Review

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Sleep, glymphatic system, and Parkinson's disease

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Abstract

Sleep is involved in regulating many aspects of the body, including cell function, physical activity, and disease. Neurodegenerative diseases are often preceded by sleep disturbance. This disturbance is not just a non-motor symptom but also an important risk factor for developing the disease. It is now understood that the glymphatic system plays important physiological functions in the human body: maintaining the balance of interstitial fluid and clearing waste products from metabolism or death in the brain. Glymphatic system dysfunction contributes to the progression of neurodegenerative diseases. Importantly, sleep is involved in regulating the glymphatic system, which affects the clearance of pathological proteins in the brain, and may be an important pathway affecting the progression of neurodegenerative diseases. Here, we review recent advances in sleep disturbances and the glymphatic system in health and Parkinson's disease, hoping to identify potentially targetable avenues for future research and treatment of Parkinson's disease.

Keywords: Sleep, Parkinson's disease, neurodegeneration, glymphatic system, α-synuclein

INTRODUCTION

Parkinson's disease (PD) has emerged as a prominent neurodegenerative disorder, exhibiting a marked increase in prevalence[1]. PD is characterized by the pathological aggregation of α-Synuclein(α-Syn) into Lewy bodies and subsequent loss of dopaminergic neurons, resulting in a cascade of motor and non-motor symptoms[2]. Motor symptoms include resting tremors, dystonia, bradykinesia, and postural gait disturbances[3], while non-motor symptoms such as sleep disturbances, hyperalgesia, hyposmia, cognitive deficits, anxiety, depression, constipation, and other autonomic symptoms (including orthostatic hypotension, urinary urgency, and erectile dysfunction) significantly decrease patients' health-related quality of life and well-being[4,5]. Among these, sleep disturbances stand out as the most prevalent non-motor symptom, typically manifesting as insomnia[6], rapid eye movement sleep behavior disorder (RBD)[7], excessive daytime sleepiness (EDS), and restless legs syndrome (RLS), affecting over half of PD patients, significantly impairing their quality of life, and imposing a substantial economic burden on society[6]. Importantly, sleep disturbances can emerge early in the prodromal disease phase and worsen as PD progresses, which are not merely regarded as a consequence of PD but also may contribute to disease progression[8,9]. Among them, the pathological progress of RBD and PD is the most close. The Oxford Discovery Cohort Study[10] found faster progression of motor, mood, and cognitive symptoms in PD patients combined with possible RBD (pRBD), confirming a more aggressive PD subtype identifiable at baseline. Additionally, numerous basic science studies support a correlation between sleep and neurodegenerative disease progression at the pathophysiological level[11], and have revealed a strong bidirectional relationship between sleep disruption and increased amyloid-beta (Aβ) deposition, as well as higher levels of α-Syn in the brain's extracellular fluid and cerebrospinal fluid[12-17]. Collectively, these findings strongly suggest a close relationship between sleep disturbances and neurodegenerative disease, and understanding the impact of sleep disturbance on PD remains an urgent avenue for further investigation.

The glymphatic system is regulated by the sleep-wake cycle, facilitating the efficient removal of accumulated waste from the brain by allowing the flow of interstitial and cerebrospinal fluid through perivascular pathways, with significantly greater efficiency at night than during the day. Aging is a well-established risk factor for glymphatic system dysfunction[18,19], which may explain the particular relevance of this system to neurodegenerative diseases affecting older populations[20]. Numerous studies have demonstrated the involvement of the glymphatic system in the clearance and spread of pathogenic proteins tau[21], amyloid-β[22-25], and α-Syn[26-28], which provides a new direction for exploring the pathogenesis of neurodegenerative diseases characterized by abnormal protein deposition in the brain. PD is known to be primarily caused by protein homeostasis imbalance. Under normal physiological conditions, α-Syn is a physiologically benign, soluble monomer consisting of 140 amino acids[29]. However, pathological conditions can trigger α-Syn oligomerization or polymerization, leading to the formation of cytotoxic aggregates with a β-lamellar structure. If the abnormally folded proteins are not efficiently cleared, this can result in the accumulation of α-Syn both inside and outside cells, along with the intercellular spread of pathological α-Syn, which contributes to dopaminergic neuron death[30,31]. Among these, the extracellular pathological proteins are more likely to be cleared through the glymphatic system[25]. Clinical studies have already confirmed damage to the glymphatic system in PD[32,33], strongly suggesting that glymphatic system dysfunction may be one of the important pathogenic mechanisms of PD.

