

Sleep and Attention in Alzheimer's Disease

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Individuals with Alzheimer's disease (AD[†]) present with a wide variety of symptoms, including sleep disruption and sleep disorders. Conversely, disordered sleep has been associated with an increased risk of developing AD. Both conditions individually have adverse effects on attention, which can be further divided into selective, sustained, divided, and alternating attention. The neural mechanisms underpinning sleep problems in AD involve the disruption of the circadian system. This review comprehensively discusses the types of attention impairments, the relationship between AD pathology and sleep disruption, and the effect of sleep issues on attention in AD. Recommendations for future research include addressing the lack of consistency among study designs and outcomes, and the need to continue exploring the biology of sleep and attention in AD.

INTRODUCTION

Sleep patterns vary across the human lifespan. Older adults in the general population report higher rates of sleep disturbances, with up to 50 percent of individuals describing daytime sleepiness, fragmented sleep, and difficulty falling, staying in, or waking up from sleep [1,2]. The American Geriatrics Society and National Institute on Aging have proposed to conceptualize these disturbances as a possible geriatric syndrome, where sleep disturbance is a result of a group of co-occurring risk factors [3]. The

documented risk factors that influence sleep disturbance include age, cognitive state, functional ability, and mobility. When it comes to cognition specifically, it has also been reported that poor sleep is a risk factor for cognitive impairment [4].

This relationship between sleep and cognition becomes more complicated in the context of Alzheimer's disease (AD). The total number of people with dementia is expected to reach 65.7 million globally by 2030, and 60 to 80 percent of those cases will be attributed to AD, the most common primary cause of dementia syndrome

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†Abbreviations: AD, Alzheimer's disease; APOEε4, Apolipoprotein E epsilon 4; Aβ, Amyloid-beta; BOLD, Blood-oxygen level dependent; CPAP, Continuous positive airway pressure; CSF, Cerebrospinal fluid; DAN, Dorsal attentional network; LC, Locus coeruleus; NFTs, Neurofibrillary tangles; OSA, Obstructive sleep apnea; PET, Positron emission tomography; REM, Rapid eye movement; SDB, Sleep-disordered breathing; VAN, Ventral attentional network.

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[5,6]. AD is marked by a clinical presentation of memory impairment, executive dysfunction, visuospatial impairment, and attention deficits [7]. Decline in attention is significantly associated with decline in functional ability and difficulty in performing activities of daily living, such as eating, grooming, and bathing in AD patients [8]. As a result, attention deficits negatively impact the quality of life for both AD patients and their caregivers.

Sleep disturbances in AD patients are also frequent. Older adults with AD often experience similar forms of sleep dysfunction as the general population, but at a greater intensity [9]. These include difficulties falling asleep, frequent awakenings during the sleep period, and overall lower sleep efficiency [10,11]. Sleep disturbances are not only associated with poorer cognition and increased behavioral symptoms, notably aggressiveness, but also predict more rapid disease progression [9,12]. This paper aims to comprehensively summarize the types of attention impairments in AD, examine major sleep disorders frequently associated with AD, and to discuss the mechanistic relationship between sleep, attention, and AD.

ATTENTION IMPAIRMENTS IN AD

Although AD is predominantly categorized as a memory disorder, many patients also develop attention impairments early in the disease [13]. Studies have typically measured attention impairments using a variety of standardized neuropsychological tests such as the color-word Stroop test [14], the digit symbol substitution test [15], the digit span task [16], the auditory target detection test, and the figural visual scanning test [17]. A specific domain of attention, selective attention, is commonly measured using a visual search task [18], whereas sustained attention can be measured using the sustained attention to response task [19] or the Conners continuous performance test [20]. Studies have used the Trail-Making Test B and the Symbol-Digit Modalities Test to measure divided attention, whereas alternating attention can be measured using multiple-object tracking tests [21]. Below, we review the four different types of attention impairments in AD; selective attention, sustained attention, divided attention, and alternating attention.

Selective Attention

Selective attention is defined as the ability to focus on a single stimulus while blocking out all other distractions [22]. To test selective attention abilities in Alzheimer's patients, Chau *et al.* used an eye tracking paradigm with relative fixation time as the primary outcome measure. The results revealed that, compared to healthy controls, Alzheimer's patients spent significantly less time fixating on novel images relative to repeated images, indicating a

decrease in selective attention abilities in AD [22]. Similarly, a study by Festa *et al.* also revealed a deficit in selective attention in Alzheimer's patients using a visual search task alone and in combination with a visuomotor tracking task [23]. Another study by Venkatesan *et al.* instructed AD participants to complete search tasks requiring either luminance-motion or color-motion binding, analogs of within and across visual processing stream binding, respectively. The participants also underwent a standardized road test and naturalistic driving data was collected. The study revealed that the Alzheimer's group performed significantly poorer on the visual search task than the control group and that performance on the task was predictive of driving ability [24].

