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Insomnia: A risk factor for Alzheimer's disease?

by

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The cover was created with Midjourney.com. The added image of the degenerated brain can be found in online form in https://assets.medpagetoday.net/media/images/97xxx/97034.jpg?width=0.6

Summary

Alzheimer's disease imposes harmful effects on nearly half of the population, with sleep disturbances such as insomnia being a common repercussion. Recently, attention has shifted towards the potential of sleep disturbances serving as a predisposing factor for the onset of Alzheimer's disease. Consequently, this thesis will concentrate on insomnia as a potential risk factor for Alzheimer's disease, rather than simply a symptom. Findings indicate a link between the two conditions, characterized by a decrease in slow-wave sleep duration and amplitude in insomnia patients, leading to elevated levels of Amyloid-beta. The thesis also explores disturbed glymphatic clearance as a potential mechanism underlying this increase. In conclusion, research suggests that Slow Wave Sleep (SWS) could potentially serve as a biomarker for early detection of Amyloid-beta accumulation. This insight could pave the way for alternative, non-invasive treatments targeting SWS enhancement.

Introduction

Dementia is a term used to describe neurodegenerative diseases that affect behavioral and cognitive aspects of one's life. Dementia is currently the seventh leading cause of death worldwide (figure 1) (58). Globally the impact of the disease is traced back to the 55 million individuals currently living with some form of dementia (58). With the expected life expectancy on the rise, this number is expected to triple by 2050, reaching 125 million individuals living with dementia (15) Alzheimer's disease (AD) contributes to 60-70% of the dementia cases (58), making it the most common type of dementia (59).

AD is a multifactorial disease with the causes of its pathogenesis still not fully known. One of the most supported hypotheses is the amyloid-beta hypothesis (as reviewed by (14), which states that the accumulation of the amyloid beta (Aβ) protein is the initiating event of the neurodegeneration seen in AD (14). Aβ is a cleavage product of the protein APP (18). If Aβ is accumulated it inferes neuronal toxicity (24). Based on the enzymes that cleavage the APP protein there is a variety of peptide residue

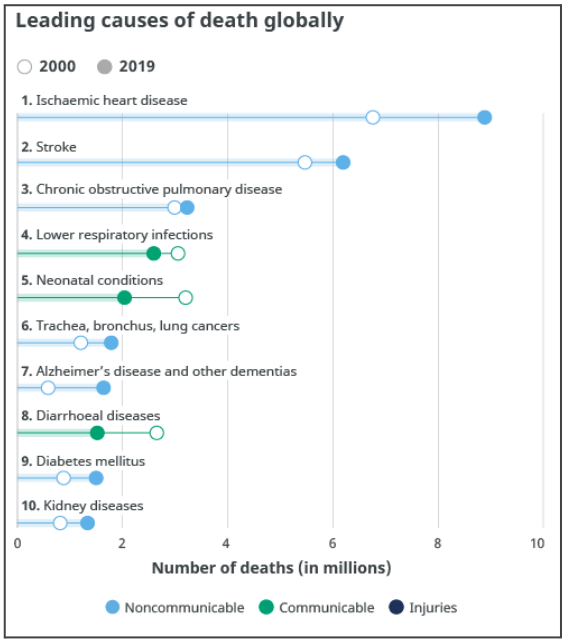

Figure 1. Top 10 leading causes of death worldwide in 2019. Death due to Alzheimer's disease and other dementias are ranked 7th. Source: WHO Global Health Estimates.

ranges that can be produced (as reviewed by (57). Specifically, the simultaneous cleavage of APP by b secretase and g secretase results in small residue molecules of Aβ that are prone to segregate (figure 2A) (as reviewed by (57). This eventually leads to the formation of amyloid oligomers which infer toxicity to the brain.

