Review Article

The Interplay between Disordered Sleep and Alzheimer's Disease: Exploring the Bidirectional Relationship

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ABSTRACT

The debilitating neurodegenerative condition referred to as Alzheimer's Disease (AD), results in severe cognitive deterioration, including deficits in memory, confusion, and abnormal behaviour. Sleep plays a crucial role in sustaining cognitive health, as it supports brain repair and performs memory consolidation. Complaints of consistently disrupted sleeping habits, such as reduced quality and fragmented sleep, are increasingly recognized as potential risk factors for AD. The fundamental elements of healthy sleep: its structure, oscillations and benefits- then considering how changes in sleep architecture, including alterations in REM and NREM stages, are associated with cognitive decline. Another significant concept is the finding that sleep deprivation is often correlated with increased levels of amyloid beta (Aβ) and tau proteins in the brain, which are two biomarkers of AD pathology and accumulate with disease progression. This review examines the connection between unhealthy sleep patterns during aging and AD development, emphasizing the need for continued research into how improving sleep hygiene could potentially moderate the effects of cognitive deterioration.

Keywords: Alzheimer's Disease, Sleep, Amyloid-beta, Tau, Circadian rhythm, Sleep disruption, Sleep/wake cycle

INTRODUCTION

Alzheimer's disease (AD) is a gradual neurodegenerative disorder characterized by the occurrence of neurofibrillary amyloid plaques and hyperphosphorylated tau tangles that results in gradual dementia, memory loss, cognitive impairment, sleep disturbances, and other behavioral deviations (1). AD accounts for more than 75% of all dementia cases and is credited as the sixth leading cause of death in the world, the field has recognized the necessity for growing research on potential risk indicators, lifestyle contributors, and environmental factors associated with Alzheimer's pathogenesis (1). Research has begun examining the bidirectional relationship between the individual's lifestyle choices and AD pathology (2). Much like how increased levels of physical activity promote proper cardiovascular health, and a balanced dietary regime aids with digestive health, our body is dependent on the quality and quantity of sleep for sustainable cognitive function. The restorative powers and

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Received September 30, 2024**; Accepted** November 8, 2024
https://doi.org/10.70251/HYJR2348.245160

complex benefits of sleep play a notable role in cognitive health and ability, as research shows this restorative state allows the body to repair the cellular elements that become depleted throughout the day (3). Research has uncovered much about the phenomena that occur in sleep, proving that adequate, consistent sleep allows for improved cognitive performance, memory processing, and hormone regulation (4). Therefore, inconsistent or fragmented sleep, which is a physiological hallmark associated with normal aging, has been proposed as a potential risk factor for cognitive decline and related neurological diseases (5).As we progress into older adulthood, both the macro-level architecture of sleep, such as sleep cycle duration, and the micro-level structure, including the quantity and quality of sleep oscillations, become abnormal (Figure 1) (6). It is also relevant to note that the age-related decline in quality and quantity of the distinctive sleep cycles, rapid eye movement (REM) and non-rapid eye movement slow wave sleep (NREM SWS), is associated with increased reports of sleep fragmentation, easy arousal, and difficulty with sleep maintenance (7). As sleep consolidation breaks down with normal aging, these changes may be part of what makes aging a risk factor for disorders like AD, where progressive memory impairment and accumulation of Aβ plaques are prominent (1). In support of these findings, there is mounting evidence of a bidirectional relationship between sleep disturbances and AD pathology where the sleep-wake cycle becomes disturbed (8). This is important as extracellular Aβ, a hallmark of AD, in brain interstitial fluid (ISF) as well as cerebrospinal fluid (CSF) fluctuates diurnally: soluble Aβ levels increase during wakefulness and decrease during sleep (8). Severe sleep deprivation in humans increases soluble Aβ in CSF by 25–30% due to increased overnight Aβ production relative to sleeping

