



Sleep Deprivation and Neuroglial Dysfunction: A Pathway to Neurodegeneration

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Abstract

Sleep disruption is a modifiable risk factor for cognitive decline and neurodegeneration, with astrocytes and microglia playing a central role in this link. This systematic review synthesizes experimental evidence on how total, selective, or fragmented sleep deprivation alters glial function and how these changes relate to executive function, memory, and neuropathology. Following PRISMA 2020, I searched MEDLINE (EBSCO) and Scopus (2010–April 2025). Eligible in vivo or ex vivo studies employed defined sleep-loss protocols, validated glial markers (e.g., GFAP, AQP4, Iba1, CD68, cytokines), and assessed cognitive or neuropathological outcomes; the risk of bias was appraised using SYRCLE (animals) and RoB-2 (humans). Twenty-six studies met the criteria. Across paradigms, sleep loss increased microglial activation (TNF- α , IL-1 β , IL-6; complement signaling), induced astrogliosis with AQP4 depolarization and enhanced astrocytic phagocytosis, and reduced synaptic proteins (PSD-95, synaptophysin), co-occurring with impaired spatial/recognition memory and, in Alzheimer's models, greater A β deposition and tau phosphorylation. Emerging evidence suggests glymphatic clearance efficiency depends on vascular and arousal factors beyond sleep stage alone. These findings highlight promising therapeutic targets spanning sleep restoration and direct glial modulation: slow-wave augmentation (acoustic stimulation, noninvasive brain stimulation), circadian alignment (timed light, melatonin agonism), treatment of sleep disorders (CBT-I, dual orexin receptor antagonists, CPAP for OSA), and glial-pathway interventions (complement blockade [C1q/C3/C3aR], microglial modulation [P2X7, NLRP3, CX3CR1/TREM2], and restoration of astrocytic AQP4 polarity and endfeet integrity). Overall, sleep deprivation disrupts glial homeostasis and aligns with cognitive impairment and neurodegenerative pathology.

Keywords: *sleep deprivation, astrocytes, microglia, neuroinflammation, glymphatic.*

Sleep Deprivation and Neuroglial Dysfunction: A Pathway to Neurodegeneration

Sleep is increasingly recognized as a critical regulator of central nervous system (CNS) health. Once considered a passive state, it is now recognized as a dynamic biological process, essential not only for cognitive performance and synaptic plasticity, but also for maintaining immune balance and efficiently clearing metabolic waste from the brain (Xie et al., 2013). Disruptions to sleep architecture, whether through total deprivation, fragmentation, or selective suppression of Rapid Eye Movement (REM) and Non-Rapid Eye Movement (NREM) stages, have been associated with an increased risk of cognitive impairment and neurodegenerative diseases, particularly Alzheimer's disease (AD) and related dementias (Santello et al., 2019).

Increasing evidence suggests that sleep disruption outcomes may be partially crystallized by the activation and dysfunction of glial cells, specifically astrocytes and microglia. Astrocytes play a crucial role in regulating synaptic transmission, maintaining extracellular ion balance, and facilitating the glymphatic clearance of neurotoxic proteins, such as amyloid-beta ($A\beta$). In contrast, microglia act as the brain's resident immune cells, involved in essential processes such as synaptic pruning, debris clearance, and neuroinflammatory signalling (Santello et al., 2019; Wang et al., 2021). Chronic or severe sleep disruption seems to interfere with the normal functions of these glial populations, leading to maladaptive processes such as chronic neuroinflammation, synaptic loss, and impaired clearance of pathogenic proteins (Xie et al., 2020; Zhang et al., 2022).

Conceptual and Historical Development

Historically, neuroscience research emphasized neurons as the primary actors in brain function, with glial cells regarded as passive support elements. This view has undergone a significant shift over the past two decades. Pioneering work has revealed that astrocytes actively participate in synaptic transmission by forming the tripartite synapse and that microglia modulate synaptic development and plasticity via activity-dependent mechanisms (Santello et al., 2019).

In parallel, advances in sleep science have shown that brain activity during sleep is essential for memory consolidation, synaptic downscaling, and the clearance of toxic proteins through the glymphatic system. The discovery that aquaporin-4 (AQP4) channels on astrocytic end-feet mediate glymphatic clearance, and that this system operates most efficiently during deep NREM sleep, provided a direct mechanistic link between sleep physiology and the regulation of neurotoxic burden in the brain (Xie et al., 2013).

However, more recent evidence has complicated this view. Using advanced in vivo imaging and tracer studies, Smith et al. (2024) reported that glymphatic transport efficiency is not solely determined by sleep stage; under specific physiological conditions, glymphatic waste removal can remain robust during wakefulness and appears to be strongly shaped by vascular pulsatility, astrocytic end-foot organization, and arousal state (Buccellato et al., 2022; Santello et al., 2019). This suggests that the relationship between sleep architecture and glymphatic function is more nuanced than initially

proposed, and that multiple physiological pathways may contribute to metabolite clearance across different vigilance states. This theme will be examined in greater detail in the Discussion section.

The convergence of glial biology and sleep research has sparked growing interest in how sleep deprivation disrupts neuroglial homeostasis and whether this contributes to long-term brain dysfunction. Studies in both animal models and humans have shown that sleep fragmentation or loss can induce astrogliosis, microglial activation, elevated expression of pro-inflammatory cytokines, and impaired neuroplasticity, key pathological features of neurodegenerative diseases (Wang et al., 2021; Zhang et al., 2022).

Experimental evidence from animal models provides compelling mechanistic insight. Chronic or repeated sleep disruption reliably induces a low-grade inflammatory state in the brain, which is associated with measurable cognitive deficits. In mice, weeks of intermittent REM-focused or total sleep deprivation increase hippocampal microglial activation, elevate pro-inflammatory cytokines, suppress synapse-related proteins, worsen spatial memory, and even accelerate β -amyloid (A β) accumulation—implicating sleep loss, especially REM loss, in both inflammatory signaling and impaired proteostasis (Zhao et al., 2023). In a longer repeated-deprivation paradigm, an innate immunity regulator, hippocampal nuclear factor kappa B (NF- κ B) signaling remains upregulated and tumor necrosis factor-alpha (TNF- α), a chemical messenger produced by the immune system that induces inflammation, is elevated even three weeks post-deprivation, with persistent microglial reactivity and enduring deficits in spatial learning and memory (Wadhwa et al., 2017). A complementary rat study that used a 21-day chronic sleep-deprivation/fragmentation protocol has revealed “anxiety-like” behavior, recognition-memory decline, and pronounced astrocyte/microglia activation in the hippocampus and piriform cortex, further reinforcing a glia-centric mechanism linking fragmented sleep to cognitive impairment (Roy et al., 2018).