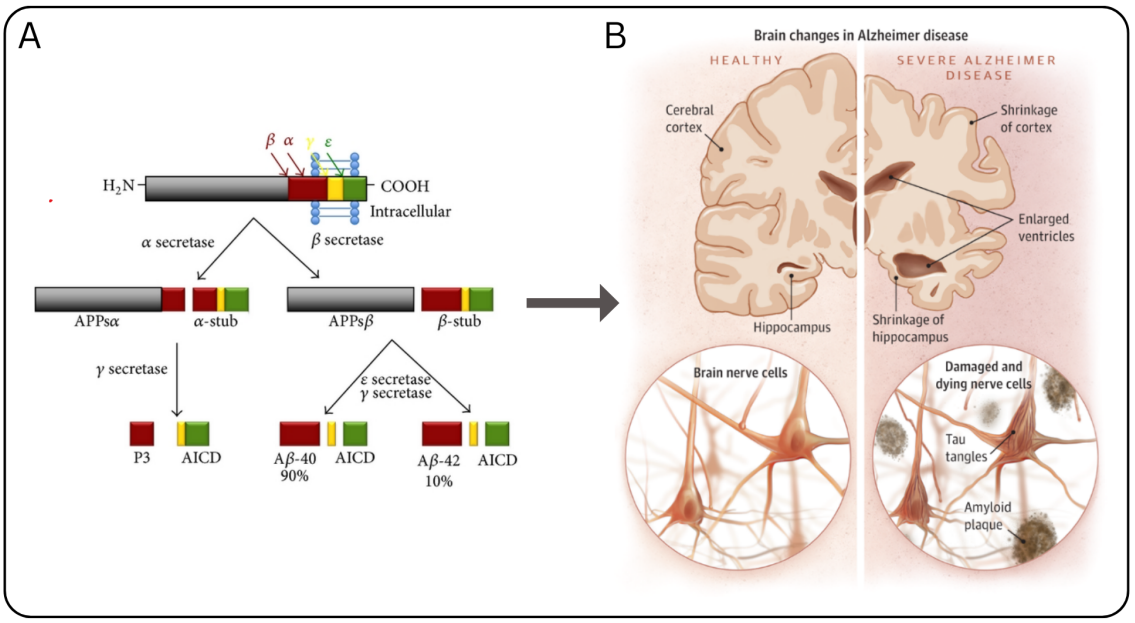

Figure 2. **A**. Amyloid Precursor Protein (APP) protein processing through the cleavage of the beta-site AβPP-cleaving enzyme (BACE1), followed by presenilin-1 (PS1). The production of the toxic Amyloid-beta (Aβ) peptide types, Aβ1-40 and Aβ1-42, occurs through the sequential cleavage of the APP by beta and gamma-secretases. *Source*: Mokhtar et al (2013), ''The Beta-Amyloid Protein of Alzheimer's Disease: Communication Breakdown by Modifying the Neuronal Cytoskeleton''. **B** Illustrative representation of a healthy (left) and a diseased Alzheimer's brain (AD) (right). The presence of Amyloid plaques in the AD brain is visible on the left along with the depiction of another hallmark of AD , the neurofibrillary tangles (not discussed here). Further features of an AD brain contain, the shrinkage of the hippocampus, the enlarged ventricles and the overall shrinkage of the cortex. *Source*: Boersma, M. (2018), ''Spectroscopic Techniques for Amyloid Plaques and Tau Tangles Observed in Dementia and Alzheimer' s Disease''.

Residues Aβ40 and Aβ42 are the ones most highly related to AD pathogenesis (figure 2A) (3).

A significant hurdle in the early treatment of AD is the premature formation of oligomers, years prior to the observable cognitive deterioration (12). This makes their early detection notably challenging. By the time AD is eventually diagnosed, neurodegeneration has already taken place (12). One of the prevalent characteristics at this stage is the presence of amyloid plaques, the end products of Aβ segregation (12) (figure 2B).

AD is predominantly observed in the elderly and is commonly known as a disease of aging (46) . Sleep architecture alterations associated with aging are increasingly being considered as a risk factor in the pathogenesis of AD. Particularly, the elderly spent less and less time in the sleep duration, sleep restoration and sleep onset (5, 13)

These behavioral manifestations are due to clinical changes regarding non-rapid eye movement sleep (NREM) and slow wave sleep (SWS). There is a noted reduced time elderly individuals spend in the deeper sleep stage of sleep NREM stage N3 contradicted by increased time spent in the lighter phases of NREM stages N1 and N2 (39). It is believed that alteration in part in the sleep spindle's frequency and density along with the changes seen in slow wave activity contribute to the difficulty experienced by the elderly in maintaining sleep during the lighter NREM stages (28) Such sleep disruption is often associated with AD symptomatology and cognitive impairment (30).

