Sleep: A Novel Mechanistic Pathway, Biomarker, and Treatment Target in the Pathology of Alzheimer's Disease?

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Sleep disruption appears to be a core component of Alzheimer's disease (AD) and its pathophysiology. Signature abnormalities of sleep emerge before clinical onset of AD. Moreover, insufficient sleep facilitates accumulation of amyloid-β (Aβ), potentially triggering earlier cognitive decline and conversion to AD. Building on such findings, this review has four goals: evaluating (i) associations and plausible mechanisms linking non-rapid-eye-movement (NREM) sleep disruption, Aβ, and AD; (ii) a role for NREM sleep disruption as a novel factor linking cortical Aβ to impaired hippocampus-dependent memory consolidation; (iii) the potential diagnostic utility of NREM sleep disruption as a new biomarker of AD; and (iv) the possibility of sleep as a new treatment target in aging, affording preventative and therapeutic benefits.

Alzheimer's Disease and the Emerging Interaction with Sleep

AD is one of the largest public health and economic challenges of the 21st century. One in 10 adults over the age of 65 suffer from AD, representing a worldwide epidemic. As a result, there is a pressing need to develop sensitive biomarkers facilitating early detection, and effective treatment interventions [1]. Only by achieving both can the goals of prevention and therapeutic intervention be accomplished [1]. One emerging candidate that may fulfill all of these objectives is sleep. In this review we evaluate evidence linking sleep disturbance with AD and its pathophysiology, especially Aβ pathology. We further outline the cognitive consequences of sleep disruption as a novel mechanistic conduit contributing to cognitive decline associated with AD pathophysiology. Finally, we explore the potential of sleep to serve as both a biomarker of AD and as a new therapeutic and preventative strategy for lowering AD risk.

Sleep, Aβ, and Alzheimer's Disease

Sleep in Aging

A physiological hallmark of advancing age is the decline of sleep, wherein NREM slow wave sleep (SWS) declines are particularly significant [2]. These impairments begin in midlife, and in many older adults age 75 years or older, less than 10% of SWS time remains [2]. Similar reductions in the quality of SWS are observed, measurable in the electroencephalographic (EEG) signature of slow wave activity (SWA; ~0.5–4.5 Hz) [3,4]. These age-related decreases in NREM SWS quantity and quality are paralleled by increasing amounts of time spent awake

Trends

A bidirectional, causal interaction exists between NREM sleep and Aβ pathophysiology that may contribute to Alzheimer's disease (AD) risk and progression.

The disruption of NREM sleep may represent a novel pathway through which cortical Aβ impairs hippocampus-dependent memory consolidation.

The disruption of NREM sleep physiology offers potential diagnostic utility in the form of a non-invasive biomarker of Aβ pathology, AD risk, and/or AD pathophysiological progression.

Evidence implicates sleep disturbance as a consequence and cause of AD progression; one that is modifiable, offering preventative and therapeutic treatment potential.

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at night, with sleep becoming more fragmented [2]. The prevalence of primary sleep disorders, including insomnia and sleep apnea, also increases with advancing age [5], further impairing the restorative quality of sleep.

Importantly, however, sleep disruption is not uniformly observed across older adults of equivalent age [5]. There are marked differences in the ability to generate sleep, including NREM SWS [2,5]. Similar variability is observed in the prevalence of sleep disorders [5–7]. This has led to the suggestion that underlying pathological factors, such as those associated with abnormal aging and AD, may partially determine the type and severity of sleep deterioration in later life and, with it, the cognitive faculties supported by sleep [4,8].

**Sleep in Abnormal Aging**

Impairments of sleep structure are markedly exaggerated in those with mild cognitive impairment (MCI), and in those suffering from AD [9–11], relative to cognitively normal older adults. Analogous sleep impairments are present in older adults at highest biological risk for developing AD, such as carriers of the APOE4 allele; the most prominent genetic risk factor for late-onset AD [9]. In addition, the decline in physiological NREM sleep quality, specifically slow wave oscillatory activity, is accelerated in AD patients relative to age-matched controls [10].

Indicating clinical and etiological relevance, the magnitude of sleep disruption progresses in unison with the severity of AD symptomatology and pathology [6,10,12]. For example, tau and Aβ protein levels measured in cerebrospinal fluid (CSF) predict the degree of reduced SWS time in AD patients, together with decreases in sleep efficiency and REM sleep [12]. Sleep disturbance also appears to be among the earliest observable symptoms of AD, being present before and soon after MCI and AD diagnosis [9,10,13–16]. Beyond sleep disruption, clinical sleep disorders are strongly co-morbid with MCI and AD. Over 60% of patients with MCI and AD have at least one clinical sleep disorder [6,7], with sleep apnea and insomnia being most common. Furthermore, APOE4 genotype is known to significantly increase the risk of developing sleep apnea [17].

The physiological decline of sleep, particularly NREM sleep quantity and quality, is therefore a common feature of advancing age, but the onset, severity, and nature of these impairments are all significantly accelerated in those with AD and in those at highest risk for AD. Although these sleep disturbances have long been considered robust symptoms of AD, new evidence indicates that this relationship between AD and sleep disruption may be causal and bi-directional, representing an integral part of the disease and potentially its treatment.

