



Review

“Glymphatic” Neurodegeneration: Is Sleep the Missing Key?

Luigi Ferini-Strambi ^{1,2,*} and Maria Salsone ^{1,3}¹ Division of Neuroscience, Vita-Salute San Raffaele University, 20132 Milan, Italy; salsone.maria@hsr.it² Sleep Disorders Center, San Raffaele Scientific Institute, 20132 Milan, Italy³ IRCCS Istituto Policlinico San Donato, 20097 San Donato Milanese, Italy

* Correspondence: ferinistrambi.luigi@hsr.it; Tel.: +39-0226433363; Fax: +39-0226433394

Abstract: Robust evidence suggests that the glymphatic system plays a key role in preserving brain health. Indeed, its activity in maintaining homeostasis by clearing neurotoxic proteins such as beta-amyloid from the human brain is essential. Sleep represents the factor that mainly influences this system, since it is selectively active during the night, in particular during non-rapid eye movement (NREM) sleep. This is true, since the sleep head position, in particular the supine position for its relationship to the status of opening/closing of the jugular veins, appears to be determinant for the development of future neurodegeneration. Growing evidence from human and animal models highlights the neurobiological link between sleep, glymphatic dysfunction and neurodegeneration. On the other hand, several modifiable factors have been recently identified modulating (improve/reduce) glymphatic system activity, such as Omega-3 polyunsaturated fatty acids, stress, hypertension, physical activity, alcohol, gender and genetic predisposition, in particular variants of aquaporin-4 (AQP4). From this viewpoint, our ambition is to discuss how the glymphatic system works in the brain, what factors mainly impact on this activity and its strict relation with the neurodegeneration. Future directions might include the analysis of factors modulating glymphatic system activity and a personalized glymphatic profile, “glymphatom”, as a natural target for preventive neurodegenerative treatment.

Keywords: glymphatic system; sleep



Citation: Ferini-Strambi, L.; Salsone, M. “Glymphatic” Neurodegeneration: Is Sleep the Missing Key? *Clin. Transl. Neurosci.* **2024**, *8*, 23. <https://doi.org/10.3390/ctn8020023>

Academic Editor: Susanne Wegener

Received: 26 April 2024

Revised: 28 May 2024

Accepted: 4 June 2024

Published: 7 June 2024



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1. Introduction

In the last two decades, one of the most fascinating challenges for researchers and clinicians has been trying to understand how the human brain removes neurotoxic metabolic waste. In this context, the glymphatic system, first described in 2012 [1] as a highly organized fluid-transporting system, plays a prominent role in maintaining brain homeostasis and, thus, represents a research priority. Indeed, the glymphatic system is now recognized as a novel brain-wide perivascular network between cerebrospinal fluid (CSF) and interstitial spaces, promoting the clearance of brain metabolic wastes. However, some important questions should be addressed when discussing this critical issue. Firstly, how does the glymphatic system work in preserving brain health? Secondly, what are the factors that can influence, compromising or promoting, the precious work of this system? Thirdly, what occurs in the human brain when this system is malfunctioning, and what are the clinical consequences with a focus on neurodegeneration? From this viewpoint, we aimed to discuss these crucial questions to offer a critical vision on the complex relationship between sleep and neurodegeneration through the “glymphatic” window.

2. The First Question: How the Glymphatic System Works

It is well known that in the peripheral tissues, there is the lymphatic system that returns soluble material, proteins and fluid coming from the interstitial space to the general circulation, thus maintaining tissue homeostasis [2]. It is also well known that, although the human brain is one of the most active organs, characterized by a high metabolic

rate, the central nervous system (CNS) has no “conventional” lymphatic system. This apparent discrepancy has been recently explained with the discovery in the human brain of a system called “glymphatic” (for functions similar to the lymphatic), based on the specific perivascular channels, which promotes the elimination of soluble proteins and metabolites [2]. The glymphatic process is complex but highly structured and can be distinguished into three main phases. The initial phase involves the inflow of CSF produced in the choroid plexus through the periarterial spaces, via periarterial Virchow–Robin spaces [3]. An intermediate phase, in which the CSF flows in the brain parenchyma, through a water channel so-called protein aquaporin-4 (AQP4), highly expressed at the end-feet of astrocytes, ensheaths the brain blood vessels [4], which is basically the outside of the perivascular space. Here, CSF-ISF exchange occurs, and CSF from the perivascular spaces mixes with the interstitial fluid (ISF) [2]. Finally, the CSF-ISF drains out of the brain through the perivenous spaces and drains into CSF compartments [2]. Thus, once within the subarachnoid CSF, solutes can exit the cranium via arachnoid granulations or meningeal lymphatic vessels or along cranial and spinal nerves to drain to systemic circulation and cervical lymph nodes [5]. CSF also directly exits the subarachnoid space through the cribriform plate and other perineural routes to reach the lymphatic system. Some authors investigated the functional relationship between CSF efflux through lymphatics and the potential influx into the brain by assessing the distribution of CSF-infused tracers in awake mice using near-infrared fluorescence imaging. These authors demonstrated that the tracers quickly exited the subarachnoid space by transport through the lymphatic system to the systemic circulation in awake mice [6].

