

# Sleep, Glymphatic Flow, and Proteostasis: Linking Sleep Physiology to Neurodegenerative Risk

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## Abstract

Sleep is essential for maintaining brain health, cognitive performance, and neurological function. Accordingly, increasing scientific attention has recently been directed toward understanding the physiological mechanisms through which sleep exerts its restorative effects. The discovery of the glymphatic system (GS) provides a new conceptual framework for understanding how the brain eliminates metabolic waste and neurotoxic aggregates. During sleep, GS facilitates the convective exchange of cerebrospinal and interstitial fluids in order to remove harmful byproducts. These processes are linked to proteostasis, the regulation of protein synthesis, folding, and degradation, ensuring cellular homeostasis and preventing the accumulation of misfolded proteins. The dysfunction of glymphatic flow or proteostasis significantly contributes to the onset and progression of neurodegenerative diseases. According to research findings, poor sleep quality and short sleep duration produce decreased glymphatic clearance of debris, contributing to protein aggregation and cellular die-off and injury. Conversely, restorative sleep impairs waste flushing while protecting neural function. The present review provides findings related to recent research about the interplay of sleep physiology, glymphatic flow, and proteostasis to simultaneously provide an understanding of these three interrelated processes in the context of risk of neurodegenerative disease. Moreover, it presents emerging treatment approaches, such as sleep optimization, pharmacological modulation of glymphatic flow, and enhancement of proteostasis pathways that may avoid age-related cognitive decline that ultimately plays a role in brain health across the lifespan.

**Keywords:** Sleep, Glymphatic system, Proteostasis, Neurodegeneration

## Introduction

Sleep is a vital physiological process, which is vital not only for restoring energy and supporting synaptic plasticity but also for maintaining metabolic, immune, and cognitive balance.<sup>1</sup> Epidemiological studies consistently associate poor sleep quality, reduced slow-wave sleep (SWS), and fragmented sleep with a higher risk of neurodegenerative disorders, including Alzheimer's disease (AD) and Parkinson's disease (PD).<sup>2</sup> The mechanisms behind this connection remained unclear for many years. Nonetheless, the recent discovery of the glymphatic system (GS), a glial-assisted waste clearance network in the brain, provides a compelling mechanistic pathway connecting sleep physiology to neural proteostasis and neurodegenerative risk.<sup>3</sup>

Proteostasis refers to the maintenance of proper protein synthesis, folding, trafficking, and degradation. This process is essential in neurons, which are long-lived

and metabolically active. When proteostasis is disrupted, misfolded and aggregated proteins, such as amyloid- $\beta$  (A $\beta$ ), tau, and  $\alpha$ -synuclein, accumulate. These features are the hallmarks of a variety of neurodegenerative diseases.<sup>4</sup> The interaction between sleep, glymphatic clearance, and proteostasis creates an integrated network. This network may explain how chronic sleep dysfunction contributes to neurodegeneration.<sup>4</sup> This review integrates current knowledge on (i) sleep architecture and its role in brain clearance, (ii) the regulatory mechanisms of the GS, and (iii) intracellular proteostasis pathways in the brain. It further examines (iv) evidence of the interplay among these three systems in neurodegenerative diseases and (v) therapeutic implications and future directions. By connecting these topics, this study aims to clarify how sleep physiology influences glymphatic and proteostatic processes, how their disruption can increase neurodegenerative risk, and where research and interventions might focus in the

coming years.

