

A Study on the Bi-directional Relationship Between Sleep Disturbance and Alzheimer's Disease

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Abstract. Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by gradual memory loss and cognitive decline. This multifactorial condition is influenced by aging, genetic predispositions, and various lifestyle factors. Among these, sleep has emerged as a critical component of overall health, with recent research highlighting a bi-directional relationship between sleep disturbances and AD. On one hand, poor sleep may contribute to the onset and progression of AD by exacerbating pathological processes; on the other hand, the accumulation of AD-related pathologies can further disrupt sleep. Notably, slow-wave sleep (SWS) has emerged as a key overlapping factor in this relationship. By examining the interplay between sleep disorders—such as insomnia, obstructive sleep apnea (OSA), and narcolepsy—and AD, this article seeks to deepen the understanding of their shared mechanisms. Ultimately, unraveling this complex relationship may provide new insights into the etiology of AD and pave the way for innovative treatment strategies aimed at mitigating the impact of sleep disturbances on disease progression.

Keywords: Sleep disturbance, Alzheimer's disease (AD), Insomnia, Obstructive sleep apnea (OSA), Narcolepsy.

1. Introduction

Alzheimer's disease (AD) is the most common cause of dementia worldwide, usually characterized by memory loss, cognitive impairments, and behavioural changes [1]. Pathologically, the extracellular deposition of amyloid (A β) peptides and intracellular tau fibrillary tangles (NFTs) are hallmarks of AD [1]. The accumulation of oligomeric A β associates with synaptic loss, contributing to the disruptions of long-term potentiation (LTP), which is critical for memory consolidation. The hyperphosphorylated tau, which composes NFTs, is also closely correlated with synaptic dysfunctions and cognitive decline [2]. The impaired clearance of A β and tau could be a key factor in their pathological aggregation in the brain. Research into various clearance mechanisms, including the ubiquitin-proteasome system, cellular uptake by microglia, and transport through the blood-brain barrier (BBB), is ongoing [3]. However, significant breakthroughs have yet to be achieved. Recently, a so-called glymphatic system has been shown to facilitate A β and tau clearance. And it works most effectively during sleep [4].

Sleep is essential for human life, contributing to energy conservation, brain waste clearance, cognition, and so on. Sleep disturbance, a condition that disrupts the normal sleep pattern, can lead to memory impairments [4]. Since 1991, studies found that up to 45 % of individuals diagnosed with AD suffered from sleep problems, and they usually experienced significant changes in sleep architectures,

such as reduced SWS and increased sleep fragmentation [5-6]. However, whether it is a cause or consequence of AD remains unclear.

Sleep disorders like insomnia, OSA, and narcolepsy reduce sleep quality and duration, potentially contributing to AD development [7-8]. These sleep problems can be detected before AD onset and are thought to impair the glymphatic system, which plays a crucial role in toxic waste product clearance [9]. A mouse model of AD showed increased A β levels and aggravated cognitive decline after a chronic sleep deprivation (SD), underscoring a positive correlation between sleep disturbance and AD [10].

Additional studies have proposed that AD may contribute to sleep disturbances due to neurodegeneration in brain regions that are responsible for regulating the sleep-wake cycle. For example, AD can lead to neuronal loss in hypothalamus and brainstem, which both play vital roles in maintaining normal sleep patterns [11]. The degeneration of these areas can result in fragmented sleep and insomnia. Furthermore, the accumulation of A β in the brain may disrupt normal sleep architecture, exacerbating sleep disturbances early in the progression of AD [11].

This article aims to analyze current findings from both perspectives to identify a convincing direction or a better explanation for this two-way association. It will specifically examine the functions of sleep and evidence from various sleep disorders to elucidate the mechanisms underlying this relationship. From there, we can gain insights into AD's etiology and accelerate the progress of finding biomarkers and therapeutic targets of AD.