However, efficient glymphatic flow and clearance depend on several variables. Animal models reveal that the cerebral arterial pulsation and vasomotion are key factors driving CSF flow through the perivascular spaces in the brain. Some authors found that unilateral ligation of the internal carotid artery significantly reduces the arterial pulsatility by 50%, slowing the rate of paravascular CSF–ISF exchange, with the systemic administration of the adrenergic agonist dobutamine increasing the pulsatility of penetrating arteries by 60%, increasing this rate [7]. Additionally, an increase in blood pressure was able to modify the pulsations of the arterial wall, thus increasing backflow and thereby reducing net flow in the perivascular spaces [8]. Moreover, low-frequency arteriolar oscillations have been proven to drive the drainage of solutes [9], and functional hyperemia (also known as neurovascular coupling) was able to improve not only the supply of metabolites but also the removal of metabolic waste [10]. Taken together, these findings suggest that cerebral arterial pulsability plays a crucial role in the glymphatic influx and clearance, thus becoming a promising natural target for the development of therapeutic treatments. Notably, the identification of these three important phases has been possible through the application of advanced and sophisticated neuroimaging tools that, “in vivo”, have allowed us to identify the mechanisms underlying the glymphatic process in the human brain. In the context of emerging tools, a recent review [11] summarized the findings to date, dividing neuroimaging investigations into those that use or do not use the administration of gadolinium-based contrast agents (GBCAs). This approach, including imaging without GBCAs, imaging with intrathecal administration of GBCAs and imaging with intravenous administration of GBCAs, has proven beneficial not only for examining the interstitial fluid movement in the brain parenchyma but also for assessing the fluid dynamics in the perivascular and subarachnoid spaces [11]. In detail, DTI-ALPS (diffusion tensor image analysis along the perivascular space) has been recently proposed for investigating the interstitial fluid as fine water movement in the brain parenchyma [11]. The hypothesis is that a higher APLS index may be correlated to higher efficiency in the clearance of waste through the glymphatic system [11]. This is even more true when we consider the “aging” of the glymphatic system in healthy adults. Interestingly, some authors [11] have recently demonstrated that the ALPS index was negatively correlated with age, since it was significantly lower in the elderly group, as compared with the young group. However, it must be stated that, although this neuroimaging tool is now widely used,

the lack of establishment and validation represents its main limitations. Finally, several studies conducted using MRI-based imaging in humans have shown that the perivascular space in the basal ganglia may also function as an outlet for solutes and CSF from the brain parenchyma [12], thus expanding the spectrum of possible targets of the glymphatic process to study.

3. The Second Question: Factors Influencing/Modulating the Glymphatic System Activity

Research focusing on the early identification of factors influencing/modulating glymphatic system activity is thriving. Growing evidence supports, first of all, the fundamental role of sleep. It is accepted that the glymphatic function is a peculiar characteristic of the sleeping brain. Indeed, human studies revealed that sleep is associated with greater glymphatic activity, as compared with wakefulness [2]. This occurs since sleep constitutes an optimal “spatiotemporal” environment for glymphatic clearance [13]. The term “spatial” refers to the interstitial space, in which CSF-ISF exchanges, a phenomenon enlarged by 60% during sleep [14]. The term “temporal” is related to the circadian optimization of the CSF influx into the interstitial space [15]. This said, not all sleep phases are essential for the correct functioning of the glymphatic system, or, perhaps, not all sleep phases contribute in the same manner to this important process. Why this occurs is a fascinating matter of discussion. Several hypotheses have been proposed in order to decode the dynamic relationship between non-rapid eye movement (NREM) sleep and the glymphatic system. Firstly, during NREM sleep (in particular N3 stage), a physiological reduction in the central noradrenergic tone occurs, leading to an increase in the interstitial fluid volume fraction and, thereby, more efficient waste transport [16]. Secondly, NREM fragmentation has been proven to reduce the AQP4 expression in the brain [17], although it is up-regulated in younger animals. Finally, the regulation of glymphatic activity appears to be significantly affected by the shift between wakefulness and NREM sleep stages rather than by the circadian rhythm [2]. It is also interesting to note that sleep is a modifiable risk factor, at least in some aspects and conditions. This is the case of the head position during sleep. Indeed, some authors [18] have demonstrated that the head position, in particular the supine position during nocturnal sleep, may have relevant clinical implications for the development of future neurodegeneration. This is probably due to the fact that, in this position, the glymphatic activity is less efficient because of the different statuses of jugular veins.