Interestingly, the glymphatic system, responsible for clearing waste products from the brain, is also physiologically regulated by sleep. Fluid transport within this system exhibits a daily rhythm, with enhanced activity during sleep and reduced activity during wakefulness[34]. Consistently, several studies have identified strong associations between glymphatic dysfunction and sleep disturbances[35], especially in aging

individuals and those suffering from age-related neurodegenerative diseases. Furthermore, similar to amyloid-β, α-Syn in the brain's extracellular fluid and cerebrospinal fluid are higher during wakefulness compared to sleep[17]. Moreover, α-Syn levels can be further exacerbated by sleep disruption[36]. These findings collectively suggest a complex interplay between sleep, the glymphatic system, and neurodegeneration[37]. Therefore, this article focuses on the link between sleep disturbances and the glymphatic system in neurodegeneration, especially regarding the clearance of pathological proteins, aiming to provide new research avenues for the pathogenesis and neuroprotection of PD.

SLEEP AND PARKINSON'S DISEASE

Sleep is a fundamental biological process essential for health, driven by different electrophysiological rhythms within the brain[38]. Sleep and wakefulness are two distinct functional states governed by the circadian rhythm[39,40]. While wakefulness allows us to perform a variety of physical and cognitive tasks, sleep serves critical restorative functions. It replenishes energy and physical strength, enhances immunity, promotes growth and development, improves learning and memory abilities, and helps to stabilize emotions[41]. With advancing age, sleep patterns exhibit a progressive disruption. In addition, growing evidence suggests that sleep disorders may even precede the onset of some neurodegenerative diseases, and abnormal sleep patterns can worsen their progression[42], including PD.

Severe sleep disturbances have been documented in PD[11,43], such as insomnia, EDS, RBD, and RLS, which can manifest in the early stages of PD. Insomnia, characterized by difficulty falling asleep, staying asleep, or early awakening, and generally poor sleep quality, is one of the most common non-motor symptoms in PD patients, significantly impacting their quality of life[44,45]. EDS refers to the inability to maintain a state of wakefulness and alertness during the day, often leading to unintentionally falling asleep at inappropriate times almost daily for at least 3 months. EDS is prevalent in PD patients, affecting approximately 20%-60% of individuals[46,47], and can worsen their quality of life and increase their risk of injury[48]. RBD is characterized by vivid or unpleasant dreams and intense body movements that may lead to acting out dreams and potential injury. Existing research suggests that RBD can be a precursor to neurodegenerative diseases characterized by α-Syn deposition, including PD, dementia with Lewy bodies, or multiple system atrophy[49,50].

Longitudinal studies indicate that most patients will gradually develop symptoms of PD or cognitive impairments over time[51]. A prospective study followed a group of patients with idiopathic RBD; after decades, the majority (82%) were ultimately diagnosed with a neurodegenerative disease characterized by α-Syn deposition[52]. RLS is a common sensorimotor disorder where patients experience unpleasant sensations in their legs at rest, typically relieved by movement. A recent meta-analysis showed a significantly higher prevalence of RLS in PD patients compared to healthy controls (2.86 times higher). Treated PD patients exhibited a prevalence of 15%, while non-medicated patients showed an 11% prevalence[53]. However, another research suggests no causal or genetic link between RLS and PD[54]. Additionally, research suggests that sleep disturbances in PD, including more disrupted sleep patterns, reduced slow wave sleep (SWS), and rapid eye movement sleep, may contribute to cognitive decline and memory consolidation difficulties. A study demonstrated that PD patients taking dopaminergic medications showed improvement in working memory after sleep. Notably, the degree of improvement correlated with the amount of SWS[55]. In conclusion, strong evidence suggests a close link between sleep disturbances and the development of PD.