**Bidirectional Links Between Sleep and Aβ Pathology**

Insomnia and sleep apnea are not only more prominent in AD, but conversely increase the risk of developing MCI and AD [15,16], suggesting a reciprocal relationship between sleep disturbance and AD pathophysiology. Furthermore, individuals with sleep apnea convert to MCI and AD at a younger age [18]. By contrast, successfully treating sleep disturbance can delay the age of onset into MCI [18] and improve cognitive function in AD [19,20]. While additional evidence is required, these findings point to a potential causal and bidirectional link between sleep disorders and AD. As this reciprocal model would further predict, older adults with superior sleep quality have a significantly lower risk of developing MCI and AD, and also maintain cognitive function for longer [13,14]. Together, these findings indicate that healthier quality of sleep in later life may confer resilience to AD.

The bidirectional link between sleep disturbance and Aβ pathology is observed before clinical onset of AD, and can occur independently of insomnia or apnea [12,14,21–23]. This indicates that the association between sleep and Aβ pathology is not merely a consequence of a primary sleep disorder or of end-stage neurodegeneration. Instead, emerging evidence links specific sleep
deficits to the defining pathological features of AD: Aβ and tau pathology. Both subjective and objective measures of poor sleep correlate with the severity of cortical Aβ burden, CSF measures of Aβ, and phosphorylated tau in CSF [12,21–23]. Such sleep–Aβ associations have been reported in cognitively normal older adults, MCI patients, and those diagnosed with AD [12,21–23]. Raising biomarker potential, the relationship between NREM sleep disruption and Aβ may be anatomically and neurophysiologically unique. First, associations with Aβ are selectively observed in the low-frequency range of NREM SWA below 1 Hz [21], unlike the more general age-related decline in broader SWA from 1–4 Hz linked to grey matter atrophy [4]. Second, the signature association with <1 Hz NREM SWA correlates most significantly with Aβ in medial prefrontal cortex [21]—one of the earliest sites to accumulate Aβ [24]; a topic we return to below.

Rodent models further support a connection between Aβ and NREM sleep (Figure 1A–F). Experimentally increasing cortical Aβ causally fragments NREM sleep [25,26], while

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**Figure 1. Reciprocal Relationship between Aβ and Sleep, and Their influence on Hippocampus-Dependent Memory Consolidation.** CSF Aβ in humans (A) and ISF Aβ in rodents (B) rise during wake and fall during sleep, and sleep restriction of APP/PS1 mutant rodents results in higher cortical Aβ plaque burden (C; adapted from [25]). Further, APP/PS1 mutant rodents (red bars) exhibit increased wake time (D) and reduced REM (E) and NREM (F) sleep time relative to wild-type rodents (blue bars; adapted from [26]). These findings represent a reciprocal relationship between sleep and Aβ: sleep and sleep disturbance can influence Aβ accumulation (A–C, blue box), while Aβ aggregation can disrupt sleep and increase wake time (D–F, red box). A potential mechanism underlying disrupted NREM SWA by Aβ pathology is the aggregation of Aβ (G, top, sagittal brain slice; adapted from [48]) within the same medial prefrontal cortical nodes crucial for the electrical source generation of NREM slow waves (G, bottom, sagittal brain slice; adapted from [47]). Indeed, medial prefrontal Aβ burden predicts the degree of disrupted <1 Hz NREM SWA [H, red scatter plot; adapted from [21]]. The disruption of <1 Hz NREM SWA by Aβ, in turn, is associated with impaired sleep-dependent consolidation of hippocampus-dependent memory. Disrupted <1 Hz NREM SWA is associated with reduced overnight development of hippocampus-independent retrieval (H, blue scatter plot), that normally fosters superior memory stabilization and thus remembering (H, turquoise scatter plot). These interactions are further supported by structural equation modeling, which revealed that the only significant path linking Aβ pathology to impaired hippocampus-dependent memory was through its intermediary disruption of <1 Hz NREM SWA (I, adapted from [21]). While the relationship between Aβ and NREM sleep is likely to be bidirectional, the strongest link between Aβ and memory was through its association with NREM SWA. Abbreviations: Aβ, amyloid-β protein; AC, anterior cingulate gyrus; APP/PS1, amyloid precursor protein and presenilin 1 mutant rodents; au, arbitrary units; CSF, cerebrospinal fluid; DVR, distribution volume ratio; FAR, false alarm rate; HC, hippocampus; ITG, inferior temporal gyrus; HR, hit rate; ISF, interstitial fluid; L, left hemisphere; LR, lure rate; LN, natural logarithm; MAX, maximum; MIN, minimum; mPFC, medial prefrontal cortex; MTG, medial temporal gyrus; PCC, posterior cingulate cortex; PHG, parahippocampal gyrus; PosC, post-central gyrus; prop., proportion; SWA, slow wave activity; WT, wild type. * P < 0.05, ** P < 0.01, *** P < 0.001.
experimentally decreasing NREM sleep and increasing wake time escalates Aβ production and corresponding cortical deposition [25]. Conversely, NREM sleep promotes the clearance of extracellular Aβ that accumulates during wakefulness [27]. Therefore, NREM sleep represents one crucial pathway through which the brain appears to manage Aβ levels: the absence of sleep contributes to the aggregation of Aβ, while the presence of NREM sleep proactively reduces Aβ burden. Within this proposed framework, disrupted NREM SWS and excess wakefulness increases Aβ aggregation, which itself impairs NREM SWS, resulting in a vicious cycle accelerating AD progression [28].

Although NREM sleep associations with Aβ are most prominent, of note are emerging links between Aβ and REM sleep (detailed in Box 1). Moreover, evidence for the impact of tau pathology on sleep is rapidly growing, highlighting multifactorial mechanistic links between sleep disturbance and AD (described in Box 2).