Indeed, it is well documented in healthy volunteers that both internal jugular veins were opened in the supine position, while in the right lateral decubitus position, the right internal jugular vein was opened, and the left one was partially collapsed, and vice versa [19]. Additionally, risk factors that should also be taken into consideration in the binomial sleep–glymphatic system include the impact of elevated ambient temperatures, affecting not only sleep but also thermoregulation and autonomic system reactivity [20]. The convergence of evidence from animal models also demonstrated that brain clearance is reduced during sleep and in the presence of anesthetics, especially dexmedetomidine, ketamine-xylazine and pentobarbital [21]. Why this occurs remains a matter of discussion. The experiments of Ma et al., using near-infrared fluorescence imaging, clearly indicate that mice in the awake group had significantly less tracer remaining at 60 min compared to mice that were under either type of anesthesia [6]. Another important question, in addition to sleep, is that the glymphatic drainage is astrocyte-dependent, and a large part of this activity is made up of AQP4, a precious channel protein regulating water movement in the brain.

Thus, it is possible to speculate that alterations in this protein, both in the sense of abnormal expression and/or polarization in the conditions of astrogliosis, could represent a potential risk factor for impaired glymphatic clearance. Indeed, a genotype characterized by the AQP4 gene deletion can result in a reduction in the clearance activity equal to about 70% [1]. Similarly, a postmortem human brain investigation in patients with AD showed that the loss of characteristic perivascular AQP4 localization was strongly associated

with an increase in neurotoxic waste, particularly in A β pathology [22]. Finally, it is also interesting to note that other modifiable factors can significantly affect glymphatic system activity, including eating patterns, in particular Omega-3 polyunsaturated fatty acids, stress, hypertension, physical activity, alcohol and gender [23]. In detail, Omega-3 polyunsaturated fatty acids, physical activity and alcohol consumed in small amounts can improve glymphatic activity, while stress and the coexistence of arterial hypertension have an inhibitory role [24].

