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Review

REVIEW

Sleep–wake regulation and the hallmarks of the pathogenesis of Alzheimer's disease

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Abstract

While efficient treatments for Alzheimer's disease (AD) remain elusive, a growing body of research has highlighted sleep–wake regulation as a potential modifiable factor to delay disease progression. Evidence accumulated in recent years is pointing toward a tight link between sleep–wake disruption and the three main hallmarks of the pathogenesis of AD, i.e. abnormal amyloid-beta (Aβ) and tau proteins accumulation, and neurodegeneration. However, all three hallmarks are rarely considered together in the same study. In this review, we gather and discuss findings in favor of an association between sleep–wake disruption and each AD hallmark in animal models and in humans, with a focus on the preclinical stages of the disease. We emphasize that these relationships are likely bidirectional for each of these hallmarks. Altogether, current findings provide strong support for considering sleep–wake disruption as a true risk factor in the early unfolding of AD, but more research integrating recent technical advances is needed, particularly with respect to tau protein and neurodegeneration. Interventional longitudinal studies among cognitively healthy older individuals should assess the practical use of improving sleep–wake regulation to slow down the progression of AD pathogenesis.

Statement of Significance

Here, we integrate within a single review the findings associating sleep–wake regulation and the three main hallmarks of Alzheimer's disease (AD) pathogenesis in the preclinical stages of the disease. The causality of these relationships is discussed and the emphasis is placed on the bidirectionality between sleep–wake quality and AD neuropathological processes. As current research provides strong support for considering sleep–wake disruption as a true risk factor in the early unfolding of AD, the practical use of improving sleep and wakefulness to hinder AD pathogenesis should be further investigated by researchers and clinicians.

Key words: sleep–wake regulation; circadian rhythms; Alzheimer's disease; cognitive decline; amyloid-beta; tau; neurodegeneration

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Introduction

The current search for an Alzheimer's disease (AD) treatment, although encouraging, is still failing to provide efficient therapies to significantly delay disease progression, and the existing ones only grant marginal symptomatic relief [1]. Indeed, several recent clinical trials were unsuccessful in developing new drug therapies against AD [2, 3]. With an estimated healthcare cost of 818 billion US dollars per year worldwide, AD, the most prevalent form of dementia, represents an important socioeconomic and scientific challenge in our ever-aging society [4]. Some consider that delaying the onset of AD by just 5 years would decrease AD costs by 40% [5]. Early detection and prevention are promising means to reach this objective [6]. However, only 30% of AD cases are considered to be associated with recognized environmental risk factors for AD (diabetes, low education, smoking, lack of physical activity, hypertension, and depression) and acting on them would only moderately attenuate the foreseen increase in AD prevalence [7]. Hence, identifying novel modifiable protective and risk factors for AD is crucially needed. These novel factors should facilitate the early detection of an increased risk for AD, even in asymptomatic individuals, and allow for more efficient prevention [6]. In the present review paper, we argue that the regulation of the sleep–wake cycle and its disruption constitute such novel factors. The last decade has indeed seen a growing body of evidence supporting the link between AD-related processes and the regulation of sleep and wakefulness [8–12]. Accordingly, a recent meta-analysis of 27 observational studies revealed that approximately 15% of AD in the population may be attributed to treatable sleep problems, and that individuals with sleep-related issues exhibit a 1.55 times higher risk of developing the disease [13].

The main pathophysiological hallmarks of AD are the abnormal accumulation in the brain of amyloid-beta (Aβ) protein in plaques and of tau protein in neurofibrillary tangles (NFTs), together with neurodegeneration, i.e. synaptic and neuronal loss [14]. These hallmarks contribute to predicting the conversion of mild cognitive impairment (MCI), a prodromal phase of AD, to fully declared AD [15, 16]. Importantly, it is now well established that Aβ and tau protein accumulations as well as brain atrophy start decades before MCI or AD symptoms onset. A period corresponding to AD "preclinical" stages has therefore been proposed and encompasses the 10 to 20 years preceding observable cognitive impairments [15, 17]. It is important to stress that AD preclinical stages reflect an increased risk for the disease rather than being a deterministic feature: whether and when one will develop symptomatic AD cannot be established based solely on the presence of AD pathophysiological hallmarks. Nevertheless, together with Apolipoprotein E (*APOE*) polymorphism, the strongest genetic risk factor for sporadic AD [18–20], these pathophysiological changes offer the current best bases for applying prevention strategies to individuals at risk of developing sporadic AD.

Here, we provide a narrative review of the evidence for the relationship between the disruption of the sleep–wake cycle and the hallmarks of AD (i.e. Aβ burden, tau burden, and neurodegeneration) during its preclinical stages, both in humans and animal models. The papers linking sleep–wake regulation and AD pathophysiology that were considered are summarized in an overview table for each hallmark, i.e. (Table 1) for the Aβ section, (Table 2)for the the tau section, and (Table 3) for the neurodegeneration section. We will only discuss the late-onset sporadic form of AD as it represents the vast majority of AD cases compared with the early-onset familial form which accounts for less than 5% of AD cases [21, 22].

