The Future of Medical Science

FSA

Article

The Bidirectional Relationship Between Sleep and Alzheimer's Disease

Siqi (Grace) Peng

Lexington High School, Lexington, Massachusetts

https://doi.org/10.37229/fsa.fjms.2025.08.10

***Corresponding author:** penggrace18@gmail.com

Future Science Association

Available online free at
www.futurejournals.org

Print ISSN: 2693-1885

Online ISSN: 2693-1907

Received: 20 June 2025
Accepted: 25 July 2025
Published: 10 August 2025

Abstract: In the United States, approximately 6.7 million adults aged 65 and older are affected by Alzheimer's disease (AD), the leading cause of dementia in the elderly. This long-term neurodegenerative condition is characterized by a decline in cognitive function and memory, and its prevalence is projected to double by 2060. While the exact causes of AD remain unknown, evidence points to multiple contributing factors, with sleep emerging as a significant and potentially reversible determinant. Sleep plays a critical role in the clearance of beta-amyloid (Aβ), a protein central to AD pathology. Disruptions to sleep, particularly a reduction in non-rapid eye movement (nREM) sleep, can impair the brain's natural waste removal processes and lead to Aβ accumulation. Furthermore, common sleep disorders like insomnia and obstructive sleep apnea exacerbate this process, accelerating disease progression. This review explores the critical, bidirectional relationship between sleep disturbances and Aβ pathology, highlighting the potential of sleep-focused interventions as a non-invasive strategy to slow the advancement of AD.

Key words: Alzheimer's disease, sleep, beta-amyloid, nREM sleep, neurodegeneration, insomnia, obstructive sleep apnea.

1. Introduction

In the United States alone, approximately 6.7 million adults aged 65 years and above have Alzheimer's disease (AD), the most common cause of dementia among elderly individuals. The estimated worth of people with Alzheimer's is expected to increase over the years. The general trend estimates that by 2060, the figure will double to about 13.8 Americans with some kind of Alzheimer's dementia **(2023 Alzheimer's disease facts and figures, 2023)**.

AD is a long-term neurodegenerative condition that is linked with decreased brain function, loss of memory, and cognitive impairment. Although the definite cause remains unknown, clinical and experimental findings indicate that there are multiple environmental and biological factors contributing to the etiology and development of the disease **(Puthiyedth *et***

***al.*, 2016)**. Among these factors, sleep was found to be a significant but also reversible determinant of Alzheimer's etiology.

2. The Link Between Sleep and Amyloid-Beta Accumulation

Sleep plays a significant function in beta-amyloid (Aβ) clearance and control, which is a protein whose deposition is typical of the pathophysiology of Alzheimer's disease. Deep sleep, specifically non-rapid eye movement (nREM) sleep, in healthy individuals is marked by the elimination of waste products of metabolism. Of these waste products, beta-amyloid is a major part as well. Disruptions to sleep, for instance, reduced nREM sleep, may hinder the natural cleaning processes of the brain and induce Aβ deposition **(Caire *et al.*, 2023)**.

Aβ is produced by the cleavage of amyloid precursor protein (APP). While it exists in multiple forms, the Aβ42 subtype is specifically neurotoxic and/aggregation-prone. As brain concentrations of Aβ42 build, it literally forms small plaques that disrupt synaptic communication, cause inflammation, and ultimately lead to neuronal death. The resultant loss of neural integrity is translated into memory and cognitive loss. Formation of such plaques has been shown to be strongly linked with genetic susceptibility and lifestyle, including sleep quality, and nREM sleep cycle disruption.

In healthy brains, Aβ levels fluctuate across the sleep-wake cycle: rising during wakefulness and falling during sleep. However, in individuals who have poor or broken sleep, the normal rhythm is broken, and there are elevated and extended levels of Aβ because the brain simply cannot perform the task of removing metabolic waste. In one study, a single night of sleep loss in healthy young adults significantly increased morning Aβ42 levels **(Ooms *et al.*, 2014)**. Correspondingly, Ju *et al*. (2013) found that preclinical amyloid deposition was correlated with worse sleep quality, even without any alteration of sleep amount. Furthermore, sleep disturbances are common in established AD patients. They include insomnia, disturbed sleep, reduced sleep efficiency, reduced REM and SWS, and increased wake after sleep onset **(Moe *et al.*, 1995; Liguori *et al.*, 2014)**. These disturbances could not only exacerbate the cognitive symptoms but also further accelerate disease development by impairing Aβ clearance.

3. Impact of Specific Sleep Disorders on Alzheimer's

Sleep disorders such as insomnia, obstructive sleep apnea (OSA), and restless legs syndrome have a significant effect on sleep quality and sleep organization by reducing the quantity and density of non-rapid eye movement (nREM) sleep.

The most prevalent sleep disorder, insomnia, is characterized by difficulty in initiating sleep or maintaining sleep. In insomnia, slow-wave sleep time and total sleep time are typically reduced. Because SWS is crucial for the clearance of glymphatic Aβ, chronic insomnia can threaten this activity and result in the accumulation of higher levels of Aβ within the brain. Long-term elevation might be the underlying cause of amyloid plaque formation, which impairs synaptic function and allows neuronal damage **(Ju *et al.*, 2013)**. Besides, longitudinal studies have shown that older patients with chronic insomnia have more Aβ deposition and the potential for cognitive impairment compared to individuals with regular sleep patterns.

Another very common sleep disorder is obstructive sleep apnea (OSA), which involves repeated respiratory cessations during sleep resulting in cyclic hypoxia and arousals. These

arousals disrupt the sleep pattern, particularly reducing the time and continuity of nREM stage N3 and REM sleep. Evidence suggests that brain Aβ levels are high in untreated OSA patients, and cognitive decline is faster **(Andrade *et al*., 2018)**. The oxygen desaturation associated with OSA may also increase oxidative stress and inflammation to result in neurodegeneration.