Mechanisms of Sleep Disruption and Aβ

While a bidirectional relationship between NREM sleep disruption and Aβ pathology is likely, the underlying mechanism(s) are unclear. Some clues are emerging, and implicate active, antagonistic mechanisms underlying the reciprocal relationship between wake, NREM sleep, and Aβ (Figure 2).

One recent discovery has described a sleep-dependent role for the glymphatic system in dictating Aβ clearance [27]. During NREM sleep, glial cells shrink by as much as 60%, facilitating a markedly increased flow of cerebrospinal fluid through interstitial space. The result is an enhanced clearance of extracellular toxins and metabolic detritus during NREM sleep. Extracellular Aβ is vacated by this mechanism at a twofold faster rate during NREM SWS than during wake [25,27] (Figure 2). Of relevance, Aβ clearance is impaired in AD [29]. The cause may, in part, be due to chronic sleep disruption and/or sleep apnea-induced hypoxia. Both can increase blood vessel stiffness by triggering chronic hypertension [30–32] which, alongside cerebral amyloid angiopathy [29], reduces clearance efficiency leading to amyloid accumulation [32].

**Box 1. REM Sleep, Aβ pathology, and AD**

Relationships between sleep, AD, and AD pathology extend beyond NREM SWS, and include REM sleep disturbance. Patients with MCI and AD demonstrate reduced REM sleep amount, delayed REM sleep onset, and blunted rebound of REM sleep following selective deprivation [9–12,84,86]. MCI and AD patients both demonstrate reductions in the EEG quality of REM sleep [86,87]; a feature that can even discriminate those with AD from cognitively normal older adults [87]. Moreover, Aβ correlates with reduced REM sleep amount in healthy older adults [21] and patients with AD [12]. The selective degeneration of cholinergic projection neurons within the brainstem and basal forebrain (BF) may underlie aspects of this disruption [88,89]. Both brainstem and BF cholinergic neurons regulate REM sleep [90,91], and BF cholinergic degeneration is an initial component of AD pathophysiological progression [88]. The degree of cortical Aβ burden correlates with the degree of BF atrophy in healthy older adults, MCI, and AD patients [92]. Aβ and tau have further been implicated in the degeneration of cholinergic neurons projecting from the BF to the cortex (Box 2) [92,93].

REM sleep disruption in AD has cognitive and affective consequences. REM sleep disruption predicts worse Mini-Mental State Examination scores in MCI and AD patients, and neuropsychological impairment in older adults and MCI patients [11,12,94]. Disrupted REM sleep also predicts more severe longitudinal decline across multiple cognitive domains in older adults and AD patients [84,94]. Another crucial function of REM sleep is the regulation of emotional reactivity and mood states [95], both of which are disturbed in AD. AD patients fail to show the normal enhancing effects of emotion on memory retention [96], and express deficits in processing of complex emotional information [97], both of which rely on REM sleep [95]. Furthermore, neuropsychiatric symptoms of AD, including depression, aggression, agitation, and anxiety [98], are all observed in sleep-deprived individuals [95]. Moreover, depression and post-traumatic stress disorder (PTSD)–associated with REM sleep disturbance [99]–are risk factors for developing AD [99,100]. Thus, REM sleep deficits may exacerbate psychiatric conditions common in AD patients [101], and this is pertinent considering the impact of these symptoms on caregiver burden and the likelihood of institutionalization [102]. While therapeutic interventions that selectively increase REM sleep are currently limited, cholinesterase inhibitors do increase REM sleep quality and duration, the success of which predicts the degree of memory improvement in AD patients [20]. Whether cholinesterase inhibitors offer similar benefits to the mood and emotional symptoms of AD remains a currently uninvestigated question.
Box 2. Sleep Disturbance Associated with Tau Pathology

Tau-associated neurofibrillary tangles (NFT) are a central neuropathological component underlying AD and its symptoms [50,88,103]. The medial temporal lobe (MTL) accumulates NFT early in AD disease progression [50]. This regional aggregation is relevant given the role of the hippocampus in generating ripples that are time-locked to the expression of NREM sleep spindles and slow waves which collectively support sleep-dependent memory processing [53,55].

Tau within the MTL diminishes the expression of hippocampal ripples in rodents, resulting in less temporally synchronized ripple events [104]. This desynchronization is, in part, due to loss of GABA-dependent inhibition that dictates patterned neural firing and thus governs neural oscillations [104]. Tau is further associated with abnormally long hyperpolarized downstates and impaired depolarizing up-states during NREM slow oscillations within the cortex [105]. Adding to reports in rodents, human studies have identified associations between CSF tau and diminished NREM SWS in patients with AD [12]. Moreover, AD patients have fewer NREM sleep spindles relative to healthy older adults, with the degree of spindle reduction predicting the severity of memory impairment [106].

In addition to tau disrupting sleep, sleep impacts tau accumulation. Preliminary evidence indicates that chronic sleep restriction may impair hippocampus-dependent memory and increase tau accumulation, particularly insoluble tau linked to NFT formation [107,108]. Conversely, the glymphatic system may also promote tau clearance [109]. Mechanistically, this may help to explain why older adults with superior sleep continuity have significantly less NFT pathology at autopsy [14]. It may further account for greater resilience against the detrimental impact of APOE4 genotype on AD risk [14], implicating sleep as a potential reserve factor countering AD pathophysiology.