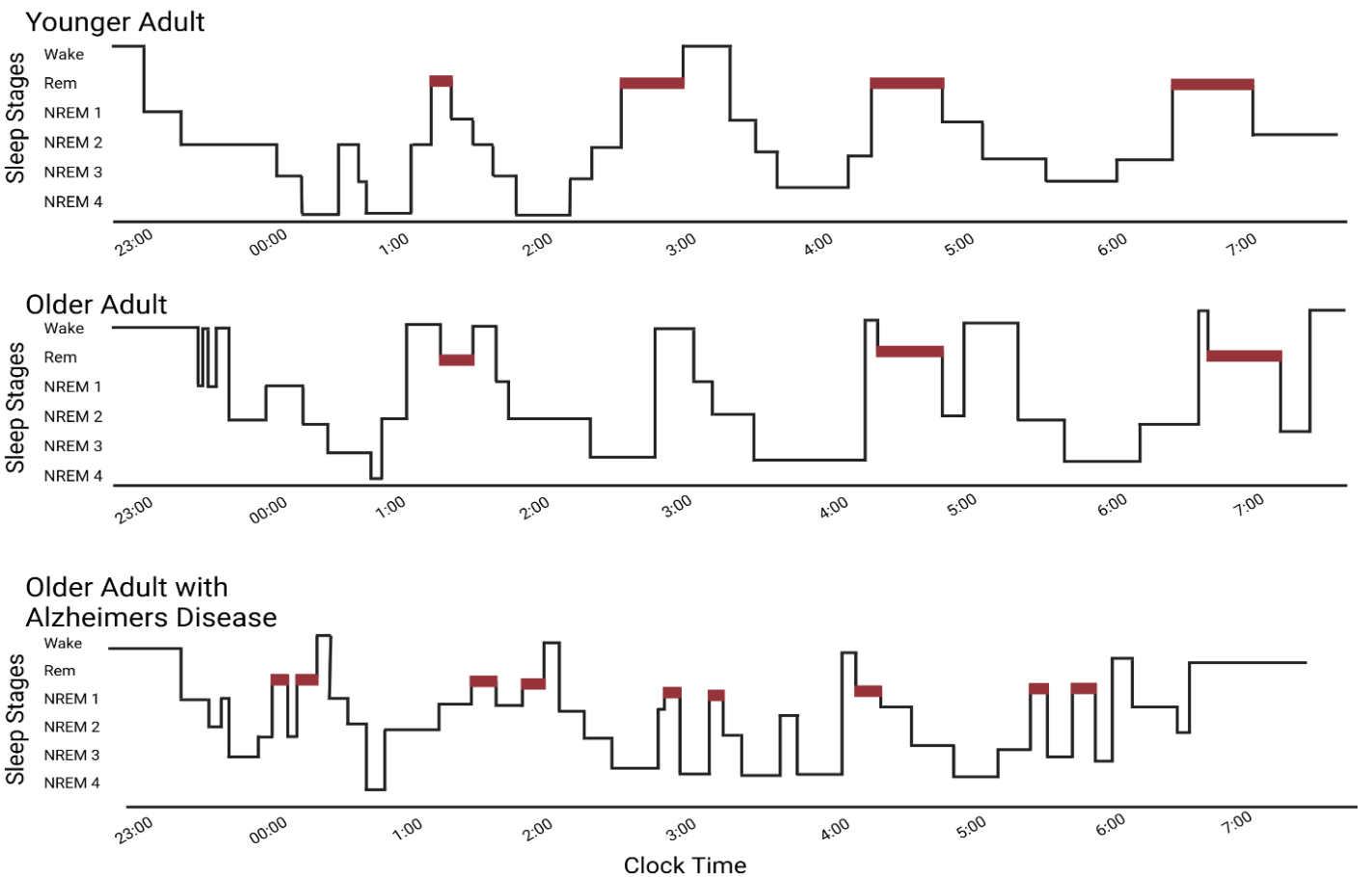

Figure 1. Comparative schematic of changes in sleep architecture when effected by age and/or disease. Visual representation of sleep cycles throughout an 8hr time frame in a younger adult (A), an older adult (B), and an older adult with AD (C). The red bars indicate periods of REM sleep and their duration. This figure is an abbreviation of figure 1A as seen in Sleep and Human Aging (dpl6hyzg28thp.cloudfront.net).

