Narrative Review Article

Sleep Disruption After Traumatic Brain Injury: Implications for Glymphatic Function and Cognitive Recovery

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ABSTRACT

Traumatic brain injury (TBI) is a major cause of neurological dysfunction and can lead to long-term cognitive impairment. While many studies focus on the immediate effects of injury, sleep disruption following TBI is a major and underrecognized barrier to recovery. Sleep plays a critical role in memory consolidation, neuronal repair, and metabolic waste clearance through the glymphatic system. Disruption of sleep, particularly slow-wave sleep, can impair these processes and contribute to ongoing neurological dysfunction. This review examines the pathophysiology of TBI, normal sleep physiology and the role of the glymphatic system in cognitive function. It also explores the prevalence of sleep disruption after TBI and its association with cognitive and emotional symptoms. Evidence from both human and animal studies suggests that impaired sleep is associated with neurological decline, while experimental studies support several biological mechanisms through which sleep disruption can influence recovery following traumatic brain injury. Targeted interventions aimed at improving sleep represent an important and modifiable factor in enhancing recovery following traumatic brain injury. The objective of this narrative review is to examine how sleep disruption following traumatic brain injury can impair glymphatic clearance and contribute to cognitive dysfunction and long-term neurological outcomes. By synthesizing evidence from human and animal studies published between 2007 and 2024, this review highlights potential mechanistic links and discusses the clinical relevance of improving sleep as a therapeutic target during TBI recovery.

Keywords: traumatic brain injury; glymphatic system; sleep disruption; slow-wave sleep; cognitive recovery; neurodegeneration; beta-amyloid; neuroinflammation

INTRODUCTION

Traumatic brain injury (TBI) is defined as a disruption in normal brain function caused by an external force, such as a blow or jolt to the head. It is a common condition that can lead to both short-term and long-term neurological complications. Although much research has focused on the acute effects of TBI, sleep disruption after injury is increasingly recognized as an important but underexplored factor in recovery.

TBI affects over 50 million people worldwide each year, costing the global economy approximately $400 billion annually (1). The consequences range from brief cognitive disruption following mild concussion to permanent neurological disability following severe injury. Despite this scale, post-injury sleep disruption remains systematically underscreened and undertreated

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in clinical practice, representing a gap with measurable consequences for recovery outcomes.

Sleep is essential for brain function, supporting memory consolidation, neuronal repair, and metabolic waste clearance (2). During sleep, especially slow-wave sleep, the brain clears metabolic waste through the glymphatic system, a network of perivascular channels that facilitates cerebrospinal fluid (CSF) flow through brain tissue (3). When sleep is disrupted, this clearance process becomes less efficient, potentially leading to the accumulation of neurotoxic substances.

Many patients with TBI report insomnia, fragmented sleep, or excessive daytime sleepiness (4). These disturbances not only reflect injury but also actively worsen neurological outcomes. The objective of this narrative review is to synthesize current evidence regarding the relationship between traumatic brain injury, post-traumatic sleep disruption, glymphatic system dysfunction, and cognitive recovery. Specifically, this review examines how alterations in sleep following TBI can impair glymphatic waste clearance, contribute to the accumulation of neurotoxic proteins, and influence long-term neurological and cognitive outcomes while highlighting potential therapeutic implications for improving patient recovery. In this review, the term sleep disruption is used as the overarching clinical term encompassing insomnia, hypersomnia, fragmented sleep, circadian rhythm disorders, and related abnormalities following traumatic brain injury. The terms sleep disturbances and sleep–wake disturbances are used only when referring to specific physiological mechanisms or when reflecting the terminology used in individual studies.

PATHOPHYSIOLOGY OF TRAUMATIC BRAIN INJURY

TBI triggers a cascade of biological processes involving metabolic stress, excitotoxicity, inflammation, and structural damage to neurons.

Following injury, excessive glutamate release leads to excitotoxicity, causing overstimulation of neurons and disruption of ion balance. This results in calcium overload, mitochondrial dysfunction, and oxidative stress, ultimately damaging or killing neurons (1).

TBI also disrupts the blood-brain barrier, allowing inflammatory molecules and immune cells to enter brain tissue, as seen in Figure 1. Maas *et al*. emphasized that this secondary injury process contributes significantly to long-term neurological damage (1). Activated microglia and astrocytes release cytokines such as interleukin-1β and tumor necrosis factor-alpha, which further amplify neuroinflammation.

