor regulating microglial phagocytic function [50]. MerTK mediates phagocytosis by recognizing phosphatidylserine (PS) on the cell membrane surface [51]. Under normal conditions, PS is located on the inner side of the cell membrane, but when synapses are damaged or experience metabolic stress (such as oxidative stress induced by prolonged wakefulness), PS may translocate to the membrane surface, emitting an "eat me" signal [52].

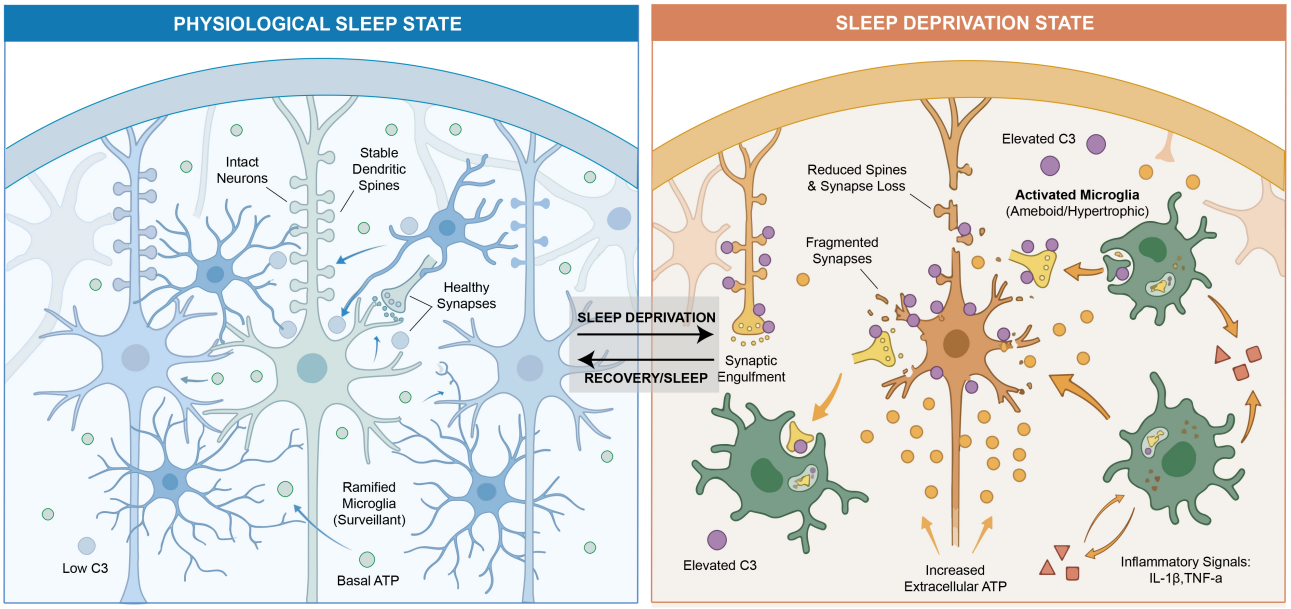

Fig. 1. Schematic representation of microglia-dependent synaptic remodeling under physiological sleep and sleep deprivation states. Under physiological sleep conditions (left panel), microglia exhibit a ramified, surveillant morphology associated with basal ATP and low complement component 3 (C3) levels, ensuring the maintenance of stable dendritic spines and intact neuronal circuits. Conversely, sleep deprivation (right panel) induces a phenotypic shift in microglia toward an activated, ameboid or hypertrophic state, driven by the accumulation of extracellular ATP (orange circles) and the release of pro-inflammatory cytokines such as IL-1β and TNF-α. This pathological activation facilitates the aberrant tagging of synapses by elevated C3 (purple circles), triggering excessive microglial engulfment of synaptic components ("over-pruning"), which results in fragmented synapses and a significant reduction in dendritic spine density. The central arrows indicate the dynamic nature of this process, suggesting that recovery sleep may help restore microglial homeostasis and synaptic integrity. Schematic diagrams were created with Adobe Illustrator (Version CC 2020; Adobe Inc., San Jose, CA, USA). ATP, adenosine triphosphate; IL-1β, interleukin-1β; TNF-α, tumor necrosis factor-α.

The local synaptic metabolic stress caused by sleep deprivation may induce PS externalization, combined with growth arrest-specific protein 6 (Gas6) as a bridging molecule, activating MerTK on microglia, thereby initiating phagocytosis of synaptic terminals [53]. In addition, sleep deprivation may also alter the expression balance of CD47-SIRPα ("don't eat me" signal), lowering the protective threshold of synapses, rendering them more vulnerable to microglial attack [18,54].

Astrocyte-Microglia Synergistic Interactions

Microglia do not act in isolation; astrocytes play a key synergistic or initiating role in SD-induced synaptic remodeling [55]. As the primary cells for synaptic metabolic support, astrocytes are particularly sensitive to extracellular glutamate and potassium ions produced by prolonged wakefulness [56]. Studies have shown that astrocytes secrete IL-33, which directly enhances microglial phagocytic capacity and establishes a feedback loop tied to synaptic maturation. They also release TGF-β, which upregulates C1q, thereby promoting complement-dependent synaptic pruning by microglia. Additionally, reciprocal mechanisms may exist, such as microglia releasing insulin-like growth factor 1 (IGF-1) to guide astrocytic phagocytosis, while both cell types coordinate the balance between synapse formation and elimination through extracellular matrix remodeling—astrocytes primarily producing extracellular matrix (ECM) components and microglia potentially degrading them via metalloproteinases [55]. Under sleep deprivation, this glial crosstalk can be disrupted or amplified: acute sleep deprivation primarily enhances astrocytic phagocytosis of synaptic elements, whereas chronic sleep deprivation further activates microglia, promoting their phagocytic activity and leading to excessive synaptic elimination with potential neuroinflammatory consequences [15]. Collectively, this glial crosstalk establishes a positive feedback loop that exacerbates the loss of synaptic density.

Impairment of Synaptic Structural Proteins and Plasticity

The ultimate consequence of the above phagocytic mechanisms is the degradation of synaptic structural proteins and impaired plasticity [57]. Sleep deprivation leads to significant downregulation of the scaffold proteins PSD-95 and Synapsin-1 in the hippocampus and PFC [38]. Functionally, excessive microglial synapse pruning directly disrupts the induction and maintenance of long-term potentia-