controls (9). Furthermore, sleep deprivation raises levels of tau protein in mouse brain ISF and human CSF, and persistent sleep deprivation accelerates the spreading of tau masses in certain brain networks (10). Moreover, disturbed sleep is not only a manifestation of AD but also contributes to disease development and cognitive deterioration as approximately 25–66% of AD patients complain of worsening fragmented or mistimed sleeping patterns (11). This review will delve into how these sleep disturbances, particularly the alterations in REM sleep, brain oscillations, and body movements, define and characterize each sleep stage. Additionally, we highlight the importance of sleep for proper cognitive function while defining the functional consequences, risks of disease, and contributing factors to age-related sleeping disorders. Lastly, we will uncover how sleep inconsistencies intertwine with AD pathology and progression, examining the ways in which disrupted sleep may accelerate cognitive decline and worsen the disease's impact.

SLEEP ARCHITECTURE

A proper sleep cycle is characterized by a rhythmic, periodic process that alternates between three stages of NREM sleep and a fourth stage of REM sleep (12). This is known as sleep architecture, and when it is disrupted, the full restorative benefits of sleep cannot be obtained (12). Each full night's sleep and phase of sleep is unique with variations in muscle tone, brain wave patterns, and eye movements; every stage builds upon one another to deepen an individual's sleep, slow down brain oscillation frequencies, and begin repair of the body (12). The four stages are cycled through approximately four to six times per night, with an average cycle lasting ninety minutes (13). As one begins to doze off, our bodies shift into the first stage of sleep, which occurs when one's eyes are closed, and interruption is easy. It is commonly known as the 'entry' level to sleep and generally occupies around 5% of a full night's sleep or about 1 to 7 minutes in the initial cycle (14). Cerebral function in stage 1 transitions from a state of wakefulness, marked by consistent high frequencies alpha waves, to low-voltage, mixed-frequency waves. As the night progresses, we undergo our first cycle of stage 2, which can be explained as a slightly deeper sleep that occurs when eye movement is limited, heart rate slows, and body temperature declines (15). This stage of sleep accounts for around 50% of a night's sleep and is represented by sleep spindles and k-complexes, which are believed to play important roles for memory consolidation and our nightlong learning process (15). Observational studies suggest that individuals who learn a new activity have a much larger density of these sleep spindles than those in a control group (12). Moving through to stage 3 sleep, also known as deep sleep, slow wave or delta sleep, which involves high amplitude slow waves and endures throughout the first half of the night (14). Typically, this phase will occupy 20–25% of the night or last 20 to 50 minutes per cycle (16). Deep sleep, the final stage of NREM sleep, is crucial for the body's nighttime repair and system strengthening. During this phase, your heartbeat and breathing slow to their lowest levels, your muscles are fully relaxed, and brain waves become notably slower, making arousal difficult. This profound state of rest is essential for physical restoration and cognitive health. Understanding these sleep characteristics not only highlights their importance for overall well-being but also offers insights into how disturbances in these stages might impact conditions such as AD, where impaired sleep patterns can impair cognitive function (3).

CLASSIFICATION OF REM AND NREM

Sleep is commonly discussed and classified by 4 distinct stages, additionally sleep is characterized in terms of REM and NREM sleep. Both sleep phases are essential for maintaining cognitive function, the ability to repair cells, and an individual's overall health. Following the change of state from wakefulness to sleep, we enter the first of three sublevels of NREM sleep: a state of slow eye / body movements, heart rate and breathing (16). The NREM stages can also be classified by sleep spindles and K-complexes – both short bursts of brain activity that help repress the influence of external stimuli and contribute to memory consolidation (16). REM sleep is described in a very different manner. The REM stage of the circadian cycle takes place after stage 3 and takes up roughly 20% of a standard sleep cycle (16). REM is credited for its impact on our overnight learning consolidation as this phase of sleep helps solidify information processing in the hippocampal and cortical regions of the brain (16). It is during this period of the night that an increase in protein synthesis and activation of learning-related brain regions, such as the prefrontal cortex, is observed. Furthermore, we can distinguish REM sleep as a state of high brain activity, rapid eye movements, and visual dreaming (16). REM typically occurs 90 minutes after falling asleep, with its first phase lasting 10 minutes and gradually increasing in duration with each cycle that passes (17). This period is distinct from that of NREM as heart and breath rates