### Sleep Physiology and Brain Clearance

Sleep is conventionally divided into rapid eye movement (REM) and non-REM (NREM) stages, with NREM further categorized into N1, N2, and N3 (also termed SWS). SWS features high-amplitude delta waves, synchronous cortical activity, reduced neuronal firing and metabolic demand, and increased interstitial space volume.<sup>1</sup> This state appears particularly conducive to brain clearance; studies indicate that the extracellular space (ECS) volume increases approximately 60% during SWS, thereby reducing resistance to interstitial fluid (ISF) flow.<sup>5</sup> SWS is generally regarded as the most restorative phase of sleep and is closely linked to sleep quality and maintenance; nevertheless, its specific functions and their consequences for daytime functioning are not fully elucidated yet.<sup>6</sup> Chronic sleep deficits are associated with impairments in cognition and memory, and current evidence demonstrates a link between reduced SWS and various clinical and psychiatric disorders. Enhancing sleep architecture by increasing SWS, regardless of changes in total sleep duration, may improve these related conditions. Continued research and the development of innovative pharmacological and non-pharmacological sleep therapies are warranted.<sup>7</sup> According to multiple animal studies, the influx of cerebrospinal fluid (CSF) into the brain parenchyma and its exchange with ISF significantly increase during sleep or anesthesia compared to wakefulness. For example, tracer research on mice reported approximately a 2-fold higher clearance of A $\beta$  during sleep.<sup>8</sup> Recent human neuroimaging studies employing diffusion tensor imaging along perivascular spaces have shown that individuals with poor sleep quality exhibit lower ALPS indices, suggesting reduced glymphatic clearance capacity.<sup>9</sup>

Chronic sleep deprivation or fragmentation directly impairs these clearance processes. In animal models, even one night of sleep deprivation rapidly increases hippocampal A $\beta$  deposition and slows tracer egress.<sup>10</sup> Similarly, human studies indicate that short sleep duration (< 6 h) or disrupted SWS correlates with elevated CSF A $\beta$ /tau and greater amyloid positron emission tomography. Mechanistically, wakefulness is associated with elevated norepinephrine levels, which constrict the ECS and suppress perivascular fluid movement, thereby reducing glymphatic flux.<sup>11</sup>

Thus, high-quality sleep, particularly with robust SWS, appears to offer greater brain clearance potential via an enlarged ECS and enhanced CSF-ISF exchange. Conversely, sleep disruption leads to decreased clearance and increased risk for protein accumulation. Accordingly, a comprehensive exploration of the GS is essential.

### Glymphatic System: Function and Regulators of Glymphatic Flow

The GS is a brain-specific fluid clearance network in

which CSF enters along periarterial channels, exchanges with ISF via astrocyte-expressed aquaporin-4 (AQP4) water channels at the end feet, and exits along perivenous or meningeal lymphatic routes.<sup>12</sup> Astrocytes are responsible for the formation of perivascular tunnels, which are instrumental in promoting convective fluid transport. Moreover, the polarized expression of AQP4 on the end-feet of astrocytes is crucial for the efficacy of fluid exchange; any disruption of this polarization significantly impairs the clearance process.<sup>13</sup> The GS is a waste-clearance system that uses perivascular tunnels to remove soluble proteins and metabolites from the CNS, facilitates the distribution of compounds throughout the brain, and primarily functions during sleep. In addition, it is involved in the removal of neurotoxic waste products, and its dysfunction may be associated with the pathogenesis of neurodegenerative diseases, cerebral trauma, and stroke.<sup>3</sup> The GS exhibits a decline in function with aging. According to research, older adults show lower DTI-ALPS indices, reduced tracer influx, and increased perivascular space (PVS) dilation.<sup>14</sup> These changes coincide with increased A $\beta$  accumulation in the aging brain. Furthermore, pathological conditions (e.g., AD and PD) are linked to even greater impairments in glymphatic flow and changes in the distribution of AQP4 channels.<sup>2</sup>

### Several factors modulate glymphatic efficacy:

- Sleep state: As noted, SWS enhances glymphatic flow. It has been demonstrated that glymphatic influx is associated with delta wave power and is the highest during deep NREM sleep.<sup>15</sup>
- Arterial pulsatility: The driving force for periarterial CSF influx is, in part, the pulsatile dilation of arteries. Aging and hypertension reduce arterial compliance and dampen pulsatile amplitude, leading to less glymphatic flow.<sup>16</sup>
- Vascular and astrocytic integrity: Impaired clearance is also related to age-related stiffening of the vasculature, astrocytic reactivity, and loss of AQP4 polarization.<sup>17</sup>
- Body posture: Interestingly, in rodent models, lateral asleep positioning increases glymphatic clearance vs. prone or supine positions.<sup>18</sup>