4. The Third Question: “Glymphatic” Neurodegeneration and Sleep

Neurodegeneration is an umbrella term used mainly to indicate the pathological protein aggregation in the human brain, although other hallmarks, such as synaptic and neuronal network dysfunction, aberrant proteostasis, cytoskeletal abnormalities, altered energy homeostasis, DNA and RNA defects, inflammation and neuronal cell death, have been recently identified [24]. The pathological protein aggregation involves proteins that first play an essential and physiological role in the cell that become badly folded and may gain toxicity [25]. Thus, this pathological protein burden leads to a group of diseases with highly heterogeneous clinical presentations, so-called proteinopathies, including Parkinson’s Disease (PD) and Alzheimer’s Diseases (AD). However, it is important to underline that the mechanism at the basis of neurodegeneration is common, independent of the accumulated protein, alpha-synuclein, as the forms of aggregates (Lewy bodies) for PD, with beta-amyloid (A β) as the forms of plaques and hyperphosphorylated tau protein for AD. The role of these proteins as a trigger for neurodegenerative diseases has been widely stressed in the literature. The most accredited hypothesis is that the brain pathological accumulation may be related to a reduced elimination of neurotoxic metabolites rather than an increase in their production. Thus, it is not surprising that the glymphatic system comes into play in neurodegeneration. This is clear since there is growing evidence for using of the term “interstitial fluidopathy” to define the influence of the glymphatic system on neurodegenerative disorders. Structural/functional impairments in glymphatic activity have been reported both in the early and prodromal stages of neurodegenerative diseases. In detail, the inefficient clearance of neurotoxic proteins from the brain drives the accumulation of α -synuclein, tau and A β , which triggers reactive astrogliosis, inflammatory activity, oxidative stress, impaired neuronal function, and synaptic transmission deficits and can result in a final common pathway to neurodegeneration [26]. There is robust evidence for glymphatic impairments in neurodegenerative disorders. A significant positive correlation between diffusivity parameters along the perivascular spaces such as the ALPS index and Mini-Mental State Examination (MMSE) score has been detected in AD patients, suggesting that lower water diffusivity along the perivascular space was in relation to the disease severity [27]. Additionally, significant differences were found in the right DTI-ALPS indices between cognitively normal and AD groups and Mild Cognitive Impairment (MCI) groups [28]. Additionally, the ALPS index was associated with the cerebral gray matter (GM) volume in the cerebellar gray, dorsolateral prefrontal, thalamus, superior frontal, amygdala and hippocampus, and these coherent regions coincided with those showing GM atrophy in young-onset AD patients. Mediation analyses of this group also suggested that the relationships between the ALPS index and cognitive performance were fully mediated by the integrity of ALPS-index-coherent GM areas [29]. Taken together, these findings support the strict relationship between altered MRI functional and structural parameters reflecting an impairment in the glymphatic system and the AD disease severity. Taking a step further to define “glymphatic” neurodegeneration, sleep has been now recognized as a fundamental functional element of the glymphatic system that highlights its state dependency [13]. Supporting this, sleep disorders, including poor sleep quality, sleep deprivation, sleep fragmentation and obstructive sleep apnea (OSA), are not only very common in PD and AD but have also been recently linked to impaired glymphatic function [29,30]. Interestingly, significantly reduced DTI-ALPS parameters have been detected both in PD patients and in those with prodromal stages, such as REM sleep

behavior disorder (RBD), suggesting an early disruption in the glymphatic activity [31,32]. Additionally, the results from a data-driven analysis of 70 studies support the notion of an interrelationship between sleep disorders and AD pathogenesis, mediated by the glymphatic system [13]. It is well documented that in AD patients, untreated sleep disorders are strongly associated with accelerated cognitive decline and phenocopy to a major neurocognitive disorder [33]. This is the case of OSA, leading to an elevated intrathoracic and intracranial pressure that can cause increased venous pressure and impedance in the outflow compartment of the glymphatic system [13]. An enlargement of the perivascular space in the bilateral frontal cortex, the basal ganglia, bilateral lateral ventricles and the fourth ventricle has been detected in OSA patients, in association with the severity and the existence of hypoxemia [34]. Different DTI-ALPS index values have been found among chronic insomnia patients with an impaired cognition group, as well as a normal cognition group and control subjects, thus suggesting that glymphatic system dysfunction may also occur in chronic insomnia among middle-aged and elderly individuals and appears to be correlated with cognitive decline [35]. Finally, different CSF tracer enrichment has been found in patients with good Pittsburgh Sleep Quality Index (PSQI) questionnaire (≤ 5) and poor PSQI (> 5) results [36]. In detail, sleep impairment was associated with increased CSF tracer enrichment in several brain regions. Moreover, the MMSE scores of chronic insomnia patients with cognitive impairment positively correlated with the DTI-ALPS index, thus suggesting that glymphatic system dysfunction may be involved in chronic insomnia, especially in the presence of cognitive decline [36]. Additionally, MRI volumetric parameters such as cortical brain volume and entorhinal cortex thickness were correlated with the severity of sleep disturbance and the degree of cortical tracer enrichment, thus suggesting that chronic sleep disturbance may be accompanied by altered glymphatic function along enlarged perivascular spaces [37]. Interestingly, some authors [38] have also demonstrated “in vivo” that one night of total sleep deprivation impaired the molecular clearance from the human brain and that humans do not catch up on lost sleep. Of note, the DTI-ALPS index was also significantly different among the chronic insomnia patients with the impaired cognition group, normal cognition group and healthy controls [38]. Finally, it is also interesting to note that AQP4 genetic variation can influence the relationship between sleep and brain A β -amyloid burden [39]. It has also been demonstrated that one AQP4 variant, rs72878776, was associated with poorer overall sleep quality, while several polymorphisms moderated the effect of sleep parameters, including sleep latency and duration of brain A β -amyloid burden [39]. Figure 1 summarizes the main mechanisms linking sleep disorders/alteration glymphatic system activity and neurodegeneration.