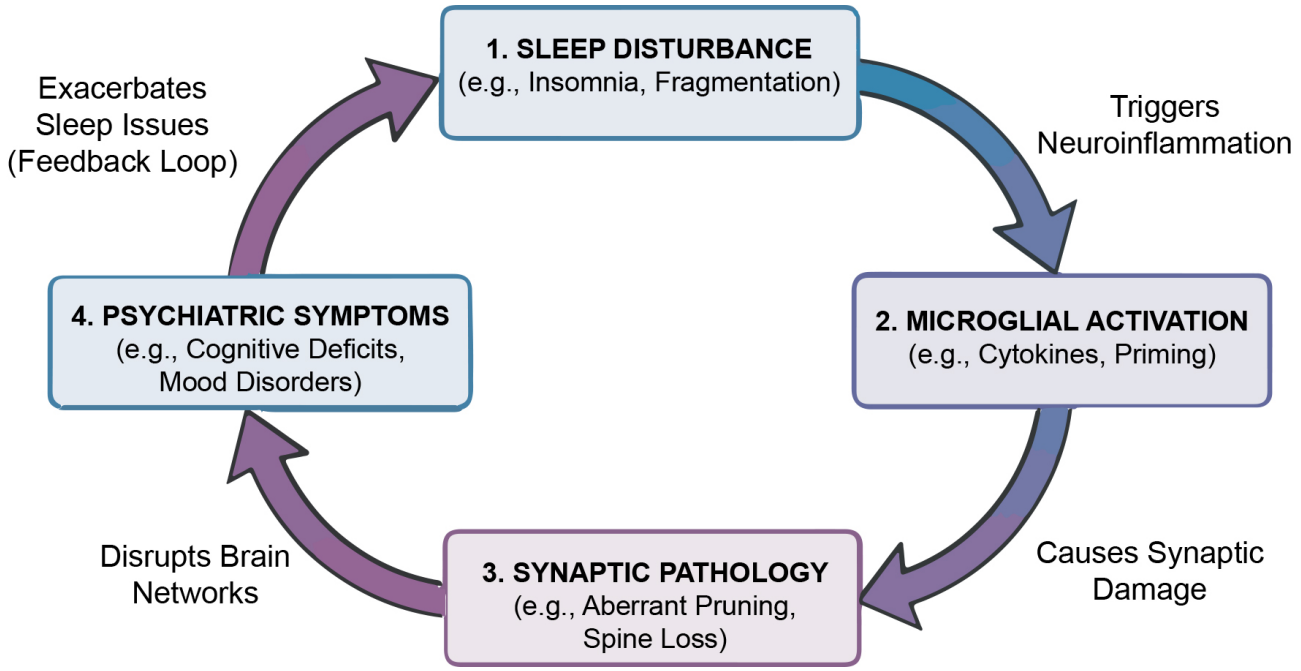

Fig. 2. The neuroimmune vicious cycle connecting sleep disturbances and psychiatric symptoms. This schematic illustrates the bidirectional mechanism of comorbidity between sleep deprivation and psychiatric disorders. (1) Sleep Disturbance (e.g., insomnia or sleep fragmentation) acts as a neurobiological stressor that triggers neuroinflammation and induces a phenotypic transition of microglia into an activated or "primed" state. (2) Activated Microglia release pro-inflammatory cytokines and exhibit enhanced phagocytic activity, erroneously eliminating healthy synaptic structures. (3) Synaptic Pathology, manifesting as reduced dendritic spine density or aberrant pruning, disrupts neural network connectivity (particularly in the PFC and hippocampus), constituting the anatomical substrate for cognitive deficits and emotional dysregulation. (4) Psychiatric Symptoms in turn exacerbate sleep quality, forming a self-sustaining "sleep–neuroimmune–synapse" pathological feedback loop. This cycle explains why sleep loss acts as both a prodromal symptom and an independent risk factor for disease exacerbation. Schematic diagrams were created with Adobe Illustrator (Version CC 2020; Adobe Inc., San Jose, CA, USA).

tion (LTP), while possibly abnormally enhancing long-term depression (LTD) [58–60]. This pathological leftward shift in synaptic efficacy weakens the information storage capacity of neural networks, highly consistent with the common phenotypes of cognitive rigidity and memory impairment in mental illnesses [59].

Pathological Implications in Major Psychiatric Disorders

Given the high prevalence of sleep disturbances in patients with psychiatric disorders [61] and the role of synaptopathy as a shared anatomical substrate across multiple mental illnesses [62], microglia-mediated abnormal synapse remodeling offers a novel perspective for understanding the mechanisms underlying comorbidity in these conditions. As illustrated in Fig. 2, this process creates a neuroimmune feedback loop where sleep disturbance and psychiatric symptoms mutually exacerbate each other through synaptic pathology.

Major Depressive Disorder (MDD)

Chronic insomnia and disruptions in sleep architecture, such as reduced slow-wave sleep and shortened rapid eye movement (REM) latency, represent core clinical features of MDD [63]. For decades, MDD has been associated with reduced gray matter volume in the PFC and hippocampus, characterized at the microscopic level by decreased dendritic spine density and loss of synaptic connections [64].

Mounting evidence suggests that a "primed" state of microglia induced by sleep deprivation may result in this synaptic loss [15]. In models of chronic stress or sleep restriction, hippocampal microglia become activated and release pro-inflammatory cytokines such as IL-1β, which not only suppress the expression of brain-derived neurotrophic factor (BDNF) but also directly phagocytose postsynaptic dendritic spine structures, leading to collapse of the excitatory/inhibitory balance in neural networks [65–67]. This glia-mediated synaptic stripping effect may constitute the neurobiological basis for anhedonia and cognitive slowing observed in treatment-resistant depression.

Schizophrenia

Schizophrenia is widely considered a neurodevelopmental disorder, with its typical peak onset in late adolescence to early adulthood, coinciding with the normal peak period of synaptic pruning in the human brain [68]. Significant reductions in synaptic density in the cerebral cortex, particularly the PFC, in patients support the plausibility of the "over-pruning" hypothesis [69,70].

Recent genome-wide association studies (GWAS) have identified variants in the complement component 4 (*C4*) gene as the strongest genetic risk factor for schizophrenia, where *C4* serves as a key molecule mediating microglial phagocytosis of synapses [71]. Meanwhile, patients with schizophrenia often exhibit marked reductions in sleep spindles and deficits in slow-wave sleep [72]. Evidence suggests that, during critical developmental periods, sleep disturbances may further activate the genetically vulnerable *C4*-microglia pathway, leading to excessive elimination of cortical synapses and ultimately disrupting neural circuits responsible for higher cognitive functions [73,74].

Anxiety Disorders and Post-Traumatic Stress Disorder (PTSD)

Unlike the synaptic loss commonly observed in schizophrenia, the pathological changes in anxiety disorders and PTSD exhibit brain region-specific heterogeneity [75]. In the amygdala, a core brain region responsible for fear and emotional processing, prolonged sleep deprivation or stress exposure often leads to an abnormal increase in dendritic spine density or pathological strengthening of synapses, whereas the PFC (responsible for emotional regulation) typically exhibits atrophy [76–78].

Microglia play a dual role in this process. Studies have shown that sleep deprivation sensitizes microglia in the amygdala, enabling them to enhance excitatory synaptic transmission by secreting mediators such as TNF-α, thereby impeding fear extinction [79,80]. This explains why sleep disturbances are not only symptoms of PTSD but also factors in a vicious cycle that makes traumatic memories difficult to erase and sustains anxiety symptoms.

Clinical Evidence From Post-Mortem and Neuroimaging Studies

To bridge the gap between mechanistic animal models and human clinical pathology, an increasing body of evidence implicates aberrant synaptic remodeling and microglial activation in the pathogenesis of psychiatric disorders. By integrating large-scale genomic data with post-mortem histological evidence, researchers have consistently quantified deficits in postsynaptic elements—most notably dendritic spine density within the PFC—thereby providing anatomical validation for the 'synaptic pruning' hypothesis in schizophrenia [68,81]. Parallelly, stereological investigations in major depressive disorder (MDD) have revealed significant reductions in synapse counts and glial cell density within key socio-emotional regulatory circuits [82–84]. These structural impairments offer a neurobiological basis for functional connectivity deficits, which are further exacerbated by sleep disturbances.