Sustained Attention

A second type of impaired attention, sustained attention, has also been shown to contribute to increased risk of falls [25] as well as unsafe driving [26,27] in AD patients. Sustained attention is defined as the ability to maintain focus on a specific task for an extended period of time [28]. Huntley *et al.* showed that early AD patients performed significantly poorer than healthy controls on tests of sustained attention [29]. Another study by Berardi *et al.* in mild AD patients reported a reduced ability to maintain concentration for an extended period of time compared to healthy age matched controls. Alzheimer's patients also had lower levels of overall vigilance and poorer concentration to stimuli over time compared to controls [30].

Divided Attention

Johannsen *et al.* reported deficits in divided attention in AD patients, which is defined as the ability to attend to multiple tasks simultaneously [31]. Using Positron Emission Tomography (PET) scans, they found that Alzheimer's patients showed decreased levels of cortical activation when attending to multiple somatosensory and visual stimuli compared to healthy age matched controls. The difference in activation patterns observed between Alzheimer's patients and control participants increased with difficulty of attention tasks. Another study by Nebes and Brady utilized a visual search task to assess divided attention ability in patients with AD. They reported that when the number of items in the search task increased, they found a disproportionate rise in search time in patients with AD compared to controls, suggesting that AD patients are less efficient than healthy controls in dividing their attention [32].

Alternating Attention

Alternating attention or attentional shifting is the ability to effortlessly move your attention between tasks

demanding different cognitive demands [33]. In a study by Gorus *et al.*, alternating attention was tested using a double task situation where participants had to alternate between responding to a visual and auditory stimulus. The results demonstrated that mild Alzheimer's patients performed significantly poorer than healthy controls both in terms of reaction speed and also in error rate [34]. Additionally, a study by Coubard *et al.* tested alternating attention in Alzheimer's patients using the Rule shift cards test. Participants are required to respond to stimuli (red or black playing cards) according to one of two rules that are presented consecutively. That study reported that Alzheimer's patients had significantly higher switch error rates compared to age-matched controls [35].

SLEEP DISORDERS ASSOCIATED WITH AD

Studies have demonstrated strong associations between disturbed sleep and incident cognitive impairment. Spira *et al.* investigated the relationship between AD biomarkers and sleep. They found that greater amyloid-beta ($A\beta$) deposition, a characteristic hallmark of AD pathology, was associated with poorer sleep quality and shorter sleep duration [36]. Lucey *et al.* also proposed that $A\beta$ deposition and sleep have a bidirectional interaction resulting in a feedback loop that can negatively affect memory function [37]. A longitudinal study by Bokenberger *et al.* revealed that the length of time in bed and the time you rise in the morning were risk factors for dementia. Specifically for older adults, sleeping less than six hours, more than nine hours or rising later than 8:00 AM predicted a greater prevalence of dementia 17 years later [38]. Additionally, Bonanni *et al.* reported that AD patients have an increased sleep propensity during the daytime [39]. Excessive daytime sleepiness has been reported as an important risk factor for cognitive impairment in the elderly population [40]. Similarly, Lim *et al.* reported that an increased risk for developing AD was due to an increase in sleep fragmentation [41]. They also demonstrated a positive association between levels of sleep fragmentation at baseline and faster cognitive decline [41].

Sleep Apnea

One of the most common sleep disorders in AD is sleep apnea [42]. Obstructive sleep apnea (OSA) is a subtype of sleep-disordered breathing (SDB) marked by laryngeal collapse that leads to periods of cessation or significant reduction of breathing during sleep [43]. OSA has been reported at levels of between 50 percent and 80 percent in patients with dementia. In the dementia population, severity of OSA has been associated with disease severity [43,44]. Carriers of the apolipoprotein E epsilon

4 (APOE ϵ 4) genotype have a higher risk of developing cognitive impairment and AD with concomitant SDB. A large-scale cross-sectional study of middle-aged individuals found that having the APOE ϵ 4 genotype was associated with poorer cognition in those who also had SDB, but not in those without SDB [45]. Another recent study produced similar findings, where in a diverse population of older adults, hypoxemia from sleep apnea was associated with poorer performance on attention tests [46]. This association was especially strong for individuals identified as high risk for AD because they were APOE ϵ 4 allele carriers, adding further support to the view that SDB may be a modifiable dementia risk factor.