Krueger *et al*. showed that these cytokines also play a role in sleep regulation, interacting with brain regions such as the hypothalamus and brainstem (5). When dysregulated, they can disrupt normal sleep architecture, particularly slow-wave sleep, which is critical for recovery.

Another key mechanism is axonal injury. Johnson *et al*. demonstrated that mechanical forces during trauma can damage axons, impairing neuronal communication and leading to long-term cognitive deficits (6). The combined effect of excitotoxicity, neuroinflammation, and axonal injury creates a neurological environment in which sleep disruption becomes especially harmful.

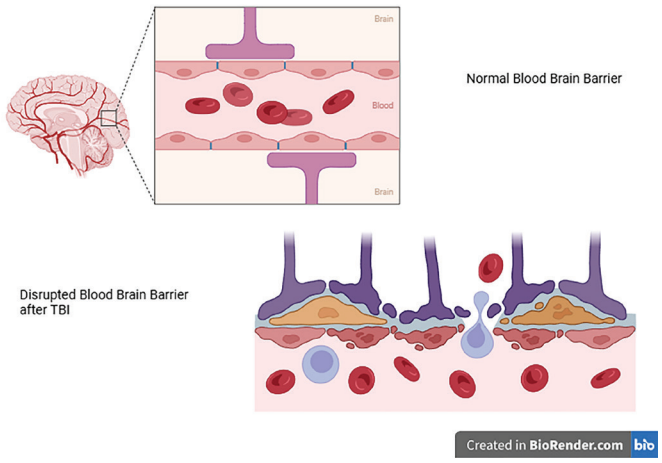

Figure 1. *Blood-brain barrier disruption following traumatic brain injury. The top image shows an intact blood-brain barrier with preserved endothelial tight junctions. Bottom image shows disrupted blood-brain barrier post-TBI, with increased permeability, infiltration of inflammatory cells into brain tissue, contributing to neuroinflammation and secondary injury.*

NORMAL SLEEP PHYSIOLOGY AND THE GLYMPHATIC SYSTEM

Sleep occurs in cycles consisting of non-rapid eye movement (NREM) and rapid eye movement (REM) stages. Slow-wave sleep (N3) is particularly important for brain recovery and memory consolidation (7).

Rasch *et al*. explained that during slow-wave

sleep, newly formed memories are reactivated in the hippocampus and gradually transferred to long-term storage in the cortex (7). This process strengthens neural connections and stabilizes learned information.

Sleep also supports metabolic clearance. As depicted in Figure 2, Iliff *et al.* identified the glymphatic system as a pathway through which CSF flows along perivascular spaces, removing waste products from brain tissue (3). Xie *et al.* further demonstrated that during sleep, interstitial space increases by approximately 60%, significantly enhancing clearance of metabolites such as beta-amyloid (2).

Experimental studies indicate that sleep deprivation can impair glymphatic clearance, whereas human studies suggest similar associations but have not yet established direct causality. Kang *et al*. showed that sleep deprivation leads to increased beta-amyloid accumulation, linking sleep disruption to neurodegenerative processes (8). In human studies, Mander *et al.* found that reduced slow-wave sleep is associated with increased amyloid deposition and worse memory performance (9).

Together, these findings show that sleep is essential for proper glymphatic system function, efficient clearance of neurotoxic substances, and limiting buildup linked to cognitive decline.

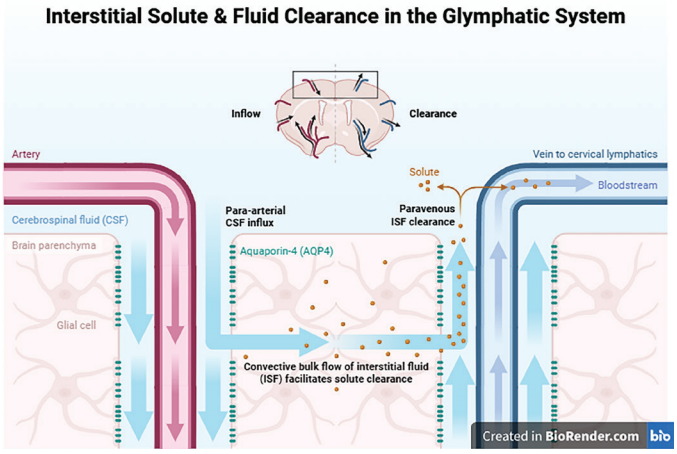

Figure 2. *Glymphatic clearance pathway during sleep. Cerebrospinal fluid enters periarterial spaces, exchanges with interstitial fluid through aquaporin-4 channels, and exits along perivenous pathways carrying metabolic waste. Following traumatic brain injury, sleep disruption and astroglial dysfunction impair this clearance system, promoting accumulation of neurotoxic solutes and delayed cognitive recovery.*