In conclusion, some intriguing points of reflection emerge from human studies. Firstly, it appears that glymphatic system activity and the accumulation of neurotoxic proteins in the human brain are mutually connected, in the sense that the impaired glymphatic system can exacerbate the brain pathological burden and vice versa, thus generating a vicious circle, leading to “glymphatic” neurodegeneration. Secondly, glymphatic system activity can be influenced by several conditions and factors, but sleep should be considered the key element. The evidence that the glymphatic system is altered early in sleep disorders, prodromal to neurodegenerative disorders, supports the hypothesis that sleep alterations can cause glymphatic dysfunction rather than vice versa. Finally, the glymphatic system, with all its structural and functional components, should be considered a potential target for the treatment of neurodegenerative diseases.

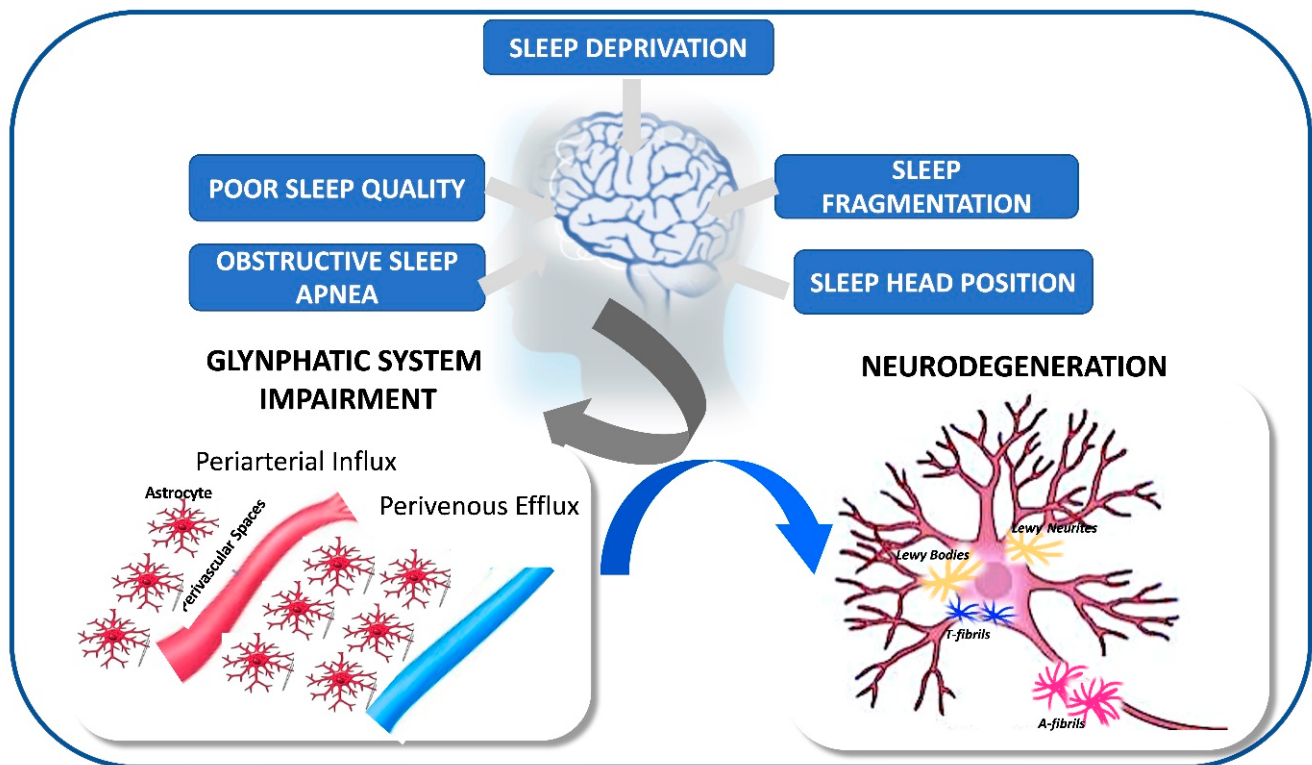


Figure 1. Schematic representation of the mechanisms linking sleep disorders, glymphatic system activity and neurodegeneration.

Author Contributions: Conceptualization, L.F.-S. and M.S.; Writing—original draft preparation; Supervision, L.F.-S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not Applicable.

Informed Consent Statement: Not Applicable.

Data Availability Statement: Not Applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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