Several crucial questions emerge from the proposed vicious cycle linking tau and sleep disruption. For example, does MTL tau aggregation proportionally disrupt the expression of, and network interaction between, NREM sleep oscillations (ripples, spindles, and slow waves), thereby contributing to memory impairment? In addition, what is the nature of relationships between sleep, Aβ, and tau pathology? Is the impact of Aβ and tau on sleep (and vice versa) inter-related or independent, and do these interactions forecast the progression of cognitive decline in aging and AD? Considering several reports that have linked NFT accumulation in the basal forebrain, brainstem, and hypothalamus with both NREM and REM sleep disruption, neuronal degeneration, and the cognitive functions sleep subserves [20,64,88,89,110–112] (Box 3), another issue regards the impact of tau on sleep beyond its accumulation within the MTL and its association with NREM sleep oscillations.

Beyond the role of NREM sleep in this model of Aβ regulation is an active impact of the waking brain state that further contributes to increases in Aβ [25], specifically through a higher neurometabolic rate relative to NREM sleep (Figure 2) [33]. Neurons consume greater levels of oxygen and ATP during wakefulness [34,35], while NREM sleep is associated with reduced oxygen consumption and the active replenishment of ATP levels [34,35]. Waking therefore represents a state of higher oxygen, ATP, and glucose consumption, resulting in higher rates of metabolic distress [36]. Ergo,
without sufficient NREM sleep to manage this waking burden, a higher risk for neurotoxic and oxidative consequences that promote AD pathophysiology occurs [36–38]. Supporting this proposal, amplified neurometabolic activity results in increased amyloid precursor protein (APP) production and β- and γ-secretase interactions, directly increasing Aβ production [39]. In addition, Aβ accumulation is promoted by oxidative stress [40] and further promotes oxidative stress itself [41]. This is in direct contrast to NREM sleep, which actively regulates oxidative stress and promotes cellular repair in the face of accumulating cellular oxidative damage [36,38].

Through its increased metabolic activity, wakefulness may therefore promote both APP and β- and γ-secretase interactions and the build-up of oxidative stress. Both of these processes cause Aβ to accumulate, with Aβ itself further potentiating its own production [40,41] (Figure 2). In an otherwise healthy system, wake-dependent build-up of metabolic and oxidative byproducts is managed by NREM sleep through at least two routes: (i) a sleep-dependent gynecologic response that promotes clearance of metabolic and neurotoxic waste, including Aβ [27], and (ii) restorative cellular processes that mitigate the impact of accumulated oxidative stress, for example replenishment of ATP and repair of DNA damage [35,36]. However, NREM sleep disturbance and/or sleep apnea-associated hypoxia [30]—both of which are more common in older adults, and especially those with MCI and AD—impairs this restorative process, leading to an escalation of Aβ. This Aβ aggregation, in turn, triggers increased sleep disruption through a positive feedback loop, and thus a vicious cycle ensues (Figure 2). Further promoting this vicious cycle, increased Aβ burden enhances neuronal excitability, with chronic sleep loss exacerbating this hyperexcitability through epileptogenic mechanisms [42]. Thus, not only does sleep loss promote Aβ aggregation while Aβ aggregation promotes sleep loss, but sleep loss also magnifies the effect of Aβ aggregation on neuronal function. This magnification has the potential to facilitate neuronal hyperexcitability [42], disrupt the impact of sleep on synaptic potentiation [23], triggering a nonlinear increase in Aβ accumulation, accelerating AD pathogenesis.

Numerous questions remain unresolved. For example, the precise mechanism(s) through which Aβ disrupts NREM sleep physiology, specifically within the slow oscillation frequency range (<1 Hz), is unknown. One tenable candidate that we offer is Aβ-disruption of NMDA and GABA A receptor function that underlies NREM slow oscillation expression in cortical regions known to accumulate Aβ early [43–45]. The low-frequency (<1 Hz) slow oscillations of NREM sleep are governed by NMDA and GABA A receptor activity, the former dictating a cellular UP state of cortical excitation, the latter the DOWN state involving prolonged hyperpolarization [44]. Any perturbation in their function, such as that caused by Aβ [43,44], should result in a selective reduction in NREM slow oscillation generation. Three lines of evidence tentatively support this possibility. First, NREM slow oscillations are impaired in rodent models of AD, with higher Aβ levels being associated with increased UP-state activity through NMDA-dependent Ca2+ influx, and thus reduced DOWN-state duration through GABA A-dependent Cl− influx [46]. Second, pharmacologically blocking cortical NMDA receptors decreases the incidence of the NREM slow oscillation while hastening its frequency [44]. Third, NMDA receptor function is disrupted in AD, particularly within the frontal lobe—the same regions in which NREM slow oscillations are predominantly generated [43,47]. While preliminary, these findings implicate an influence of Aβ on GABA and NMDA receptor function that may underlie the selective impairment of frontal NREM SWA expression in the <1 Hz frequency range in older adults. Although more empirical evidence is required, this hypothesis offers at least one, receptor-dependent, pathway through which Aβ pathology impairs the qualitative expression of NREM slow oscillations, resulting in a sleep state more vulnerable to fragmentation.

The Role of Sleep Disruption in AD and Aβ-dependent Cognitive Decline

Individuals with higher cortical Aβ burden have proportionally worse hippocampus-dependent memory [21,48–52]. While Aβ aggregates significantly within specific medial and lateral
prefrontal, posterior cingulate, and precuneus cortical regions [48,50], all of which generate NREM slow oscillations [47] (Figure 1G). Aβ does not accumulate substantively within the hippocampus until relatively late in AD. How, then, does a largely cortical-based pathology produce a subcortical, hippocampus-dependent memory impairment? While tauopathy and synaptic loss undoubtedly play crucial roles [50], it remains possible that Aβ pathology influences hippocampus-dependent memory indirectly, acting through intermediary factor(s) including disturbed NREM sleep.