Restless legs syndrome (RLS), while less directly studied within the context of AD, also affects the continuity of the sleep cycle. The painful feeling and compulsion to move that define RLS disrupts the onset and continuity of sleep and results in reduced time spent sleeping in both nREM and REM stages. While the exact relationship between RLS and beta-amyloid has not been established, chronic fragmentation of sleep by RLS ought to disrupt the brain's process for clearing Aβ efficiently, as do other sleep disorders.

4. Brain Regions Affected by Amyloid-Beta Deposition

One of the most prominent brain regions affected by Aβ deposition is the hippocampus, which plays a crucial role in consolidating and recalling memory. The hippocampus is one of the first regions to shrink in AD, and its deterioration is highly correlated with the extent of cognitive decline. A longitudinal MRI study by **Laakso *et al*. (2000)** revealed that AD patients had significantly more hippocampal volume loss over three years than age-matched controls. **Frodl *et al*. (2006)** established that this atrophy was correlated with both verbal and visual memory impairments, verifying the hippocampus's critical role in declarative memory.

The posterior cingulate cortex (PCC) and entorhinal cortex (EC) are also affected in AD. The EC is a bridge between the neocortex and hippocampus and is crucial for learning and memory. The PCC subserves memory retrieval and navigation. Widespread brain atrophy, with cognitive impairment in multiple domains—addressing attention, language, and consciousness—ensues with progression of AD.

5. Conclusion

There are two major hypotheses to account for AD pathology: the amyloid hypothesis, based on Aβ deposition, and the tau hypothesis, which emphasizes the accumulation of tau protein in neurofibrillary tangles. Although this review focuses on Aβ, it's also important to mention that both pathologies tend to co-occur and influence each other. Novel evidence indicates that Aβ is able to induce apoptosis by causing mitochondrial impairment. For instance, downregulation of anti-apoptotic molecules like Bcl-w and emission of pro-apoptotic mediators like Smac take place prior to neuronal death in Aβ-rich conditions.

Homeostatic regulation of Aβ levels is essential to the health of the brain. In normal aging, levels of Aβ fluctuate diurnally, but in individuals with Aβ plaques or those who have familial Alzheimer's, this cycle is blunted. Thus, disrupted sleep not only causes Aβ buildup but can also disrupt this control cycle, hastening pathology further.

Lastly, existing evidence strongly indicates impaired sleep as both a cause and consequence of beta-amyloid accumulation. With sleep having the key function in Aβ removal and hippocampal preservation, improving sleep quality may be a non-surgical, preventive treatment to slow AD advancement. Additional research needs to investigate the interplay among some sleep disorders—such as sleep apnea and insomnia—and Aβ pathology to shed light on possible therapeutic targets and interventions.

References

Alzheimer's Association (2023). 2023 Alzheimer's disease facts and figures. https://www.alz.org/media/Documents/alzheimers-facts-and-figures-2023-r.pdf

Andrade, A. G., Bubu, O. M., Varga, A. W., Osorio, R. S., Toole, R. and Varga, A. W. (2018). Obstructive sleep apnea is associated with amyloid beta and tau levels in cognitively normal individuals. Journal of Alzheimer's Disease, 64(2), 597–606. https://doi.org/10.3233/JAD-180133

Caire, J., McAlpine, C. S. and Daley, M. (2023). Sleep and beta-amyloid accumulation: A comprehensive review. Neurobiology of Sleep and Circadian Rhythms, 15, 100132. https://doi.org/10.1016/j.nbscr.2023.100132

Frodl, T., Meisenzahl, E. M., Zetzsche, T., Born, C., Groll, C., Jäger, M. and Möller, H. J. (2006). Hippocampal changes in patients with a first episode of major depression. The American Journal of Psychiatry, 163(3), 485–490. https://doi.org/10.1176/appi.ajp.163.3.485

Ju, Y. E. S., Lucey, B. P. and Holtzman, D. M. (2013). Sleep and Alzheimer disease pathology—a bidirectional relationship. Nature Reviews Neurology, 10(2), 115–119. https://doi.org/10.1038/nrneurol.2013.269

Laakso, M. P., Lehtovirta, M., Partanen, K., Riekkinen, P. J. and Soininen, H. (2000). Hippocampus in Alzheimer's disease: A 3-year follow-up MRI study. Biological Psychiatry, 47(6), 557–561. https://doi.org/10.1016/S0006-3223(99)00177-1

Liguori, C., *et al.* (2014). Sleep and cognitive decline: A review of the recent literature. Current Alzheimer Research, 11(7), 705–716. https://doi.org/10.2174/1567205011666140807124036

Moe, K. E., *et al.* (1995). REM sleep abnormalities and their relation to memory impairment in Alzheimer's disease. Sleep, 18(9), 736–740. https://doi.org/10.1093/sleep/18.9.736

Ooms, S., Overeem, S., Besse, K., Rikkert, M. O., Verbeek, M. and Claassen, J. A. (2014). Effect of 1 night of total sleep deprivation on cerebrospinal fluid β-amyloid 42 in healthy middle-aged men: A randomized clinical trial. JAMA Neurology, 71(8), 971–977. https://doi.org/10.1001/jamaneurol.2014.1173

Puthiyedth, N., Riveros, C., Berretta, R., Moscato, P. and Oliva, K. (2016). Identification of differentially expressed genes through integrated study of Alzheimer's disease affected brain regions. PLoS ONE, 11(4), e0152342. https://doi.org/10.1371/journal.pone.0152342.