There are several lines of treatment that have been introduced to treat SDB and specifically OSA. Surgical treatments target sites along the pharynx that prevent airway passage, such as anatomical abnormalities or swelling, to reduce size or alter shape and restore regular breathing [47]. However, the less invasive treatment option is the continuous positive airway pressure (CPAP), and it is often used as a first line treatment. This involves attaching a mask to the patient's nose overnight, where pressure forces the airways to remain expanded, thus preventing the collapse and obstruction [48]. Sustained CPAP use resulted in less cognitive decline, stabilization of depressive symptoms and daytime somnolence, and improvement in subjective sleep quality in AD patients. Caregivers of patients using CPAP also reported improvements in their own sleep [49].

Insomnia

Another common sleep disorder is insomnia. An insomnia diagnosis includes complaints of difficulty falling or staying asleep, or experiencing non-restorative sleep, for a minimum of one month or a minimum of three months, depending on the edition of the Diagnostic and Statistical Manual of Mental Disorders used [50]. Due to the inconsistency in diagnostic criteria across manuals, it is difficult to estimate the prevalence of insomnia in the general population [51]. In patients with AD, insomnia-related symptoms have been reported to be present in 25 to 35 percent of the population [52]. A recent meta-analysis showed evidence for an increased risk of developing dementia in individuals with a pre-existing diagnosis of insomnia [53]. Insomnia in individuals with AD has been shown to increase caregiver burden and has been cited as one of the most frequent reasons that caregivers seek institutional care [54]. Some possible explanations include the sleep disruption this causes for caregivers themselves, as well as the association of insomnia with more frequent incidents of night-time wandering, which leads to a higher risk of falls and injuries [55].

Pharmacologic and non-pharmacologic interventions continue to be investigated for the treatment of

AD patients with insomnia and related symptoms. Recommendations from meta-analyses are in support of non-pharmacologic interventions as first line treatment, as the risk of inducing an adverse event is greatly reduced [56,57]. One study reported positive findings of reduced sleep complaints following a behavioral intervention that included sleep hygiene practice, daily walking, and light therapy in patients with AD [58]. Light therapy, particularly, has been shown to improve duration and quality of sleep in patients with AD [57].

Pharmacologic treatments for insomnia in AD are limited. Many treatments used to typically treat insomnia in the general population may not be appropriate for use with older adults because of increased risk of adverse events. For example, benzodiazepines are associated with an increased risk of adverse events, such as worsened cognition, dizziness, falls, and hypotension [59,60], and many clinicians consequently discourage long-term benzodiazepine use in the geriatric population [61]. Z-drugs, a class of hypnotics, include zolpidem, zopiclone, and zaleplon, work on the same receptor as benzodiazepines [62]. Despite being perceived as “safer” due to a reduced profile of side-effects, Z-drugs pose similar risks in older adults. A recent meta-analysis reported an association between the use of z-drugs and an increase in fractures, injuries, and falls in older adults [63]. In the dementia population, evidence from some systematic reviews and meta-analyses have supported low dosages of trazodone for sleep problems [64] and melatonin for increasing sleep duration [65]. The melatonin receptor agonist, ramelteon, has also been associated with improvements in behavioral symptoms and sleep-wake rhythm disturbance in AD [66]. However, those findings are from small studies and larger trials are needed to better determine the efficacy and safety of pharmacotherapies for sleep problems in dementia.

THE MECHANISTIC RELATIONSHIP BETWEEN ATTENTION, SLEEP, AND AD

Attentional Systems in AD

Attention incorporates the use of several neural circuits to successfully carry out cognitive operations. A prominent model of attention classifies two separate systems: the dorsal attention network (DAN) and ventral attention network (VAN). DAN has been implicated in goal-driven processes, employing a top-down approach, whereas VAN has been shown to specialize in bottom-up functioning [67]. The two networks show differential responding based on task demands, but even during rest, there appears to be spontaneous fluctuations in blood oxygen level-dependent (BOLD) signals that validate the presence of two networks [68]. Another study examining BOLD levels reported that DAN is specifically impacted

during the course of AD. Compared with healthy older adults, participants with AD showed reduced functional connectivity in DAN but not VAN [69]. This finding is in line with clinical presentations of attention-specific decline in AD, where top-down processes such as divided and selective attention are significantly impaired, as discussed above. Decline in functional connectivity within attention networks that result in attention impairments has also been shown to be linked with A β pathology [70].