Together, these findings underline a paradigm shift: sleep is not merely a restorative state but a dynamic neurobiological process whose disruption can initiate and accelerate glial-driven pathways to neurodegeneration.

Defining Key Concepts and Pathologies

Sleep Deprivation and Sleep Architecture Disruption

Sleep deprivation refers to a partial or total loss of sleep that can occur acutely or chronically, including the stage-specific suppression of rapid eye movement (REM) or non-rapid eye movement (NREM) sleep. In rodent models, chronic sleep deprivation (CSD) refers to repeated or prolonged insufficiency that can be continuous or fragmented. A selective reduction of REM sleep in rodents, experimental paradoxical sleep deprivation (PSD), is the most commonly induced via the modified multiple platform (MMP) method, in which animals are placed on small platforms in a water-filled tank so that REM-related muscle atonia leads to brief water contact and REM disruption (Wadhwa et al., 2017). Disruption of REM, an epoch linked to synaptic plasticity, memory consolidation, and affective

regulation, can exacerbate neuropathology in animal models. In Alzheimer's disease (AD) mice, REM loss has been linked to increased microglial activation (Liu et al., 2023).

Neuroglial Cells

Glial cells (particularly astrocytes and microglia) are central to neural homeostasis. Astrocytes regulate neurotransmitter uptake, support the blood–brain barrier via perivascular endfeet, and contribute to glymphatic clearance of metabolic waste. Microglia are the CNS's resident immune cells, mediating synaptic pruning, host defense, and injury responses. Under pathological or sustained stress conditions, both cell types can shift from surveillance states to reactive phenotypes, namely astrogliosis and microgliosis, marked by morphological remodeling and altered gene-expression programs that amplify inflammatory signalling (Manchanda et al., 2018).

Neuroinflammation

Neuroinflammation denotes activation of the brain's innate immune system, largely mediated by glial cells. Chronic or repeated sleep loss provokes a low-grade, persistent inflammatory state characterised by activation of transcription factors such as nuclear factor- κ B (NF- κ B) and activator protein-1 (AP-1), with consequent upregulation of pro-inflammatory cytokines, including tumour necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6) (Manchanda et al., 2018). These mediators disrupt synaptic signalling, bias astrocytes and microglia toward reactive phenotypes, impair neurogenesis, and contribute to pathways implicated in neurodegenerative disease.

NLRP3 Inflammasome and Innate Immune Activation

The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is a cytosolic multiprotein complex that is predominantly expressed in microglia and, under pathological conditions, can be induced in astrocytes. It acts as a sensor for cellular disturbance within the brain's innate immune system. Activation follows a two-step model. First, priming, often mediated through pattern-recognition receptors such as Toll-like receptors, induces NF- κ B–dependent transcription of NLRP3, pro-IL-1 β , and pro-IL-18. Systemic inflammation, stress hormones, or persistent sleep loss can provide this initial signal. Second, activation is triggered by danger-associated molecular patterns and metabolic stressors; in the context of sleep deprivation, these include mitochondrial dysfunction, elevated reactive oxygen species (ROS), ion fluxes (notably K⁺ efflux and Ca²⁺ influx), and lysosomal rupture.

Upon activation, NLRP3 oligomerises and recruits the adaptor ASC (apoptosis-associated speck-like protein containing a CARD), which binds pro-caspase-1 to form the active inflammasome. Autocatalytic processing yields caspase-1, which cleaves pro-cytokines to mature IL-1 β and IL-18, enabling their secretion and the amplification of neuroinflammatory signalling (Ren et al., 2024). Sustained NLRP3 activity in the CNS promotes a self-perpetuating inflammatory state, enhancing

microgliosis and astrocytic inflammatory programmes. In Alzheimer's disease (AD) models, chronic inflammasome signalling has been linked to increased A β ₄₂ burden—partly through impaired microglial phagocytic clearance—and to tau hyperphosphorylation via kinase cascades, converging on synaptic dysfunction and cognitive decline (Ren et al., 2024). These mechanisms position NLRP3 as a key bridge between sleep deprivation, neuroinflammation, and neurodegeneration.

Pathological Consequences of Sleep Loss

Across rodent models, sleep deprivation in both acute and chronic paradigms, including total and REM-selective protocols, is associated with hippocampal inflammation, reduced synaptic protein expression, and impairments in learning and memory. For example, repeated and intermittent REM sleep deprivation in mice results in persistent activation of hippocampal microglia, increases inflammatory cytokines, and impairs spatial learning, with effects that can persist for weeks after deprivation ends (Wadhwa et al., 2017). In APP/PS1 mice that are genetically predisposed to Alzheimer's disease (Appendix A), disruption of REM sleep, which is critical for synaptic plasticity, memory consolidation, and affective regulation, exacerbates neuropathological progression. In APP/PS1 Alzheimer's disease mice, REM sleep disturbance increases microglial activation and inflammatory signaling (Liu et al., 2023). Together, these findings delineate a mechanistic pathway by which sleep loss initiates neuroinflammatory cascades and glial dysfunction, thereby sharpening the interpretation of experimental results and their relevance to the development and progression of neurodegenerative diseases.

Current State of Research

Over the last decade, research on the interplay between sleep deprivation, neuroglial function, and neurodegeneration has accelerated, drawing on mechanistic animal studies and translational human work. Early descriptive links between poor sleep and cognitive decline have evolved into controlled experimental models that dissect the cellular and molecular pathways mediating this relationship.

Animal studies provide the most direct evidence that sleep loss disrupts glial homeostasis and accelerates neuropathology. Multiple murine paradigms, ranging from intermittent REM sleep deprivation, formerly termed paradoxical sleep deprivation, to chronic REM suppression and total sleep deprivation, consistently show increased astrocytic activation, microglial reactivity, and pro-inflammatory cytokine release (Manchanda et al., 2018; Liu et al., 2022; Yin et al., 2017). These glial responses are accompanied by deficits in spatial learning, recognition memory, and anxiety-like behavior that often persist for weeks after recovery sleep (Wadhwa et al., 2017; Roy et al., 2018). In genetically susceptible models, such as APP/PS1 mice, sleep fragmentation exacerbates amyloid- β accumulation, synaptic protein loss, and hippocampal inflammation, suggesting a feed-forward loop between sleep disruption and Alzheimer-like pathology (Liu et al., 2022; Wang et al., 2021).