Mounting evidence supports this proposition, implicating the disruption of NREM sleep as one intermediary factor brokering the influence of cortical Aβ on impaired hippocampus-dependent long-term memory consolidation. First, NREM sleep causally enhances episodic memory consolidation in healthy adults through the coordinated interaction of three associated oscillations: (i) hippocampal ripples, (ii) cortical slow oscillations (<1 Hz), and (iii) thalamocortical sleep spindles [53–55]. Cortical NREM slow oscillations coordinate a time-locked expression of sleep spindle and ripple events, with hippocampal ripples nested in temporal synchrony within the troughs of the sleep spindle oscillation [53]. Through this interaction, the hippocampus and neocortex are proposed to engage in a coordinated dialogue, allowing memory representations to become increasingly cortically-dependent and hippocampally-independent—a transformation that offers resistance to interference and minimizes forgetting [55]. This innate physiological system can be experimentally manipulated. Stimulation methods in humans that causally enhance <1 Hz slow oscillations and sleep spindles, as well as their coupling, enhance overnight memory consolidation and associated next-day retention [54,56]. Conversely, both sleep deprivation and the selective deprivation of slow waves impairs episodic memory [57,58]. It is therefore possible that any pathological disruption of this set of coordinated NREM oscillations—such as that associated with Aβ and/or tau pathology—could impair numerous aspects of sleep-dependent memory processing that contribute to cognitive decline in aging, including those of initial encoding and subsequent offline consolidation [4,8,21].

Consistent with this prediction, cognitive impairment in MCI and AD is associated with quantitative measures of poor sleep quality, particularly the deterioration of NREM sleep [11,12,21]. Moreover, CSF Aβ, tau, and orexin levels correlate with both sleep and cognitive measures, suggesting that sleep may be linked to both disease pathology and the memory decline associated with that pathology (further orexin details in Box 3) [12]. The degree of disruption in slow wave activity further predicts the severity of memory impairment in both healthy and Aβ+ older adults [4,21]. Perhaps most compelling are recent findings demonstrating that the severity of Aβ burden within medial prefrontal cortex significantly predicts the degree of impairment in <1 Hz NREM SWA generation [21] (Figure 1H). Moreover, this reduced <1 Hz NREM SWA generation is further associated with impaired overnight memory consolidation (and thus retention), together with impoverished hippocampal–neocortical memory transformation. Finally, structural equation models demonstrate that the association between cortical β-amyloid pathology and impaired hippocampus-dependent memory consolidation statistically depended on the degree of diminished <1 Hz NREM SWA (Figure 1). An important next challenge will be to understand if and how AD-related sleep disruption impacts memory processing before and beyond consolidation, considering that sleep has been associated with all key stages of long-term memory: encoding [8], integration [59], reconsolidation (post-retrieval) [60], and retrieval [61].

Disrupted sleep therefore represents a novel, but clinically underappreciated, mechanistic conduit through which cortical Aβ contributes to hippocampus-dependent cognitive decline in the initial stages of AD progression. However, this same disruption of NREM SWA, integral to AD pathophysiology, offers new diagnostic and therapeutic opportunities that we now address in the remaining sections.
Box 3. The Role of Orexin in AD

The hypothalamic orexin system contributes to the regulation of sleep and wake states. Degeneration of the orexin system in AD has long been recognized [110–112]. However, hypothalamic orexin dysfunction may actively contribute to AD pathophysiology, a possibility supported by the finding that individuals carrying a polymorphism of an orexin receptor gene show increased AD risk [113]. Nevertheless, controversies remain. Some studies reported higher orexin levels in AD [12,114]. Others, by contrast, reported either no difference [115–117] or lower orexin levels [110]. A potential explanation is that orexin changes across AD stages are not linear. In early stages [12,114], orexin levels may increase in response to orexinergic neurodegeneration. In later AD stages, degeneration of orexinergic neurons may overtake compensation [110]. In MOI and early AD, higher orexin levels predicted longer sleep latency, more fragmented sleep, and shorter REM sleep duration [12], while lower orexin levels in late-stage AD predicted more fragmented daytime wakefulness [118]. Whether increased orexin is unique to AD, separating it from other conditions such as frontotemporal and Lewy body dementia, remains unclear. While some data support this differential distinction [117,118], there is also evidence that hypothalamic tau burden predicts the severity of orexin neurodegeneration independently of dementia type [112].

While the precise pathway(s) through which alteration of orexin impacts AD remain unclear, Aβ and tau are implicated. Orexin levels predict CSF Aβ [114] and tau levels [12,115] in AD, although tau relationships are not AD-specific [112,115]. In rodents, orexin infusion increases Aβ levels, while Aβ levels decreased following the blockage of orexin receptors [25,83]. Aβ levels are also reduced in orexin knockout mice [25,83]. However, orexin knockout mice slept more, and sleep deprivation still increased Aβ deposition [83]. Thus, orexin alters Aβ through its impact on sleep/wake behavior. AD pathophysiology may therefore induce hypothalamic orexin neurodegeneration, while orexinergic degeneration, and the sleep–wake dysfunction associated with it, may instigate AD pathophysiology. Why tau pathology preferentially accumulates within hypothalamic orexin neurons, and how tau triggers increased orexin levels, remain unknown. Another perplexing finding is that patients with narcolepsy, who have profound orexinergic system degeneration, do not show an elevated risk for AD [119]. This despite the fact that CSF tau and Aβ levels are altered in narcoleptic patients [120], with two thirds of narcoleptic patients having tau pathology [119]. Such disparity may suggest that the neurobiology of narcolepsy is more indicative of a general increased risk for tauopathies, rather than AD specifically, although a more complex mechanistic explanation may emerge.