Complementing these post-mortem findings, recent advancements in Positron Emission Tomography (PET) targeting Synaptic Vesicle Glycoprotein 2A (SV2A) have enabled the *in vivo* quantification of synaptic density. Specifically, studies employing the [^{11}C]UCB-J radiotracer have demonstrated widespread reductions in synaptic terminal density within the frontal and anterior cingulate cortices of patients with schizophrenia [85,86]. These deficits significantly correlate with the severity of cognitive impairment, reinforcing the clinical relevance of synaptic loss. Furthermore, translocator protein (TSPO)-targeted PET imaging has provided evidence of neuroinflammation and microglial activation across major psychiatric disorders. Crucially, these human neuroimaging findings often align with the severity of sleep disturbances, providing robust clinical validation for the 'sleep-microglia-synapse' axis originally conceptualized in preclinical models [87–89].

Therapeutic Perspectives

Elucidating the pathological mechanisms by which sleep deprivation mediates abnormal synaptic remodeling through microglia not only deepens our understanding of the etiology of psychiatric disorders but also provides highly promising interventional targets for clinical treatment. The core of therapeutic strategies lies in blocking the pathological activation and excessive phagocytosis of microglia and promoting the recovery and reconstruction of synaptic homeostasis.

Sleep Intervention and Recovery of Synaptic Homeostasis

The most direct therapeutic approach is to address the sleep disorders themselves. Cognitive Behavioral Therapy for Insomnia (CBT-I) is currently the first-line non-pharmacological treatment regimen [90]. Preclinical studies have shown that providing sufficient recovery sleep after acute sleep deprivation partially restores microglial morphology to a resting state, with levels of synaptic phagocytosis markers also decreasing [91]. This indicates that early intervention can be reversible. However, in the case of long-term chronic sleep restriction, simply catching up on sleep may not fully reverse the "primed" state of microglia [92]. Epigenetic modifications induced by prolonged sleep deprivation may render microglia more sensitive to subsequent stressors [93]. Therefore, in the treatment of chronic psychiatric disorders, simply improving sleep may need to be combined with immunomodulatory strategies to achieve optimal efficacy [94].

Targeted Pharmacological Interventions on Microglia

Given the central role of microglia in synaptic pathology, the development of drugs that specifically modulate their function has become a hotspot in translational medicine.

Minocycline: As a highly lipophilic tetracycline antibiotic, minocycline effectively crosses the blood-brain barrier and exhibits broad-spectrum anti-inflammatory effects along with inhibition of microglial activation [95]. Multiple animal experiments have confirmed that minocycline pretreatment can prevent sleep deprivation-induced release of pro-inflammatory factors and synaptic loss [96]. Although clinical trials in depression and schizophrenia have shown heterogeneous results, it still holds promise as an adjunctive therapy [97–101].

CSF1R Inhibitors: Colony-stimulating factor 1 receptor (CSF1R) is a key signaling pathway for maintaining microglial survival. Use of CSF1R inhibitors, such as PLX3397/5622, can eliminate the vast majority of microglia in the brain within a short period [102]. Studies have found that after microglial depletion, sleep deprivation-induced dendritic spine loss is significantly ameliorated, and newly regenerated microglia upon drug withdrawal often revert to a healthier phenotype [16,103]. Although whole-brain cell elimination raises safety concerns for clinical application, this validates blocking microglia as a feasible pathway to rescue synaptic structure.

Complement and Purinergic Pathway Antagonists: Specific antagonists targeting the C3-CR3 axis or P2Y12 receptors are under development, aiming to precisely block the "synaptic phagocytosis" process without affecting other physiological functions of microglia, such as neurotrophic support, representing the direction of future precision medicine [104,105].

Lifestyle Interventions

In addition to pharmacological approaches, lifestyle modifications represent an effective means to maintain microglial rhythmicity and function.

Aerobic Exercise: Regular physical exercise has been demonstrated to significantly downregulate neuroinflammation levels in the brain, promote polarization of microglia toward an anti-inflammatory (M2-like) phenotype, and increase the release of BDNF, thereby counteracting synaptic damage induced by sleep deprivation [106,107].

Light Therapy: Given that microglia possess independent clock gene mechanisms, timed and quantitative light exposure, such as morning blue-enriched light irradiation, helps recalibrate the circadian rhythms of the suprachiasmatic nucleus (SCN) and microglia, improves sleep architecture, and indirectly maintains synaptic homeostasis [108,109].

Current Challenges and Future Perspectives

While the "sleep-microglia-synaptic remodeling" axis offers a compelling framework for understanding psychiatric comorbidities, several critical knowledge gaps remain. Bridging these gaps is essential for translating preclinical findings into effective therapeutic strategies.

Unresolved Mechanisms in Microglial Synaptic Regulation

A fundamental unresolved question is how microglia distinguish synapses designated for elimination from those meant for preservation or potentiation. While the complement cascade (C3-CR3) [45,48] and phosphatidylserine-mediated "eat-me" signals [51,52] are well-established, the molecular safeguards that prevent aberrant "over-pruning" in the mature brain remain elusive. Emerging evidence underscores a critical equilibrium between pro-phagocytic and anti-phagocytic ("don't-eat-me") signals, such as the CD47-SIRPα axis [54]. However, it remains to be determined how SD disrupts this homeostatic balance at the single-synapse level. Furthermore, microglia exhibit functional duality, ranging from synaptic stripping to spine formation via BDNF-dependent mechanisms [65,106]. The regulatory "switch" governing these divergent roles—and whether SD biases microglia toward a detrimental phagocytic phenotype at the expense of their trophic functions—warrants detailed investigation using high-resolution *in vivo* imaging.

Heterogeneity in Sleep Deprivation Paradigms

Most extant studies utilize rodent models of total sleep deprivation (TSD), which may not fully capture the profound heterogeneity of human sleep disorders.

Temporal Dynamics—Acute Astrocytic Phagocytosis vs. Chronic Microglial Priming: Current evidence suggests a distinct cellular handoff in synaptic remodeling depending on the duration of sleep deprivation. While acute sleep deprivation primarily triggers astrocytic phagocytosis of synaptic components—a process often serving a compensatory metabolic function and largely reversible upon recovery sleep—chronic sleep restriction is hypothesized to drive microglia into a "primed" or hyperreactive state [92]. This chronic activation, potentially maintained by epigenetic modifications, leads to sustained microglial-mediated synaptic elimination that is resistant to homeostatic recovery. Identifying the critical temporal threshold where this adaptive glial remodeling transitions into maladaptive pathology is essential.

Sleep Architecture—Synaptic Vulnerability in REM vs. NREM Deprivation: Microglial motility and morphology are fine-tuned by sleep-stage-specific oscillations, with NREM sleep particularly facilitating glymphatic clearance. Given that distinct psychiatric conditions exhibit characteristic sleep deficits—such as diminished slow-wave sleep in

schizophrenia versus REM dysregulation in depression—it is imperative to understand how selective REM or NREM deprivation differentially modulates microglial-mediated synaptic refinement [14,30,63,72].