frequently quicken, blood flow to the brain increases and an increase in brain metabolism by 20% (18). This escalation of brain activity, sometimes reaching high energy levels then those experienced throughout the day, results in the state of vivid dreaming that is thought to contribute to a substantial portion of memory consolidation (16). To best understand the process of REM sleep, we must be familiar with the small structure located near the centre of the brain, referred to as the thalamus, which acts as a transmit for sensory information to the cerebral cortex (the covering of the brain that decodes and develops information from short-term to long-term memory) (19). During most stages of NREM sleep, this information interpreter becomes quiet, allowing you to tune out your external environment; but during REM sleep, the thalamus is a high-functioning structure – sending the cortex sounds, images, and other sensory information that your dreams are composed of (19). Other important components of the brain, including the brain stem (especially the pons and medulla), are currently active to execute a specific role during REM sleep; they prevent the muscles in your body from physically enacting your dreams (19). It sends out signals to relax muscles critical for body posture and limb movements, which effectively disables your ability to move (i.e. flail your arms and legs around).

BRAIN OSCILLATIONS

Brain oscillations, sometimes referred to as brainwaves, can be thought of as rhythmic or repetitive bursts of electrical activity generated by stimuli in the central nervous system (20). Oscillations are most recorded using an electroencephalogram (EEG), which visually represents the various frequencies of brain oscillations: beta, alpha, theta, and delta (20). In a state of arousal and active engagement in mental activity is the generation of beta waves. These low amplitude, fast-paced waves have a frequency ranging from 14 to 15 cycles per second, or Hertz (Hz) (20). Beta waves are associated with a strongly engaged mind, such as an individual in active conversation, a test taker, or a debater; tasks that require plenty of brain power. The next brainwave classification in order of frequency is alpha, a slower and higher amplitude wave. Alpha waves have a frequency of between 9 and 14 Hz and could be exemplified with an individual completing a task, sitting down, and resting shortly after (20). Theta waves, are characterized as having even slower frequencies and greater amplitudes than both alpha and beta; the range of theta waves is typically between 5 and 8 Hz. Someone who has taken time off from a task and begins to daydream or a person who is driving on a freeway and realizes that they can't recall the last five miles are often in this state (20). The final brainwave class is delta. Delta brainwaves are of the slowest frequency and greatest amplitude among the four different states; they typically center around a range of just 1.5 to 4 Hz (20). From the beginning of the sleep cycle straight to the end, our brains are transitioning and cycling through these four states of brain oscillations. As one attempts to fall asleep, possibly staring at a phone or reading a book, they are likely to be in low beta, the state of high mental activity. When one decides to put the book down, turn off the light, and shut their eyes, they descend from beta brainwaves to alpha, to theta and finally, once asleep, to delta. Once a cycle completes, the order of brainwave frequency once again increases, moving in the opposite direction (20). As the delta deep sleep frequencies transition into the frequency of theta waves, active dreaming as well as REM behind the eyelids occurs (20). When an individual awakens from a restful night – in preparation for waking up, the brainwave stages will increase one last time, ascending from delta all the way through to beta as the sleep cycles ends (20). During this transition phase, it is possible for an individual to hit the snooze button and slowly descend back down to the theta state for an extended period – which allows the free-flowing of ideas and yesterday's memories or to contemplate the activities of the approaching day. This can be an extremely productive and important time for creative mental activity and mental preparation (20).