2. Functions of sleep

2.1. Memory consolidation

Memory consolidation integrates newly encoded memories into long-term storage, a process most effective during sleep [11]. The two states of sleep, SWS and rapid eye movement (REM) sleep, play different roles in memory consolidation. During SWS, the brain reactivates and redistributes newly learned information, transferring it from the hippocampus to the neocortex for long-term storage [11]. During REM sleep, the high frequency brain waves facilitate synaptic consolidation through LTP [12]. Notably, the NMDA receptor is involved in the LTP process. Study on SD rats showed a reduced NMDA /AMPA ratio and an altered surface expression of NMDA receptors in the hippocampal cells, suggesting a negative impact of SD on LTP-mediated memory consolidation [13]. Other animal models of SD showed impaired memory performance in cognitive assessments, such as the Morris water maze (MWM), contextual fear-conditioning task (CFC), and object-location memory task (OLM) [14].

2.2. Glymphatic clearance of A β and tau

The abnormal build-up of A β and tau proteins are hallmarks for AD, contributing to neuronal damage. To maintain homeostasis, the timely clearance of these proteins is as crucial as their production. Emerging evidence suggests the glymphatic system is responsible for A β and tau clearance [4,15]. The glymphatic system, mainly active during sleep, is a drainage process that allows the extracellular proteins or metabolic waste products be carried by the flow of cerebrospinal fluid (CSF) and interstitial fluid (ISF) to the vasculature and out of the brain [4,15]. The CSF-ISF flow is mainly facilitated by aquaporin 4 (AQP4) water channels on the end-feet of astrocytes, which closely surround the blood vessels [4,15]. Animals without AQP4 exhibit a ~70% reduction in CSF influx and a ~55% reduction in parenchymal solute clearance [16]. Moreover, in AQP4-deficient mice, there is an increased level of A β and tau found in the brain, along with cognitive decline [4,15].

Sleep is vital for glymphatic functions as it highly correlates with increased CSF influx, interstitial volume, and improved A β clearance [4,15]. A study proposed that sleep could enhance glymphatic activity by expanding the interstitial space, while adrenergic signaling during wakefulness contracts it, reducing clearance efficiency [4]. Additionally, animal models of SD showed increased A β levels and an impaired AQP4 polarisation, suggesting that sleep could cause abnormal protein build-up through AQP4 damage [15].

2.3. Regulation of neuroinflammation

Neuroinflammation is characterized by the activation of microglia and an increase in pro-inflammatory cytokines within the brain, playing a critical role in the pathogenesis of AD [17]. Emerging evidence suggests that sleep is integral to immune system regulation, with several studies demonstrating this connection through SD models [17-18]. For instance, research has shown elevated levels of pro-inflammatory cytokines, such as TNF α , IL-6, and IL-1 β , accompanied by reactive gliosis in the brains of mice after 3-day SD [17]. Another study reported an overexpression of microglial markers and accompanying cognitive impairments in C57BL/6J male mice following 24 hours of SD [18]. Furthermore, the pro-inflammatory cytokines and activated microglia can exacerbate one another, leading to further damage to hippocampus-dependent memory and learning [18].

3. Sleep disorders and their associations with AD

3.1. Insomnia

Insomnia is defined as difficulty with falling asleep or maintaining sleep, which can cause daytime fatigue, low energy, and difficulty in maintaining attention [19-20]. The severity of the symptoms can increase with age and are common in AD patients, with more than half of the AD patients report experiencing insomnia [19]. In addition, AD patients usually experience more severe symptoms of insomnia, such as reduced sleep maintenance and instability of circadian rhythms, compared to their age controls [19].

Research indicated that insomnia could raise the CSF levels of A β , tau proteins, and pro-inflammatory cytokines, all of which are implicated in AD pathology [20-25]. Chen et al.'s study applying SD on Sprague-Dawley rats showed a significant increase in A β 1-42 and A β 1-40 [21]. Rothman et al. assessed the correlation between SD and tau and found an increased level of tau in 3xTgAD mice following sleep restriction (6h/day for 6 weeks) [22]. Another study showed a similar effect of SD on 3xTgAD mice with increased tau protein fraction and accompanied cognitive decline [23]. Moreover, sleep might play an important role in cytokine and immune cell regulation as their fluctuations follow the sleep-wake cycle [20]. A study demonstrated that prolonged sleep loss could lead to elevated levels of IL-6, which is closely related to AD [24].