Sleep Disruption as an Early Diagnostic Biomarker of AD Risk

There is urgent need to identify biomarkers that predict which individuals are at greatest risk for developing AD, motivated by at least two goals: (i) offering the chance for preventative measures, pre-disease onset, and (ii) allowing nascent treatment intervention, early in the disease process [1,50]. Several lines of evidence now suggest that selective impairments of NREM sleep quality may serve both of these goals, representing a novel, non-invasive, relatively inexpensive, and specific biomarker of AD pathology.

First, disruptions of NREM SWS have been detected at early stages in those declining into AD, before clinical onset [9,11,21]. Second, the degree of sleep disruption is exaggerated in individuals with a genetic risk for developing AD, specifically APOE4+ older adults [9]. Third, even in healthy older adults without mild cognitive impairment, subjective and objective measures of sleep quality significantly predict the degree of existing cortical Aβ burden [21–23]. Fourth, reduced <1 Hz NREM SWA predicts Aβ in medial prefrontal cortex [21]–one of the earliest cortical sites to accumulate Aβ pathology [24]. Of note, this association is independent of the general age-related reductions in SWA (1–4 Hz) associated with grey matter loss [4].

Frequency-specific quantitative EEG measures of NREM sleep, particularly that in the <1 Hz signature range, may therefore represent an early biomarker of Aβ burden. Alongside other established biomarkers [50], sleep EEG may significantly aid in identifying an individual’s risk for developing AD years or even decades before onset of clinical symptoms. However, before this can be accepted, rigorous examination of this NREM spectral EEG signature must be undertaken. Specifically, its diagnostic utility must be characterized beyond its ability to distinguish between otherwise healthy Aβ+50- older adults. For example, while sleep disturbance is present among many other psychiatric and neurological conditions [5,62], it remains unclear to what degree this selective <1 Hz NREM SWA disturbance is also present. Targeted examinations in a variety of clinical populations will ultimately determine the accuracy of sleep EEG for differential
In addition to quantitative EEG measures of NREM sleep, wrist actigraphy-measured sleep fragmentation and sleep efficiency may be independent or additive candidate biomarkers of AD pathology and risk. Actigraphy-defined low sleep efficiency and high sleep fragmentation in older adults predicts higher CSF-measured Aβ42 levels, declining cognitive status, and higher risk for developing AD within 6 years [13,63]. In addition, the degree of actigraphy-measured sleep fragmentation in aging and AD tracks the magnitude of neuronal degeneration within hypothalamic sleep regulatory regions, with AD patients showing the greatest sleep fragmentation and neuronal degeneration [64]. By contrast, individuals with more consolidated measures of actigraphy-determined sleep exhibit superior cognitive function, reduced risk for developing MCI or AD, and a reduced impact of APOE4 genotype on both cognitive outcomes and AD risk [14]. These findings are consistent with rodent models with high Aβ production, which express a phenotype of marked sleep fragmentation [26].

Therefore, the association between Aβ and actigraphy-measured sleep fragmentation, in conjunction with EEG-assessed deficits in <1 Hz NREM SWA, may offer more meaningful sleep-related diagnostic utility in individuals at risk for developing AD. As actigraphy devices become more accessible, and if corresponding accuracy in tracking sleep quality sufficiently improves, the ramifications of this biomarker proposal could scale dramatically. However, to evaluate this possibility at a population scale, current mass-marketed wearable actigraphy devices will need to substantially improve upon currently reported accuracy, which appears to be low [65].

**Treatment Implications—Sleep Intervention as Preventative and Therapeutic**

Unlike many other consequences of AD pathology, such as structural brain atrophy or reductions in cerebral blood flow, sleep is a modifiable factor, and thus a treatable target [64,56,66]. This is especially important considering that Aβ-related sleep disruption may impair hippocampus-dependent memory, thus contributing to cognitive decline [21] (Figure 3A). Therapeutic interventions that restore NREM slow wave sleep quantity and/or quality offer at least two new treatment possibilities. First, NREM sleep enhancement in mid- to late-life may deliver a preventative benefit that reduces AD risk, in part, through improved Aβ clearance [27] and/or enhanced cellular restitution processes to combat accumulated oxidative stress [36]. While sleep enhancement should benefit all older adults, it may prove especially efficacious in high-vulnerability populations, such as APOE4 individuals, who express marked sleep deficits [14]. Second, sleep restoration may help to minimize the degree of cognitive decline in those with already extant Aβ pathology through two non-mutually exclusive mechanistic pathways: (i) increased Aβ clearance and cellular restitution, and (ii) enhanced long-term memory consolidation that helps to counteract cognitive decline associated with AD pathophysiology.