SLEEP ALTERATION RELATED TO NORMATIVE AGING

Aging causes normal physical changes, noticeably deficits in sleep physiology, including shortened sleep cycle duration, reduced sleep quality, and decreased circadian rhythmicity (6). Although irregular sleeping patterns are commonly associated with normal aging, it is important to understand the neurobiological mechanisms of age-related sleep impairment to best understand the functional consequences that could follow (6). As adults progress into later life, both the macro-level and micro-level architecture of sleep are altered: such as disordered sleep timing, increased sleep fragmentation, easy arousals, shorter and less frequent NREM /REM cycles, and increased time spent awake throughout the night (6). This is not to imply that all individuals experience the same degree of sleep disruption; it can be evident that some older adults exhibit little sleep alteration, while others show dramatic impairment (21). An example of a

change in sleep architecture is the reduced time an older adult spends in a period of slow wave activity (SWA); which is characterized as smaller frequency waves that range from 0.5-4.5 Hz throughout NREM sleep and is closely bound with the homeostatic need to sleep following sustained wakefulness (22). This is tied to the idea of sleep pressure- the longer an individual stays awake, the stronger the pressure to sleep and the greater the subsequent SWA during sleep (23). Nevertheless, aging causes disruptions to this homeostatic sleep control process. The drop in sleep pressure is caused by the substantial loss of adenosine A1 receptors brought about by aging (23). A portion of the homeostatic pressure to sleep, which includes SWS and the EEG characteristic of SWA that goes along with it, is controlled by raising extracellular adenosine, a metabolic byproduct that builds up during awake time (24). With fewer receptors to receive the adenosine, older adults experience shifted and irregular sleep timing. Another mechanism that leads to the decreased rhythm of the circadian cycle and sleep disruption is the reduction of galanin-expressing neurons in the preoptic region of the hypothalamus, a key regulator of sleep start and maintenance (25). The degree of this cell loss at post-mortem inspection is a good indicator of how severely older individuals' sleep fragmentation was assessed in the years before (25). The form and function of various hypothalamic and brainstem nuclei, which control sleep and wake brain states, are known to alter with age, and this decline in sleep and wake regulation is observed throughout the adult lifetime (6). It's equally important to point out that while SWS latency significantly decreases with age, age-related sleep impairments also affect how much time an individual spends in deep or REM sleep. Given that sleep is necessary for memory consolidation and cognitive function, a decline in the percentage of REM sleep in elderly individuals may have significant functional effects (26).

FUNCTIONAL CONSEQUENCES OF AGE-RELATED SLEEP IMPAIRMENT

Age-related sleep disruption can give rise to detrimental consequences and effects regarding an older adult's brain and body health. The phenomenon of sleep in earlier life supports every major physiological bodily system, including metabolic, thermoregulatory, endocrine, cardiovascular and immune (27); as well as several brain processes related to cognition and affect, including learning and memory, emotional control, focus, motivation, motor control, and decision-making (28). Therefore, it is not surprising that an expanding body of research reveals sleep disorders related to aging can be linked to deficits in learning and memory (28). Sleep quantity and oscillatory quality prior to learning enhance the restoration of next-day hippocampal-dependent encoding capacity and thus initial learning; sleep after learning stabilizes new memory representations (29). The subsequent offline consolidation of hippocampal-dependent memory processing has been repeatedly associated with characteristics of non-REM sleep following encoding (30). The formation of new hippocampal based memories is reliant on adequate sleep both before and after the initial formation of a potential memory: these processes have become impaired in older adults. As the positive association between proper sleep hygiene and cognitive function is observed, one can formulate conclusions about the effects on memory processing when sleep is compromised. A meta-analysis of research has established a correlation between insufficient sleep habits and the severity of impairment in various cognitive performance tests (31). This means the degree of evaluated sleep disturbance in older individuals predicts progressively lower results on standardized neuropsychological tests (31). Additionally, in younger adults, the density of NREM oscillations predicts the recovery of hippocampal encoding activity and learning capacity, while in older adults, the level of impairment in fast-frequency spindle density significantly predicts the subsequent day's failure of the hippocampus to engage in episodic associative memory encoding, which in turn determines the success of learning ability (32). Thus, sleep disturbance in later life may have several pathways that decrease hippocampal dependent learning and contribute to cognitive decline, given the intra-hippocampal structural and functional alterations associated with aging (6). Supporting these observations, various clinical follow-up studies have shown that cognitively normal older adults with severe sleep fragmentation exhibit a 1.5 times higher risk of developing AD, and those with self-reported sleep deterioration face a doubled risk of AD onset (1).