Conversely, insomnia in AD could be caused by the neurodegeneration at suprachiasmatic nucleus (SCN) and pineal gland, which are critical structures to maintain the circadian rhythm [25-26]. SCN is the “master clock” in our body that governs the sleep-wake cycle and related hormone secretion, including melatonin secreted by pineal gland [25]. “Sundowning”, a common phenomenon appearing in the middle or late stages of AD, is marked by an aggravated confusion, wandering, and agitation during late afternoon to evening. And it has been suggested due to disrupted circadian rhythm [26]. The behavioral and psychological symptoms co-expressed in AD patients, such as anxiety, depression, and agitation, can significantly interfere with their ability to fall and stay asleep [26]. Medications that are used to alleviate these symptoms can also negatively contribute to sleep disturbance due to side effects [26].

3.2. Obstructive sleep apnea (OSA)

OSA is characterized by repeated episodes of partial or complete obstruction of the upper airway during sleep, which can lead to breathing pauses, reduced oxygen levels, and frequent awakenings, disrupting normal sleep patterns [27]. People who suffer OSA usually have anatomical abnormalities, such as naturally small airways, or the reduced muscle tone in throat muscles during sleep [27]. A meta-analysis showed that individuals with AD are five times more likely to develop OSA compared to their age-matched controls. And approximately half of AD patients experience OSA following their initial diagnosis [28].

Studies suggest that OSA contributes to intermittent hypoxia, sleep fragmentation, and cardiovascular comorbidities, all closely linked to AD [29-31]. OSA-induced intermittent hypoxia, characterized by repeated low oxygen levels due to airway obstruction, is associated with increased

reactive oxygen species (ROS) production, leading to oxidative stress and neuronal damage [29]. Research using 3xTg-AD mice showed that chronic intermittent hypoxia raised A β levels, while APP/PS1 mice exposed to chronic hypoxia demonstrated enhanced tau pathology via calpain-mediated tau hyperphosphorylation [30-31]. Additionally, OSA disrupts sleep architecture, reducing REM sleep, which is crucial for synaptic plasticity and memory consolidation [32]. A prospective study found that reduced REM sleep and delayed REM onset significantly correlate with a higher incidence of AD over 12 years [33]. OSA also decreases SWS, a stage critical for memory, learning, and glymphatic clearance. A study investigated SWS in older patients with severe OSA and found a decrease in total percentages of SWS in their sleep cycle [34]. Other studies associated reduced SWS with higher levels of A β [35-36]. Cardiovascular comorbidities like atrial fibrillation and coronary heart disease, common in OSA patients, further increase AD risk [37]. And treatment with continuous positive airway pressure (CPAP) has shown improvements in cognitive function, SWS, and reduced cardiovascular risk in OSA patients with AD [38-40].

AD can contribute to or worsen OSA through neurodegeneration at respiratory centers and the disruption of sleep stages. A review has identified that brain areas impacted by AD—such as the ventral respiratory group (VRG) in the medulla oblongata, the nucleus tractus solitarius (NTS), the parabrachial nucleus, the reticular formation nuclei, and the ambiguous nucleus, all of which are crucial for respiratory rhythm and muscle control—may be responsible for the respiratory dysfunction observed in OSA [41]. Additionally, the accumulation of A β plaques and NFTs in AD can alter sleep patterns, particularly by reducing SWS, which can, in turn, exacerbate the severity of OSA [29].

3.3. Narcolepsy

Narcolepsy is a sleep disorder characterized by excessive daytime sleepiness and disturbed sleep patterns [42]. Pathologically, it is characterized by a deficiency in orexin (or hypocretin), a neuropeptide that regulates sleep-wake cycle [42].

Studies indicated that the neurons producing orexin were substantially lost in the hypothalamus of human narcoleptics [42]. This deficiency in orexin and orexinergic neurons can lead to changes in sleep patterns, especially the SWS in NREM sleep. Studies on narcoleptic patients and orexin knock-out mice both showed decreased SWS [43-44]. Sleep fragmentation was also found in narcolepsy type 1 (NT1) patients with unstable REM and NREM sleep [45]. In addition, orexin might play an important role in hippocampal-dependent memory. The mouse model with orexin deficiency showed memory impairments in the two-way active avoidance task, which could be rescued by orexin-A (OXA) treatment [46]. Interestingly, OXA level was positively correlated with A β and tau pathology in AD patients, with orexin deficiency decreasing A β pathology in AD mice. However, the rescue of orexin levels increased the levels of A β in the brain [47].