Sleep Disruption and AD Pathology

In AD patients, the mechanistic relationship between sleep disruption and AD has been frequently reported as bidirectional. The pathology of AD emerges several years prior to the onset of cognitive symptoms. Two main molecules, A β and tau, can be detected in the cerebrospinal fluid and are associated with the development and progression of AD. Amyloid plaques are primarily composed of A β peptides, and high levels of A β in the brain result from poor clearance of A β [71]. A β levels in the cerebrospinal fluid (CSF) can be used to predict incident AD [72]. Tau proteins have also been a biomarker of interest as they are key initiators of neuronal death when there are abnormalities during the phosphorylation process [73]. Recent studies have begun exploring the role these biomarkers play in disordered sleep.

Ju *et al.* reported that in a group of cognitively-normal individuals, sleep disruption during non-rapid eye movement (REM) sleep leads to increased A β levels, which in turn, poses an increased risk of developing amyloid plaques [74]. Amyloid plaques frequently accumulate in cortical layers III and V, where they can disrupt acetylcholine-mediated oscillations in slow wave sleep [75]. The authors concluded that their findings contribute to the growing literature by providing evidence that sleep disturbance affects the same biochemical processes as the neuropathology of AD. On the other hand, amyloid accumulation resulting from AD pathology has been shown to induce sleep problems [76]. That study found that in a cognitively healthy group, individuals with higher levels of amyloid buildup showed lower levels of sleep efficiency, supporting the notion that amyloid deposition may increase levels of sleep fragmentation due to its interference with neuronal functioning in sleep-modulating brain regions. Neurofibrillary tangles (NFTs), the result of tau aggregation, have been linked to sleep as well. Lim *et al.* reported that in a group of older adults without dementia, uninterrupted sleep diminished the negative impact APOE ϵ 4 has on NFT formation and density [77]. They reported that the reduction in density at death may mediate the link between cognition measured close to time of death and APOE ϵ 4.

A region highly susceptible to developing NFTs is the locus coeruleus (LC) [78]. Levels of NFTs in this

brain region is linked to sleep disturbances in early AD, as the LC and connected neural regions play a significant role in the sleep-wake cycle [79]. Additionally, NFTs may be transmitted to other sleep-regulating brain regions from the LC, spreading neurodegeneration and disrupting the sleep-wake cycle further [80]. The LC is an especially important region of the brainstem because it also has a critical role in cognition. Lower neural density in the LC has been linked to cognitive decline in older adults, including decline in attention [81]. Lower neural density in brain regions associated with sleep has also been implicated in sleep disruption. Specifically, Lim *et al.* reported that lower amounts of neurons in the intermediate nucleus, located in the anterior hypothalamus, were associated with higher levels of sleep fragmentation [82]. The intermediate nucleus plays a major role in sleep-wake function as it releases galanin, an inhibitory neurotransmitter that inhibits wakefulness [83]. Lim *et al.* reported that lower levels of sleep fragmentation were associated with higher levels of galaninergic neurons, regardless of whether AD was present, but also that the AD sample had an overall smaller quantity of those neurons in the intermediate nucleus [82].

Sleep is also regulated by the circadian system. The suprachiasmatic nucleus, another region in the anterior hypothalamus, has been shown to house the master circadian clock, where chemical and hormonal signals are sent to peripheral clocks in other organs to regulate their rhythmic activity based on approximate 24-hour periods [84]. Abnormalities in the circadian system are implicated in the development and progression of AD. A β levels in the brain have been shown to closely overlap with the sleep-wake cycle, and plaque build-up interferes with the normal physiology of A β dynamics. Huang *et al.* tracked the circadian rhythm via electroencephalography while collecting CSF on an hourly basis from younger adults, older adults with amyloid deposition, and older adults without amyloid deposition [85]. The results of that study supported other findings in the current literature that state that patterns of A β levels are more dynamic in healthy, young adults, and the dynamic fluctuation decreases in the presence of amyloid deposition [86]. Huang *et al.* concluded that this phenomenon can be attributed to the plaques serving as a buffer, thus hindering the dynamic changes in A β concentrations that would have been otherwise observed.

Another mechanism underlying how sleep impacts A β levels has been studied in cases of prolonged wakefulness with forced sleep deprivation. One study collected CSF samples overnight from a group of cognitively healthy men that were allowed either unrestricted sleep or forced wakefulness and reported that A β levels were higher in the forced wakefulness group [87]. Another study supported this finding by comparing A β levels in

the same sample across a night of rested sleep followed by a night of forced wakefulness [88]. Adverse effects of one night of sleep deprivation were associated with higher A β levels in the CSF. One explanation for this relationship between sleep and A β levels is that neuronal activity influences A β production. Slow-wave activity is a component of non-REM sleep which is characterized by reduced neuronal activity [88]. Disruption of this particular phase of sleep was shown to amplify A β levels, suggesting that sleep may mediate A β production by providing a period of reduced neuronal activity, supporting the theory that higher levels of neuronal activity lead to greater A β production, increasing the risk for AD [74].