A particular focus is the phagocytic function of microglia and their role in synaptic pruning. Chronic sleep deprivation biases microglia toward a pro-inflammatory shift from surveillance to reactive states, increasing complement-tagged synaptic engulfment and disrupting CX3C chemokine receptor 1 (CX3CR1) signaling, both of which are linked to cognitive impairment (Wang et al., 2023; Zhai et al., 2023). Overlapping pathways involving triggering receptor expressed on myeloid cells 2 (TREM2) and Siglec-3 (CD33) further suggest impaired amyloid clearance and disrupted synaptic maintenance under sleep loss (Tan et al., 2023). Astrocytes, beyond their metabolic and homeostatic roles, also remodel synapses under prolonged wakefulness: Bellesi et al. (2017) reported increased astrocytic phagocytosis of synaptic elements, while Holth et al. (2019) and subsequent studies linked disrupted astrocytic endfoot organization and aquaporin-4 (AQP4) polarity, defined as the preferential localization of AQP4 to perivascular endfeet critical for glymphatic exchange, to impaired interstitial solute clearance. These findings initially supported the glymphatic hypothesis, that the deep NREM sleep is uniquely efficient at removing neurotoxic proteins such as A β and tau (Hauglund et al., 2020; Xie et al., 2013). However, more recent *in vivo* imaging work (e.g., Choi et al., 2024) nuances this view, indicating that solute clearance can remain robust during wakefulness under certain physiological conditions, and that vascular pulsatility, arousal state, and astrocytic architecture are key determinants, alongside sleep stage.

Sleep deprivation also intersects with post-translational protein modification relevant to neurodegeneration. Chronic REM sleep loss reduces O-GlcNAc cycling, a regulatory modification that protects against tau hyperphosphorylation and amyloidogenesis (Kim et al., 2024). In parallel, Holth et al. (2019) demonstrated that both acute and chronic sleep disruption increase extracellular tau in mice and humans, potentially accelerating neurofibrillary tangle formation.

Therapeutic studies provide proof of principle that restoring sleep or modulating glial responses can diminish pathology. Optogenetic re-establishment of REM sleep in APP/PS1 mice reduced microglial activation and improved cognition (Zhao et al., 2023). Pharmacological interventions, including Hsp70 administration through intranasal delivery of the molecular chaperone heat shock protein 70, which stabilizes misfolded proteins, limits proteotoxic stress, and reduces pro-inflammatory signaling in glia; dexmedetomidine-mediated complement suppression; and adenosine A1 receptor modulation, have each shown promise in mitigating sleep-loss-induced neuroinflammation and cognitive deficits (Kang et al., 2023; Thondala et al., 2024; Zhai et al., 2023).

While there are fewer studies involving humans, those that do exist are demonstrating significant translational relevance: observational cohorts have linked chronic short sleep and sleep fragmentation to higher CSF A β and tau levels, elevated neuroinflammatory markers, and a greater risk of mild cognitive impairment (Buccellato et al., 2022; Santello et al., 2019). Functional neuroimaging reveals sleep-loss-related changes in hippocampal activation and network connectivity that parallel the structural and molecular alterations observed in animal models.

In summary, the evidence suggests that sleep deprivation disrupts the function of astrocytes and microglia, impairing synaptic maintenance, dysregulating immune signaling, and reducing the clearance of misfolded proteins, changes that converge on neurodegenerative pathways. However, the precise contribution of glymphatic dysfunction remains a topic of debate. This review systematically

evaluates how both acute and chronic sleep deprivation, including total and REM-selective protocols, affects astrocyte and microglial function in both animal and human studies, and how these alterations relate to cognition and Alzheimer's disease.

Methods

Search Strategy

This systematic review was conducted in accordance with the PRISMA 2020 guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) to ensure methodological transparency and reproducibility. The review was not preregistered; to mitigate potential bias, eligibility criteria, screening procedures, and synthesis plans were finalised prior to study selection and are documented in the Supplementary Material.

A systematic literature search was performed in April 2025 in two databases: MEDLINE (via EBSCOhost) and Scopus. The strategy combined Medical Subject Headings (MeSH)/subject headings and keyword terms spanning three domains-sleep disturbance, glial cell biology, and cognitive or pathological outcomes-using Boolean operators (AND/OR) and truncation where appropriate. Search terms included combinations of "sleep deprivation," "REM sleep," "sleep fragmentation," "astrocyte*," "microglia*," "GFAP," "Iba1," "cognitive dysfunction," "Alzheimer*," "synaptic plasticity," and "neuroinflammation." The search was limited to peer-reviewed journal articles published in English between 2010 and 2025. Full, database-specific search strings are provided in the Appendix B section of the review. Reference lists of included studies and relevant reviews were hand-searched to identify additional articles.

Inclusion and Exclusion Criteria

Eligibility criteria were prespecified to ensure a rigorous and focused selection of studies relevant to the research question. Original experimental investigations conducted in vivo (animal or human) or ex vivo have been included when they are directly linked to a prior in vivo sleep manipulation. Eligible studies had to (i) clearly describe a sleep-disruption protocol such as total sleep deprivation, selective REM or NREM restriction, or chronic sleep fragmentation; (ii) report at least one glial outcome indexing astrocyte or microglia function; and (iii) include either behavioral measures of cognition or neuropathological outcomes. Astrocyte outcomes included GFAP (reactive astrogliosis) and AQP4 (endfoot polarity/lymphatic clearance). Microglial outcomes included Iba1 (a microglial cytoskeletal marker), CD68 (a marker of lysosomal/ phagocytic activity), and cytokine profiling (e.g., TNF- α , IL-1 β , IL-6). Cognitive outcomes encompassed validated tasks (e.g., Morris water maze for spatial learning; novel object recognition for recognition memory). Neurodegenerative outcomes included A β deposition, tau pathology, and synaptic proteins (e.g., synaptophysin as a proxy for synaptic density)

(Santello et al., 2019; Zhang et al., 2022).

Exclusion criteria included: review articles, meta-analyses, editorials, conference abstracts/proceedings, and methodological papers without original data; in vitro-only studies not tied to an in vivo manipulation; studies lacking glial-specific analyses; and studies without measurable cognitive or neuropathological outcomes. Duplicate publications and re-analyses of previously published datasets were excluded unless they presented substantially new findings or extended prior results.