Deprivation Paradigms—Total Sleep Deprivation vs. Fragmentation and Hypoxia: Clinical conditions, notably obstructive sleep apnea, are characterized by fragmentation and intermittent hypoxia rather than total deprivation [17,58]. The synergistic effects of these insults on microglial polarization remain largely uncharted, with profound clinical significance.

Translational Challenges and Safety Concerns

While microglial modulation presents a compelling therapeutic avenue, translating preclinical findings into clinical practice is fraught with challenges regarding specificity and systemic safety.

Pan-microglial vs. Targeted Inhibition: Global microglial depletion—achieved via CSF1R antagonism—effectively mitigates dendritic spine loss in murine models [16,102]. However, this approach carries significant clinical risks, as microglia are indispensable for neuroprotective surveillance and the clearance of cellular debris [10,30]. Prototypical long-term depletion may predispose the CNS to secondary infections or accelerate neurodegeneration due to impaired homeostatic maintenance [29,104].

The Temporal Window of Intervention: Synaptic pruning is a highly choreographed, time-sensitive process [22,45]. Therapeutic intervention following irreversible structural damage may prove futile. Conversely, suppressing pruning during critical neurodevelopmental windows—particularly in the context of schizophrenia—risks disrupting essential circuit refinement and network maturation [7,73].

Precision Targeting of Downstream Signaling: Rather than broad immunosuppression (e.g., via minocycline), a more nuanced strategy involves uncoupling pathological phagocytosis from homeostatic functions. By specifically targeting downstream cascades, such as the C3-CR3 axis or P2Y12 signaling, it may be possible to arrest aberrant synaptic stripping while preserving the cell's vital reparative roles [48,104].

Conclusion

In summary, sleep deprivation reshapes the CNS's immune microenvironment, transforming microglia from physiological maintainers of synaptic homeostasis into pathological, excessive phagocytes. Through mechanisms including the complement cascade, purinergic signaling, and glial cell crosstalk, sleep deprivation leads to abnormal synaptic pruning and impaired neural circuit function, thereby playing a key pathogenic role in depression, schizophrenia, and anxiety-related disorders. Although current evidence primarily derives from animal models, with ongoing challenges in human translational research, imaging technologies, and sex differences, the "sleep–microglia–synaptic remodeling" axis provides a novel integrative framework for understanding the comorbid mechanisms of psychiatric disorders. Future research urgently needs to integrate longitudinal clinical cohorts, multimodal imaging, and precise molecular intervention strategies to differentiate the effects of acute versus chronic sleep deprivation and to target blockade of pathological synaptic phagocytosis pathways, with the aim of opening new directions in the prevention and treatment of psychiatric disorders based on sleep and neuroimmune regulation.

Availability of Data and Materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions

YYL, YKS and LLH designed the research study. YYL and YW performed the literature retrieval. YKS and HY conducted the literature analysis. LLH drafted the article. All authors contributed to important editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This research was supported by the following grants: the Natural Science Foundation of Heilongjiang Province (No. LH2019H106), the "Excellent Young Teachers Basic Research Support Program" for Provincial Undergraduate Colleges in Heilongjiang Province (YQJH2023152), Heilongjiang Province Traditional Chinese Medicine Research Project (No. ZHY2025-009).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Fang H, Tu S, Sheng J, Shao A. Depression in sleep disturbance: A review on a bidirectional relationship, mechanisms and treat-

ment. Journal of Cellular and Molecular Medicine. 2019; 23: 2324–2332. https://doi.org/10.1111/jcmm.14170.

[2] Krystal AD. Psychiatric disorders and sleep. Neurologic Clinics. 2012; 30: 1389–1413. https://doi.org/10.1016/j.ncl.2012.08.018.

[3] Medic G, Wille M, Hemels ME. Short- and long-term health consequences of sleep disruption. Nature and Science of Sleep. 2017; 9: 151–161. https://doi.org/10.2147/NSS.S134864.

[4] Van Someren EJW. Brain mechanisms of insomnia: new perspectives on causes and consequences. Physiological Reviews. 2021; 101: 995–1046. https://doi.org/10.1152/physrev.00046.2019.

[5] Tononi G, Cirelli C. Sleep and the price of plasticity: from synaptic and cellular homeostasis to memory consolidation and integration. Neuron. 2014; 81: 12–34. https://doi.org/10.1016/j.neuron.2013.12.025.

[6] Berdenis van Berlekom A, Muflihah CH, Snijders GJLJ, MacGillavry HD, Middeldorp J, Hol EM, *et al*. Synapse Pathology in Schizophrenia: A Meta-analysis of Postsynaptic Elements in Postmortem Brain Studies. Schizophrenia Bulletin. 2020; 46: 374–386. https://doi.org/10.1093/schbul/sbz060.

[7] Germann M, Brederoo SG, Sommer IEC. Abnormal synaptic pruning during adolescence underlying the development of psychotic disorders. Current Opinion in Psychiatry. 2021; 34: 222–227. https://doi.org/10.1097/YCO.0000000000000696.

[8] Zhang MM, Guo MX, Zhang QP, Chen XQ, Li NZ, Liu Q, *et al*. IL-1R/C3aR signaling regulates synaptic pruning in the prefrontal cortex of depression. Cell & Bioscience. 2022; 12: 90. https://doi.org/10.1186/s13578-022-00832-4.

[9] Raven F, Van der Zee EA, Meerlo P, Havekes R. The role of sleep in regulating structural plasticity and synaptic strength: Implications for memory and cognitive function. Sleep Medicine Reviews. 2018; 39: 3–11. https://doi.org/10.1016/j.smrv.2017.05.002.

[10] Augusto-Oliveira M, Verkhratsky A. Lifestyle-dependent microglial plasticity: training the brain guardians. Biology Direct. 2021; 16: 12. https://doi.org/10.1186/s13062-021-00297-4.

[11] Deurveilher S, Golovin T, Hall S, Semba K. Microglia dynamics in sleep/wake states and in response to sleep loss. Neurochemistry International. 2021; 143: 104944. https://doi.org/10.1016/j.neuint.2020.104944.

[12] Soteros BM, Sia GM. Complement and microglia dependent synapse elimination in brain development. WIREs Mechanisms of Disease. 2022; 14: e1545. https://doi.org/10.1002/wsbm.1545.

[13] Paolicelli RC, Bisht K, Tremblay MÈ. Fractalkine regulation of microglial physiology and consequences on the brain and behavior. Frontiers in Cellular Neuroscience. 2014; 8: 129. https://doi.org/10.3389/fncel.2014.00129.

[14] Corsi G, Picard K, di Castro MA, Garofalo S, Tucci F, Chece G, *et al*. Microglia modulate hippocampal synaptic transmission and sleep duration along the light/dark cycle. Glia. 2022; 70: 89–105. https://doi.org/10.1002/glia.24090.