ROLES OF AMYLOID-B AND TAU

The progressive loss of cognitive abilities including memory, reasoning, and speech are hallmarks of AD (2). AD may manifest itself in two distinct groups, with early onset targeting those younger than 65, the majority of those affected are diagnosed with sporadic AD and are 65 or older (2). The destructive and fatal implications of AD are caused by the accumulation of tau tangles and

proteins that form amyloid plaques in the brain, which impair normal brain activity and cause a loss of neuronal connections (2). Individuals with AD eventually need full-time care as their condition worsens and they become more and more difficult to assist with everyday tasks. The diagnosis of AD has gone from a purely pathological one, in the days of Alois Alzheimer (1864–1915), to a clinical, exclusionary approach in 1984 (33). The clinical diagnosis was based on the criteria defined by the stage of dementia, a clinical syndrome characterized by substantial progressive cognitive impairment affecting several domains, or neurobehavioral symptoms of enough severity to cause evident functional impact on daily life (34). Given the developments in the biomarker field and the desire to make them usable in a diagnostic setting, researchers grouped the biomarkers into A (amyloid), T (phosphorylated tau), and N (neurodegeneration, measured by total tau where applicable): the ATN framework. In this research framework, the diagnosis of AD is defined by the presence of Aβ and phosphorylated tau (34). In the course of AD, tau becomes hyperphosphorylated, forming aggregates that deposit as neurofibrillary tangles (NFT) and neuropil threads (35). Tau can also form aggregates in the absence of an overt Aβ pathology, inferring that tau pathology in AD might be induced by Aβ – but the question of whether tau or Aβ is responsible for triggering the other, remains unresolved (35). Aβ is synthesized from a larger protein known as amyloid precursor protein (APP) using enzymes such as beta-secretase and gamma-secretase (36). Aβ is produced in excess and accumulates excessively as a result of abnormal APP processing (36). Aβ plaque buildup is thought to impair cell-to-cell transmission and initiate inflammatory reactions, which in turn results in neuronal death and general cognitive deterioration (37). AD also has these neurofibrillary tangles as a major characteristic. Tau, becomes hyperphosphorylated in AD, resulting in the formation of twisted tangles within neurons (38). The formation of tau tangles disrupts the normal function of microtubules, which are critical for nutrient and organelle transport within neurons. This disruption leads to neuronal dysfunction and cell death (39). While there is controversy over whether the presence of Aβ plaques can exacerbate tau pathology or vice versa, the sequential relationship between these two types of protein abnormalities evidently contributes to the overall neurodegenerative process in AD (40). Numerous investigations have demonstrated how the sleep-wake cycle contributes to the development of AD (40). Extracellular Aβ in the brain's ISF and CSF fluctuates throughout the day; levels of soluble Aβ are higher when awake and decrease when sleeping (8). This suggests that excessive daytime wakefulness and decreased sleep quantity with higher levels of this disease hallmark. In humans, acute sleep deprivation causes a 25–30% rise in soluble Aβ in CSF due to an increase in Aβ synthesis overnight compared to sleeping controls (41). Furthermore, Aβ deposition causes APP transgenic mice's sleep–wake cycle to be disturbed, resulting in longer periods of wakefulness (42). Similarly, recent research has also discovered the diurnal fluctuation of tau in ISF; chronic sleep deprivation speeds up the growth of tau protein aggregates in particular brain networks in a tau seeding/spreading model, and raises the levels of tau in human CSF and mouse brain ISF (10). The fluctuating level dependent on sleep-wake cycle is strong evidence that the physiology of AD and sleep disruption are related in both directions.