At full-text assessment, the same prespecified criteria were applied to refine the final set, emphasizing well-defined animal models (e.g., C57BL/6, APP/PS1) or clearly defined human cohorts; validated glial markers (GFAP for astrocytes; Iba1/CD68 and pro-inflammatory cytokines for microglia); and functional outcomes relevant to learning and memory. Studies also had to demonstrate relevance to neurodegenerative conditions, with particular emphasis on Alzheimer's disease models or human populations at risk for cognitive decline (Niazi et al., 2024; Wu et al., 2023). This full-text screening reduced the pool from 50 to 21 studies, ensuring that only methodologically rigorous and conceptually relevant research was included in the synthesis.

Data Extraction

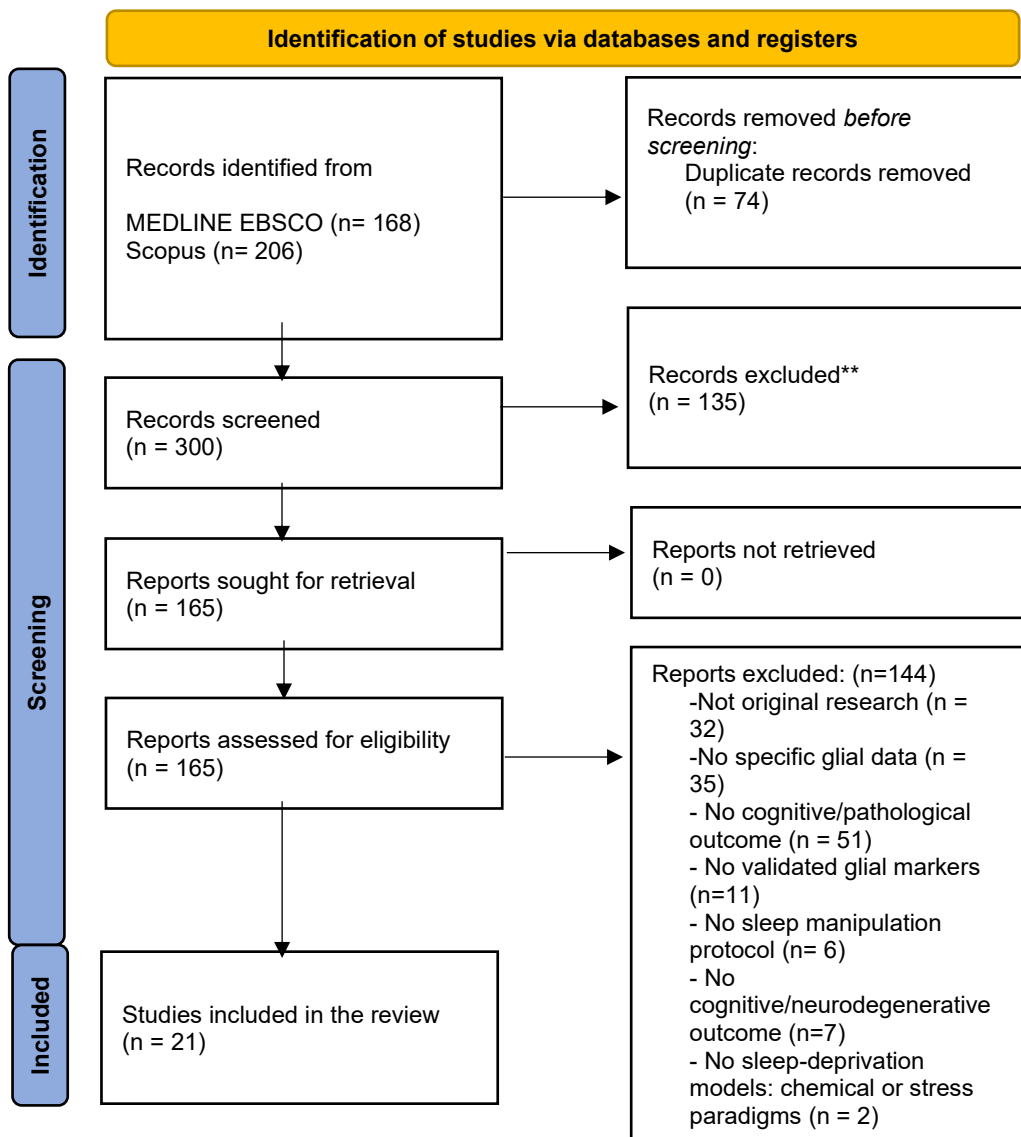
All search results were exported into Microsoft Excel for screening and deduplication, with duplicates identified through matching of DOI, title, and author. Screening was performed in two stages. In the first stage, titles and abstracts were reviewed to determine preliminary eligibility. In the second stage, full texts of potentially eligible studies were retrieved and assessed against both the primary and refined inclusion criteria. The literature search and screening process is illustrated in Figure 1.

For each included study, data were extracted using a structured template. Extracted information included publication metadata (author, year, journal), experimental model (species, strain, or human cohort), type and duration of sleep manipulation, targeted sleep phase (e.g., REM, NREM, or total sleep deprivation), and glial markers assessed. Cognitive or neuropathological outcomes were recorded, including behavioral performance metrics, quantification of amyloid-beta and tau, and measures of synaptic density. Main findings, reported limitations, and any interventions used were documented. Each study was also annotated according to the primary focus on glial cells (astrocytes or microglia) and the strength of association with cognitive outcomes. A long-form characteristics table, including all extraction fields (authors/year, sample, protocol, controls, glial markers, cognitive and neurodegenerative outcomes, and principal findings), is provided in Supplementary Table S1.

Given the heterogeneity in methodologies, outcome measures, and experimental designs, a quantitative meta-analysis was not performed. Instead, a qualitative synthesis was undertaken to identify recurring mechanistic patterns and conceptual insights. The risk of bias was evaluated by examining the clarity of the experimental design, sample sizes, use of control conditions, blinding or randomization procedures, and transparency in the reporting of glial and cognitive data. Studies with methodological limitations were noted but not excluded if they provided relevant mechanistic or conceptual contributions.

Figure 1

PRISMA Flow Chart



Note. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses. Records were identified in April 2025 from MEDLINE (EBSCOhost) and Scopus (n = 374). After de-duplication by DOI, title, and author (n = 74), 300 records were screened for title/abstract and 135 were excluded. Full texts assessed for eligibility (n = 165); 144 were excluded for primary reasons including no experimental sleep manipulation, no glial outcomes, no cognitive/neuropathological outcomes, in vitro-only without preceding in vivo manipulation, absence of sleep-deprivation models (e.g., AlCl₃/D-gal AD model), or non-original research (including review articles; n = 3). Twenty-one studies were included in the qualitative synthesis. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. (2021). The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>.