[15] Bellesi M, de Vivo L, Chini M, Gilli F, Tononi G, Cirelli C. Sleep Loss Promotes Astrocytic Phagocytosis and Microglial Activation in Mouse Cerebral Cortex. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2017; 37: 5263–5273. https://doi.org/10.1523/JNEUROSCI.3981-16.2017.

[16] Ni RJ, Yuan WJ, Wang YY, Yang X, Wei JX, Zhao LS, *et al*. Microglia-mediated inflammation and synaptic pruning contribute to sleep deprivation-induced mania in a sex-specific manner. Translational Psychiatry. 2025; 15: 285. https://doi.org/10.1038/s41398-025-03525-x.

[17] Nadjar A, Wigren HKM, Tremblay ME. Roles of Microglial Phagocytosis and Inflammatory Mediators in the Pathophysiology of Sleep Disorders. Frontiers in Cellular Neuroscience. 2017; 11: 250. https://doi.org/10.3389/fncel.2017.00250.

[18] Cornell J, Salinas S, Huang HY, Zhou M. Microglia regulation of synaptic plasticity and learning and memory. Neural Regeneration Research. 2022; 17: 705–716. https://doi.org/10.4103/1673-5374.322423.

[19] Nandi S, de Deus JL, Faborode OS, Nandi S. Synaptic Pruning by Microglia: Lessons from Genetic Studies in Mice. Developmental Neuroscience. 2025; 47: 362–382. https://doi.org/10.1159/000541379.

[20] Wang C, Yue H, Hu Z, Shen Y, Ma J, Li J, *et al*. Microglia mediate forgetting via complement-dependent synaptic elimination. Science (New York, N.Y.). 2020; 367: 688–694. https://doi.org/10.1126/science.aaz2288.

[21] Huo A, Wang J, Li Q, Li M, Qi Y, Yin Q, *et al*. Molecular mechanisms underlying microglial sensing and phagocytosis in synaptic pruning. Neural Regeneration Research. 2024; 19: 1284–1290. https://doi.org/10.4103/1673-5374.385854.

[22] Nelson N, Miller V, Broadie K. Neuron-to-glia and glia-to-glia signaling directs critical period experience-dependent synapse pruning. Frontiers in Cell and Developmental Biology. 2025; 13: 1540052. https://doi.org/10.3389/fcell.2025.1540052.

[23] Gunner G, Cheadle L, Johnson KM, Ayata P, Badimon A, Mondo E, *et al*. Sensory lesioning induces microglial synapse elimination via ADAM10 and fractalkine signaling. Nature Neuroscience. 2019; 22: 1075–1088. https://doi.org/10.1038/s41593-019-0419-y.

[24] Camacho-Hernández NP, Peña-Ortega F. Fractalkine/CX3CR1-Dependent Modulation of Synaptic and Network Plasticity in Health and Disease. Neural Plasticity. 2023; 2023: 4637073. https://doi.org/10.1155/2023/4637073.

[25] Naffaa MM. Mechanisms of astrocytic and microglial purinergic signaling in homeostatic regulation and implications for neurological disease. Exploration of Neuroscience. 2025; 4: 100676. https://doi.org/10.37349/en.2025.100676.

[26] Gómez Morillas A, Besson VC, Lerouet D. Microglia and Neuroinflammation: What Place for P2RY12? International Journal of Molecular Sciences. 2021; 22: 1636. https://doi.org/10.3390/ijms22041636.

[27] Nakanishi H, Ni J, Nonaka S, Hayashi Y. Microglial circadian clock regulation of microglial structural complexity, dendritic spine density and inflammatory response. Neurochemistry International. 2021; 142: 104905. https://doi.org/10.1016/j.neuint.2020.104905.

[28] Guzmán-Ruiz MA, Guerrero-Vargas NN, Lagunes-Cruz A, González-González S, García-Aviles JE, Hurtado-Alvarado G, *et al*. Circadian modulation of microglial physiological processes and immune responses. Glia. 2023; 71: 155–167. https://doi.org/10.1002/glia.24261.

[29] Iweka CA, Seigneur E, Hernandez AL, Paredes SH, Cabrera M, Blacher E, *et al*. Myeloid deficiency of the intrinsic clock protein BMAL1 accelerates cognitive aging by disrupting microglial synaptic pruning. Journal of Neuroinflammation. 2023; 20: 48. https://doi.org/10.1186/s12974-023-02727-8.

[30] Hristovska I, Robert M, Combet K, Honnorat J, Comte JC, Pascual O. Sleep decreases neuronal activity control of microglial dynamics in mice. Nature Communications. 2022; 13: 6273. https://doi.org/10.1038/s41467-022-34035-9.

[31] Parhizkar S, Gent G, Chen Y, Rensing N, Gratuze M, Strout G, *et al*. Sleep deprivation exacerbates microglial reactivity and Aβ deposition in a *TREM2*-dependent manner in mice. Science Translational Medicine. 2023; 15: eade6285. https://doi.org/10.1126/scitranslmed.ade6285.

[32] Hu Y, Wang Y, Wang Y, Zhang Y, Wang Z, Xu X, *et al*. Sleep Deprivation Triggers Mitochondrial DNA Release in Microglia to Induce Neural Inflammation: Preventative Effect of Hydrox-

ytyrosol Butyrate. Antioxidants (Basel, Switzerland). 2024; 13: 833. https://doi.org/10.3390/antiox13070833.

[33] Gu X, Zhao Z, Chen X, Zhang L, Fang H, Zhao T, *et al*. Imaging microglia surveillance during sleep-wake cycles in freely behaving mice. eLife. 2023; 12: RP86749. https://doi.org/10.7554/eLife.86749.

[34] Ni RJ, Wang YY, Pu WJ, Wei YY, Wei JX, Zhao LS, *et al*. Differential effects of sleep deprivation on behavior and microglia in a brain-region-specific manner in young and aged male mice. Brain, Behavior, and Immunity. 2024; 117: 12–19. https://doi.org/10.1016/j.bbi.2023.12.031.

[35] Liu H, Yang C, Wang X, Yu B, Han Y, Wang X, *et al*. Propofol improves sleep deprivation-induced sleep structural and cognitive deficits via upregulating the BMAL1 expression and suppressing microglial M1 polarization. CNS Neuroscience & Therapeutics. 2024; 30: e14798. https://doi.org/10.1111/cns.14798.

[36] Niazi NUK, Huang C, Yang Z, Zhang Y, Song C. Comparison between sub-chronic and chronic sleep deprivation-induced behavioral and neuroimmunological abnormalities in mice: Focusing on glial cell phenotype polarization. Behavioural Brain Research. 2024; 470: 115067. https://doi.org/10.1016/j.bbr.2024.115067.

[37] Zielinski MR, Gibbons AJ. Neuroinflammation, Sleep, and Circadian Rhythms. Frontiers in Cellular and Infection Microbiology. 2022; 12: 853096. https://doi.org/10.3389/fcimb.2022.853096.

[38] Zhang YM, Wei RM, Feng YZ, Zhang KX, Ge YJ, Kong XY, *et al*. Sleep deprivation aggravates lipopolysaccharide-induced anxiety, depression and cognitive impairment: The role of pro-inflammatory cytokines and synaptic plasticity-associated proteins. Journal of Neuroimmunology. 2024; 386: 578252. https://doi.org/10.1016/j.jneuroim.2023.578252.