Indeed, sleep architecture alterations are even more prominent in patients affected by the prodromal phase of AD, mild cognitive impairment and also in AD patients (as reviewed by (35). Specifically, a range of 8.8 to 45.5% of MCI patients suffer from sleep disturbances (31). Additionally, 25% to 60% (19) of AD patients suffer much more frequently with sleep problems than cognitively normal individuals (52). One of the most common sleep disturbances associated with MCI and AD is insomnia (4, 19, 45)

Insomnia is characterized as the second most common sleep disorder. Insomnia's prevalence, like AD's, is significantly higher in older individual's than insomnia prevalence in younger individuals (as reviewed by (43). Specifically, it is seen in 30-48% of the elderly (10, 40) in contrast to the 12-20% of the younger population (50). Chronic insomnia has been linked to an increased risk of developing AD later in life. individuals with insomnia are in general more likely to have cognitive impairments(17, 9) and are at a higher risk of developing AD (20).

Sleep disturbances in AD have long been mainly considered as part of its symptomatology. However, in recent years the bidirectional relationship between sleep and Alzheimer's disease is increasingly explored. Following that notion, in this review, I aim to explore the extent of the relationship of insomnia disorder as a risk factor for Alzheimer's disease. Modifying sleep quality could then potentially be an easily accessible method of delaying the onset of AD. Thus, further exploring their relationship is of the utmost importance. By critically evaluating the current literature, this review seeks to shed light on the potential use of insomnia as a biomarker for the early detection of AD and identify potential therapeutic or preventative interventions for this prominent disease.

Exploring the Association Between Sleep Disturbances and Amyloid Accumulation in Alzheimer's Disease Progression

As alluded to earlier, a decrease in slow-wave sleep is a common occurrence with aging. However, this reduction is markedly more pronounced in AD and the precursory phase of Mild Cognitive Impairment (MCI) (as reviewed by (35). An increasing amount of studies suggest the potential association between SWS and Aβ accumulation seen in AD. Indeed, Winer et al, showcased this association indicating the effect of reduction of SWA below 1Hz in predicting long term Aβ accumulation (54). Interestingly this is a drastic effect, with only one night of disturbed sleep efficiency linked to the initiation of Aβ accumulation.

The accumulation of Aβ due to sleep disturbances appears to start before the onset of clinical symptoms of AD. Reportedly, individuals that are considered cognitively healthy, but with noted sleep disturbances, have accumulated Aβ protein. Specifically, cognitively healthy individuals with reduced SWS duration were linked to increased Aβ42 levels (53) (figure 3). Aβ production is hypothesized to be neuronal activity dependent with diurnal activity. Its levels are believed to decrease at night during SWS where neuronal activity is low (53). Thus a disturbed SWS can be the reason behind such elevated levels.

