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Sleep: A novel mechanistic pathway, biomarker, and treatment target in the pathology of Alzheimer's disease?

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Abstract

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 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.

Keywords

Sleep; Alzheimer's disease; Amyloid-β; Aging; Cognitive decline

Alzheimer's Disease and the Emerging Interaction with Sleep

Alzheimer's disease (AD) is one of the largest public health and economic challenges of the 21st century. One in ten 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, the former before disease onset[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 amyloid-β (Aβ) pathology. We further outline the cognitive consequences of sleep

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disruption as a novel mechanistic conduit potentially contributing to cognitive decline associated with AD pathophysiology. Finally, we explore the potential of sleep to serve as both a biomarker of AD, and 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 75 years of age 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; ~0.5–4.5Hz)[3, 4]. These age-related decreases in NREM SWS quantity and quality are paralleled by increasing amounts of time spent awake 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]. Marked differences in the ability to generate sleep, including NREM SWS, exist[2, 5]. Similar variability is observed in the prevalence of sleep disorders[5–7]. This has lead 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 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]. Additionally, 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, 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, yet the onset, severity, and nature of these impairments are all significantly accelerated in those with AD and those at highest risk for AD. Although these sleep disturbances have long been considered a robust symptom 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]. In 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 independent of insomnia or apnea[12, 14, 21–23]. This indicates that the association between sleep and Aβ pathology is not just a consequence of a primary sleep disorder, or 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 phospohorylated tau in CSF[12, 14, 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 1Hz[21], unlike the more general age-related decline in broader SWA from 1–4Hz linked to grey matter atrophy[4]. Second, the signature association with <1Hz NREM SWA correlates most significantly with Aβ in medial prefrontal cortex[21]—one of the earliest sites to accumulate Aβ[24].

Rodent models further support a connection between Aβ and NREM sleep (Fig. 1A–F). Experimentally increasing cortical Aβ causally fragments NREM sleep[25, 26], while 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 critical pathway through which the brain appears to manage Aβ levels: sleep's absence 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].

Though 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, however, implicating active, antagonistic mechanisms underlying the reciprocal relationship between NREM sleep and Aβ, as well as the facilitatory relationships between wake-dependent processes and Aβ production (Fig. 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 two-fold faster rate during NREM SWS than during[25, 27] wake (Fig. 2). Of relevance, Aβ clearance is reduced 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[32].

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], in particular through its higher neurometabolic rate relative to NREM sleep (Fig. 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 is suffered[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] (Fig. 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: (1) a sleep-dependent glymphatic response that promotes clearance of metabolic and neurotoxic waste, including Aβ[27], and (2) active restorative cellular processes that mitigates the impact of accumulated oxidative stress, e.g. replenishment of ATP, 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 (Fig. 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], and even trigger nonlinear increases in Aβ accumulation, accelerating AD pathogenesis.

Nevertheless, numerous questions remain unresolved. For example, the precise mechanism(s) through which Aβ disrupts NREM sleep physiology, specifically within slow oscillation frequency range (<1Hz), is unknown. One tenable candidate that we offer is Aβ-disruption of frontal 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 (<1Hz) 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], could 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 associated with increased UP state activity through NMDA-dependent Ca^{2+} 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 <1Hz 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] (Fig. 1G), Aβ does not accumulate substantively within the hippocampus until relatively late in AD. How then does a largely cortical-based pathology engender a sub-cortical, hippocampus-dependent memory impairment? While tauopathy and synaptic loss undoubtedly play critical roles[50], it remains possible that Aβ pathology influences hippocampus-dependent memory indirectly, through intermediary factor(s) including disturbed NREM sleep.

Mounting basic and translational evidence suggests that NREM sleep disruption represents one potential 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: (1) hippocampal ripples, (2) cortical slow oscillations (<1 Hz), and (3) thalamo-cortical 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 <1Hz 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 <1Hz NREM SWA generation[21] (Fig. 1H). Moreover, this reduced <1Hz NREM SWA generation was further associated with impaired overnight memory consolidation (and thus retention), together with impoverished hippocampal-neocortical memory transformation. Finally, structural equation models revealed that the association between cortical β-amyloid pathology and impaired hippocampus-dependent memory consolidation statistically depended on the degree of diminished <1Hz NREM SWA (Fig. 1I). An important next challenge will be to understand if and how AD-related sleep disruption impacts memory processing before and beyond consolidation, since sleep has been associated with all key stages of long-term memory: encoding[8], integration[59], reconsolidation (post-retrieval)[60], and retrieval of long-term memory[61].

Disrupted sleep therefore could be a novel, yet 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 translational opportunities, the diagnostic and therapeutic aspects of which we outline in the remaining sections.