SLEEP DISRUPTION AFTER TRAUMATIC BRAIN INJURY

Sleep disruption is highly prevalent following TBI, including insomnia, fragmented sleep, hypersomnia, and circadian rhythm disruptions. Castriotta *et al*. found abnormal sleep studies in 46% of adults evaluated at 3 months post-TBI (10), while Baumann *et al*. reported new-onset sleep–wake disturbances in 72% of patients six months after injury, indicating that these problems can persist beyond the acute phase (11). Objective studies using polysomnography and actigraphy have confirmed reduced slow-wave sleep and altered sleep architecture in traumatic brain injury patients (4, 11).

Sleep disruption is closely linked to cognitive and emotional symptoms. Traumatic brain injury patients frequently report attention deficits, memory problems, fatigue, irritability, anxiety, and depression (12-13). Lim *et al.* demonstrated that mild TBI in rodents produces persistent deficits in maintaining wakefulness, linked to reduced orexin neuron activation, a finding that may help explain the fragmented sleep architecture observed in human TBI patients (14).

The high prevalence of sleep disruption after TBI is consistent across both civilian and military populations. Collen *et al*. reported that 97.4% of soldiers with combat-related TBI described sleep complaints, most commonly insomnia, frequent nocturnal awakenings, nightmares, and daytime sleepiness (15). These findings suggest that sleep disturbance is a widespread and persistent consequence of brain injury across multiple patient populations (Table 1).

However, limitations exist. Many studies rely on self-reported data, and sample sizes are often relatively small, typically ranging from 50 to 120 participants (4, 11, 15). Confounding factors such as pain, depression, and medication use may also influence sleep outcomes (10).

SLEEP-RELATED COGNITIVE DYSFUNCTION AFTER TBI

Cognitive impairment after TBI is well-documented, affecting memory, attention, processing speed, and executive function (18). These deficits often persist long after the initial injury and significantly impact daily functioning. Disrupted sleep further worsens these impairments, and in TBI patients this effect is amplified due to underlying neuronal and axonal damage (7). Mavroudis *et al.* reviewed evidence that

Table 1. *Summary of representative studies investigating sleep disruption, glymphatic system function, cognitive dysfunction, and therapeutic interventions following traumatic brain injury (TBI). The table highlights the study population, key findings, and the relevance of each study to the relationship between post-traumatic sleep disruption and neurological recovery.*

Study/Reference	Population	Key Finding
Xie *et al*. 2013 (2)	Mice	Sleep expands interstitial space ~60%, enhancing glymphatic clearance
Kang *et al*. 2009(8)	Mice	Amyloid-beta rises during wakefulness and falls during sleep
Castriotta *et al*. 2007 (10)	TBI adults	46% had abnormal sleep studies at 3 months post-injury
Baumann *et al*. 2007 (11)	TBI patients	72% had sleep-wake disturbances at 6 months post-injury
Lim *et al*. 2013 (14)	TBI rodents	Mild TBI caused persistent wake deficits linked to reduced orexin neuron activation; dietary BCAA supplementation improved wake deficits
Collen *et al*. 2012 (15)	Military TBI	97.4% reported sleep complaints post-injury
Mander *et al*. 2017 (9)	Older adults	Reduced slow-wave sleep linked to greater amyloid deposition
Grima *et al*. 2016 (16)	TBI patients	Meta-analysis found significantly reduced sleep efficiency and increased sleep disturbance in TBI patients compared to healthy controls
Grima *et al*. 2018 (17)	TBI patients	Melatonin improved sleep efficiency compared to placebo in randomized controlled trial

persistent cognitive deficits after mild traumatic brain injury are associated with diffuse axonal injury, chronic neuroinflammation, mitochondrial dysfunction, and impaired neuronal recovery process, which together disrupt recovery of memory, attention and executive function (18).

These findings also point to a self-reinforcing cycle unique to TBI. Neuronal damage, blood-brain barrier disruption, and neuroinflammation impair sleep architecture, which in turn reduces the glymphatic clearance described above (1,5). The resulting accumulation of neurotoxic metabolites worsens neuronal function and cognitive symptoms, further disrupting sleep. Elevated inflammatory cytokines also directly interfere with hypothalamic and brainstem sleep regulation, prolonging this disruption well beyond the acute injury phase (5). Whether this cycle directly contributes to cognitive decline in humans remains an area of ongoing investigation (2-3).