[39] Andjelkovic AV, Situ M, Citalan-Madrid AF, Stamatovic SM, Xiang J, Keep RF. Blood-Brain Barrier Dysfunction in Normal Aging and Neurodegeneration: Mechanisms, Impact, and Treatments. Stroke. 2023; 54: 661–672. https://doi.org/10.1161/STROKEAHA.122.040578.

[40] Avilez-Avilez JJ, Medina-Flores MF, Gómez-Gonzalez B. Sleep loss impairs blood-brain barrier function: Cellular and molecular mechanisms. Vitamins and Hormones. 2024; 126: 77–96. https://doi.org/10.1016/bs.vh.2024.02.003.

[41] Zielinski MR, Gerashchenko D, Karpova SA, Konanki V, McCarley RW, Sutterwala FS, *et al*. The NLRP3 inflammasome modulates sleep and NREM sleep delta power induced by spontaneous wakefulness, sleep deprivation and lipopolysaccharide. Brain, Behavior, and Immunity. 2017; 62: 137–150. https://doi.org/10.1016/j.bbi.2017.01.012.

[42] Lazarus M, Oishi Y, Bjorness TE, Greene RW. Gating and the Need for Sleep: Dissociable Effects of Adenosine A_1 and A_{2A} Receptors. Frontiers in Neuroscience. 2019; 13: 740. https://doi.org/10.3389/fnins.2019.00740.

[43] Peng W, Liu X, Ma G, Wu Z, Wang Z, Fei X, *et al*. Adenosine-independent regulation of the sleep-wake cycle by astrocyte activity. Cell Discovery. 2023; 9: 16. https://doi.org/10.1038/s41421-022-00498-9.

[44] Woźny-Rasała I, Ogłodek EA. NLRP3 Inflammasome in Stress-Related Neuropsychiatric Disorders: Mechanisms of Neuron-Microglia-Astrocyte Crosstalk, HPA Axis Dysregulation, and Therapeutic Perspective. Biomolecules. 2025; 15: 1344. https://doi.org/10.3390/biom15091344.

[45] Schafer DP, Lehrman EK, Kautzman AG, Koyama R, Mardinly AR, Yamasaki R, *et al*. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron. 2012; 74: 691–705. https://doi.org/10.1016/j.neuron.2012.03.026.

[46] Wang L, Ling H, He H, Hu N, Xiao L, Zhang Y, *et al*. Dysfunctional synaptic pruning by microglia correlates with cognitive impairment in sleep-deprived mice: Involvement of CX3CR1 signaling. Neurobiology of Stress. 2023; 25: 100553. https://doi.org/10.1016/j.ynstr.2023.100553.

[47] Fatoba O, Itokazu T, Yamashita T. Complement cascade functions during brain development and neurodegeneration. The FEBS Journal. 2022; 289: 2085–2109. https://doi.org/10.1111/febs.15772.

[48] Han QQ, Shen SY, Liang LF, Chen XR, Yu J. Complement C1q/C3-CR3 signaling pathway mediates abnormal microglial phagocytosis of synapses in a mouse model of depression. Brain, Behavior, and Immunity. 2024; 119: 454–464. https://doi.org/10.1016/j.bbi.2024.04.018.

[49] Tuan LH, Tsao CY, Lee LJH, Lee LJ. Voluntary exercise ameliorates synaptic pruning deficits in sleep-deprived adolescent mice. Brain, Behavior, and Immunity. 2021; 93: 96–110. https://doi.org/10.1016/j.bbi.2020.12.017.

[50] Park J, Choi Y, Jung E, Lee SH, Sohn JW, Chung WS. Microglial MERTK eliminates phosphatidylserine-displaying inhibitory post-synapses. The EMBO Journal. 2021; 40: e107121. https://doi.org/10.15252/embj.2020107121.

[51] Lemke G. Phosphatidylserine Is the Signal for TAM Receptors and Their Ligands. Trends in Biochemical Sciences. 2017; 42: 738–748. https://doi.org/10.1016/j.tibs.2017.06.004.

[52] Scott-Hewitt N, Perrucci F, Morini R, Erreni M, Mahoney M, Witkowska A, *et al*. Local externalization of phosphatidylserine mediates developmental synaptic pruning by microglia. The EMBO Journal. 2020; 39: e105380. https://doi.org/10.15252/embj.2020105380.

[53] Yilmaz C, Korovina I, Witt A, Abdallah F, Müller B, Hentsche C, *et al*. Modulation of microglial phagocytosis via the GAS6-MERTK pathway regulates pathological angiogenesis in the mouse oxygen-induced retinopathy model. Cell Death & Disease. 2025; 16: 428. https://doi.org/10.1038/s41419-025-07744-4.

[54] Ding X, Wang J, Huang M, Chen Z, Liu J, Zhang Q, *et al*. Loss of microglial SIRPα promotes synaptic pruning in preclinical models of neurodegeneration. Nature Communications. 2021; 12: 2030. https://doi.org/10.1038/s41467-021-22301-1.

[55] Vainchtein ID, Molofsky AV. Astrocytes and Microglia: In Sickness and in Health. Trends in Neurosciences. 2020; 43: 144–154. https://doi.org/10.1016/j.tins.2020.01.003.

[56] Sriram S, Carstens K, Dewing W, Fiacco TA. Astrocyte regulation of extracellular space parameters across the sleep-wake cycle. Frontiers in Cellular Neuroscience. 2024; 18: 1401698. https://doi.org/10.3389/fncel.2024.1401698.

[57] Havekes R, Park AJ, Tudor JC, Luczak VG, Hansen RT, Ferri SL, *et al*. Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. eLife. 2016; 5: e13424. https://doi.org/10.7554/eLife.13424.

[58] Jiang R, Zhao Y, Liu L, Yin X, Yang J, Tian Z, *et al*. Oleoylethanolamide supplement attenuates postweaning sleep fragmentation-induced social behavioral deficits via inhibiting hippocampal microglial reactivity in adult mice. Brain, Behavior, and Immunity. 2026; 132: 106231. https://doi.org/10.1016/j.bbi.2025.106231.

[59] John A, Reddy PH. Synaptic basis of Alzheimer's disease: Focus on synaptic amyloid beta, P-tau and mitochondria. Ageing Research Reviews. 2021; 65: 101208. https://doi.org/10.1016/j.arr.2020.101208.

[60] Zhang J, Malik A, Choi HB, Ko RWY, Dissing-Olesen L, MacVicar BA. Microglial CR3 activation triggers long-term synaptic depression in the hippocampus via NADPH oxidase. Neuron. 2014; 82: 195–207. https://doi.org/10.1016/j.neuron

.2014.01.043.

[61] Freeman D, Sheaves B, Waite F, Harvey AG, Harrison PJ. Sleep disturbance and psychiatric disorders. The Lancet. Psychiatry. 2020; 7: 628–637. https://doi.org/10.1016/S2215-0366(20)30136-X.

[62] Howes O, Marcinkowska J, Turkheimer FE, Carr R. Synaptic changes in psychiatric and neurological disorders: state-of-the art of in vivo imaging. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2024; 50: 164–183. https://doi.org/10.1038/s41386-024-01943-x.