Results

Overview of Findings

This review included 21 experimental studies (published between 2010 and 2025) that met all the criteria; full characteristics are presented in Supplementary Table S1. Across models, sleep deprivation, whether total, REM-selective/NREM-restricted, or chronic fragmentation, was consistently associated with disrupted astrocytic and microglial function, reflected by Iba1/CD68 increases and pro-inflammatory cytokines (e.g., TNF- α , IL-1 β , IL-6), frequent GFAP upregulation and AQP4 endfoot polarity changes, and concomitant deficits on standard cognitive tasks (Morris water maze, Y-maze, novel object recognition) (Liu et al., 2023; Manchanda et al., 2018; Wadhwa et al., 2017; Wang et al., 2021). Several studies have linked these glial changes to Alzheimer-related pathology, including increased A β burden, p-tau accumulation, and loss of synaptic proteins (PSD-95, synaptophysin) (Kim et al., 2024; Liu et al., 2023; Wang et al., 2021; Zhang et al., 2022).

Human data were limited but directionally aligned, associating poor sleep with higher CSF A β /tau levels, elevated inflammatory markers, and measurable cognitive decline (e.g., Buccellato et al., 2022). Methodological heterogeneity across protocols and biomarker panels precluded the calculation of a pooled effect estimate; therefore, the findings are synthesized qualitatively and summarized in the text and Supplementary Table S1(ST1).

Detailed Synthesis

Across rodent models, sleep loss consistently provoked microglial reactivity, astrocytic changes, and cognition-relevant deficits. Repeated, intermittent REM sleep deprivation produced enduring anxiety-like behavior and spatial/working-memory impairments alongside selective hippocampal microgliosis and elevated TNF- α /IL-1 β , with several effects persisting for weeks after the last deprivation (Wadhwa et al., 2017). The total sleep deprivation (72 h) reduced synaptic proteins (PSD-95, synaptophysin) and impaired memory via altered CD33/TREM2 signalling and microglial phagocytosis (Zhang et al., 2022), while a complementary line showed that 72 h SD disrupted CX3CR1-mediated synaptic pruning: microglia became hyperactivated with reduced branching, PSD95/CD68 co-localization fell, dendritic spines increased, and spatial memory declined (Wang L. et al., 2023). At the astrocyte–microglia interface, sleep loss increased astrocytic phagocytosis of synaptic elements and, under chronic restriction, additionally induced microglial activation with C3 upregulation. C3 is the central hub of the complement cascade; its cleavage products, C3b and iC3b, opsonize synapses and recruit microglial CR3, facilitating complement-tagged synapse engulfment. These findings indicate that prolonged wakefulness primes glia for synapse-directed immune signalling (Bellesi et al., 2017).

Links to Alzheimer relevant pathology were strongest in AD-prone mice. In APP/PS1 mice, chronic deprivation (20 h/day for 21 days) exacerbated working/spatial/fear-memory deficits, suppressed hippocampal LTP, decreased PSD-95, increased microgliosis, and elevated A β deposition; wild-type littermates showed milder parallel effects (Wang C. et al., 2021). In APP/PS1 mice exposed to

48 h deprivation, both REM-selective and total deprivation impaired spatial memory, heightened microglial activation (CD68, CD40, IRF7), increased C3, and reduced plaque clearance (greater A β burden), with soluble A β highest in TSD > RD > controls (Liu S. et al., 2023). Downstream molecular pathways also shifted: chronic REM-SD decreased brain O-GlcNAc cycling, increased GFAP/IBA-1 and pro-inflammatory markers, raised A β and p-Tau, and reduced dendritic complexity; normalizing O-GlcNAc (glucosamine or OGT overexpression) or dampening neuroinflammation (minocycline) rescued pathology and behavior (Kim et al., 2024). Phenotype-level polarization data showed that chronic (vs. sub-chronic) SD induced microglia toward M1 and astrocytes toward A1 states, exacerbated depressive-like behavior, and disrupted APP processing (Niazi et al., 2024). Early-life sleep fragmentation had lasting consequences: neonatal fragmentation resulted in persistent hippocampal/cortical microgliosis and astrogliosis, sustained elevation of IL-1 β and TNF- α , and long-term recognition/spatial-memory deficits months later (Bertrand et al., 2020).

Intervention studies provide initial evidence that targeting sleep or glia can reverse these phenotypes. Hsp70 (intranasal) reduced microglial activation, shifted cytokines toward anti-inflammatory profiles, restored p-CREB/BDNF, and rescued memory and anxiety after sleep deprivation (Kang et al., 2023). Dexmedetomidine attenuated C3/C3aR1 activation, reduced astro/microgliosis, stabilized synaptic proteins (PSD-95, SYP), and improved spatial and working memory (Zhai et al., 2023). Adenosine A1 receptor agonism (CCPA) mitigated REM-SD-induced glial activation and cytokines and normalized fear-extinction recall, whereas antagonism worsened outcomes (Thondala et al., 2024). Restoring sleep architecture itself was beneficial: optogenetic slow-wave augmentation in APP mice improved NREM sleep, reduced plaques, normalized neuronal Ca²⁺ dynamics, and reprogrammed microglia toward plaque-engaged, phagocytic states, the precise outcomes that were suppressed due to concurrent sleep deprivation (Zhao et al., 2023). A pharmacologic approach that improved sleep structure (propofol) upregulated BMAL1/BDNF, shifted microglia away from M1, and rescued spatial/working memory after 48 h SD (Liu H. et al., 2024).

Conceptual and narrative reviews (Buccellato et al., 2022; Carvalhas-Almeida et al., 2023; Santello et al., 2019) align with these experimental findings by framing the roles of astrocytes and microglia, AQP4/glymphatic contributions, and circadian-glia interactions; however, they were not treated as primary evidence. Likewise, non-sleep disease or stress models (e.g., isoliensinine in AlCl₃/D-gal mice; chronic noise/NLRP3) were not included in the core synthesis, although they provide a convergent mechanistic context for glial-neurodegenerative pathways. Overall, the experimental corpus supports a model in which sleep loss drives microglial activation and complement signaling, astrocytic phagocytosis/AQP4 perturbation, as well as synaptic/AD-relevant pathology. Multiple orthogonal interventions demonstrate reversibility when either sleep architecture or glial pathways are restored.