Sleep–Wake Regulation and Amyloid-Beta

Aβ refers to peptides of 36–43 amino acids that normally exist in the brain in a soluble form but become toxic when aggregated into diffusible oligomers [23] and eventually form extracellular insoluble amyloid plaques [24]. In nonpathological conditions, the physiological role of Aβ is uncertain but is suspected to participate to normal synaptic function [23]. Aβ40 is the major Aβ species (~80%–90%) produced by β- and γ-secretase in the sequential enzymatic cleavage of the larger transmembrane amyloid precursor protein (APP). Aβ42, one of the minor species (~5%–10%), plays a crucial role in the aggregation of amyloid into plaques because of its hydrophobic and fibrillogenic properties [25–27]. One can monitor AD pathophysiology progression with positron emission tomography (PET) using Aβ ligands, but Aβ42 assay in the cerebrospinal fluid (CSF) is also a sensitive and common biomarker for AD. In fact, lower CSF Aβ42 concentration is thought to reflect and even to precede amyloid plaque formation in the brain [28, 29].

The AD-related pathophysiological process of Aβ follows a stereotyped progression pattern, with Aβ deposits first found in the neocortex. As the disease progresses, allocortical brain regions (e.g. entorhinal cortex and hippocampus) are involved as well as nuclei from the basal forebrain. Ultimately, Aβ burden encompasses brainstem nuclei and the cerebellum [30]. The prevailing theory of AD pathogenesis hypothesizes that the accumulation of Aβ into insoluble plaques is the key initiator of a series of pathogenic processes that eventually lead to AD [31, 32]. At first, changes in Aβ levels caused by an increase in total Aβ production and/or a reduced clearance result in Aβ deposits that impede synaptic function and diminish long-term potentiation of neuronal circuits. Inflammatory responses and plaque formation further amplify synaptic and neuronal damage, precipitating widespread neuronal dysfunction, cell death, and ultimately dementia with plaque and tangle pathology [33]. Although the broad outlines of the so-called "amyloid cascade hypothesis" have been supported by the work of many researchers, whether Aβ accumulation is the prime event in the development of AD neuropathological processes is still not clearly established [34–38]. Furthermore, soluble forms of Aβ, i.e. the precursors that subsequently lead to Aβ plaques, might be more toxic than the aggregated insoluble forms: oligomeric neurotoxic species of Aβ bind to different components of neuronal and non-neuronal plasma membranes and induce complex patterns of synaptic dysfunction and synapse loss [23].

The striking role of the sleep–wake cycle in the unfolding of Aβ pathology finds its roots in two landmark findings: the discovery that soluble Aβ dynamics are strongly associated with sleep and wakefulness [39, 40], and the existence of a sleep-related metabolite clearance system in the brain [41, 42]. Using in vivo microdialysis, Kang and colleagues [39] investigated hippocampal Aβ levels during wakefulness and sleep in wild-type mice and Tg2576 mice, a well-characterized mouse model of AD known to overexpress a mutant form of human APP [43, 44]. First, they found that interstitial fluid (ISF) Aβ levels of Tg2576

Table 1. Summary table of studies considered in this review and directly linking sleep–wake regulation to amyloid-beta