Sleep Disruption as an Early Diagnostic Biomarker of AD Risk

There is urgent need to identify and develop early biomarkers that determine which individuals are at greatest risk for developing AD, motivated by at least two goals: (1) offering the chance for preventative measures, pre-disease onset, and (2) allowing nascent treatment intervention, early in the disease process[1, 50]. Several lines of evidence now suggest that selective diminutions of NREM sleep quality may serve both of these goals, potentially representing a novel, non-invasive, relatively inexpensive, and potentially specific biomarker of AD pathology. First, disruptions of NREM SWS have been detected at early stages of 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, i.e. 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 <1Hz 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 (1–4Hz) associated with grey matter loss[4].

Frequency-specific quantitative EEG measures of NREM sleep, particularly that in the <1 Hz signature range, therefore offer signs of being an early biomarker of Aβ burden. Alongside other established biomarkers[50], sleep EEG may therefore 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+/− 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 <1Hz NREM SWA disturbance is also present. Targeted examinations in a variety of clinical populations will ultimately determine the accuracy of sleep EEG for differential diagnosis, and for assessing clinical risk regarding the development of specific medical conditions, including AD.

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 six years[13, 63]. Additionally, 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]. In 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 NREM sleep fragmentation[26]. Therefore, the association between Aβ and actigraphy-measured sleep fragmentation, in conjunction with EEG-assessed deficits in <1Hz NREM SWA, may offer more meaningful sleep-related diagnostic utility in individuals at risk for developing AD. This hypothesis will

need to be tested in future clinical investigations. Nevertheless, 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, in order 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[54, 56, 66]. This is especially important considering that Aβ-related sleep disruption may impair hippocampus-dependent memory, thus contributing to cognitive decline[21] (Fig. 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-vulnerable populations, such as APOE4+ individuals, which express marked sleep deficits[14]. Second, sleep restoration may help 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, or (ii) enhance long-term memory consolidation that helps counteract cognitive decline associated with AD pathophysiology.

Currently, there are several promising methods for achieving a NREM SWA enhancement benefit, particularly <1Hz NREM SWA. Several non-pharmacological methods represent the most tenable candidates for NREM sleep enhancement. Among the most well studied is transcranial direct current stimulation (tDCS) in the <1Hz range, which can double the overnight sleep-dependent memory benefit in young adults[56]. A few reports have successfully enhanced <1Hz NREM SWA and memory consolidation 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 <1Hz 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.

Other, more non-invasive, non-pharmacological methods include auditory closed-loop stimulation during NREM SWS that significantly enhances <1Hz NREM SWA and improves overnight hippocampus-dependent memory consolidation[54]. Preliminary findings in older adults have reported similar improvements in <1Hz NREM SWA using this same method[73]. Another method, kinesthetic stimulation during sleep—through slow, rhythmic bed rocking—has been shown to significantly increase low frequency NREM SWA in young

adults, though 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 of them 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]. As 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 <1Hz 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 lowering of 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 (>1Hz) 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]. Since the coupling between slow waves and sleep spindles is known to be critical 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 not promote memory consolidation, and 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] (see Box 3). Nevertheless, it remains unclear 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.

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 life-style factors—offers AD prophylaxis, limits AD progression upon development, and/or ameliorates disease symptomatology.

Concluding Remarks

As evidence for causal, bi-directional links between sleep disturbance and AD pathophysiology continues to grow, new key questions are emerging. 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 critical 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 Fig. 3B, include 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 <1Hz 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 those with AD. A first step would be to focus on those aspects of sleep known to be especially impacted by AD pathology, and 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 critical 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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Highlights

1. A bidirectional, causal interaction exists between NREM sleep and Aβ pathophysiology that may contribute to Alzheimer's disease (AD) risk and progression.
2. The disruption of NREM sleep may represent a novel pathway through which cortical Aβ impairs hippocampus-dependent memory consolidation.
3. 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.
4. Evidence implicates sleep disturbance as a consequence and cause of AD progression; one that is modifiable, offering preventative and therapeutic treatment potential.

Box 1

REM sleep, Aβ pathology, and Alzheimer's Disease

Relationships between sleep, AD, and AD pathology extends beyond NREM SWS, and includes 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, 85]. 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 (see 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 critical 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[95]—are risk factors for developing AD[99, 100]. Thus, REM sleep deficits may exacerbate psychiatric conditions common in AD patients[101], 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 considering 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 desynchrony 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 down states 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 insoluable tau linked to NFT formation[107, 108]. Conversely, the glymphatic system may also promote tau clearance[109]. Mechanistically, this may help 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 the APOE4 genotype on AD risk[14], implicating sleep as a potential reserve factor countering AD pathophysiology.