Discussion

Contextualizing the Findings within the Current State of Research

Collectively, the 21 studies synthesized here reinforce and extend the view that sleep actively regulates glial homeostasis, rather than being merely permissive for brain health (Carvalho-Almeida et al., 2023; Santello et al., 2019). Prior work frames astrocytes and microglia as central nodes linking sleep–wake state to synaptic remodeling, immune tone, and proteostasis; the present review integrates these threads by showing that experimental sleep loss—whether total, REM-selective/NREM-restricted, or fragmented—consistently shifts glia toward reactive phenotypes, coincident with impaired cognition and Alzheimer related pathology (Kim et al., 2024; Liu et al., 2023; Manchanda et al., 2018; Wadhwa et al., 2017; Wang et al., 2021). The oncergent evidence implicates complement signaling and microglial phagocytic programs (e.g., CX3CR1, TREM2/CD33 axes), astrocytic synapse engulfment and AQP4 endfoot polarity, and metabolic stress pathways (including reduced O-GlcNAc cycling) as sleep-sensitive levers that shape synaptic integrity and amyloid/tau dynamics (Bellesi et al., 2017; Kim et al., 2024; Liu et al., 2023; Zhai et al., 2023; Wang et al., 2023; Zhang et al., 2022).

The findings also refine prevailing models. While the glymphatic hypothesis emphasizes deep NREM as optimal for solute clearance (Buccellato et al., 2022; Xie et al., 2013), emerging *in vivo* work suggests that vascular pulsatility, arousal state, and astrocytic architecture modulate clearance efficiency beyond sleep stage alone; the balance of evidence here aligns with that nuance, with AQP4 polarity/endfoot organization appearing critical and reliably perturbed by sleep loss (Buccellato et al., 2022; Santello et al., 2019). Likewise, microglial responses are not uniformly pro-phagocytic; depending on the pathway engaged, sleep deprivation can either exaggerate synapse removal (complement upregulation) or lead to pruning failure (CX3CR1 disruption), resulting in distinct cognitive signatures (Liu et al., 2023; Wang et al., 2023; Zhai et al., 2023). Such heterogeneity likely reflects stage-specific deprivation, dose/duration, developmental timing, and region-specific vulnerability (Niazi et al., 2024; Raviv et al., 2021; Wadhwa et al., 2017).

Translationally, the rodent evidence aligns with human observations, which link short or fragmented sleep to higher CSF amyloid/tau and inflammatory markers, as well as cognitive decline (Buccellato et al., 2022; Holth et al., 2019). Notably, several included experiments show reversibility: restoring sleep architecture or targeting glial pathways, including complement dampening, adenosine A1 modulation, heat-shock responses, normalization of O-GlcNAc-ameliorated molecular and behavioral phenotypes (Kang et al., 2023; Kim et al., 2024; Thondala et al., 2024; Zhao et al., 2023; Zhai et al., 2023). This aligns with clinical directions already in motion (behavioral sleep therapies, circadian alignment, sleep-apnea treatment, slow-wave augmentation) while pointing toward adjunctive, glia-targeted strategies to test alongside sleep restoration (Kang et al., 2023; Zhai et al., 2023; Zhao et al., 2023;).

Agreement and Conflict Across Studies

Across animal models, there is strong agreement that experimental sleep loss, whether total, REM-selective/NREM-restricted, or fragmented, induces microglial activation (Iba1/CD68) and elevations in pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6), accompanied by cognitive deficits on spatial and recognition tasks (Liu et al., 2023; Manchanda et al., 2018; Wadhwa et al., 2017; Wang et al., 2021). Multiple studies also converge on Alzheimer relevant outcomes; namely, increased A β burden, p-tau, and loss of synaptic proteins (PSD-95, synaptophysin) with effects most pronounced in APP/PS1 models (Kim et al., 2024; Liu et al., 2023; Wang et al., 2021). Technically speaking, there is broad alignment that sleep loss perturbs glial phagocytic programs and complement signaling (e.g., C3/C3aR1), and that these processes are reversible in intervention paradigms (e.g., dexmedetomidine, Hsp70) with parallel improvements in behavior (Kang et al., 2023; Zhai et al., 2023). Independent lines of evidence further agree that astrocytic synapse engulfment increases with prolonged wakefulness and that early-life sleep disruption leaves a long-lasting glial “priming” state with enduring memory costs (Bellesi et al., 2017; Raviv et al., 2021).

However, despite the strong agreement, several inconsistencies are observable. First, astrocytic readouts vary: some studies report robust GFAP upregulation, whereas others highlight AQP4 endfoot polarity changes in the absence of marked GFAP shifts, the differences that likely reflect trial selection, brain region, and timing post-deprivation (Bellesi et al., 2017; Kim et al., 2024). Second, the direction of microglial pruning is not uniform: evidence supports both exaggerated, complement-mediated synapse removal (C3) and pruning failure via CX3CR1 disruption, the mechanisms that might dominate at different doses/durations, developmental windows, or circuits (Wang et al., 2023; Zhai et al., 2023). Third, comparisons of REM-SD versus total SD yield mixed results: some measures separate on a very minimal level (Liu et al., 2023), while others reveal pathway-specific differences (e.g., O-GlcNAc cycling under chronic REM-SD) (Kim et al., 2024). Fourth, behavioural sensitivity differs by analysis; Y-maze/object-location tasks frequently detect deficits while NOR can be spared, suggesting domain-specific or ceiling/familiarity effects (Wang et al., 2023; Zhang et al., 2022). Finally, persistence varies, with some effects resolving after recovery sleep and others persisting for weeks, particularly following repeated or fragmented paradigms (Wadhwa et al., 2017).

Much of this heterogeneity is possibly attributable to paradigm-specific confounds. Deprivation paradigms such as gentle handling, multiple-platform water tanks, and rotating bars introduce stress, motor activity, light, and environmental factors that can independently activate glia (Manchanda et al., 2018; Wang et al., 2021). Additional variability arises from dose/duration, circadian timing (ZT), recovery-sleep allowance, age/sex/strain, brain region analysed, and the post-SD sampling window (Lim & Dinges, 2008; Liu et al., 2023; Wadhwa et al., 2017). Outcome panels also differ (morphology versus function; cytokines versus complement versus phagocytosis analysis), and repeated behavioural testing (e.g., water-maze familiarity) can mask true impairments (Wadhwa et al., 2017).