### Proteostasis in the Brain

#### Influence of Sleep on Proteostasis

Proteostasis is the maintenance of the proteome through coordinated regulation of protein synthesis, chaperone-mediated folding, post-translational modifications, trafficking, and degradation via the ubiquitin-proteasome system and autophagy-lysosomal pathways.<sup>19</sup> In post-mitotic, long-lived neurons, robust proteostasis is essential for preventing the accumulation of misfolded or aggregated proteins and maintaining synaptic and metabolic functions.<sup>20</sup> Recent findings suggest that sleep plays a supportive role in proteostatic mechanisms. For

instance, studies in animal models demonstrate that sleep enhances the expression of molecular chaperones and increases autophagic flux in brain tissue. In contrast, sleep deprivation reduces autophagy markers, causes the accumulation of ubiquitinated proteins, and increases endoplasmic reticulum stress. Overall, these perturbations may impair the degradation of A $\beta$ , tau,  $\alpha$ -synuclein, and other aggregation-prone proteins.<sup>21</sup> Ortiz-Vega et al found that sleep modulation plays a critical role in maintaining proteostasis and mitigating neurodegeneration in *Drosophila* models of tauopathy. Research also shows that sleep deprivation worsens neurodegenerative outcomes, whereas inducing sleep has a beneficial effect by enhancing autophagy and decreasing the accumulation of toxic tau proteins.<sup>22</sup>

### Proteostasis and Aging

Proteostasis functions at the intracellular level, thereby facilitating the removal of misfolded proteins. However, the GS is responsible for the clearance of extracellular solutes and interstitial aggregates.<sup>23</sup> Thus, efficient clearance requires the impairment of both systems; impairment of either may result in the buildup of toxic proteins. According to evidence, disruptions in glymphatic flow exacerbate proteostatic stress and vice versa.<sup>24</sup>

With advanced age, the proteostasis capacity reduces, as indicated by a decline in autophagy efficiency, a decrease in chaperone expression and proteasome activity, as well as an increase in oxidative damage.<sup>25</sup> These modifications facilitate the aggregation of A $\beta$ , tau, and  $\alpha$ -synuclein, a phenomenon that is further exacerbated by compromised glymphatic clearance.<sup>26</sup> The deficiency of AQP4 disrupts clearance mechanisms in AD models, leading to failures in proteostasis and dysfunction within neuronal circuits. Proteostasis acts as an essential intracellular defense mechanism against the aggregation of proteins, with its effectiveness augmented during sleep and adversely affected by aging and sleep disturbances. The interplay between proteostasis and glymphatic clearance suggests that the simultaneous dysfunction of these systems may signify a credible mechanistic pathway for the inception of neurodegenerative diseases.<sup>27</sup>

### Interplay Between Sleep, Glymphatic Flow, and Neurodegeneration

In AD, hallmark pathologies include A $\beta$  plaques and tau neurofibrillary tangles. Evidence shows that reductions in SWS and sleep fragmentation precede cognitive deficits and link with increased amyloid burden.<sup>28</sup> Neuroimaging studies have associated a lower ALPS index (impaired glymphatic flow) with greater A $\beta$  deposition and cognitive decline.<sup>29</sup> In transgenic mouse models, the lack of AQP4 polarization results in a 25%–50% increase in A $\beta$  accumulation despite unchanged production rates.<sup>30</sup>

Sleep disorders, especially REM-sleep behavior disorder, often appear early in prodromal PD. Recent

studies have reported that patients with PD have reduced glymphatic function and greater PVS burden.<sup>31,32</sup>  $\alpha$ -synuclein clearance may depend on glymphatic flow; AQP4 deficiency has been involved in the acceleration of  $\alpha$ -synuclein aggregation and dopaminergic neuron loss, which are the main pathological features of PD.<sup>33</sup> Similar mechanisms are proposed for other neurodegenerative conditions (e.g., Huntington's disease and amyotrophic lateral sclerosis), where protein clearance and sleep disturbances are present.<sup>34</sup>