Reference	Target population (*N*, age)	Sleep–wake variable(s)	Aβ variable(s)	Main outcome(s)
Branger et al., 2016	Cognitively normal participants (51, 64.1 ± 10.6 years)	Self-reported sleep latency and sleep quality	Cortex Aβ burden	Longer sleep latency and poorer sleep quality were associated with increased Aβ burden
Brown et al., 2016	Cognitively normal participants (184, 75.5 ± 6.1 years)	Sleep latency	Cortex Aβ burden	Longer sleep latency was associated with increased Aβ burden
Busche et al., 2015	APP23xPS45 mice (5, 6–8 months), wild-type mice (6, 6–8 months)	Long-range SWA coherence	Cortex, hippocampus, and thalamus Aβ burden, exogenous Aβ infusion	SWA coherence between cortex and hippocampus was disrupted in transgenic mice Aβ administration was associated with impaired SWA coherence in wild-type mice
Carvalho et al., 2018	Cognitively normal participants (283, 77.1 ± 4.8 years)	ESS	Longitudinal Aβ accumulation	Excessive daytime sleepiness was associated with increased Aβ accumulation over 7 years of follow-up
Chen et al., 2017	Male Sprague-Dawley rats (40, 3 months)	2–4 days of paradoxical sleep deprivation	Hippocampus Aβ burden	Acute sleep deprivation was associated with increased Aβ burden
Dissel et al., 2017	Adult UAS-APP:BACE flies (30, 7 days)	Sleep latency, sleep fragmentation, sleep duration	Human APP and BACE co-expression	Co-expression of APP and BACE was associated with reduced sleep duration and increased sleep fragmentation
Elias et al., 2018	Male cognitively normal OSA patients (42, 67.69 ± 5.37 years) and controls (77, 68.3 ± 3.86 years)	Apnea–hypopnea index	Cortex Aβ burden	Aβ burden was increased in OSA patients compared to controls
Ju et al., 2013	Cognitively normal participants (142, 65.6 ± 8.2 years)	2 weeks of at-home actigraphic recording	CSF-Aβ level	Worse sleep efficiency was associated with abnormal CSF-Aβ level
Ju et al., 2016	Cognitively normal OSA patients (10, 48–62) and controls (31, 45.8–65.7 years)	Apnea-hypopnea index, NREM SWA	CSF-Aβ level	Reduced NREM SWA was associated with increased CSF-Aβ level in controls Higher apnea–hypopnea index was associated with abnormal CSF-Aβ level
Ju et al., 2017	Cognitively normal participants (14, 35–65 years)	1 night of specific SWA disruption	CSF-Aβ level	Specific SWA disruption was associated with higher CSF-Aβ level
Kang et al., 2009	Tg2576 mice (16, 3–9.5 months), C57BL6/SJL mice (20, 4 months), $APP^{SWE}/PS1^{\Delta E9}$ mice (38, 1.7–3.5 months) Male cognitively normal participants (10, 20–50 years)	Acute sleep deprivation, sleep restriction to 4h/day for 3 weeks, almorexant injection (1/day for 8 weeks)	ISF-Aβ level, CSF-Aβ level, cortex and hippocampus Aβ burden	ISF- and CSF-Aβ levels showed fluctuations over a 24 hr period Acute and chronic sleep deprivation were associated with increased ISF-Aβ level and increased Aβ burden, respectively Chronic almorexant injection was associated with reduced Aβ burden
Lucey et al., 2018	Cognitively normal participants (8, 30–60 years)	1 night of sleep deprivation, 1 night of SWS augmentation	CSF-Aβ level	Total sleep deprivation was associated with increased CSF-Aβ level No association between SWS augmentation and CSF-Aβ level
Mander et al., 2015	Cognitively normal participants (26, 75.1 ± 8.2 years)	NREM SWA	Medial prefrontal cortex Aβ burden	Increased Aβ burden was associated with impaired NREM SWA
Molano et al., 2017	Cognitively normal participants (98, 69 ± 7.1 years	2 weeks of at-home actigraphic recording	CSF-Aβ level	The interaction between worse sleep efficiency and abnormal CSF-Aβ level was associated with poorer cognition
Musiek et al., 2018	Cognitively normal participants (148, 66.6 ± 8.3 years)	1 week of at-home actigraphy	Cortex Aβ burden	Higher fragmentation of rest-activity circadian rhythm was associated with increased Aβ burden

Table 1. Continued

Reference	Target population (*N*, age)	Sleep–wake variable(s)	Aβ variable(s)	Main outcome(s)
Ooms et al., 2014	Male cognitively normal participants (26, 40–60 years)	1 night of total sleep deprivation	CSF-Aβ level	Total sleep deprivation was associated with increased CSF-Aβ level
Roh et al., 2012	$APP^{SWE}/PS1^{\Delta E9}$ mice (32, 3–9 months)	Wakefulness duration, NREM/REM sleep duration	Hippocampus Aβ burden, active immunization to Aβ	Increased Aβ burden was associated with increased wakefulness duration and decreased NREM/REM duration Active immunization to Aβ restored the sleep–wake cycle
Roh et al., 2014	$APP^{SWE}/PS1^{\Delta E9}/OR^{-/-}$mice (12, 3–6 months), APP/PS1-21/$OR^{-/-}$ mice (12, 3.5–8.5 months)	Orexin modulation, sleep restriction to 4 hr/day for 3 weeks	Cortex and hippocampus Aβ burden	Transgenic orexin knockout mice displayed decreased Aβ burden and increased sleep duration Chronic sleep restriction was associated with increased Aβ burden
Sharma et al., 2018	Cognitively normal OSA patients (111, 69.26 ± 7.41 years) and controls (97, 67.56 ± 7.32 years)	Apnea–hypopnea index	CSF-Aβ level, longitudinal Aβ accumulation	Higher apnea-hypopnea index was associated with abnormal CSF-Aβ level and increased Aβ accumulation over 2 years of follow-up
Shokri-Kojori et al., 2017	Cognitively normal participants (24, 22–72 years)	1 night of total sleep deprivation, self-reported sleep history	Hippocampus and thalamus Aβ burden	Total sleep deprivation and poorer self-reported sleep history were associated with increased Aβ burden
Spira et al., 2013	Cognitively normal participants (70, 53–91 years)	Self-reported sleep duration and sleep quality	Cortex and precuneus Aβ burden	Poorer sleep quality and shorter sleep duration were associated with increased Aβ burden
Spira et al., 2018	Cognitively normal participants (123, 36.2–82.7 years)	Self-reported excessive daytime sleepiness and napping habits	Longitudinal Aβ accumulation	Excessive daytime sleepiness was associated with increased Aβ burden over 15.7 years follow-up No association between napping and Aβ burden
Sprecher et al., 2015	Cognitively normal participants (98, 50–73 years)	ESS, MOS	Cortex Aβ burden	Greater somnolence and sleep disturbances were associated with increased Aβ burden
Sprecher et al., 2017	Cognitively normal participants (101, 62.9 ± 6.2 years)	MOS, ESS	CSF-Aβ level	Poorer sleep quality, greater sleep disturbance and daytime somnolence were associated with abnormal CSF-Aβ level
Varga et al., 2016	Cognitively normal participants (36, 66.8 ± 8.2 years)	SWA, SWS duration	CSF-Aβ level	Reduced SWA and SWS duration were associated with higher CSF-Aβ level
Xie et al., 2013	C57BL6 mice (12, 3 months)	Natural and induced sleep	Aβ glymphatic clearance rate	Natural and induced sleep were associated with a 60% increase in interstitial space volume, resulting in easier glymphatic clearance

