

## Microbiome Meets Glymphatics: Conceptual Advances

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### Abstract

The glymphatic system facilitates brain waste clearance in a sleep-dependent manner, a process largely mediated by astrocytic AQP4 (astrocytic aquaporin-4) channels. Recent research suggests that the gut microbiome influences glymphatic function via metabolites such as short-chain fatty acids, bile acids, and tryptophan derivatives, which govern blood-brain barrier (BBB) integrity, astrocyte activity, and circadian rhythms. Age-related gut dysbiosis and consequent systemic inflammation may impair both the quantity and quality of slow-wave sleep, reducing glymphatic clearance and promoting the accumulation of neurotoxic proteins, ultimately contributing to cognitive decline. Interventions targeting the gut-brain axis—including dietary modification, prebiotics, probiotics, exercise, and GLP-1 (Glucagon-Like Peptide-1) analogs—have the potential to enhance glymphatic function and preserve cognitive resilience during aging. A comprehensive understanding of the microbiome-glymphatic axis could inform integrative strategies for healthy brain aging.

**Keywords:** blood-brain barrier; glymphatic system; aging

### Introduction

The glymphatic system, a brain-wide waste-clearance pathway, removes metabolic byproducts, toxic proteins, and inflammatory mediators from the brain via the exchange of cerebrospinal fluid (CSF) and interstitial fluid along perivascular routes, facilitated by AQP4 channels, with directional flow dependent on AQP4 polarization [1,2]. Glymphatic influx moves CSF into perivascular spaces, while interstitial fluid that contains waste is drained along perivenous pathways into meningeal lymphatics and then into cervical lymph nodes. This is all done by arterial pulsations that are in sync with the heart cycle. Clearance is strongly sleep-dependent, peaking during deep slow-wave sleep, and is essential for maintaining brain homeostasis, including nutrient delivery, waste removal, and ionic balance [3,4]. Impairment of this system is implicated in neurodegenerative and neurovascular diseases, sleep disturbances, and other disorders, where reduced clearance leads to the accumulation of neurotoxic proteins such as amyloid beta (A $\beta$ ), resulting in cognitive deficits and disrupted sleep [5,6]. Age-related sleep disturbances may be linked to gut dysbiosis, which can compromise glymphatic efficiency and exacerbate cognitive decline, potentially promoting neurodegeneration [7]. The gut microbiome regulates BBB permeability, astrocyte function, and neuroinflammatory processes through microbial metabolites such as short-chain fatty acids (SCFAs), bile acids, and tryptophan

derivatives, mediated by both direct and circadian-regulated mechanisms affecting sleep and glymphatic activity [8,9]. Dysbiosis may interfere with clearance processes via inflammation, altered microbial signaling, or circadian disruption, while impaired glymphatic function can, in turn, affect overall homeostasis, including gut health, potentially through bidirectional communication mediated by the vagus nerve [10,11]. Together, these observations support a microbiome-glymphatic axis, highlighting the integrated regulation of brain clearance, sleep quality, and cognitive function, offering a novel perspective for investigating sleep disorders in aging and their cognitive consequences [7,12].

### The Microbiome-Glymphatic Axis in Aging

The gut microbiota, the glymphatic system, and sleep architecture work together to keep the brain stable and able to adapt. Gut microbial metabolites, such as SCFA, bile acids, and tryptophan derivatives, regulate astrocyte function, the polarization of AQP4, and the integrity of the BBB [13,14]. SCFAs interact with the aryl hydrocarbon receptor (AhR), subsequently stabilizing the localization of AQP4 and facilitating glymphatic transport, offering an illustration of the microbiome's ability to modulate brain physiology at a distance [15]. Age-related dysbiosis shifts systems of microbial communities toward a predominance of pro-inflammatory Gram-negative bacteria and can result in increased systemic lipopolysaccharide (LPS) exposure [16]. The disrupted gut barrier allows for