Currently, there are several candidate methods for achieving a NREM SWA enhancement benefit, particularly <1 Hz NREM SWA. Non-drug methods represent the most tenable candidates for NREM sleep enhancement. Among the best-studied is transcranial direct current stimulation (tDCS) in the <1 Hz range, which can double the overnight sleep-dependent memory benefit in young adults [56]. Successful enhancement of <1 Hz NREM SWA and memory consolidation has been demonstrated in young and older adults [56,66], patients with temporal lobe epilepsy [67], individuals with attention deficit hyperactivity disorder [68], and patients with schizophrenia [69]. A similar effect has also been reported in rodents [70]. Nevertheless, it is important to note that some failures to enhance <1 Hz NREM SWA and associated memory consolidation have been described in young and older adults as well [71,72], suggesting that further refinement of the technique is required before this method can be recommended.
Circumstances, increase improves is often anti-convulsive and SWS stimulation dependent improvements even associated made possible through consolidation. thereby potential Pharmacological Other

Figure (A) Non-invasive methods to assess SWA have been tested in young adults and been shown to significantly increase low-frequency NREM SWA in young adults, although no memory assessments were made [74]. Whether older adults would show similar low-frequency NREM SWA enhancement, and whether such sleep improvement transacts a functional memory benefit, remains untested.

Other non-pharmacological methods include auditory closed-loop stimulation during NREM SWS that significantly enhances <1 Hz NREM SWA and improves overnight hippocampus-dependent memory consolidation [54]. Preliminary findings in older adults have reported similar improvements in <1 Hz NREM SWA using this same method [73]. In addition, kinesthetic stimulation during sleep—through slow, rhythmic bed rocking—has been shown to significantly increase low-frequency NREM SWA in young adults, although no memory assessments were made [74]. Whether older adults would show similar low-frequency NREM SWA enhancement, and whether such sleep improvement transacts a functional memory benefit, remains untested.

A limitation of all of these methods is that none have been tested for long-term efficacy. It remains unknown if any could foster enhanced NREM SWA and cognition for a sustained period. An alternative in this regard is cognitive behavioral therapy for chronic insomnia (CBT-i): a non-pharmacological, non-invasive method that can successfully enhance long-term sleep quality and cognitive outcomes in patients suffering from chronic insomnia [75]. Because insomnia is more prominent in aging, MCI, and AD [5,7], and increases the risk for developing AD [15], CBT-i is another candidate opportunity for intervention. However, it remains unknown whether CBT-i improves physiological sleep oscillations, including <1 Hz NREM SWA, relevant for cognition and AD-pathology regulation.

Pharmacological methods for selective NREM sleep enhancement have so far proved less promising in the context of aging and cognition. Although multiple GABA-targeting hypnotic and anti-convulsive drugs that increase NREM SWA in a dose-dependent manner exist [76–79], they often fail to trigger any corresponding sleep-dependent memory benefit in the elderly, and many even have amnestic effects [77,78,80,81]. Moreover, such medications have actually been associated with an increased rather than reduced dementia risk [82]. Two related mechanisms
may explain these outcomes. First, many GABA-targeting drugs trigger faster-frequency increases in NREM sleep spectral power, rather than enhancing slow frequencies that support memory and are disrupted by Aβ pathology [77–79]. Indeed, older adults expressing faster-frequency NREM SWA (>1 Hz) demonstrate significantly worse overnight hippocampus-dependent memory consolidation, highlighting the importance of attention to the slow frequencies in the context of AD therapy [21]. Current GABA-targeting medications may therefore enhance sleep EEG features that are not only non-optimal for memory consolidation, but counter to it. A second explanation is that many of these medications alter sleep spindles and their coupling with NREM slow waves [77], with fewer spindles predicting worse memory [81]. Because the coupling between slow waves and sleep spindles is known to be crucial for promoting hippocampal-neocortical communication that supports memory consolidation [53–55], enhancing NREM SWA at the expense of sleep spindles and/or spindle–slow wave coupling may fail to promote memory consolidation or may even disrupt sleep-dependent memory processing.

Little is currently known regarding the impact of non-GABA-targeting sleep medications on enhancing sleep-dependent memory in elderly populations at risk for dementia. For example, alterations in the orexin system have been implicated in both rodent models of AD and in human patients with AD [12,25,83] (Box 3). Whether therapies targeting orexin ameliorate sleep disruption in AD or in individuals at risk for developing AD, and whether such sleep improvement offers cognitive benefits, is similarly unknown.

Although considerably more research is necessary, it appears tenable that older adults and those with AD are permissive to sleep intervention. Indeed, treatment of sleep apnea in AD patients improves some cognitive outcomes [19]. Moreover, sleep apnea treatment before onset into MCI significantly delays the age of onset into MCI [18]. One goal of future research programs will be to determine whether experimentally enhancing NREM sleep—on its own or in combination with other intervention and lifestyle factors—offers AD prophylaxis, limits AD progression upon development, and/or ameliorates disease symptomatology.

Concluding Remarks
As evidence for causal, bidirectional links between sleep disturbance and AD pathophysiology continues to grow, new key questions are emerging (see Outstanding Questions). We close by outlining a select few that, to us, appear pressing and potentially transformative.

First, most studies examining the relationship between sleep and AD pathology have used cross-sectional designs. No study to date has gathered longitudinal sleep EEG recordings alongside measures of AD pathophysiology and sleep-dependent memory. Such data are not only crucial to establish the impact of sleep disturbance on AD risk within a given individual over time but also to tease apart the directionality of these sleep–AD relationships and their relationship with varied stages of memory processing and retention. Furthermore, longitudinal designs offer a powerful test of the biomarker utility of sleep disturbance as an accurate forecasting tool of AD risk and AD pathological progression. Thus, longitudinal studies examining the diagnostic utility of sleep disturbance to forecast features of AD are now imperative. Such a scheme, outlined in Figure 3B, includes predictive changes in AD pathological burden, AD risk, conversion to MCI or AD, and/or the cognitive decline associated with AD.