Several critical 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? Additionally, 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 tau's impact on sleep beyond its accumulation within the MTL and its association with NREM sleep oscillations.

Box 3

The role of orexin in Alzheimer's Disease

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, in 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 MCI 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[116]. Whether increased orexin is unique to AD, separating it from dementias such as frontotemporal and Lewy body dementia, remains unclear. While some data supports this differential distinction[117, 118], there is also evidence that hypothalamic tau burden predicts the severity of orexin neurodegeneration independent 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, though 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 remains unknown. Another perplexing finding is that patients with narcolepsy, who have profound orexingic 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, though a more complex mechanistic explanation may emerge.

Outstanding Questions Box

1. Longitudinally, what is the impact of sleep disturbance on AD risk and cognitive decline associated with AD, and what are the directionality of these relationships?
2. What is the contribution of distinct sleep disorders and age-associated sleep disturbance to AD risk and AD pathophysiology?
3. Are there distinct sleep biomarkers that predict unique aspects of AD pathophysiology and AD risk, and further track AD progression?
4. Are there therapeutic sleep interventions and innovations that enhance sleep in the elderly and those with AD, offering preventative and therapeutic value, respectively?

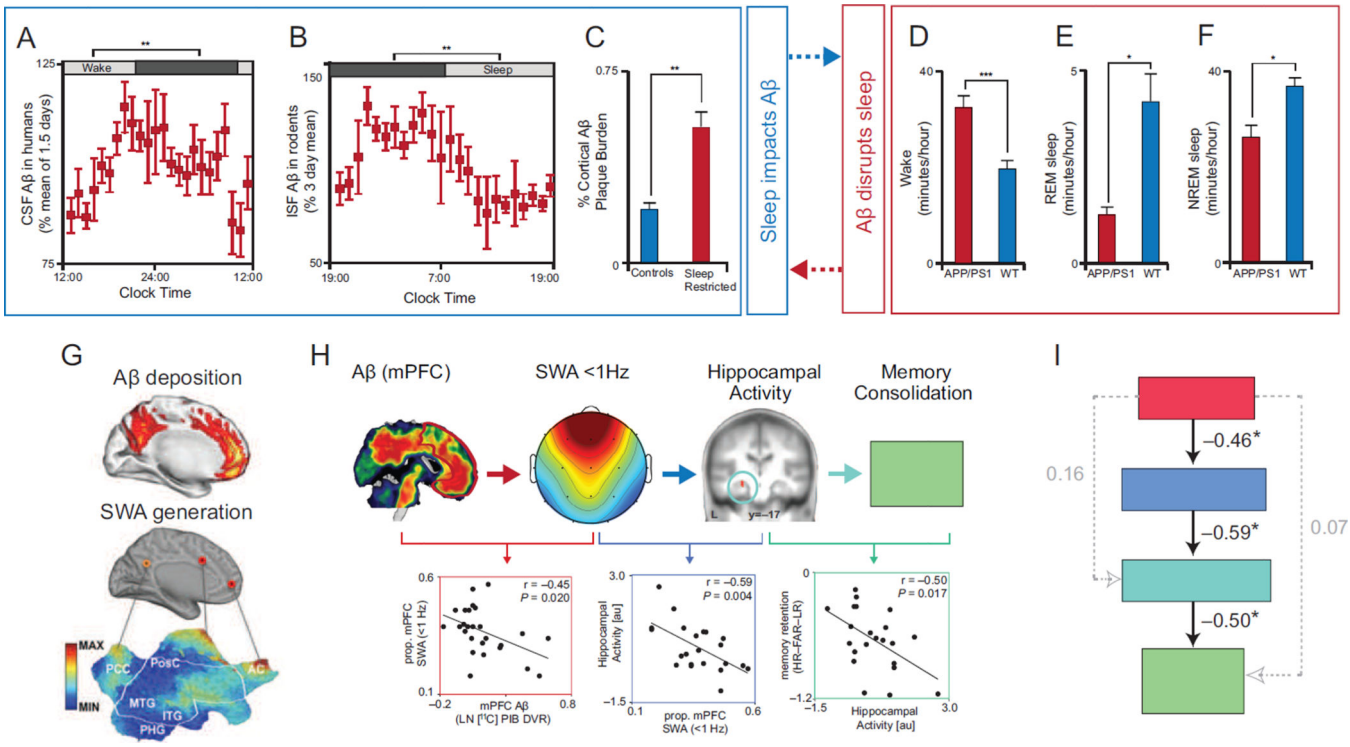

Figure 1.