LPS to traverse into the systemic circulation, activating Toll-like receptor 4 (TLR4) signaling, which triggers microglial activation, neuroinflammation, and synaptic dysfunction [17]. These conditions can inhibit restorative slow-wave sleep, which disrupts glymphatic transport efficiency, leading to ongoing neurotoxic accumulation and cognitive impairment [18]. In turn, dysbiosis-induced inflammation alters hippocampal and cortical circuits essential for long-term mechanisms of memory formation, linking a dysbiotic microbiome to memory dysfunction [19]. The degeneration of the suprachiasmatic nucleus (SCN) and neuroendocrine and inflammatory changes associated with aging add to the disruption of circadian regulation, leading to more sleep fragmentation and metabolic dysfunction [20]. In elderly individuals and those with mild cognitive impairment or Alzheimer's disease, poor sleep is associated with increased amounts of cortical A $\beta$ , higher levels of tau in cerebrospinal fluid, and decreased amounts of posterior Non-Rapid Eye Movement (NREM) sleep—all of which predict impairment in memory function [21]. Collectively, these findings suggest a highly interconnected network whereby the aging process, microbiome, sleep disruption, and impaired glymphatic clearance worsen neurodegenerative changes. Interventions that promote increased balance of the microbiome by using probiotics, prebiotics, or dietary changes, as well as approaches that enhance slow wave sleep and rhythm, may limit inflammation from LPS, preserve AQP4 polarization, and enhance glymphatic flow [22,23].

In essence, with the growing recognition of the gut-brain axis in regulating sleep and glymphatic waste clearance, longitudinal investigations integrating microbiome profiling, LPS quantification, sleep metrics, and neuroimaging of glymphatic flow could advance our understanding of how these interacting determinants contribute to the maintenance of brain homeostasis over time. This line of research may further elucidate the biological pathways through which microbial ecology and metabolic integrity support healthy cognitive aging.

### Therapeutic and Lifestyle Interventions

The emerging data points to the modification of the gut-brain axis as a way to promote sleep quality and cognitive resilience. Dietary approaches, including prebiotics and probiotics, to systematically influence the gut microbiome enhance metabolites, including SCFAs and tryptophan derivatives, which regulate

astrocyte function, AQP4 polarization, and BBB integrity. GLP-1 and GLP-1 analogs reduce sleep fragmentation and promote non-rapid eye movement (NREM) sleep, which likely influences glymphatic clearance. GLP-1 also alters mesolimbic reward circuits, which could affect memory and may influence hippocampal plasticity, but human data for influence on long-term memory is preliminary [24]. Exercise, particularly aerobic types, increases circulating GLP-1 and influences hippocampal plasticity and influences gut microbiota composition and SCFA production. Resistance exercise consistently improves sleep quality and provides an additive effect to aerobic exercise on aspects of metabolic and cognitive health [25,26]. The potential combined interventions and pharmacological strategies that facilitate sleep, glymphatic, and cognitive health likely act synergistically, but additional longitudinal and mechanistic human studies are required to establish causal relationships.

### Research Gaps and Future Directions

Notwithstanding significant conceptual advancements, fundamental questions remain regarding the role of the glymphatic system in aging and cognition. It remains unclear which specific microbial taxa and metabolites modulate glymphatic activity, whether age- or disease-related impairments are reversible, and how circadian rhythms and microbial metabolites interact to influence glymphatic function. Emerging evidence indicates that age-related circadian disruption can impair glymphatic clearance, leading to the accumulation of neurotoxic proteins such as A $\beta$  and tau, which contribute to neurodegenerative processes. Microbial metabolites may further modulate circadian regulation via epigenetic mechanisms, illustrating the important effect of the gut microbiome on circadian rhythms and brain health [27,28]. To address these gaps, longitudinal and translational studies integrating neuroimaging, microbiome profiling, and sleep assessments are necessary to elucidate causal relationships and identify biomarkers for early intervention. Such integrative, transdisciplinary research could ultimately inform novel therapeutic strategies to preserve cognitive function across the lifespan.

### Broader Implications

The emerging recognition of a microbiome-glymphatic axis underscores the value of a holistic perspective on brain health. Diet, sleep, and gut

microbial composition are modifiable factors that significantly influence cognitive function and the risk of brain disorders. Considering these factors concurrently has the potential to advance personalized medicine and inform public health strategies aimed at promoting healthy aging, reducing the societal burden of dementia, and enhancing cognitive performance and workplace productivity.

## Conclusion

The microbiome-glymphatic axis integrates gut microbial composition, sleep, and brain waste clearance to support cognitive health. Age-related changes, including gut dysbiosis, systemic inflammation, and circadian disruption, can impair glymphatic function and contribute to cognitive decline. Interventions that restore gut microbial balance, enhance slow-wave sleep, or modulate AQP4 polarization may improve glymphatic circulation and cognitive performance. The societal relevance of this framework is substantial: such strategies have the potential to reduce the incidence of dementia, enhance cognitive function, improve quality of life across the lifespan, and inform public health policies aimed at promoting lifelong brain health.

## Declarations

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### Conflict of Interest

The author declares no conflict of interest.

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