APP = amyloid precursor protein; BACE = beta-secretase cleaving enzyme; CSF = cerebrospinal fluid; ESS = Epworth sleepiness scale; MOS = medical outcomes study sleep scale; NREM = nonrapid eye movement; REM = rapid eye movement.

mice exhibit a diurnal variation, with a significant decrease of approximately 25% during the light period (i.e. when mice sleep most) relative to the dark period. Crucially, they observed that the same pattern of variation is also present in the ISF of wild-type mice and in the CSF of young healthy humans, indicating that Aβ fluctuation over a 24 hr period is inherent to normal cellular physiology. Furthermore, sleep-deprived mice showed significantly increased Aβ levels that were promptly reduced after sleep recovery. To unravel the underlying molecular mechanisms, the potential role of orexin, a peptide promoting arousal and wakefulness [45–47], was put forward. Interestingly, orexin infusion increased ISF Aβ levels during the light period, whereas an orexin receptor antagonist abolished the previously observed diurnal variation. At a broader level, chronic sleep restriction in mice (20 hr daily for 21 days) was associated with greater Aβ plaque burden among several brain regions, whereas enhancing sleep via chronic orexin antagonist treatment (once daily for 8 weeks) was related to reduced Aβ plaque deposition.

The characterization of the sleep–wake modulation of Aβ dynamics was further expanded to include a recently described process of brain cellular waste regulation, called the "glymphatic system" [42, 48]. This system consists in convective fluxes from the para-arterial CSF through ISF and toward the para-venous space that allow neuronal products to be transported to the systemic circulation for clearance [48, 49]. The glymphatic process can be altered by genetic variations affecting aquaporin 4 water channels [50] and has been linked to AD and other dementias [51]. Using two-photon imaging of the brain of living

Table 2. Summary table of studies considered in this review and directly linking sleep–wake regulation to tau