The orexinergic system is disturbed in various neurodegenerative diseases, including AD. Sleep disruptions in AD could lead to increased A β accumulation, which can cause neuronal loss that further alters the orexinergic system [47]. It was suggested that the degeneration of basal forebrain cholinergic neurons are important projection targets for orexin neurons. The loss of this communication could lead to a dysregulation of orexinergic signaling, potentially leads to or exacerbate narcolepsy [47].

4. Discussion

While there are many possible factors that can cause sleep problems like stress, poor sleep habits, mental health disorders, medications and so on, the most common ones are age and gender. A study reported that there is a direct, inverse relationship between age and sleep quality. And the prevalence of poor sleep quality is higher in females [48].

A common phenomenon among sleep disorders is disrupted or reduced SWS, which could be a core factor for AD development. SWS facilitates memory consolidation and the clearance of A β and tau proteins via the glymphatic system. Impaired SWS could result in cognitive impairments and accumulation of A β peptides and NFTs, which are hallmarks of AD [49]. Sleep fragmentation found in various sleep disorders can lead to SWS [28]. However, this disrupted sleep stage is also found

commonly in AD patients, which was suggested due to A β and tau deposition [46]. A possible mechanism underlying the reduced SWS in AD could be A β -led hyperactivity that results in neuronal network dysfunction [50]. Notably, the inhibitory tone was disabled in AD mice. And treating them with GABA_A receptor agonists can rescue this imbalance and the SWS [50].

Since the changes in SWS usually occur in early stage of AD or even before the AD onset, it is potential to be a biomarker for AD. Targeting SWS then becomes a promising treatment for AD. Recent studies have incorporated optogenetics in restoring the slow wave oscillations. A study used light to activate channelrhodopsin-2 (ChR2) excitatory neurons at the endogenous frequency of slow waves in APP mice and restored slow wave oscillations [51]. Additionally, they showed that chronic restoration of slow-wave activity (SWA), a representation of the amount and intensity of slow-wave oscillations during SWS, can stop A β deposition [51]. At the same time, the effects of transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS), and auditory stimulations on slow-wave restoration are also under research. And they all showed promising results in enhancing SWA and memory consolidation [52-54].

5. Conclusion

In conclusion, the bidirectional relationship between sleep disturbances and AD highlights a complex interplay that exacerbates each other as the disease progresses. Sleep disturbances such as insomnia, OSA, and narcolepsy can lead to the pathogenesis of AD, while AD pathology, in turn, worsens the sleep problems. SWS might be a critical factor in this relationship as it was found in both conditions and serves a role in waste clearance and memory consolidation. Although the specific mechanism remains undetermined, it could be the reduced SWS due to sleep disorders or AD pathologies leads to less glymphatic clearance, thus, the increased accumulation of A β and tau.

Although supported by ample studies, the evidence of AD contributing to sleep disturbance is mostly based on self-report from patients, which can be inaccurate due to bias and their disease conditions. Co-morbidities of AD, including depression, anxiety, and the side effects of medications, can complicate patient's report and the dependent relationship between AD and sleep disturbance. In addition, the translation of finding can be limited by the animal models. It should be noticed that animal models do not fully represent human conditions. Mice are nocturnal animals and their sleep patterns, such as SWS and REM duration, deviate from humans as aging, which can affect the generation of findings from sleep-related studies.

Future research should prioritize identifying the initial causal factors linking sleep disturbances to AD. While SWS has been highlighted as a critical component in this relationship, its precise functions and potential as a biomarker or therapeutic target require further validation. Given the current lack of effective treatments to cure or significantly slow AD progression, it is imperative to deepen our understanding of sleep's role in neuroprotection and how to use it to control AD development. Moreover, it will be crucial to explore the distinct mechanisms by which different sleep disorders—such as insomnia, obstructive sleep apnea, and narcolepsy—contribute to AD pathology. This exploration should be paired with the development of targeted therapeutic strategies that address these mechanisms.

This review provides insights for the current understanding of sleep disturbance and AD, highlighting the importance of sleep for maintaining health and well-being. At the same time, it reveals an urgent need to find the biomarkers and therapeutic targets of AD.

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