Basic scientific research also confirms that PD model mice exhibit sleep disturbances and disrupted circadian rhythms[56]. Interfering with sleep or circadian rhythms significantly exacerbates pathological protein deposition, excessive neuroinflammation, dopaminergic neuronal loss in the substantia nigra, and

motor impairments in PD model mice[57-59]. However, while circadian rhythms and sleep disorders are strongly linked to the progression of neurodegenerative diseases, the specific mechanisms underlying this connection remain poorly understood. It is well known that the sleep-wake cycle plays a crucial regulatory role in the glymphatic system[60]. Intriguingly, growing interest has emerged regarding the function of the glymphatic system in central nervous system diseases, which plays an important role in the removal of metabolic waste, including pathological proteins[23,61]. Taken together, this all suggests that the glymphatic system may serve as a potential bridge between sleep and neurodegenerative diseases[17].

GLYMPHATIC SYSTEM AND SLEEP

Sleep is a crucial human life activity, accounting for about one-third of our lifespan, and plays a significant role in maintaining overall health. Despite the recognized importance of sleep, its complex effects on the body are not yet fully understood. The glymphatic system, a recently discovered waste clearance pathway in the brain, plays a critical role in maintaining metabolic balance and brain health by removing metabolic byproducts. Notably, the glymphatic system is primarily active during sleep and exhibits a close link to the regulation of circadian rhythms[60].

The lymphatic network, a low-pressure, unidirectional flow system found throughout the vertebrate body, removes interstitial fluid (ISF) formed by capillary filtrate and plays a role in tissue immune surveillance[62]. In the brain, however, there is a lack of parenchymal lymphatic vessels. Until 2012, Iliff *et al.*[63] observed the flow pathway of a fluorescent CSF tracer injected into the cerebral space of mice using a two-photon laser scanning microscope. For the first time, they visualized the active and directional flow of CSF into brain cell spaces to remove waste products, a system they termed the glymphatic system. The anatomical foundation of the glymphatic system is the perivascular space. This space arises from the extension of the soft meninges that accompany penetrating arteries and draining veins into and out of the brain parenchyma. It is surrounded by a barrier formed by the adherent astrocyte endfeet[64]. Within the brain tissue, this space is filled with an extracellular matrix rich in type IV collagen and laminin, secreted by pericytes and fibroblasts. Platelet-derived growth factor β (PDGF-β) secreted by endothelial cells recruits pericytes, which in turn induce high expression of aquaporin 4 (AQP4) water channels in the endfeet of neighboring astrocytes[65]. CSF travels along the surface of cerebral arteries and the perivascular spaces of penetrating arterioles. It enters the brain parenchyma through the space between astrocyte endfeet or via aquaporin-4 (AQP4), facilitating CSF-ISF exchange, as well as solute and metabolite transport. Finally, convective flow carries CSF and ISF to the venous perivascular spaces, ultimately draining them out of the brain. This process maintains the stability of extracellular ions and fluids[66].