Reference	Target population (N, age)	Sleep–wake variable(s)	Tau variable(s)	Main outcome(s)
Arnulf et al., 2005	PSP patients (15, 68 ± 8 years) and cognitively normal controls (15, 67 ± 10 years)	Sleep fragmentation, REM sleep without atonia, RBD	Brain tau accumulation without abnormal Aβ burden	Higher sleep fragmentation, longer REM sleep without atonia duration, and RBD in PSP patients compared to controls
Bu et al., 2015	Cognitively normal OSA patients (45, 44.31 ± 9.96 years)	Apnea–hypopnea index	Serum tau level	Higher apnea–hypopnea index was associated with higher serum tau level
Di Meco et al., 2014	Male 3xTG mice (18, 10 months)	Sleep restriction to 4 hr/day for 8 weeks	Brain insoluble tau burden	Chronic sleep restriction was associated with increased insoluble tau level
Elias et al., 2018	Male cognitively normal OSA patients (42, 67.69 ± 5.37 years) and controls (77, 68.3 ± 3.86 years)	Apnea–hypopnea index	Cortex tau burden	No difference in tau burden in OSA patients compared with controls
Fjell et al., 2017	Cognitively normal participants (91, 64–89 years)	PSQI	CSF-tau level	Higher CSF-tau level was predictive of worse sleep quality in Aβ positive individuals
Holth et al., 2017	Male P301S mice (40, 3–12 months)	Wake bout duration, NREM/REM sleep duration	Brainstem tau burden	Higher brainstem tau burden was associated with increased wakefulness, decreased NREM and REM sleep duration
Ju et al., 2017	Cognitively normal participants (14, 35–65 years)	1 week of at-home actigraphic recording, 1 night of specific SWA disruption	CSF-tau level	No association between SWA disruption and CSF-tau level. Better home sleep quality was associated with lower CSF-tau level
Jyoti et al., 2015	$PLB1_{triple}$ mice (14, 5–21 months)	Wake bout duration, NREM/REM sleep duration	Cortex and hippocampus tau burden	Tau burden was associated with increased wakefulness, and reduced NREM and REM sleep duration
Lim et al., 2013	Cognitively normal participants (201, 85.9 ± 6.3 years)	10 days of actigraphic recordings	Brain NFTs density at autopsy	Better sleep consolidation was associated with decreased NFTs density
Motamedi et al., 2017	Cognitively normal OSA patients (50, 34.9 ± 8 years)	Apnea–hypopnea index	Plasma tau level	Higher apnea-hypopnea index was associated with higher plasma tau level
Musiek et al., 2018	Cognitively normal participants (148, 66.6 ± 8.3)	1 week of at home actigraphy	CSF-tau level	Higher fragmentation of rest-activity circadian rhythm was associated with higher CSF-tau level
Ooms et al., 2014	Cognitively normal men (26, 40–60 years)	1 night of total sleep deprivation	CSF-tau level	No association between total sleep deprivation and CSF-tau level
Osorio et al., 2016	Cognitively normal participants (63, 69.59 ± 8.55 years)	CSF-orexin level	CSF-tau levels	Higher CSF-orexin level was associated with higher CSF-tau levels
Platt et al., 2011	$PLB1_{triple}$ mice (11, 5–12 months)	Wake bout duration, NREM sleep duration	Cortex and hippocampus tau burden	Tau burden was associated with increased wakefulness and reduced NREM sleep duration
Qiu et al., 2016	$APP^{SWE}/PS1^{\Delta E9}$ mice (40, 4–10 months), wild-type littermates (40, 4–10 months)	Sleep restriction to 4 hr/day for 8 weeks	Frontal cortex and hippocampus tau burden	Chronic sleep deprivation was associated with long-lasting increased tau burden in both transgenic and wild-type mice
Rothman et al., 2013	Male 3xTG mice (10, 14 months)	Sleep restriction to 6 hr/day for 6 weeks	Cortex and hippocampus tau burden	Chronic sleep restriction was associated with increased cortical tau burden
Sprecher et al., 2017	Cognitively normal participants (101, 62.9 ± 6.2 years)	MOS, ESS	CSF-tau level	Higher excessive daytime sleepiness and worse subjective sleep quality were associated with higher CSF-tau level
Stevanovic et al., 2017	Tg4510 mice (11, 8–13 months)	Rest-activity circadian rhythm, clock gene (*BMAL1, PER2*) expression	SCN and hippocampus tau burden	Tau burden was associated with altered SCN circadian outputs and clock protein (PER2) rhythm in the hippocampus
Walsh et al., 2017	PSP patients (19, 70.94 ± 5.3 years) and cognitively normal controls (16, 72.50 ± 1 years)	Sleep latency, sleep duration, sleep fragmentation, subjective sleepiness	Brain tau accumulation without abnormal Aβ burden	Longer sleep latency, lower sleep duration, higher sleep fragmentation, and higher subjective sleepiness were found in PSP patients compared with controls

CSF = cerebrospinal fluid; ESS = Epworth sleepiness scale; MOS = medical outcomes study sleep scale; NREM = nonrapid eye movement; PSQI = Pittsburgh sleep quality index; RBD = rapid eye movement sleep behavior disorder; REM = rapid eye movement; SCN = suprachiasmatic nucleus.

adult mice, Xie et al. [42] found that the glymphatic system is strongly regulated by the sleep–wake cycle. They observed that the CSF influx was highly increased in the brain of sleeping and anesthetized mice compared with awake littermates. In turn, the larger CSF influx led to a more efficient glymphatic clearance, as illustrated by a rate of interstitial Aβ removal up to twice

Table 3. Summary table of studies considered in this review and directly linking sleep–wake regulation to neurodegeneration

Reference	Target population (N, age)	Sleep–wake variable(s)	Neurodegeneration variable(s)	Main outcome(s)
Carvalho et al., 2017	Cognitively normal participants (1374, 72.16 ± 8.8 years)	ESS, fatigue	Grey matter integrity	Higher excessive daytime sleepiness and fatigue were associated with lower cortical thickness
Dubé et al., 2015	Cognitively normal participants (63, 20–70 years)	Sleep slow waves density and amplitude	Grey matter integrity	Higher sleep slow waves density and amplitude were associated with higher grey matter integrity in sleep slow waves–related regions
Lo et al., 2014	Cognitively normal participants (66, 69.5 ± 5.7 years)	Self-reported sleep duration	Longitudinal ventricles expansion rate	Reduced sleep duration was associated with faster annual expansion rates of the ventricles over 2 years of follow-up
Sanchez-Espinosa et al., 2014	aMCI participants (21, 69.8 ± 5.5 years)	REM sleep duration	Grey matter integrity	Lower REM sleep duration was associated with reduced grey matter integrity in brain regions involved in early stages of AD
Sexton et al., 2014	Cognitively normal participants (147, 20.4–84.2 years)	PSQI	Longitudinal grey matter decline	Worse sleep quality was associated with higher rates of grey matter atrophy over 3.5 years of follow-up
Spira et al., 2016	Cognitively normal participants (122, 51–86 years)	Self-reported sleep duration	Longitudinal grey matter decline	Sleep durations of less or more than 7 hr were associated with higher rates of grey matter atrophy over 8 years of follow-up
Takeuchi et al., 2018	Cognitively normal participants (1201, 18–27 years)	Self-reported sleep continuity and sleep duration	White matter integrity	Higher sleep continuity and lower sleep duration were associated with higher white matter integrity
Van Someren et al., 2018	Cognitively normal participants (138, 69.1 ± 8.5 years)	1 week of at-home actigraphic recording	Medial temporal lobe atrophy	Higher fragmentation of rest-activity circadian rhythm was associated with higher medial temporal lobe atrophy
Zhang et al., 2014	Male SirT3 wild-type mice (5, 2 months)	Sleep restriction to 4 hr/day	Number of locus coeruleus neurons	Extended wakefulness was associated with a loss of neurons in the locus coeruleus
Zhu et al., 2007	Male C57BL/6J mice (10, 2 months)	Long-term intermittent hypoxia exposure for 8 weeks, sleep duration, sleep latency	Number of locus coeruleus neurons	Chronic sleep disruption was associated with a loss of neurons in the locus coeruleus that had long-lasting effects on sleep duration and sleep latency