Collectively, the available evidence suggests that sleep disruption may represent an important secondary contributor to cognitive dysfunction following TBI. Experimental studies indicate that impaired slow-wave sleep reduces glymphatic clearance, whereas clinical studies consistently report associations between persistent sleep disruption and poorer cognitive performance. Although causality has not yet been established in humans, these complementary findings support the hypothesis that optimizing sleep can represent a modifiable target for improving neurological recovery after TBI.

POTENTIAL LONG-TERM COGNITIVE CONSEQUENCES

Human studies primarily show correlations between sleep disruption and cognitive decline, rather than direct causation (9). It remains unclear whether poor sleep causes cognitive impairment or whether both arise from the underlying injury, such as TBI. Most likely the initial insult, such as TBI, causes sleep disruptions and cognitive impairment, and sleep disruptions then further exacerbate cognitive impairments. While human studies are more observational, animal studies provide stronger evidence for a causal relationship, as demonstrated by the controlled sleep deprivation experiments in mice described earlier (2, 8).

The potential link between chronic post-TBI sleep disruption and long-term neurodegeneration warrants further investigation. Persistent beta-amyloid accumulation is a hallmark of Alzheimer's disease, and prolonged impairment of glymphatic clearance accelerates pathological protein deposition (8). Tau protein, another neurotoxic substance cleared during sleep, also accumulates following TBI and has been linked to axonal degeneration and chronic traumatic

encephalopathy (CTE), a progressive neurodegenerative condition seen in individuals with repetitive brain injuries (6). A direct causal link in humans has not been established, but the convergence of these findings raises an important question: does untreated post-TBI sleep disruption increase the risk of accelerated neurodegeneration later in life?

Overall, current evidence supports a biologically plausible pathway linking post-traumatic sleep disruption with impaired glymphatic clearance and subsequent cognitive decline. However, most human studies remain observational, and it is still uncertain whether improving sleep directly reduces long-term neurodegenerative risk. Future longitudinal and interventional studies are therefore needed to establish causal relationships and determine whether sleep-targeted therapies can modify disease progression following TBI.

CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Sleep disruption is common after TBI but often goes unaddressed in clinical care. A meta-analysis by Grima *et al*. confirmed that TBI patients experience significantly poorer sleep efficiency than healthy controls, underscoring the need for routine clinical attention to post-traumatic sleep problems (16). Melatonin has also been investigated as a pharmacological option. Grima *et al*. conducted a randomized controlled trial showing that melatonin improved sleep efficiency and reduced sleep onset latency in TBI patients compared to placebo (17). Cognitive behavioral therapy for insomnia has also shown promise in this population and carries no pharmacological side effects. Yet routine sleep screening is still not standard practice in TBI care. Emerging research on orexin system dysfunction following TBI suggests that orexin-based therapies represent a promising future treatment, though clinical evidence in TBI populations remains limited.

The number of patients receiving effective sleep treatment could be increased through routine screening questionnaires, referral pathways to sleep medicine, integration of sleep specialists into neurorehabilitation programs, and greater clinician awareness of post-traumatic sleep disorders.

Future research should focus on larger prospective studies using objective measurements such as polysomnography and actigraphy. Long-term trials are needed to determine whether improving sleep directly improves neurological and cognitive outcomes after TBI.

CONCLUSION

Sleep disruption is a common and clinically significant consequence of traumatic brain injury (TBI) and is consistently associated with persistent cognitive and neurological impairments. Experimental evidence indicates that sleep, particularly slow-wave sleep, plays a critical role in memory consolidation, neuronal repair, and glymphatic clearance of metabolic waste, whereas disruption of these processes can adversely affect brain recovery. Although mechanistic studies, primarily in animal models, support a biological link between post-traumatic sleep disruption, impaired glymphatic function, and the accumulation of neurotoxic proteins, the available human evidence remains largely observational and does not establish a direct causal relationship. Nevertheless, the convergence of findings from both experimental and clinical studies suggests that sleep disruption can represent an important and potentially modifiable factor influencing neurological recovery following TBI. Routine assessment and management of sleep disorders should therefore be considered as part of comprehensive neurorehabilitation. Future longitudinal and interventional studies incorporating objective sleep assessments and biomarkers of glymphatic function are needed to clarify causal mechanisms and determine whether sleep-targeted therapies can improve long-term cognitive and neurological outcomes after traumatic brain injury.

CONFLICT OF INTEREST

The author declares that there are no conflicts of interest related to this work.

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