Normal sleep can be broadly categorized into alternating stages of REM and non-rapid eye movement (NREM) sleep, based on recordings from polysomnography (PSG), which include electroencephalogram (EEG), electrooculogram, and electromyogram (EMG)[67]. REM sleep is associated with vivid dreaming and is characterized by desynchronized brain waves with a mix of low frequencies (similar to the waking state), rapid eye movements, and minimal muscle tone as measured by EMG[68]. In contrast, NREM sleep is characterized by slow or no eye movements, increased activity of the parasympathetic nervous system, and little dreaming[69,70]. NREM is further divided into three stages (N1-N3)[67]. N1, the lightest stage, is marked by a significant decrease in the alpha waves (8-12 Hz) that dominate brain activity during wakefulness. Stage N2 is characterized by the presence of sleep spindles (brief transient oscillations within the range of 12-14 Hz, sometimes referred to as "σ" bands) and K-complex waves (sharp, high-pressure biphasic waves lasting more than 0.5 seconds). N3, also known as SWS, is the deepest sleep stage, with slow delta waves (0.5-2 Hz) dominating brain activity for at least 20% of total sleep time[67,70-72]. Interestingly, cerebral fluid transport begins and progresses during NREM sleep, with the inflow of cerebrospinal fluid tracers

coinciding with SWS activity measured by EEG[34]. Slow-wave activity is most prominent in early sleep and reflects sleep pressure, increasing with prior sleep deprivation[73]. Studies suggest that waste removal from the brain may be most efficient during these early NREM stages, particularly during restorative sleep after long periods of wakefulness. However, patients with PD experience reductions in the total amount and percentage of N2[74,75] and N3[76] sleep, as well as decreased sleep stability. Notably, N2 sleep also appears to be abnormal in terms of electrical activity in PD patients[77], with a decrease in SWS with disease progression[78]. These reductions in NREM and SWS sleep may contribute to impaired clearance of brain waste products, including α-Syn aggregates[7], potentially explaining the bidirectional relationship between sleep disturbances and disease progression. In PD, lower SWS sleep is associated with faster worsening of motor symptoms, and poor sleep quality predicts a more rapid decline in gait function[79,80].

The glymphatic system's function is closely tied to waking and sleeping states. Studies have revealed glymphatic influx and clearance exhibit endogenous circadian rhythms, peaking during the mid-rest phase in mice, with the highest perivascular polarization of AQP4 observed during this phase, while loss of AQP4 abolishes the day-night difference in both glymphatic influx and drainage to the lymph nodes[60]. During sleep, the glymphatic system operates at a doubled cerebrospinal fluid (CSF) clearance rate and shows a 60% increase in brain interstitial space compared to wakefulness[81]. Research has also shown that both peri-arterial inflow and overall flow within brain tissue are significantly higher during anesthesia, akin to sleep[34]. This translates to a more efficient waste clearance by the glymphatic system during sleep[81]. On the contrary, sleep deprivation impedes the glymphatic system's function, notably reducing the peri-arterial inflow from the space surrounding arteries into brain tissue compared to normal sleep states, thereby compromising the brain's clearance efficiency[82,83]. The suprachiasmatic nucleus (SCN), located within the hypothalamus, acts as the body's master circadian clock, controlling sleep and wake timing through the release of specific neurotransmitters and hormones[84,85]. Interestingly, a recent study revealed that glymphatic fluid transport peaks during sleep and decreases during wakefulness, independent of light exposure[60]. In conclusion, sleep plays a critical role in maintaining brain homeostasis and clearing out CNS metabolites through the glymphatic system.

It is worth noting that the glymphatic system can also regulate sleep in reverse. The influence of AQP4 genetic variations appears to affect sleep[86]. Studies have shown that a common single nucleotide polymorphism (SNP) in AQP4 is associated with changes in slow-wave activity during NREM sleep[87]. Taken together, these findings point to a strong link between the glymphatic system and sleep patterns.

GLYMPHATIC SYSTEM AND PARKINSON'S DISEASE

Notably, most age-related primary neurodegenerative diseases are characterized by impaired protein processing and aggregation, with a hallmark feature being the formation of misfolded or hyperphosphorylated protein aggregates[88]. In PD, pathological α-Syn not only accumulates within neurons but also spreads between cells. The glymphatic system is thought to eliminate waste products by channeling them to the cervical lymphatic vessels for disposal. However, lymphatic vessel function declines with age[89], leading to a decrease in glymphatic flow[19,90,91]. Dysfunction of the glymphatic system is increasingly recognized as a potential factor in the occurrence and progression of neurodegenerative diseases. While the precise mechanisms remain under investigation, research suggests that impaired glymphatic function may contribute to the buildup of toxic proteins and inflammatory substances in the brain, hallmarks of these diseases[92]. Given the crucial role of the glymphatic system in clearing waste from cerebrospinal fluid and interstitial fluid, the relationship between the glymphatic system and the pathological progression of PD has aroused significant interest. This section will provide a focused review of this topic.