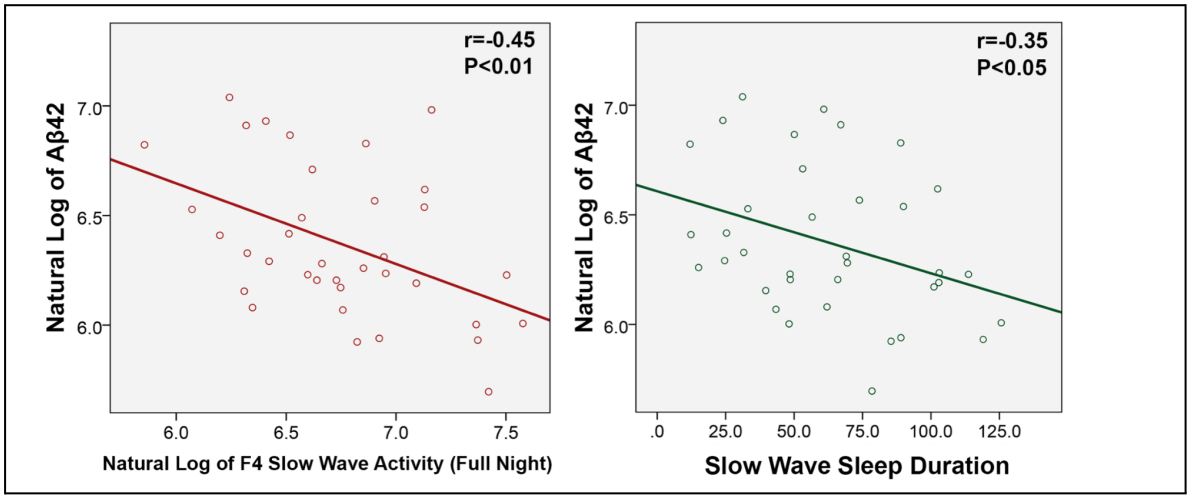

Figure 3. Correlation between CSF Ab42 and SWS duration in cognitively healthy elderly. In the figure the inverse correlation between slow wave duration and the increase in CSF Ab42 is depicted. Source: Varga et al. (2016), "Reduced Slow-Wave Sleep Is Associated with High Cerebrospinal Fluid Aβ42 Levels in Cognitively Normal Elderly"

The preliminary association between sleep disturbances and the onset of cognitive decline is further highlighted by studies involving individuals diagnosed with MCI. MCI refers to the slight changes in cognitive abilities seen in individuals that do not interfere with daily life or independent function (44). MCI is considered as an intermediate stage between healthy aging and dementia (44). In their research, Carnicelli and team delved into the disparities in sleep patterns between two groups: individuals initially identified with amnestic Mild Cognitive Impairment (MCI), and a control group of healthy senior citizens. After a period of two years, the subjects were classified as either amnestic MCI converters, indicating a likely AD onset, or non-converters (6). Even though the study was with a limited sample size, the researchers did observe that MCI converters presented with a significant reduction in A1 phase and A3 phase of the cyclic alternating pattern which is shown to take part in SWS build up and maintenance (6). It is thus suggested that SWS disturbances commences to differences in Aβ accumulation and subsequent cognitive declines prior to the emergence of clinically noticeable AD symptoms.

Adding to the evidence regarding sleep disturbances and the presence of AD, in their recent meta analysis Zhang et al, examined potential variables that might modulate the alterations seen in Polysomnography (PSG) outcomes when contrasting patients with AD and healthy individuals (56). Specifically, AD patients were found to have a decreased total sleep time sleep efficiency, SWS and REM sleep percentage and increased number of awakenings in comparison to the healthy control groups. Consequently making SWS duration and amplitude a probable biomarker for Aβ detection.

In this section, the correlation is shown between the decrease in slow-wave sleep duration and the hallmarks of AD; cognitive decline and Aβ accumulation. Insomnia, affecting 50% of Alzheimer patients, has traditionally been viewed as a byproduct of the disease. Given the discussed link between slow-wave activity and amyloid buildup, coupled with the observed alterations in sleep architecture in MCI, it becomes plausible to consider insomnia not merely as a result, but potentially as a contributing factor to the disease as well.

Insomnia and Alzheimer's Disease: Delving into the Role of Slow Wave Sleep Disruptions

Longitudinal studies have been conducted on individuals suffering from insomnia disorder to assess their possible heightened susceptibility to AD. According to (8, 9, 41), these studies have found that people with insomnia disorder are more likely to experience AD or cognitive decline than those without the disorder. The research suggests that there may be a connection between insomnia disorder and impaired cognitive function (9). These findings are noteworthy as they indicate distinct performance issues when evaluating declarative memory. Particularly, participants over the age of seventy one who are suffering from insomnia exhibit pronounced memory impairment (9) Memory impairments is one of the main domain impaired in the pathophysiology of AD (34), thus suggesting the predisposing risk of insomnia.