[63] Leitner C, Dalle Piagge F, Tomic T, Nozza F, Fasiello E, Castronovo V, *et al*. Sleep alterations in major depressive disorder and insomnia disorder: A network meta-analysis of polysomnographic studies. Sleep Medicine Reviews. 2025; 80: 102048. https://doi.org/10.1016/j.smrv.2025.102048.

[64] Duman RS, Sanacora G, Krystal JH. Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. Neuron. 2019; 102: 75–90. https://doi.org/10.1016/j.neuron.2019.03.013.

[65] Wohleb ES, Terwilliger R, Duman CH, Duman RS. Stress-Induced Neuronal Colony Stimulating Factor 1 Provokes Microglia-Mediated Neuronal Remodeling and Depressive-like Behavior. Biological Psychiatry. 2018; 83: 38–49. https://doi.org/10.1016/j.biopsych.2017.05.026.

[66] Afridi R, Suk K. Microglial Responses to Stress-Induced Depression: Causes and Consequences. Cells. 2023; 12: 1521. https://doi.org/10.3390/cells12111521.

[67] Chen X, Zhang K, Li Y, Wang C, Lou H, Yu S. Stress induces behavioral disorders by promoting microglial phagocytosis via decreasing neuronal Dkk3. Molecular Psychiatry. 2025; 30: 5731–5748. https://doi.org/10.1038/s41380-025-03314-4.

[68] Howes OD, Onwordi EC. The synaptic hypothesis of schizophrenia version III: a master mechanism. Molecular Psychiatry. 2023; 28: 1843–1856. https://doi.org/10.1038/s41380-023-02043-w.

[69] De Jager JE, van der Weijden-Germann M, van Dellen E, de Vries EFJ, Sommer IEC, Nuninga JO. Relationship between synaptic density and cortical (micro)structure in healthy subjects, patients with schizophrenia spectrum disorder and unaffected siblings: a multimodal [^{11}C]UCB-J PET and MRI study. Biological Psychiatry. Cognitive Neuroscience and Neuroimaging. 2025. https://doi.org/10.1016/j.bpsc.2025.11.008. (online ahead of print)

[70] Onwordi EC, Whitehurst T, Shatalina E, Mansur A, Arumuham A, Osugo M, *et al*. Synaptic Terminal Density Early in the Course of Schizophrenia: An In Vivo UCB-J Positron Emission Tomographic Imaging Study of SV2A. Biological Psychiatry. 2024; 95: 639–646. https://doi.org/10.1016/j.biopsych.2023.05.022.

[71] Sapienza J, Spangaro M, Comai S, Sabé M, La Torre J, Buonarroti M, *et al*. Microdosing Psychedelics to Restore Synaptic Density in Schizophrenia. International Journal of Molecular Sciences. 2025; 26: 8949. https://doi.org/10.3390/ijms26188949.

[72] Zhang Y, Quiñones GM, Ferrarelli F. Sleep spindle and slow wave abnormalities in schizophrenia and other psychotic disorders: Recent findings and future directions. Schizophrenia Research. 2020; 221: 29–36. https://doi.org/10.1016/j.schres.2019.11.002.

[73] Keshavan M, Lizano P, Prasad K. The synaptic pruning hypothesis of schizophrenia: promises and challenges. World Psychiatry: Official Journal of the World Psychiatric Association (WPA). 2020; 19: 110–111. https://doi.org/10.1002/wps.20725.

[74] Yilmaz M, Yalcin E, Presumey J, Aw E, Ma M, Whelan CW, *et al*. Overexpression of schizophrenia susceptibility factor human complement C4A promotes excessive synaptic loss and behavioral changes in mice. Nature Neuroscience. 2021; 24: 214–224. https://doi.org/10.1038/s41593-020-00763-8.

[75] Appelbaum LG, Shenasa MA, Stolz L, Daskalakis Z. Synaptic plasticity and mental health: methods, challenges and opportunities. Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology. 2023; 48: 113–120. https://doi.org/10.1038/s41386-022-01370-w.

[76] Rexrode L, Tennin M, Babu J, Young C, Bollavarapu R, Lawson LA, *et al*. Regulation of dendritic spines in the amygdala following sleep deprivation. Frontiers in Sleep. 2023; 2: 1145203. https://doi.org/10.3389/frsle.2023.1145203.

[77] Zhang HH, Meng SQ, Guo XY, Zhang JL, Zhang W, Chen YY, *et al*. Traumatic Stress Produces Delayed Alterations of Synaptic Plasticity in Basolateral Amygdala. Frontiers in Psychology. 2019; 10: 2394. https://doi.org/10.3389/fpsyg.2019.02394.

[78] Arnsten AFT. Stress signalling pathways that impair prefrontal cortex structure and function. Nature Reviews. Neuroscience. 2009; 10: 410–422. https://doi.org/10.1038/nrn2648.

[79] Yu Z, Fukushima H, Ono C, Sakai M, Kasahara Y, Kikuchi Y, *et al*. Microglial production of TNF-alpha is a key element of sustained fear memory. Brain, Behavior, and Immunity. 2017; 59: 313–321. https://doi.org/10.1016/j.bbi.2016.08.011.

[80] Pinto MJ, Bizien L, Fabre JMJ, Đukanović N, Lepetz V, Henderson F, *et al*. Microglial TNFα controls daily changes in synaptic GABAARs and sleep slow waves. The Journal of Cell Biology. 2024; 223: e202401041. https://doi.org/10.1083/jcb.202401041.

[81] Sellgren CM, Gracias J, Watmuff B, Biag JD, Thanos JM, Whittredge PB, *et al*. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. Nature Neuroscience. 2019; 22: 374–385. https://doi.org/10.1038/s41593-018-0334-7.

[82] Ongür D, Drevets WC, Price JL. Glial reduction in the subgenual prefrontal cortex in mood disorders. Proceedings of the National Academy of Sciences of the United States of America. 1998; 95: 13290–13295. https://doi.org/10.1073/pnas.95.22.13290.

[83] Kim R, Healey KL, Sepulveda-Orengo MT, Reissner KJ. Astroglial correlates of neuropsychiatric disease: From astrocytopathy to astrogliosis. Progress in Neuro-psychopharmacology & Biological Psychiatry. 2018; 87: 126–146. https://doi.org/10.1016/j.pnpbp.2017.10.002.

[84] Kang HJ, Voleti B, Hajszan T, Rajkowska G, Stockmeier CA, Licznerski P, *et al*. Decreased expression of synapse-related genes and loss of synapses in major depressive disorder. Nature Medicine. 2012; 18: 1413–1417. https://doi.org/10.1038/nm.2886.

[85] Onwordi EC, Halff EF, Whitehurst T, Mansur A, Cotel MC, Wells L, *et al*. Synaptic density marker SV2A is reduced in schizophrenia patients and unaffected by antipsychotics in rats. Nature Communications. 2020; 11: 246. https://doi.org/10.1038/s41467-019-14122-0.