Numerous studies have shown a close connection between glymphatic dysfunction and AQP4[21,22,24,25]. Alterations of AQP4 can largely reflect changes in the glymphatic system in PD. Autopsy findings have revealed a negative correlation between AQP4 expression levels and the α-Syn content in the neocortical regions of PD, suggesting a potential role for AQP4 in regulating α-Syn deposition[93]. Numerous clinical studies have shown that AQP4 mononucleoside polymorphism affects brain activity in PD patients, correlating with PD susceptibility and cognitive function[94,95]. Basic research has found that A53T transgenic mice display decreased polarization of AQP4 and reduced glymphatic activity in the brain, and knocking out the AQP4 gene accelerates the α-Syn accumulation and dopaminergic neurons loss in the substantia nigra of A53T transgenic mice, resulting in motor impairments[27]. One study by Zou *et al.*[26] found that AQP4 deletion decreased the brain's clearance rate of α-Syn, evidenced by an increase in protein monomers but not an increase in oligomer clusters, which suggests that within the glymphatic system, AQP4 facilitates the clearance of soluble, single α-Syn molecules. Additionally, Cui *et al.*[28] found that reduced AQP4 expression accelerated the pathological deposition of α-Syn and worsened dopaminergic neuron loss and behavioral deficits in AQP4 knockout mice injected with α-Syn preformed fibers (PFFs) into the striatum. Multiple studies have confirmed that knocking out the AQP4 gene or inhibiting the production of cerebrospinal fluid with acetazolamide reduces the clearance of exogenously injected α-Syn in the substantia nigra or striatum brain regions of mice[27,96]. In the MPTP-induced PD mouse model, impaired AQP4 polarization and reduced flow and effusion in the perivascular space were also found, while inhibition of MMP-9 restored AQP4 integrity at the end of astrocytes and alleviated MPTP-induced dopaminergic neuron loss[97]. Taken together, studies suggest a close relationship between the AQP4-mediated glymphatic system and α-Syn within brain tissue, and a disrupted glymphatic system can slow down the clearance of large molecules from the brain and exacerbate the pathological processes, hinting that restoring glymphatic activity could be a potential therapeutic target to slow PD progression[27,28].

As a functional and classical lymphatic system in the CNS, meningeal lymphatic vessels are distributed along the dural venous sinuses and cranial nerves, allowing the cerebrospinal fluid and its solutes in the perivascular spaces to enter the meningeal lymphatic vessels. These solutes are transported to the deep cervical lymph nodes, ultimately reaching peripheral metabolism[98,99]. Studies have found that the flow of meningeal lymphatic vessels along the superior sagittal sinus and transverse sinus is significantly reduced in patients with PD, and there is a significant delay in the perfusion of deep cervical lymph nodes. In PD model mice injected with α-Syn preformed fibrils, delayed meningeal lymphatic drainage was also observed, along with loss of tight connections between meningeal lymphatic endothelial cells, increased meningeal inflammation, and blocking of blood flow through meningeal lymphatic vessels, leading to increased α-Syn pathology and exacerbated motor and memory deficits[100]. Another study involved ligating deep cervical lymph nodes to block meningeal lymphatic drainage in 18-week-old A53T mice, revealing a reduction in tracer influx of cerebrospinal fluid, accompanied by aggregation of α-Syn around blood vessels and impaired polarization expression of AQP4 in the substantia nigra, with more severe loss of dopaminergic neurons and motor deficits[26]. Additionally, researchers found that oligomeric α-Syn in cerebrospinal fluid effectively activates macrophages located in deep cervical lymph nodes via endoplasmic reticulum stress, and inhibiting endoplasmic reticulum stress can effectively suppress this activation, thereby inhibiting peripheral inflammation in PD mice[101]. These indicate a close connection between the meningeal lymphatic drainage and PD. To thoroughly understand the relationship between the glymphatic system and PD or other neurodegenerative diseases, the malfunction of the meningeal lymphatic system in neurological conditions should be considered carefully in future works.