The Effect of Sleep Disruption on Attention Impairments in AD

Studies investigating the relationship between sleep disruption and attention is limited in the AD population. In young adults, forced wakefulness did not affect performance on tests of attention [89,90]. Yet, night workers who face chronic disruption of the circadian system, experience heightened distractibility, or reduced attention, as seen in electrophysiological data because of chronic disruption of the circadian system [91]. Additionally, a dose-response sleep study showed that the severity of sleep deprivation changes performance on vigilance tasks [92]. Mixed findings regarding the relationship between sleep and attention is also seen in studies with older adults. Where some studies found that self-reported sleep complaints negatively impact performance on attention tests [93,94], other studies showed only specific sleep problems, particularly daytime sleepiness, correlated with cognitive decline [95,96]. Those inconsistent findings may be attributed to differences in neuropsychological testing, definitions of attention, baseline cognition of the participants, and tools for collecting sleep-related variables. Recent neuroimaging studies reported that sleep deprivation was linked to a decline in task-related brain activation using functional magnetic resonance imaging following extended sleep deprivation in a group of healthy young adults [97,98].

In patients with mild cognitive impairment, where cognitive decline is significant but does not impede on daily functioning, increased duration of wake arousals after sleep onset was associated with impairments in several cognitive domains, including attention [99]. Increased duration of REM sleep also improved immediate recall performance in those with the APOE ϵ 4 allele [99]. Ancoli-Israel *et al.* conducted a randomized double-blind control study to assess effectiveness of the CPAP in patients with both AD and OSA [100]. They reported that patients using CPAP showed an improvement on neuropsychological tests of attention, when compared with those using a CPAP-placebo. Another study examined

long-term effects of CPAP in comorbid AD and sleep apnea and reported an association between compliance with CPAP for at least three months and a lower rate of decline in cognition, particularly of attention-demanding functions, in comparison to AD patients who did not use CPAP [101].

CONCLUSIONS AND OUTLOOK

Four types of attention impairments have been shown to be present throughout the course of AD. Alternating attention and divided attention impairments have been reported as predictive of AD [34,102]. Selective attention and sustained attention show prominent decline throughout the progression of AD, and may explain behavioral symptoms that are observed in patients with AD. For example, deteriorating sustained attention has been associated with an increased risk of falls [25] and decline in selective attention is implicated in reduced driving competency in patients with AD [24]. Therefore, it is important to address attention deficits to understand the outcomes associated with the disease and tailor diagnosis or treatment options as necessary.

The complications of AD pathology and symptomology that result from sleep disruption also require further investigation to more strongly support findings discussed above. Patients with AD commonly present with complaints of poor sleep, difficulty falling or staying asleep, or shorter sleep duration. In many cases, these complaints result from a comorbid sleep disorder, such as insomnia, or SDB, resulting from OSA. Ongoing research suggests that alleviating sleep-related symptoms in AD may lead to improved daytime functioning and cognitive function including attentional performance [100,101].

Existing studies provide valuable insight into the shared mechanisms underlying sleep disruptions and AD, but literature on their impact on attentional performance is limited. Currently, research on attention and sleep disturbance has been heavily based on subjective complaints of patients, but investigating more objective methods, such as using biomarkers via functional magnetic resonance imaging or non-verbal eye-tracking technologies, may provide more objective measures of attention impairments in AD patients with communication difficulties. The importance of continuing research on biomarkers is emphasized in the literature in order to not only better predict the risk of disease development, but also to personalize care for optimal treatment. Additionally, cognitive measures used to address the level of cognitive impairment vary from study to study. The establishment of a battery of standardized and validated attentional tests will allow for a more reliable interpretation of the findings across the field.

The prevalence of AD will continue to rise over the

upcoming decades [5]. Sleep disruption, which plays a significant role in the pathology of AD, both as a risk factor and a symptom, is also expected to become increasingly prominent in the geriatric population. The effects both of those conditions have on attention are important as current research has demonstrated an association between the decline in attention and increasing functional impairment, leading to greater caregiver burden. AD alone imposes substantial costs on the health care system and social services, as well as the quality of life of individuals affected by the disease and their caregivers [103]. However, it remains unclear whether there is an additive decline when both sleep disorders and AD are present, and whether alleviating attention-related symptoms caused by sleep issues can reduce disease progression. Working towards understanding the interplay of attention, sleep, and AD pathology will allow contemporary medicine to develop stronger screening tools and management options.

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