Overall, the evidence supports a model in which sleep loss drives microglial activation and astrocytic remodelling, disrupting synaptic maintenance and, in vulnerable genotypes, accelerating A β /p-tau pathology. Apparent conflicts are most simply interpreted as pathway or stage-specific effects,

for example complement upregulation versus CX3CR1 disruption and GFAP elevation versus AQP4 polarity change, rather than true contradictions. Studies that standardise deprivation stress, report precise timing and region, and pair morphology with functional gauging (pruning/engulfment, plaque clearance) show the greatest internal coherence; moreover, interventional data (dexmedetomidine, Hsp70, sleep restoration) strengthen causal inference by demonstrating phenotypic reversibility (Kang et al., 2023; Zhai et al., 2023; Zhao et al., 2023).

Strengths and Weaknesses of the Included Studies

Across the included animal studies, experimental control was generally strong. Most investigations used clearly defined, reproducible sleep-loss paradigms (e.g., multiple-platform, gentle handling, rotating-bar) with explicit dosing schedules, supporting causal inference on the effects of sleep deprivation on glial function and behavior. Construct validity was reinforced through validated markers for microglia (Iba1/CD68) and astrocytes (GFAP/AQP4), together with Alzheimer-relevant readouts ($A\beta$, p-tau) and synaptic proteins (PSD-95, synaptophysin) (Bellesi et al., 2017; Kim et al., 2024; Liu et al., 2023; Wang et al., 2021; Zhang et al., 2022). Many reports paired molecular or histological outcomes with standardized behavioral analysis (Morris water maze, Y-maze, novel object recognition), linking mechanism to function (Liu et al., 2023; Wadhwa et al., 2017; Wang et al., 2021; Zhang et al., 2022). Inclusion of disease-susceptible genotypes (e.g., APP/PS1) increased translational relevance by testing whether sleep loss accelerates pathology in vulnerable backgrounds (Liu et al., 2023; Wang et al., 2021). Several interventional experiments (sleep restoration, complement dampening, adenosine A1 modulation, Hsp70, normalization of O-GlcNAc) demonstrated partial or complete reversibility of phenotypes. A subset also incorporated post-deprivation follow-ups, distinguishing transient from persistent effects (Niazi et al., 2024; Wadhwa et al., 2017).

The methodological limitations, however, reduced the reliability and overall confidence in the findings. Common deprivation paradigms can introduce stress, locomotor load, light/noise exposure, and water-tank effects that independently activate glia; stress-matched controls were inconsistently used (Lim & Dinges, 2008; Manchanda et al., 2018; Wang et al., 2021). Heterogeneity in exposure dose and duration, circadian timing (zeitgeber time), allowance for recovery sleep, brain region sampled, and post-deprivation sampling windows complicated cross-study comparisons and precluded a reliable meta-analysis (Liu et al., 2023; Wadhwa et al., 2017; Wang et al., 2021). Objective sleep verification (EEG/EMG) was inconsistently applied, with some studies inferring REM/NREM loss from apparatus rather than polysomnography (Liu et al., 2023; Wang et al., 2021). Small sample sizes, without a priori power calculations, and variable reporting of randomization and blinding raised risk-of-bias concerns (Manchanda et al., 2018; Wadhwa et al., 2017). Several studies emphasized morphology or cytokines without functional gauging of pruning/engulfment, plaque clearance, or in vivo clearance/glymphatic flow (Bellesi et al., 2017; Wang et al., 2023; Zhai et al., 2023). Behavioral batteries varied in sensitivity and were susceptible to practice or familiarity effects (e.g., repeated water maze trials), and primary outcomes were not always prespecified. External validity was further constrained by predominant use of young, male C57BL/6 mice and limited attention to sex, aging, strain differences, or comorbid states;

reporting gaps (e.g., effect sizes, confidence intervals, standardized AQP4 polarity metrics) also reduced comparability (Kim et al., 2024; Liu et al., 2023; Wang et al., 2021).

Considering these strengths and weaknesses together, the overall certainty of evidence can best be described as moderate. Directional consistency across models and demonstrations of reversibility support a causal role for sleep loss in glial dysregulation, synaptic disruption, and cognition-relevant outcomes. At the same time, internal validity is limited by paradigm confounds, incomplete sleep verification, and small sample sizes, and external validity is limited by narrow sampling frames and sparse human mechanistic replication.

Limitations of This Review

This review has several limitations that should be taken into account when interpreting the findings. First, the search strategy. Although conducted in accordance with PRISMA 2020, the study was limited to two databases (MEDLINE via EBSCOhost and Scopus), English language publications, and the 2010–2025 time frame. These choices may have introduced language, database, and time-lag biases, and relevant studies in other databases or the grey literature (e.g., preprints, conference abstracts) may have been missed. The review was not registered (PROSPERO), which raises the possibility of unplanned analytic decisions. Second, study selection and data extraction were performed by a single reviewer (with internal cross-checks), which increases the risk of selection and extraction bias.

Third, the evidence base itself is heterogeneous. Deprivation paradigms, dosing/duration, circadian timing, allowance for recovery sleep, and species/strain/sex varied widely, as did outcome panels (e.g., morphology vs. cytokines vs. complement/phagocytosis). Due to this heterogeneity and the frequent occurrence of incomplete sleep verification (limited EEG/EMG), a quantitative meta-analysis was not possible. Fourth, reporting quality was inconsistent across primary studies (e.g., missing effect sizes and confidence intervals, limited details on randomization/blinding, non-standardized AQP4 polarity metrics), which may have weakened the precision in the qualitative synthesis.

Finally, validation is severely limited: most included experiments used young, male C57BL/6 mice and a subset of AD-prone transgenics (e.g., APP/PS1), with relatively few data from females, aged animals, other strains, or comorbid models; human studies were fewer and largely correlational.

Societal and Ethical Aspects

The societal relevance of this research is profound, given the global prevalence of chronic sleep restriction driven by lifestyle, occupational demands, and environmental factors. Understanding how sleep loss primes the brain for neurodegeneration could inform public health initiatives aimed at promoting sleep hygiene as a modifiable risk factor for dementia. Ethical considerations arise in experimental designs involving sleep deprivation, particularly in human research, where the well-being of participants must be safeguarded. Furthermore, pharmacological interventions aimed at mitigating sleep loss related pathology must be evaluated not only for efficacy but also for long-term safety and accessibility.