Dysfunction of the glymphatic system can not only affect the clearance of pathological proteins but also lead to increased sensitivity of dopaminergic neurons to toxins. Studies have shown that AQP4 deficiency

exacerbates MPTP-induced degeneration of dopaminergic neurons in the substantia nigra and ventral tegmental area in mice[102]. However, it is worth noting that the dopaminergic system can also in turn regulate the glymphatic system. Dopamine has been shown to reduce the proliferation of glial cells in the striatum, as well as the expression of AQP4 within these cells[103]. Moreover, dopamine receptors are involved in regulating the inflow and outflow of interstitial fluid, thus participating in the regulation of cerebrospinal fluid volume[104]. Therefore, since dopaminergic neurons seem to regulate AQP4 function, and AQP4 deficiency exacerbates the loss of dopaminergic neurons, the two process damage may exacerbate and promote each other, ultimately leading to protein clearance disorders.

Previous studies of the glymphatic system have focused on animal models, and there is a relative lack of indicators for assessing the function of the human glymphatic system due to safety and technical feasibility. Nowadays, with the rapid development of neuroimaging technology, diffusion tensor image along the perivascular space (DTI-ALPS) has appeared, which indirectly reflects the functional alterations of the glymphatic system by measuring the diffusion of H_2O within the perivascular space (PVS). Meanwhile, the structural changes of the glymphatic system can be assessed by calculating the PVS burden in the relevant brain regions. In recent years, many clinical studies have shown that the ALPS index is negatively correlated with the onset, progression, and severity of PD. At the same time, a decrease in DTI-ALPS was correlated with an increased PVS burden, which is associated with the development of gait freezing, a more rapid increase in dopaminergic medications, and even a higher risk of dementia conversion [Table 1]. The development of DTI-ALPS provides evidential support for the promise of an impaired glymphatic system as a predictor of progression in PD.

SLEEP, GLYMPHATIC SYSTEM AND PARKINSON'S DISEASE

As age increases, sleep quality gradually declines, leading to insomnia, fragmentation, and other issues. This may also be a result of dysfunction in the elderly glymphatic system, potentially contributing to the onset and progression of age-related neurodegenerative diseases, including PD[114]. Furthermore, there is an increasing amount of direct evidence confirming a close interplay between sleep, the glymphatic system, and PD.

REM sleep behavior disorder, or RBD, is the sleep disorder most closely associated with the onset and progression of PD. Clinical studies have shown that RBD often appears before the typical motor symptoms of PD, sometimes even decades earlier, and 90% of individuals with RBD will eventually progress to PD, suggesting that RBD is a significant risk factor for the development of PD[115]. Recent research indicates that the glymphatic system in patients with RBD is severely impaired. Using DTI-ALPS to assess glymphatic system activity, Si *et al.*found damage to the glymphatic system in both iRBD patients and PD patients[32]. Another study also confirmed that the median ALPS index was reduced in the RBD group and PD compared to the control group[105]. These findings suggest that the progression of alpha-synucleinopathies may be related to damage to the glymphatic system. In addition to REM sleep, NREM sleep disorders have also been shown to be closely related to the pathological progression of PD. Morawska *et al.*[116] found that the deprivation of slow-wave sleep increased the pathological protein load in VAMT2 knockout mice while increasing slow-wave sleep significantly reduced the deposition of pathological α-Syn in the brains of VAMT2 knockout mice and A53T transgenic PD model mice[116]. More importantly, slow-wave sleep increased the expression of AQP4 around blood vessels, suggesting that slow-wave sleep may play an important role in regulating the glymphatic system in the extracellular clearance of pathological proteins[116]. Therefore, sleep disorders affect the onset and progression of PD through the glymphatic system, and maintaining healthy sleep habits and circadian rhythms is essential for optimal glymphatic function and overall brain health.