Furthermore, Chen and his team (2018) evaluated the Cerebrospinal Fluid (CSF) Aβ levels in twenty three patients suffering from chronic insomnia, aiming to instigate the possible impacts of persistent sleep deprivation on AD pathogenesis (20). Their findings revealed a notable increase in CSF Aβ42 levels among patients with insomnia. The heightened susceptibility to AD was further explored in a study conducted by Hung and their team (20). The researchers examined the predisposing risk that primary insomnia patients had in converting to AD patients. In a follow-up study with Taiwanese insomnia patients, it was found that there was a 2.14 fold increased risk of developing dementia (20). Overall, these findings suggest the connection between primary insomnia and pathophysiological characteristics of AD.

Reduced SWS appears to be a major factor behind such correlation. Baglioni and colleagues were one of the first studies to mention the sleep architecture changes seen in elderly individuals with primary insomnia (2). Polysomnographic assessments revealed that the primary insomnia-affected elderly had a shortened sleep duration and an altered sleep architecture (2) (Table 1). Specifically, they were found to sleep 23 minutes less in total and took 6 minutes more to fall asleep than healthy counterparts (2). The changes in their sleep architecture were highlighted by a reduction in duration of SWS and reduced duration of REM sleep, accounting for 600 minutes and 300 minutes monthly respectively (2). Microscopic changes related to the duration of the SWS could thus be suspected of being the risk factor for AD pathogenesis. In a study by Tao et al, the researchers set out to analyze the differences in polysomnographic profiles over one thousand older individuals that suffer from insomnia (age range 55-80) (51). Findings reveal that the main differences between individuals that during the follow up presented with AD are reduced duration of SWS, decrease in density of sleep spindles and reduction in EEG power in waves associated with those stages. Consequently adding to the notion that SWS reduction predisposes an individual to AD (51).

The aforementioned evidence points towards a potential risk factor for AD, specifically the alterations in SWS tied to insomnia disorder. However, the underlying mechanisms regarding this possible association remain to be fully elucidated. In the ensuing section, I will delve into one possible mechanism that might connect reduced slow-wave sleep, a symptom associated with insomnia, to an elevated risk for AD.

The connection between Insomnia and Alzheimer's disease enhanced risk: Underlying mechanisms.

With the association between SWS reduction in insomnia and predisposition to AD, the question arises about the mechanism underlying such an effect. Sleep and glymphatic clearance interaction is the first pillar of such a system.During SWS, the brain undergoes glymphatic clearance which involves the removal of waste products, including Aβ protein, from the brain (22, 21, 23). The glymphatic clearance system in the last year has been reported as having a significant role in the clearance of Aβ from the brain (33). It acts in line with the lymphatic system in order to clear toxic metabolites. This is achieved by the use of convective flow that allows the exchange between cerebrospinal fluid that enters the arteries and the interstitial fluid that exits (33). Reports support the notion that this system is responsible for clearing 65% of Aβ protein of the brain (5). In recent decades, studies further support the contributing role of sleep in the clearance system. Sleep is reported to maintain homeostasis in the brain and it causes an increase of 60% in the ISF which further increases the convective exchanges of CSF with ISF thus increasing the toxic product removal (55) (figure 4). Hence, sleep is considered to have the restorative function due to this increased clearance effect (55).

Disrupted slow wave activity inhibits the function of the glymphatic clearance system which eventually leads to the accumulation of Aβ protein in the brain (48). Both human and animal studies report that SWS disruption leads to the increase of Aβ in the brain. In animal studies sleep deprivation enforced in mice lead to augmented soluble Aβ and subsequently increased the deposition of