Final Conclusions

Synthesizing 21 experimental studies, this review demonstrates that sleep loss, total, REM-selective/NREM-restricted, or chronically fragmented, reliably shifts astrocytes and microglia toward reactive states, disrupts synaptic maintenance, and impairs learning and memory. In vulnerable genotypes (e.g., APP/PS1), these glial disturbances align with Alzheimer relevant pathology, including greater A β burden, p-tau accumulation, and loss of synaptic proteins. Convergent mechanistic signals implicate complement engagement (C3/C3aR1), microglial phagocytic pathways (CX3CR1, TREM2/CD33), astrocytic synapse engulfment and AQP4 endfoot polarity, and metabolic stress (e.g., reduced O-GlcNAc cycling). Importantly, multiple orthogonal interventions-sleep restoration (including slow-wave augmentation), complement dampening, adenosine A1 modulation, Hsp70 delivery, and normalization of O-GlcNAc-demonstrate at least partial reversibility of molecular and behavioral phenotypes, underscoring both causality and therapeutic applications.

At the same time, heterogeneity in paradigms, incomplete sleep verification, and narrow sampling frames temper certainty and limit validity. Moving forward, the most promising path looks to be combining foundational sleep restoration (behavioral, circadian, and disorder-targeted care) with glia-focused therapeutics that modulate complement, purinergic/NLRP3 signaling, microglial state transitions, and astrocytic AQP4 polarity. Standardized, stress-minimized models with polysomnographic verification, balanced sex/age cohorts, functional glial analysis, and alignment with human biomarkers (e.g., CSF/serum GFAP, sTREM2, neuroinflammation PET) are essential for translating these insights. Overall, the evidence supports a clear and actionable message: protecting and restoring sleep, and directly stabilizing glial homeostasis, represents a credible strategy to preserve cognition and potentially slow neurodegenerative trajectories.

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Appendix

Appendix A

Definitions of Specialized Neuropathological Terms

1. Experimental Models

APP/PS1 Transgenic Mouse Model

A double-transgenic model co-expressing human amyloid precursor protein (APP) with familial Alzheimer's disease (AD) mutations (e.g., Swedish mutation) and human presenilin-1 (PS1) variants that accelerate amyloid- β ($A\beta$) plaque formation. These mice develop early amyloid pathology, synaptic dysfunction, and cognitive deficits, making them valuable for studying interactions between genetic susceptibility, sleep deprivation, and glial dysfunction in neurodegeneration (Jankowsky et al., 2004; Radde et al., 2006).

2. Brain Clearance Mechanisms

Glymphatic System

A perivascular network that facilitates clearance of interstitial solutes, including amyloid- β and tau, through cerebrospinal fluid (CSF) influx, exchange with interstitial fluid (ISF), and efflux along perivenous pathways. Astrocytic endfeet enriched with aquaporin-4 (AQP4) channels are key structural components. Initially believed to operate most efficiently during deep non-rapid eye movement (NREM) sleep (Xie et al., 2013), more recent findings suggest clearance can also occur during wakefulness under specific physiological conditions (Smith et al., 2024).

3. Protein Pathology

Tau Hyperphosphorylation

An abnormal increase in phosphate groups attached to tau protein, mediated by kinases such as glycogen synthase kinase-3 β (GSK-3 β) and cyclin-dependent kinase 5 (CDK5). This process disrupts tau's ability to stabilize microtubules, leading to aggregation into paired helical filaments (PHFs) and neurofibrillary tangles (NFTs), the key hallmarks of Alzheimer's disease and related tauopathies (Wang & Mandelkow, 2016). Sleep deprivation may exacerbate tau hyperphosphorylation via neuroinflammation, oxidative stress, and impaired glymphatic clearance (Zhao et al., 2020).

4. Neuroinflammatory Phenotypes

Inflammatory (M1-like) Phenotype

A pro-inflammatory activation state of microglia characterized by high inducible nitric oxide synthase (iNOS) activity and secretion of cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-1 beta (IL-1 β), and interleukin-6 (IL-6). Chronic M1-like activation contributes to synaptic loss, neuronal injury, and blood–brain barrier disruption (Orihuela et al., 2016). Persistent M1 bias during sleep deprivation promotes complement-mediated synaptic pruning and accelerates neurodegeneration (Wadhwa et al., 2017).

5. Microglial Signaling Pathways

CX3CR1 (C-X3-C Motif Chemokine Receptor 1)

A receptor expressed on microglia that binds neuronal fractalkine (CX3CL1). This signaling axis regulates microglial homeostasis, synaptic pruning, and neuroinflammatory responses (Paolicelli et al., 2011). Disruption, by genetic deficiency, disease, or sleep deprivation, can lead to excessive microglial activation, increased synaptic engulfment, and heightened inflammation (Wang et al., 2021).

TREM2 (Triggering Receptor Expressed on Myeloid Cells 2)

A transmembrane receptor on microglia that promotes survival, proliferation, and phagocytosis of debris and amyloid- β . TREM2 supports a neuroprotective microglial phenotype (Ulrich et al., 2017). Impairment in TREM2 function, observed in both Alzheimer's disease and sleep deprivation, reduces amyloid clearance and promotes neuroinflammation (Zhang et al., 2022).

CD33 (Siglec-3)

An inhibitory receptor on microglia that suppresses phagocytic activity via ITIM (immunoreceptor tyrosine-based inhibitory motif) signaling. High CD33 expression is linked to reduced amyloid clearance and increased Alzheimer's disease risk (Griciuc et al., 2013). Sleep deprivation can upregulate CD33, worsening amyloid accumulation and inflammation (Zhao et al., 2023).

Appendix B

Search Strings

Search String for Medline (EBSCO):

("sleep deprivation" OR "sleep loss" OR insomnia OR "circadian disruption")

AND

(astrocyte* OR microglia* OR "glial cell*" OR "neuroglial cell*")

AND

("cognitive dysfunction" OR "executive function" OR memory OR "behavioral changes" OR neuroinflammation OR "neurodegenerative disease*" OR Alzheimer* OR Parkinson*)

Search String for Scopus:

TITLE-ABS-KEY("sleep deprivation" OR "sleep loss" OR insomnia OR "circadian disruption")

AND

TITLE-ABS-KEY(astrocyte* OR microglia* OR "glial cell*" OR "neuroglial cell*")

AND

TITLE-ABS-KEY("cognitive dysfunction" OR "executive function" OR memory OR "behavioral changes" OR neuroinflammation OR "neurodegenerative disease*" OR Alzheimer* OR Parkinson*)

TITLE = the article's title

ABS = the article's abstract

KEY = the article's keywords