Table 1. Clinical evidence of lymphatic system impacting Parkinson's disease

Author, year	Target group	Index measured	Finding
Si *et al.*, 2022[32]	RBD, PD patients	DTI-ALPS	Patients with PD exhibited a lower ALPS index than those with BDs, and both patient groups showed a lower ALPS index than HC. The ALPS index and disease severity were negatively correlated in the BD and PD subgroups
Bae *et al.*, 2023[105]	RBD, PD patients	DTI-ALPS	The median ALPS index was lower in the group with BD versus controls but showed no evidence of a difference compared with the group with PD, and the conversion risk decreased with an increasing ALPS index
Qin *et al.*, 2023[106]	PD patients	DTI-ALPS	The DTI-ALPS index of PD patients was significantly lower than normal controls. UPDRS-III score and subscore for rigidity were negatively correlated with DTI-ALPS index
Bae *et al.*, 2023[107]	PD patients	DTI-ALPS	The ALPS-index was lower in the PD group than in the controls. In the PD group, the ALPS-index negatively correlated with the UPDRS-III score, and positively correlated with the MMSE and MoCA scores
He *et al.*, 2023[108]	PD patients	DTI-ALPS	Patients were classified into the low or high ALPS index group based on the baseline ALPS index. The low ALPS index group experienced faster deterioration in UPDRS, Symbol Digit Modalities Test, and Hopkins Verbal Learning Test
Meng *et al.*, 2024[109]	PD patients	DTI-ALPS, EPVS	The DTI-ALPS indices were lower bilaterally in PD patients than in the HC group, and EPVS numbers in any of the bilateral centrum semiovale, basal ganglia, and midbrain were higher, especially for the medium- to late-stage group.
Gu *et al.*, 2022[110]	ET, PD patients	DTI-ALPS, EPVS	The ALPS index was lower in patients with PD than in patients with ET and HC. Patients with PD showed a more severe EPVS burden in the centrum semiovale, basal ganglia, and midbrain compared to ET and HC.
Shen *et al.*, 2022[33]	PD patients	DTI-ALPS, PVS	lower DTI-ALPS in the subgroup of patients relative to controls, and the differences were more pronounced in patients with Hohn & Yahr stage greater than two. The decreased DTI-ALPS correlated with increased PVS burden, and both indexes correlated with PD severity.
Donahue *et al.*, 2023[111]	PD patients	PVS	Higher white matter rostral middle frontal PVS was associated with lower scores in both global cognitive and visuospatial functions. In the basal ganglia, higher PVS was associated with lower scores for memory, with a trend toward lower global cognitive composite scores
Jeong *et al.*, 2023[112]	PD patients	CPV	CPV was negatively associated with DAT availability and was positively associated with the UPDRS score. A larger CPV was associated with the future development of freezing of gait and a more rapid increase in dopaminergic medication.
Jeong *et al.*, 2023[113]	PD patients	CPV	CPV negatively correlated with composite scores of the frontal/executive function domain. A larger CPV was associated with a higher risk of dementia conversion

RBD: Rapid eye movement sleep behavior disorder; PD: Parkinson's disease; DTI-ALPS: diffusion tensor image analysis along the perivascular space; HC: health control; UPDRS: unified Parkinson's disease rating scale; MMSE: mini-mental state examination; MoCA: montreal cognitive assessment; (E)PVS: (enlarged) perivascular spaces; ET: essential tremor; CPV: The choroid plexus volume.