aMCI = amnestic mild cognitive impairment; ESS = Epworth sleepiness scale; PSQI = Pittsburgh sleep quality index; REM = rapid eye movement.

as fast in sleeping mice. Interestingly, the authors found that the volume of the interstitial space was over 60% greater when mice were sleeping or anesthetized, thus allowing easier CSF movement and, therefore, more efficient glymphatic clearance of neuronal by-products such as Aβ. Moreover, elevated Aβ levels as a consequence of sleep deprivation have been observed in CSF samples both in humans [52] and in adult rats [53]. One night of sleep deprivation also appeared to significantly increase PET Aβ plaque burden in the hippocampus and the thalamus in humans [54], although it is unclear how acute sleep deprivation may affect short-term plaque formation.

It seems that slow-wave sleep (SWS; or "deep sleep", dominated by large amplitude and low-frequency EEG oscillations [55]) is a key component of the association between sleep–wake regulation and Aβ aggregation. The release of soluble Aβ in the interstitial space was shown to depend on endogenous neuronal activity, with extended wakefulness leading to an overall increase in neuronal firing and thus to elevated Aβ levels [56–58]. In addition, slow-wave activity (SWA; a quantification of sleep slow waves during sleep) in frontal regions was associated with higher CSF Aβ42 levels in cognitively normal older individuals [59]. Finally, a recent study showed that specific disruption of SWS during one night induced higher levels of CSF Aβ40 on the following morning [60]. Altogether, these results suggest that reduction of SWS may lead to a relative augmentation in neuronal activity during sleep that, in turn, increases the production of Aβ and/or reduces the effectiveness of its clearance. Recent evidence shows that Aβ concentration in the CSF increases following sleep deprivation, whereas it does not decrease when attempting to enhance SWS, which may suggest that altered Aβ production, rather than its clearance, underlies the link between altered sleep and Aβ levels [61]. It remains to be determined whether the well-established modification in sleep structure in older people, including a significant reduction of SWS duration [62, 63], contributes to or is, in part, a consequence of the age-related increase in Aβ burden in healthy individuals [64].

The depicted relationship between sleep–wake disruption and Aβ deposition is indeed most likely bidirectional [65–67]. Albeit we emphasized that sleep–wake disorganization accelerates Aβ accumulation, it seems that Aβ deposits conversely impede sleep–wake regulation. A transgenic APP mouse model showed changes in the sleep–wake cycle that closely followed the emergence of Aβ plaques, and the intensity of these changes correlated with the extent of Aβ deposits [58]. Interestingly, active Aβ immunization prevented these sleep–wake modifications, suggesting a direct impact of the presence of Aβ aggregates on sleep–wake regulation. Likewise, Aβ accumulation impaired slow waves propagation during sleep in AD mice, whereas exogenous Aβ infusion disrupted SWA in wild-type mice until wash-out [68]. In a Drosophila model of AD including human APP and beta-secretase cleaving enzyme expression, sleep is significantly disrupted when these proteins are co-expressed [69].