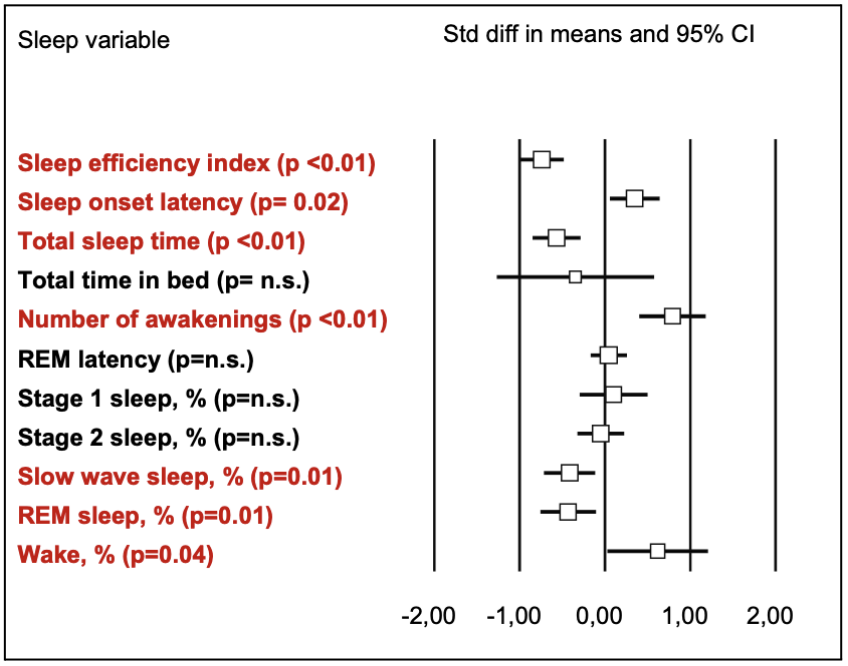

Table 1. Polysomnographic traits of patients diagnosed with primary insomnia in comparison to healthy sleep age matched individuals. Std diff, standardized difference; CI, confidence interval. Adapted from: Baglioni et al. (2014), ''Sleep changes in the disorder of insomnia: A meta-analysis of polysomnographic studies''.

Aβ (49). Further studies in humans who had a reported SWS amplitude of less than 1Hz further suggest the interaction between reduced slow wave amplitude and the impairment of glymphatic clearance (54).

The relationship between disrupted SWS and Aβ related glymphatic clearance becomes important in regards to the risk

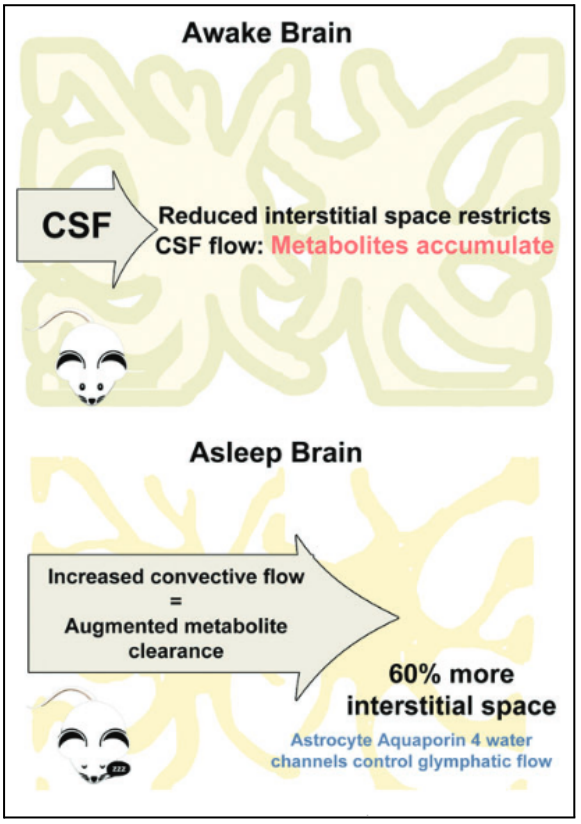

Figure 4. Sleep induced augmentation in the glymphatic flow through the increase in interstitial space. (Top) During awake hours, the brain interstitial space is minimized leading to a reduction in cerebrospinal fluid (CSF) flow. This then leads to the accumulation of metabolites such as Ab protein. (Bottom) During sleep there is an increase in convective flow which increases metabolite clearance. Source www.liebertpub.com/rej

that insomnia infers for cognitive impairments and AD. According to Chen and their team, insomnia similar to wakefulness may induce the dislocation of Aβ metabolism in the brain, leading to an increase in cerebrospinal fluid Aβ situations. This may involve an imbalance between Aβ product and concurrence due to disintegrated metabolism (7). The study found that there was an advanced concurrence rate of Aβ during sleep in comparison with the awake status, which suggests that sleep plays an important part in the concurrence of Aβ from the brain (7). Thus, habitual sleep diseases such as insomnia may disrupt this concurrence process and contribute to the accumulation of Aβ in the brain, which is a major pathological agent in AD (7).