REGULATE SLEEP TO IMPROVE GLYMPHATIC FUNCTION

Enhancing sleep can improve the efficiency of the glymphatic system, thereby reducing protein aggregation in the brain, as shown in both mouse and human studies[81,117]. A cross-sectional study involving 84 participants used an imaging technique called DTI-ALPS to assess glymphatic function. This study found that a higher DTI-ALPS index correlated with a longer duration of deep sleep (N2 sleep), suggesting a strong link between sleep quality and glymphatic system function[35]. Sleep modulation therapies also hold promise. In a study using a PD mouse model, researchers found that treatment with sodium hydroxybutyrate, a drug known to enhance slow-wave sleep, improved the organization of AQP4, a key protein in the glymphatic system, around blood vessels (perivascular AQP4 polarization)[116]. This treatment also specifically increased proteostasis and ultimately reduced the buildup of the abnormal α-Syn protein, a hallmark of PD. Supporting this link between sleep and disease progression, another study involving 129 PD patients found a correlation between the amount of slow-wave sleep measured by polysomnography and motor function scores. Patients with higher levels of slow-wave sleep showed a slower decline in motor function over a mean period of approximately 4.6 ± 2.3 years[80]. Melatonin, a hormone known to regulate circadian rhythms and improve sleep quality[118], may also play a role in glymphatic function. Studies in mice genetically modified to develop Alzheimer's disease (Tg2576 mice) have shown that melatonin treatment can inhibit the buildup of Aβ precursor protein (APP) Aβ). This effect may be due to melatonin's ability to

restore glymphatic system function. Melatonin appears to achieve this by regulating the expression of a circadian protein called Per2 and by maintaining the daily cycle of AQP4 distribution in astrocytes[119]. Interestingly, certain anesthetics may also enhance glymphatic function. A study in rats showed that combining the anesthetic dexmedetomidine with low-dose isoflurane anesthesia increased cerebrospinal fluid volume by 2% and improved glymphatic system efficiency by 32% compared to isoflurane alone. This enhanced function may be linked to dexmedetomidine's ability to inhibit the norepinephrine system, which is known to suppress glymphatic activity[81]. Another study using mice investigated the effects of different anesthetics on the glymphatic system. The researchers found that anesthetics that promote slow-wave sleep also increased the flow of cerebrospinal fluid into the brain tissue, facilitating the removal of waste products[34]. In conclusion, promoting healthy sleep patterns appears to enhance the function of the glymphatic system, which in turn helps clear away abnormal proteins from the brain. This two-way relationship suggests that improving sleep may offer a potential therapeutic target for slowing the progression of neurodegenerative diseases.

CONCLUSIONS

In summary, a significant relationship exists among sleep disturbances, the glymphatic system, and PD. Damage to the glymphatic system may serve as a pivotal factor contributing to impaired clearance, deposition of pathological proteins, and subsequent degeneration of dopaminergic neurons in PD due to sleep disturbances. In the realm of neurodegenerative diseases, extensive research has been conducted on the glymphatic system's role in clearing brain Aβ and tau proteins[21,61], yet investigations into the clearance of pathological α-Syn by the glymphatic system remain relatively limited. The precise mechanisms linking sleep disorders, glymphatic dysfunction, and PD are still under exploration. Moreover, there is a growing necessity for the implementation of more advanced, non-invasive MRI and PET technologies in the future. These technologies will aid in assessing the glymphatic system's function and the deposition of pathological proteins in the brains of individuals with sleep disturbances and PD. Additionally, they will contribute to investigating the potential impact of improving sleep on the glymphatic system and the pathological progression of PD.

DECLARATIONS

Authors' contributions
Wrote the manuscript: Wang Y, Zou W, Jin Z
Contributed to the literature search: Yin S, Chi X, Li J
Reviewed the manuscript: Sun Y, Wu J
Conceived the structure of the manuscript and participated in the entire writing process: Kou L, Xia Y, Wang T

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