Many other associations between sleep–wake regulation and Aβ are described below. We stress, however, that it is unclear whether these associations result from a causal impact of sleep–wake dysfunction or whether the latter may be a consequence of abnormal presence of Aβ. For instance, several studies showed that self-reported sleep quality is associated with Aβ deposition measured with PET and CSF markers in healthy older individuals [28, 70–72]. In two longitudinal studies, self-reported excessive daytime sleepiness at baseline was linked to increased accumulation of Aβ over 7 and 15.7 years in cognitively normal older individuals [73, 74]. Self-reported sleep latency was also associated with brain Aβ deposition in a well-characterized cohort of older men and women [72, 75], whereas poor self-reported sleep history was associated with increased Aβ burden in the hippocampus and the thalamus [54]. Objective measures of sleep efficiency, based on actigraphic recordings, were also linked to abnormal levels of amyloid in the CSF in healthy older adults [76]. Likewise, an association was reported between PET Aβ pathology in the medial prefrontal cortex and slow waves generation [77]. Obstructive sleep apnea (OSA), a well-established sleep disruption factor associated with a higher risk of developing cognitive impairments and AD [78], has been linked to increased CSF and PET Aβ burden in cognitively normal older adults [79, 80]. One hypothesis is that glymphatic clearance processes are altered by mechanical changes during respiratory efforts in people with OSA, thus promoting protein accumulation [78, 81]. Finally, rest-activity rhythm fragmentation, objectively estimated by actigraphic measures, has recently been associated with PET Aβ plaque burden, suggesting the implication of a circadian regulation of proteostasis [82]. This relationship remained significant after adjusting for age, implying that aging and preclinical Aβ pathology likely have separate contributions on sleep–wake disturbances.

Crucially, the interaction between worse sleep efficiency and abnormal CSF amyloid levels may account for worse memory function in the preclinical stages of AD [83]. This could mean that beyond the respective negative impact of poor sleep–wake quality [84] and of Aβ burden [85] on cognitive function, there may be an interaction effect that would lead to a multiplicative impact of both, at least when exceeding a certain threshold. However, isolating their respective contributions on cognition may constitute a difficult challenge since they are both changing importantly in aging.

The numerous findings reviewed here make a strong case for the bidirectional link between sleep–wake regulation and Aβ deposition. Interestingly, low-dose benzodiazepine administration to AD mice improved SWS and cognition, suggesting a potential role for γ-aminobutyric acid inhibition to alleviate part of Aβ negative impact through sleep [68]. It is unknown, however, whether acting on Aβ per se and reducing its burden would result in an improved sleep–wake regulation. Likewise, no studies have yet attempted to act on sleep–wake quality to reduce Aβ burden or to slow down its increase.

Sleep–Wake Regulation and Tau

Tau is a microtubule-associated protein whose primary role is to maintain the stability of the axonal cytoskeleton [86]. In the course of several neurodegenerative diseases, including AD, tau undergoes abnormal hyperphosphorylation, oligomerization, and then conversion into insoluble filamentous state [87, 88]. Unable to interact with microtubules, hyperphosphorylated tau assembles into toxic oligomers which eventually form intracellular NFTs [89]. Whether these NFTs are toxic remains debated [90], as they may not impede normal neuronal function once released in the extracellular space upon neuron death [91]. As for Aβ, the AD-related pathophysiological process of tau follows a stereotyped progression pattern [92]. As early as in the first decades of life, hyperphosphorylated tau can be found in the brainstem locus coeruleus and other subcortical nuclei [64, 93], which are key sites in sleep–wake regulation [94]. During the preclinical stages of AD, tau pathology is observed in the medial temporal lobe and further spreads to the neocortex as the disease progresses [95–97]. Interestingly, abnormal levels of tau protein in the CSF in preclinical AD constitute an accurate proxy measure of tau deposition in the temporal lobe, which in turn is a strong predictor of subsequent cognitive trajectory [98].

Critically, Yamada et al. [99] demonstrated using in vivo microdialysis in wild-type mice that increasing neuronal activity significantly elevated ISF tau levels within hours. Similar to Aβ regulation processes, this indicates that a relative increase in neuronal activity, as observed during extended wakefulness or chronic sleep restriction, could lead to an increase in extracellular tau production that would ultimately be reflected in CSF measures. However, tau is a relatively stable protein with a slow turnover rate so that around 11 days are required before CSF changes can be observed [99, 100]. This may explain why, contrary to Aβ, one night of acute sleep disruption could not be linked to an increase in CSF tau levels assessed on the subsequent morning in humans [52, 60]. In fact, worse home sleep quality measured with actigraphic recordings during the week preceding in-lab sleep disruption was positively associated with higher CSF tau levels [60]. In mouse models with plaques and tangles pathology, restricting sleep to 4 hr per day for 8 weeks [101], or to 6 hr per day for 6 weeks [102], led to elevated insoluble tau levels. Accordingly in humans, a large longitudinal cohort study found that actigraphic measures of better sleep consolidation in older individuals significantly attenuated the effect of *APOE* genotype on observed NFTs density at autopsy [103].

As for Aβ, the link between sleep–wake regulation and tau is likely bidirectional. A longitudinal study in cognitively normal older individuals showed that higher CSF tau levels were predictive of overall poorer sleep quality after 3 years [104]. However, this association was only present in individuals with significant Aβ deposition, further supporting the deleterious nature of tau and Aβ co-existence [105]. In addition, a human tau and amyloid knock-in mouse model of AD exhibits increased wake bout duration combined with decreased rapid eye movement (REM) and non-REM sleep duration [106, 107]. Transgenic mice expressing tau without Aβ abnormal accumulation display similar sleep–wake alterations, suggesting that tau pathology alone can induce impaired sleep and wakefulness in such animal models [108]. Of particular interest, the extent of the observed sleep impairments correlated with tau pathology intensity in brainstem regions regulating sleep [109]. Likewise, progressive supranuclear palsy, a tau only form of frontotemporal dementia that mainly involves brainstem and thalamic regions, was associated with more fragmented sleep and increased daytime sleepiness [110, 111], further suggesting a causal role for abnormal tau aggregation and sleep dysfunction.