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 restricting 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 increases wake time (**d–f**, red box). A potential mechanism underlying disrupted NREM SWS by Aβ pathology is the aggregation of Aβ (**g**, top sagittal brain slice adapted from[48]) within the same medial prefrontal cortical nodes critical 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 <1Hz NREM SWA (**h**, red scatter plot, adapted from[21]). The disruption of <1Hz NREM SWA by Aβ, in turn, is associated with impaired sleep-dependent consolidation of hippocampus-dependent memory. Disrupted <1Hz 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 <1Hz NREM SWA (**i**, adapted from[21]). While the relationship between Aβ and NREM SWA is likely to be bidirectional, the strongest link between Aβ and memory was through its association with NREM SWA. Abbreviations: Aβ, amyloid-β protein; CSF,

cerebrospinal fluid; ISF, interstitial fluid; APP/PS1, amyloid precursor protein and presenilin 1 mutant rodents; SWA, slow wave activity; MAX, maximum; MIN, minimum; PCC, posterior cingulate cortex; PosC, post-central gyrus; MTG, medial temporal gyrus; ITG, inferior temporal gyrus; PHG, parahippocampal gyrus; AC, anterior cingulate gyrus; mPFC, medial prefrontal cortex; prop., proportion; LN, natural logarithm; DVR, distribution volume ratio; L, left hemisphere; HR, hit rate; FAR, false alarm rate; LR, lure rate; au, arbitrary units; and HC, hippocampus.

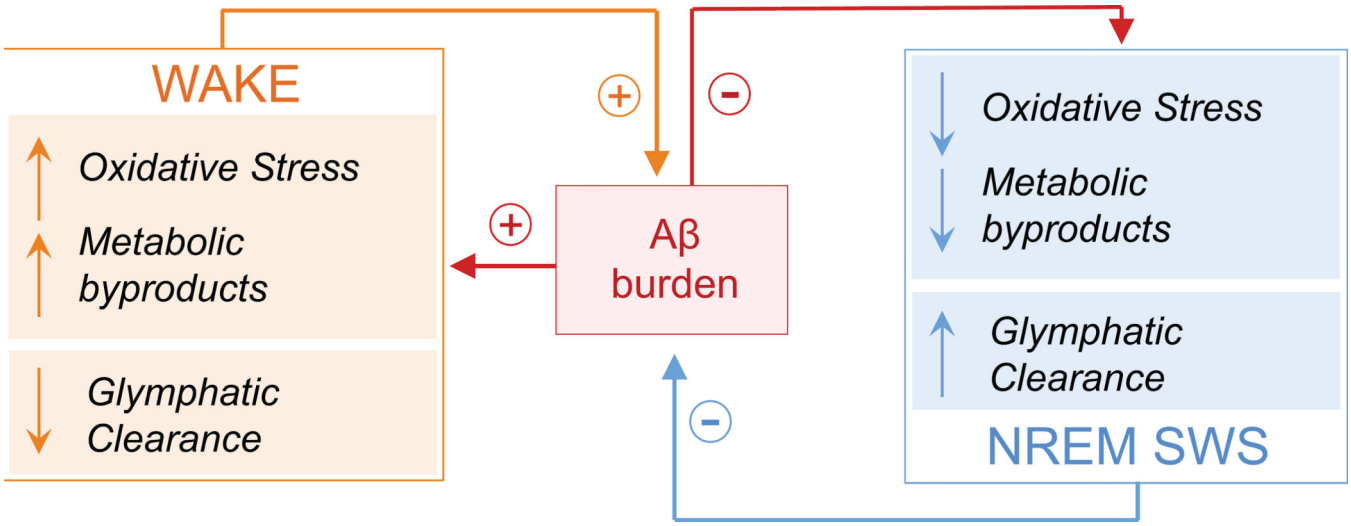

Figure 2.

Proposed theoretical schematic of active mechanistic processes regulating the reciprocal nature between NREM sleep and wake with respect to Aβ burden. During wake (orange box), glymphatic Aβ clearance is low[27], neurometabolic and neuronal spiking activity is high[34, 42], and oxidative stress is high[38], fostering higher Aβ burden (red box)[25, 27, 28, 40]. Aβ, in turn, promotes greater oxidative stress[41], neuronal hyperexcitability[42], and reduces glymphatic clearance through processes including cerebral amyloid angiopathy[29] and, presumably, NREM sleep disturbance[21, 26]. Thus, a facilitatory process is created where Aβ may promote its own accumulation. During NREM sleep (blue box), glymphatic Aβ clearance is high[27], neurometabolic rate is low[34,35], and active cellular processes promote cellular restitution that reduces oxidative damage[36]. This balances both Aβ accumulation and the negative consequences of Aβ accumulation under conditions of healthy sleep. However, under pathological conditions, Aβ burden may actively disrupt NREM sleep[21, 26]. This disruption, alongside reduced Aβ clearance due to cerebral amyloid angiopathy[29], theoretically creates an environment whereby NREM sleep can no longer successfully suppress Aβ accumulation. This once again exacerbates the vicious cycle, triggering greater Aβ aggregation and accelerating AD pathophysiological progression. Abbreviations: Aβ, amyloid-β protein; and NREM SWS, non-rapid-eye-movement slow wave sleep.