Therefore, it can be concluded that the way that insomnia leads to increased risk of Alzheimer's is through the inhibition of clearance due to the disruption of SWS over time (figure 5). These findings suggest that perfecting sleep quality may be an important factor in precluding or decelerating down the progression of Alzheimer's complaint.

Potential Non-invasive treatment interventions.

Restoring SWS on insomnia patients could potentially be a potential non-invasive intervention for AD predisposition.

The involvement of SWS in AD makes enhancement of SWS a promising non intrusive technique for the treatment of AD. There are already certain treatment options explored which target SWS enhancement for AD treatment. Auditory stimulation, transcranial magnetic stimulation, and transcranial direct current stimulation being explored for their potential to the reversal of Aβ accumulation. Transcranial magnetic

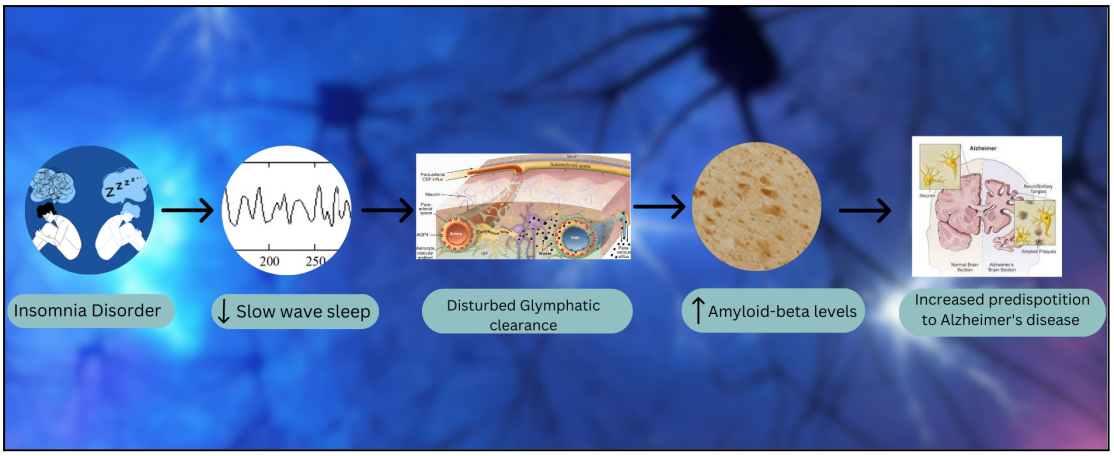

Figure 5. Graphical abstract of the thesis proposed underlying mechanism leading to increased predisposition for Alzheimer's disease as noted in insomnia patients. The effect of reduced SWS on the disruption to the glymphatic clearance are instigated as being the reason behind such effect.
Sources: (images from left to right)
1. Available from: thiswayup.org.au, '' Chasing the Dream: Do I treat my insomnia or Anxiety first?'' **2**. Available from: https://www.researchgate.net/figure/Processed-sleep-EEG-of-awake-slow-save-sleep-and-REM_fig1_247919335 . 3. Available from: Kylkilahti et al. (2021), ''Achieving brain clearance and preventing neurodegenerative diseases—A glymphatic perspective''. **4**. Available from:Available from: https://www.researchgate.net/figure/The-neuronal-Ab40-level-does-not-increase-in-the-brain-of-rhesus-monkeys-with-aging-a_fig3_308348369. **5**. Available from: stanfordhealthcare.org,'' Alzheimer's disease''.

stimulation (TMS) was performed in individuals diagnosed with MCI and led to an improved slow wave power and also improved memory performance (27). TMS has been shown to increase swa power in healthy individuals (32). Another promising method to enhance SWA is through performance of Closed Loop Acoustic Stimulation when SWS is going on (29, 37, 42). It has promising results in improving memory retention and encoding capacity in both MCI and AD patients (29, 37, 42). Even though there is no information present of whether they infer Aβ accumulation reduction, these methods have the potential of inhibiting cognitive decline in a non-invasive way. Improving SWS sleep could potentially lead to restoring the physiological glymphatic clearance of Aβ in patients already which potentially leads to less neurodegeneration.