Second, there is a need to systematically compare the relative impact of distinct sleep disorders and the varied signatures of sleep disturbance on AD risk. For example, are patients with sleep apnea, relative to otherwise healthy older adults or older adults with insomnia, at greater AD risk because they suffer from both chronic intermittent hypoxia and disrupted NREM slow oscillation expression? Furthermore, do co-morbid sleep disorders interact with other clinical risk factors, such as genetics, depression, cardiovascular disease, immune deficiencies or diabetes, to
accelerate AD onset and/or progression? Is the sleep fragmentation associated with AD a symptom of co-morbid sleep disorders, such as sleep apnea or insomnia? While older adults at risk for AD can still show increased sleep fragmentation without having sleep apnea or insomnia, it remains unclear how much either diagnosed or undiagnosed sleep disorders explain this symptom.

A third unresolved question is whether specific electrophysiological signatures of sleep disruption, such as decreases in <1 Hz NREM SWA, are unique to Aβ pathology or if they similarly track tau pathological burden. If so, characterizing how the interaction of these factors leads to deficits in sleep-dependent learning, memory, and plasticity will be essential to obtain a complete understanding of the role of sleep in AD. The recent development of tau PET imaging in vivo in humans, combined with existing PET-amyloid imaging, now makes answering these questions viable.

Finally, there is urgent need for therapeutic sleep interventions and innovations that enhance sleep in the elderly and in those with AD. A first step would be to focus on those aspects of sleep known to be especially impacted by AD pathology, and that have functional cognitive consequences, such as NREM slow oscillations, sleep spindles, REM sleep, and sleep continuity. Moreover, given the multifaceted nature of sleep disturbance associated with AD, examining combinatorial approaches that target multiple underlying mechanisms of sleep disturbance in AD may be most effective. Clinical trials will then need to determine whether such targeted sleep improvement reduces AD risk, delays AD onset, slows AD pathophysiological progression, or alleviates the cognitive decline associated with AD.

Should any of the above be true, it would require that medical practice be more diligent in inquiring about, diagnosing, and treating sleep difficulties across the lifespan, especially in the elderly. More generally, such findings would argue for improved public health policies highlighting the crucial need for sufficient quality sleep throughout adulthood—a memorandum that may lower dementia risk and maintain cognitive health across the population.

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References
51. Mattsson, N. et al. (2015) Brain structure and function as mediators of the effects of amyloid on memory. Neurology 84, 1136–1144
61. Dunw, N. (2016) Sleep not just protects memories against forgetting, it also makes them more accessible. Cortex 74, 289–296
64. Lim, A.S. et al. (2014) Sleep is related to neuron numbers in the ventrolateral preoptic/intermediate nucleus in older adults with and without Alzheimer’s disease. Brain 137, 2847–2861
68. Fiath-Kristensen, A. et al. (2014) Transcranial oscillatory direct current stimulation during sleep improves declarative memory.
consolidation in children with attention-deficit/hyperactivity disorder to a level comparable to healthy controls. Brain Stimul. 7, 793–799


71. Eggert, T. et al. (2013) No effects of slow oscillatory transcranial direct current stimulation (tDCS) on sleep-dependent memory consolidation in healthy elderly subjects. Brain Stimul. 6, 938–945

72. Sahlem, G.L. et al. (2015) Oscillating square wave transcranial direct current stimulation (tDCS) delivered during slow wave sleep does not improve declarative memory more than sham: a randomized sham controlled crossover study. Brain Stimul. 8, 528–534


76. Betti, P. et al. (2012) Differential effects of a dual orexin receptor antagonist (SB-649866) and zolpidem on sleep initiation and consolidation, SWA, REM sleep, and EEG power spectra in a model of situational insomnia. Neuropsychopharmacology 37, 1224–1233

77. Feld, G.B. et al. (2013) Slow wave sleep induced by GABA agonist taglbine fails to benefit memory consolidation. Sleep 36, 1317–1326


79. Walsh, J.K. et al. (2013) Enhancing slow wave sleep with sodium oxybate reduces the behavioral and physiological impact of sleep loss. Sleep 35, 1217–1225


83. Rich, J.H. et al. (2014) Potential role of orexin and sleep modula-
tion in the pathogenesis of Alzheimer’s disease. J. Exp. Med. 211, 2487–2496


97. Torres, B. et al. (2015) Facial expression recognition in Alz-
heimer’s disease: a longitudinal study. Arq. Neuropsiquiatr. 73, 380–389


99. Cherbuin, N. et al. (2015) Dementia risk estimates associated with measures of depression: a systematic review and meta-
analysis. BMJ Open 5, e008853


104. Wiltgen, J. et al. (2014) Disrupted hippocampal sharp-wave rip-
lle-associated spike dynamics in a transgenic mouse model of dementia. J. Physiol. Published online December 2014. http://dx.doi.org/10.1113/jphysiol.2014.292689


107. Di Meco, A. et al. (2014) Sleep deprivation impairs memory, tau metabolism, and synaptic integrity of a mouse model of Alz-


120. Heier, M.S. et al. (2014) Increased cerebrospinal fluid levels of nerve cell biomarkers in narcolepsy with cataplexy. Sleep Med. 15, 614–618