HOW DOES SLEEP MANIFEST DIFFERENTLY IN AD?

The association between sleep disruption and cognitive deterioration is best described as bidirectional, with sleep abnormalities contributing to neurodegenerative diseases and neurodegeneration itself having a causal relationship with sleep disturbances (43). Sleep and its underlying circadian rhythm are disturbed in patients with AD and these disturbances worsen with disease progression. Sleep–wake disruption tends to occur in the moderate stages of the disease and can be multifaceted (44). AD patients tend to undergo disruptions in the timing and duration of their sleep cycle. This is primarily evident in increased nighttime wakefulness, due to longer sleep onset and more frequent awakenings, and increased daytime sleepiness, which might cause confusion between day and night. Furthermore, a common symptom seen in AD patients includes dysfunction of circadian rhythms, such as increased nocturnal activity, decreased diurnal activity, and core body temperature phase delay and amplitude decrease (45). Neuronal and synaptic damage from AD pathology in circadian regulating areas (e.g. hypothalamic suprachiasmatic nucleus (SCN)) increases the dysfunction of cellular circadian rhythms, which lies at the root of parts of the sleep disturbances seen in AD (46). In terms of sleep architecture, the duration of REM sleep bouts is decreased in AD patients compared with age-matched controls, leading to a cumulative lack of REM sleep. These changes can occur very early in the course of the disease (47). Observations demonstrate that amyloid deposition (and in some cases tau aggregation) in transgenic mice brains can be associated with disruption of

normal sleep architecture, an effect that often precedes the appearance of amyloid plaques (Figure 2) (48). According to these findings, mice with an overproduction of APP/Aβ exhibit increases in awake time and decreases in both NREM and REM sleep, which in some respects mirrors the sleep patterns observed in AD patients (48). With regular abnormalities to the sleep-wake cycle, we detect aberrant fluctuations in tau and Aβ levels, the disease's two key indicators (48). When production levels become inconsistent, it further impairs an individual's sleep – which explains why sleep impairment is a commonly observed characteristic of AD as it exacerbates the disease's pathology (48). Insomnia at night and excessive daytime sleepiness affects 25%–40% of patients with mild to moderate AD and their caretakers (49). It has been estimated that the frequency of sleep disruptions in mild cognitive impairment (MCI) patients varies from 8.8 to 45.5% (50). Furthermore, sleep disordered breathing (SDB) and sleep behavior disorders: excessive daytime sleepiness (EDS), insomnia and sleep apnea occur more frequently in MCI patients than in normal subjects (51). Sleep behavior disorders have been found to originate from changes in sleep architecture and the circadian rhythm which significantly impact an AD patient's daily routines and quality of life (51). The exact reason for changes in sleep architecture in AD is still unknown, but it possibly originates from AD pathology-induced neuronal and synaptic damage in crucial sleep regulating areas and pathways in the brain (44). The relationship between the pathology of AD and disturbed sleep-wake cycles is complex and reciprocal; poor sleep not only makes cognitive decline worse, but it also emphasizes the need for more research into focused interventions to enhance sleep quality and manage the disease as a whole (Figure 3) (44).

CONCLUSION

The complex relationship between inconsistent sleeping patterns and AD highlights a foundational aspect of cognitive condition: the quality of sleep. As individuals age, alterations in sleep architecture—the structure of sleep cycles, including variations in SW sleep, REM sleep, as well as NREM sleep—can significantly affect overall brain function. Research has shown that these age-related changes can compromise the restorative properties of sleep, potentially creating the foundation for development of neurodegenerative disorders, including AD. Sleep disturbances not only hinder the ability to achieve restful sleep but may also contribute to cognitive decline. Throughout a restful night, the brain engages in