Animal research provides preliminary evidence of a possible restoration of Aβ levels through manipulation of SWS. Optogenetic excitation of cortical neurons influences slow oscillation activity and halts the formation of Aβ plaques that leads to a reduction of Aβ concentration (25). Recently Ogbeide-Latario et al modeled SWS enhancement in adult mice providing the base to further explore such enhancement techniques and the underlying mechanism by which they could work (38). Thus, measures directed at regulating slow oscillatory activity in patients diagnosed with AD could potentially stave off the onset of neurodegenerative features and hinder the forward march of the disease (25).

Discussion

In this analysis, I delved into the role of insomnia disorder as a potential catalyst for an elevated risk of AD. The proposed linkage between the two conditions appears to be the disturbance of slow-wave sleep, leading to an accumulation of Aβ.

Both AD and insomnia disorder are complicated disorders with various possible underlying mechanisms.

Accordingly the mechanism discussed here is only a small part of the equation. Accumulation of Aβ is hypothesized to be the initiating event of pathogenesis (as reviewed by (14). However, insomnia has an effect on further aspects of brain function that can lead to development of AD. For instance, insomnia also has a postulated effect on tau protein levels, the other hallmark of AD. Tau protein is a microtubule-linke protein found in neuronal cells (16). Hyperphosphorylation of the tau protein leads to its detachment from the microtubules leading to dysregulated neuronal cytoskeleton morphology (1) and eventually cell death. Multiple studies have investigated the effect of sleep deprivation in mice in regards to the levels of tau protein (11, 47). The results indicate that sleep deprivation leads to a significant increase in insoluble tau protein levels. Thus, the enhancement of aspects of sleep architecture in insomnia patients can be beneficial for the prevention of AD from both the perspective of Aβ accumulation and tau hyperphosphorylation.

Interestingly, the importance of slow oscillations in the progress of neurodegeneration seen in AD is furthermore supported by the suggested action of NREM in memory consolidation (reviewed by 26). NREM sleep and in particular its components sleep spindles (seen in stage N2) and slow waves (seen in stage N3) have been shown to play a significant role in memory consolidation (26). The theory of active systems consolidation regards long term memory formation in relation to hippocampus dependent episodic memory during sleep (36). It focuses on the importance of neuronal replay in memory consolidation. During sleep memories encoded in the hippocampus are reactivated and through propagation throughout the entire memory network they are strengthened thus facilitating long term memory formation (26). Oscillations occurring during SWS such as slow oscillations, spindles and ripples all contribute to the memory enhancing effect seen in sleep (26). Long term declarative consolidation is one of the first memory impairments to happen in AD patients. Impaired SWS seen in insomnia patients could potentially be leading to an early disturbed declarative memory consolidation.

Non-invasive interventions are promising of halting the neurodegeneration associated with the reduced duration of SWS. However, up to this date there are no studies specifically enforcing auditory stimulation, transcranial magnetic stimulation and transcranial direct current stimulation in insomnia patients. Developing such studies and exploring whether there is a longitudinal effect on the halt of neurodegeneration and clearance of Aβ accumulation, will be central in developing the best possible treatment in eliminating insomnia’s AD associated elevated risk.

In conclusion, Slow Wave Sleep (SWS) appears to be intricately involved in the accumulation of Amyloid-beta (Aβ). As SWS disturbances occur early in the pathogenesis of Alzheimer's disease, it provides an opportunity not only to employ SWS as a biomarker for Aβ detection but also to explore it as an alternative therapeutic strategy.

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