## Therapeutic Implications

### Sleep Optimization Interventions

Enhancing the quality and quantity of sleep, particularly by increasing SWS, represents a primary avenue for intervention aimed at promoting cerebral clearance via the GS and augmenting protein homeostasis. Recent studies indicate that electrical or acoustic slow-oscillation stimulation during sleep can potentially amplify SWS power, subsequently leading to improved clearance of accumulated metabolites and proteins.<sup>35</sup> For instance, research demonstrated that sensory stimulation (e.g., low-frequency acoustic) or transcranial stimulation during sleep may bolster CSF and ISF flow.<sup>36</sup> Additionally, behavioral interventions have been proposed, including stabilizing sleep timing, reducing sleep fragmentation, managing sleep apnea, and optimizing sleep posture (e.g., sleeping laterally).<sup>37</sup> It has been demonstrated that the lateral sleeping position is related to increased glymphatic efficiency compared to the supine (on the back) or prone (on the stomach) positions.<sup>38</sup>

### Targeting Glymphatic Function Directly

Beyond optimizing sleep, several interventions are being explored to directly enhance GS function:

1. **Modulation of AQP4 channels:** Preclinical studies have revealed that decreased AQP4 expression or the loss of its polarity on astrocytic endfeet is associated with diminished CSF/ISF flow and increased A $\beta$  accumulation.<sup>39</sup> Therefore, pharmacological agents capable of regulating AQP4 or restoring its polarization are a key focus of research.<sup>40</sup>
2. **Augmenting arterial pulsation/enhancing vascular function:** Considering that arterial pulsation is considered one of the primary driving forces for fluid flow within the PVS, improving vascular health (e.g., through exercise, blood pressure reduction, and mitigation of atherosclerosis) is posited to enhance glymphatic performance. This approach directly addresses the mechanical propulsion required for efficient glymphatic clearance.<sup>41</sup>
3. **Imaging and monitoring of glymphatic function:** The use of imaging techniques (e.g., tracer-based magnetic resonance imaging, the ALPS index, and other advanced methodologies) is emerging for the early detection of impaired glymphatic function,

even before the onset of clinical symptoms. These diagnostic tools are vital for facilitating the design of future *preventive* interventions.<sup>42</sup>

### Combined Interventions and Precision Approaches

Given the complex interplay among sleep, the GS, and proteostasis, a combination of multiple interventions that simultaneously improve sleep, augment clearance flow, and boost cellular protein-elimination capacity may yield the maximum effect. A comprehensive strategy for reducing the risk of neurodegeneration in high-risk individuals might involve combining behavioral sleep therapy with regular exercise and an astrocyte/AQP4-modulating pharmacological agent.<sup>43</sup> Moreover, personalized strategies are critical; people should be selected based on specific risk indicators (e.g., age, APOE4 genotype, baseline ALPS function index, and sleep quality) and then assigned targeted interventions.<sup>44</sup> Eventually, the use of biomarkers, advanced imaging, and pre-intervention or post-intervention assessments can help quantify and validate the effectiveness of these combined approaches.

### Conclusion

Evidence suggests that the interrelationship between sleep, the GS, and proteostasis is essential for sustaining nervous system homeostasis. Adequate and high-quality sleep, particularly the enhancement of SWS, optimizes glymphatic clearance, while vascular integrity and astrocytic AQP4 polarization modulate this process. In addition to intracellular proteostasis pathways, these mechanisms form an integrated defense against neurotoxic protein accumulation. However, impairments in any of these systems may shorten the onset and/or progression of neurodegenerative diseases. Consequently, multi-modal interventions, including the regulation of sleep behaviors to improve sleep and sleep physiology with exercise (i.e., regular aerobic training) to maintain vascular health and modulation of astrocyte reflection or AQP4 with pharmacology, are potential protective strategies to target neurodegeneration. It is recommended that future research focus on longitudinal human studies, the use of standardized imaging biomarkers, and mechanistic studies to support clinical application, further validating the potential of the sleep-glymphatic-alterations in the proteostasis framework. This study, therefore, identified significant opportunities on the frontiers of the prevention and treatment of neurodegenerative disorders.

### Authors' Contribution

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### Competing Interests

None.

### Ethical Approval

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