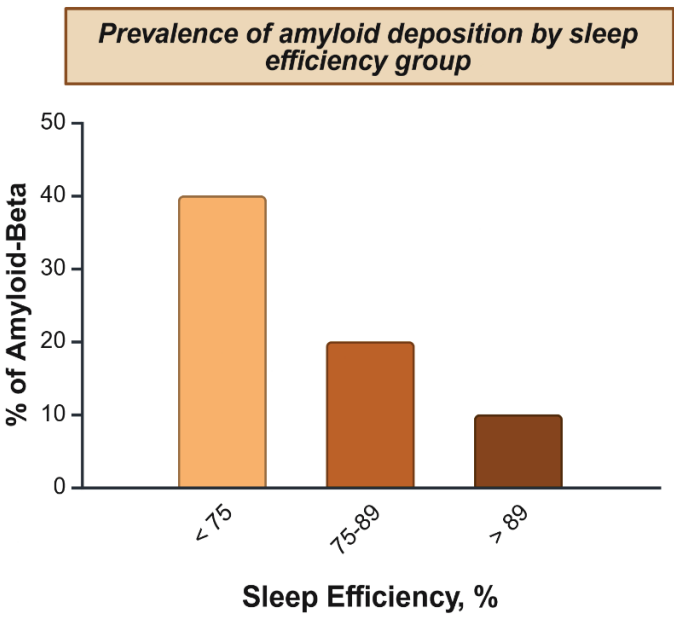

Figure 2. Graphical representation comparing percentage of amyloid deposition to sleep efficiency. This figure is an abbreviation of figure 1 as seen in Bidirectional relationship between sleep and Alzheimerâ€™s disease: role of amyloid, tau, and other factors (dpl6hyzg28thp.cloudfront.net).

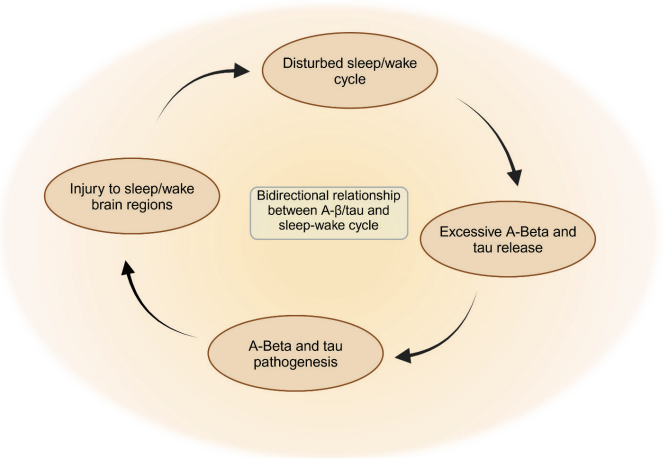

Figure 3. Model of bidirectional relationships between sleep-wake cycle and AD hallmark proteins, Aβ and tau. This figure is an abbreviation of figure 5 in Bidirectional relationship between sleep and Alzheimerâ€™s disease: role of amyloid, tau, and other factors (dpl6hyzg28thp.cloudfront.net)

homeostatic processes like memory formation and the cleaning of metabolic waste accumulated throughout the day, including Aβ. Constant disruptions to the sleep cycle could aggravate the accumulation of such proteins, creating a vicious cycle where poor sleep quality leads to deteriorating cognitive deficits. As a result, continued research in this area is necessary for full comprehension of the mechanisms through which sleep patterns impact cognitive abilities. This research could provide important insights into the possibility for treatment strategies that focus on improving sleep quality to delay cognitive decline. Researchers may be able to lessen the effects of age-related neurodegenerative processes by creating techniques to enhance older individuals' sleep quality through a better knowledge of the relationship between sleep disruptions and AD. Prioritization of sleep health may be essential to maintaining cognitive function and improving the quality of life for people with AD or at risk for developing the disease.

ABBREVIATIONS

AD	Alzheimer's disease
APP	Amyloid precursor protein
REM	Rapid eye movement
NFT	Neurofibrillary tangles
NREM	Non-rapid eye movement
Aβ	Amyloid-beta
SWS	Slow wave sleep
EEG	Electroencephalogram
SWA	Slow wave activity
Hz	Hertz
CSF	Cerebrospinal fluid
MCI	Mild Cognitive Impairment
ISF	Interstitial fluid

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