[86] Radhakrishnan R, Skosnik PD, Ranganathan M, Naganawa M, Toyonaga T, Finnema S, *et al*. In vivo evidence of lower synaptic vesicle density in schizophrenia. Molecular Psychiatry. 2021; 26: 7690–7698. https://doi.org/10.1038/s41380-021-01184-0.

[87] Setiawan E, Attwells S, Wilson AA, Mizrahi R, Rusjan PM, Miler L, *et al*. Association of translocator protein total distribution volume with duration of untreated major depressive disorder: a cross-sectional study. The Lancet. Psychiatry. 2018; 5: 339–347. https://doi.org/10.1016/S2215-0366(18)30048-8.

[88] Liu YD, Chang YH, Xie XT, Wang XY, Ma HY, Liu MC, *et al*. PET Imaging Unveils Neuroinflammatory Mechanisms in Psychiatric Disorders: From Microglial Activation to Therapeutic Innovation. Molecular Neurobiology. 2025; 62: 15318–15335. https://doi.org/10.1007/s12035-025-05177-w.

[89] Meyer JH, Cervenka S, Kim MJ, Kreisl WC, Henter ID, Innis

RB. Neuroinflammation in psychiatric disorders: PET imaging and promising new targets. The Lancet. Psychiatry. 2020; 7: 1064–1074. https://doi.org/10.1016/S2215-0366(20)30255-8.

[90] Riemann D, Espie CA, Altena E, Arnardottir ES, Baglioni C, Bassetti CLA, *et al*. The European Insomnia Guideline: An update on the diagnosis and treatment of insomnia 2023. Journal of Sleep Research. 2023; 32: e14035. https://doi.org/10.1111/jsr.14035.

[91] Gentry NW, McMahon T, Yamazaki M, Webb J, Arnold TD, Rosi S, *et al*. Microglia are involved in the protection of memories formed during sleep deprivation. Neurobiology of Sleep and Circadian Rhythms. 2021; 12: 100073. https://doi.org/10.1016/j.nbscr.2021.100073.

[92] Hall S, Deurveilher S, Robertson GS, Semba K. Homeostatic state of microglia in a rat model of chronic sleep restriction. Sleep. 2020; 43: zsaa108. https://doi.org/10.1093/sleep/zsaa108.

[93] Lyons LC, Vanrobaeys Y, Abel T. Sleep and memory: The impact of sleep deprivation on transcription, translational control, and protein synthesis in the brain. Journal of Neurochemistry. 2023; 166: 24–46. https://doi.org/10.1111/jnc.15787.

[94] Irwin MR. Sleep and inflammation: partners in sickness and in health. Nature Reviews. Immunology. 2019; 19: 702–715. https://doi.org/10.1038/s41577-019-0190-z.

[95] Garrido-Mesa N, Zarzuelo A, Gálvez J. Minocycline: far beyond an antibiotic. British Journal of Pharmacology. 2013; 169: 337–352. https://doi.org/10.1111/bph.12139.

[96] Ahmed A, Misrani A, Tabassum S, Yang L, Long C. Minocycline inhibits sleep deprivation-induced aberrant microglial activation and Keap1-Nrf2 expression in mouse hippocampus. Brain Research Bulletin. 2021; 174: 41–52. https://doi.org/10.1016/j.brainresbull.2021.05.028.

[97] Zheng W, Zhu XM, Zhang QE, Cheng G, Cai DB, He J, *et al*. Adjunctive minocycline for major mental disorders: A systematic review. Journal of Psychopharmacology (Oxford, England). 2019; 33: 1215–1226. https://doi.org/10.1177/0269881119858286.

[98] Deakin B, Suckling J, Barnes TRE, Byrne K, Chaudhry IB, Dazzan P, *et al*. The benefit of minocycline on negative symptoms of schizophrenia in patients with recent-onset psychosis (BeneMin): a randomised, double-blind, placebo-controlled trial. The Lancet. Psychiatry. 2018; 5: 885–894. https://doi.org/10.1016/S2215-0366(18)30345-6.

[99] Levkovitz Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, *et al*. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. The Journal of Clinical Psychiatry. 2010; 71: 138–149. https://doi.org/10.4088/JCP.08m04666yel.

[100] Husain MI, Chaudhry IB, Husain N, Khoso AB, Rahman RR, Hamirani MM, *et al*. Minocycline as an adjunct for treatment-resistant depressive symptoms: A pilot randomised placebo-controlled trial. Journal of Psychopharmacology (Oxford, England). 2017; 31: 1166–1175. https://doi.org/10.1177/0269881117724352.

[101] Hellmann-Regen J, Clemens V, Grözinger M, Kornhuber J, Reif A, Prvulovic D, *et al*. Effect of Minocycline on Depressive Symptoms in Patients With Treatment-Resistant Depression: A Randomized Clinical Trial. JAMA Network Open. 2022; 5: e2230367. https://doi.org/10.1001/jamanetworkopen.2022.30367.

[102] Elmore MRP, Najafi AR, Koike MA, Dagher NN, Spangenberg EE, Rice RA, *et al*. Colony-stimulating factor 1 receptor signaling is necessary for microglia viability, unmasking a microglia progenitor cell in the adult brain. Neuron. 2014; 82: 380–397. https://doi.org/10.1016/j.neuron.2014.02.040.

[103] Willis EF, MacDonald KPA, Nguyen QH, Garrido AL, Gillespie ER, Harley SBR, *et al*. Repopulating Microglia Promote Brain Repair in an IL-6-Dependent Manner. Cell. 2020; 180: 833–846.e16. https://doi.org/10.1016/j.cell.2020.02.013.

[104] Werneburg S, Jung J, Kunjamma RB, Ha SK, Luciano NJ, Willis CM, *et al*. Targeted Complement Inhibition at Synapses Prevents Microglial Synaptic Engulfment and Synapse Loss in Demyelinating Disease. Immunity. 2020; 52: 167–182.e7. https://doi.org/10.1016/j.immuni.2019.12.004.

[105] Zhang Y, Tang Y, Illes P. Modification of Neural Circuit Functions by Microglial P2Y6 Receptors in Health and Neurodegeneration. Molecular Neurobiology. 2025; 62: 4139–4148. https://doi.org/10.1007/s12035-024-04531-8.

[106] Strohm AO, Majewska AK. Physical exercise regulates microglia in health and disease. Frontiers in Neuroscience. 2024; 18: 1420322. https://doi.org/10.3389/fnins.2024.1420322.

[107] Hu J, Huang B, Chen K. The impact of physical exercise on neuroinflammation mechanism in Alzheimer's disease. Frontiers in Aging Neuroscience. 2024; 16: 1444716. https://doi.org/10.3389/fnagi.2024.1444716.

[108] Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. Somnologie: Schlafforschung Und Schlafmedizin = Somnology: Sleep Research and Sleep Medicine. 2019; 23: 147–156. https://doi.org/10.1007/s11818-019-00215-x.

[109] Vanuk JR, Pace-Schott EF, Bullock A, Esbit S, Dailey NS, Killgore WDS. Morning blue light treatment improves sleep complaints, symptom severity, and retention of fear extinction memory in post-traumatic stress disorder. Frontiers in Behavioral Neuroscience. 2022; 16: 886816. https://doi.org/10.3389/fnbeh.2022.886816.