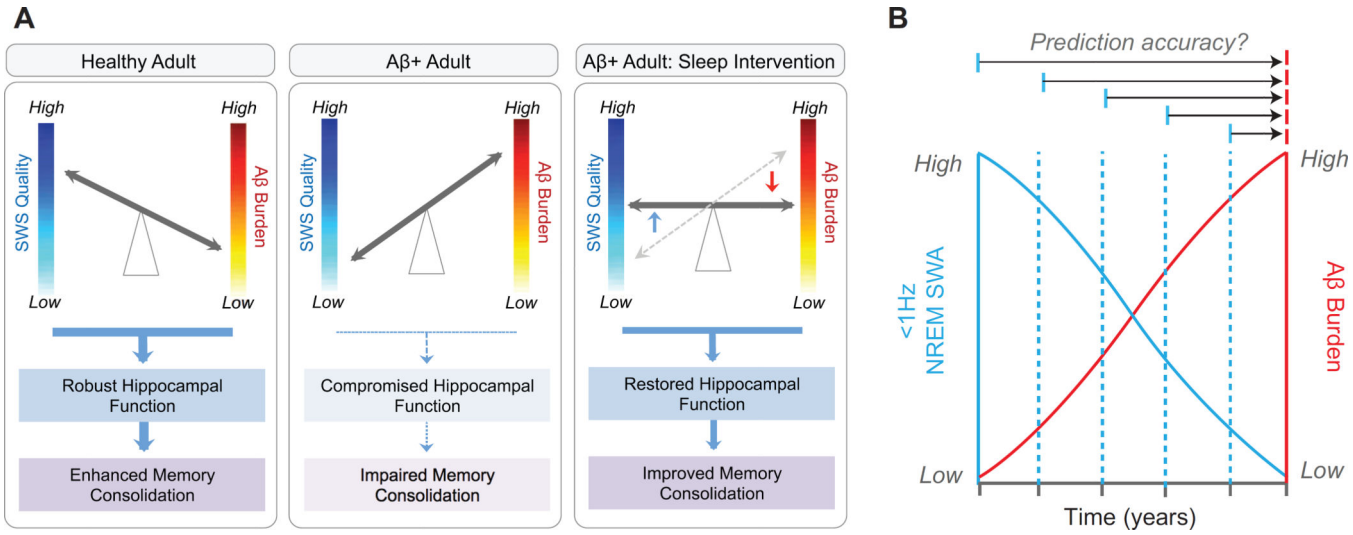

Figure 3.

Proposed consequences of the reciprocal relationship between Aβ, <1Hz NREM SWA and memory functioning under different circumstances, and the potential utility of sleep as a novel biomarker. In healthy older adults with low Aβ burden (**a**, left panel), NREM SWS quality is high, thereby facilitating hippocampus-dependent memory consolidation. In Aβ+ older adults (**a**, middle panel), NREM SWS quality is low, resulting in compromised memory consolidation. However, should NREM SWS quality be rescued through therapeutic sleep intervention in Aβ+ older adults (**a**, right panel), memory consolidation should be improved through two non-mutually exclusive pathways: i) by minimizing the negative impact of Aβ burden on sleep-dependent memory processing, and/or ii) through facilitating greater glymphatic Aβ clearance. (**b**) Since <1Hz NREM SWA is associated with Aβ burden in healthy older adults before MCI or AD onset, it is possible that this measure may offer diagnostic utility as a noninvasive biomarker of Aβ burden and AD risk. Longitudinal studies have the ability to examine the diagnostic potential of <1Hz NREM SWA, not only as a static, surrogate marker of *current* Aβ burden, but as a predictive biomarker that forecasts Aβ accumulation or risk of conversion to AD years in advance (multiple horizontal arrow tests). Abbreviations: Aβ, amyloid-β protein; Aβ + adult, an older adult with Aβ pathology; SWS, slow wave sleep; and NREM SWA, non-rapid-eye-movement slow wave activity.