Again similar to Aβ, many other associations between tau pathology and sleep–wake regulation have been reported, but

it is difficult to identify the directionality of their interplay. In young and middle-aged individuals, OSA has been associated with elevated levels of tau protein concentration in blood [112, 113]. However, a recent study did not find any significant association between tau burden measured with PET and sleep-disordered breathing in a cohort of 119 older males [79]. In cognitively normal older people, CSF levels of phosphorylated tau were positively correlated with an increase in orexin concentration, potentially because elevated orexin levels favor fragmented sleep [114] as previously observed in people with AD [115, 116]. Akin to Aβ, both objective and subjective measures of sleep quality (respectively, sleep efficiency derived from actigraphic recordings, and multidimensional self-reported scales) have been associated with elevated CSF tau levels [28, 60]. Finally, the fragmentation of the circadian rhythmicity of sleep and wakefulness positively correlates with the ratio between CSF phosphorylated tau and Aβ42, a sensitive predictor of cognitive decline in nondemented older individuals [82, 117].

Although convincingly demonstrated, proofs of the bidirectionality of the link between tau pathology and sleep–wake regulation are less numerous than for Aβ. This probably resides in part in the absence of in vivo radiotracers for tau until very recently [118, 119], implying that one could only rely on CSF measures to infer tau burden in vivo. Although the first PET markers suffered from relatively unspecific bindings, the new generation seems to be particularly specific to tau [120] such that our understanding of the association between tau and the sleep–wake cycle is likely to grow swiftly.

Critically, chronic sleep–wake disruption was consistently associated with tau phosphorylation changes and long-lasting memory deficits not only in AD mouse models, but also in wild-type littermates [121]. This suggests that recurrent sleep deprivation plays a significant role in tau-related measures as well as cognitive outcomes, beyond at least some genetic AD predispositions. Whether improving sleep–wake quality would reduce tau burden, or slow down its progression to then improve cognition, has however not been tested yet. Likewise, no attempt has been made until now to address whether pharmacologically reducing tau burden would improve cognition via an enhancement of sleep–wake quality.

Sleep–Wake Regulation and Neurodegeneration

Synaptic and neuronal loss represents one of the strongest pathological correlates of dementia [14, 122], and a reliable predictor of conversion from MCI to AD [123–125]. Neurodegeneration of the medial temporal lobe can be detected up to 4 years before the clinical diagnosis of AD and correlates with tau deposition as well as early memory deficits [126, 127]. The dynamic of brain atrophy mirrors the propagation of NFTs in early stages, and then neuronal loss is progressively observed in temporo-parietal cortices, and ultimately in frontal regions [128]. In asymptomatic individuals, it was suggested that baseline rates of brain atrophy are accelerated in those that further transition to MCI [129]. Although no magnetic resonance imaging (MRI) marker has been proved efficient to identify alone the preclinical stages of the disease, recent combinations of neuroimaging techniques hold strong potential for the early detection of preclinical AD [130].

As for tau and Aβ burden, sleep–wake regulation is associated with neurodegeneration. In young adults, sleep continuity and sleep duration were associated with brain white matter integrity, based on measures of mean diffusivity derived from diffusion-weighted imaging [131]. In healthy older individuals, self-reported excessive daytime sleepiness and fatigue were associated with MRI measures of global and regional atrophy, as well as hippocampal volume reduction [132]. Similarly, MRI-based cortical thinning of several brain areas was linked to an age-related decrease in slow-wave density and amplitude, based on electroencephalographic measures during sleep [133]. In addition, reduction of REM sleep duration in participants with MCI was associated with grey matter loss in regions that are affected early in AD, such as the precuneus, the posterior cingulate, and the postcentral gyrus [134]. Likewise, actigraphic assessment of sleep–wake rhythm fragmentation was related to the atrophy of the medial temporal lobe measured by expert visual evaluation (use of visual scale, i.e. no computerized quantification of MRI images) [135].

In cognitively normal older individuals, sleep durations shorter and longer than 7 hr have been associated with higher rates of frontotemporal grey matter decline in longitudinal assessments over 8 years [136]. Others found that short sleep duration similarly affects the expansion rates of the ventricles [137]. Moreover, self-reported sleep quality indices correlated with the rate of cortical atrophy measured over an average of 3.5 years, in a widespread set of frontal, temporal, and parietal areas [138]. These longitudinal data suggest that sleep quality directly affects cortical atrophy. This view is further reinforced by the report of decreased neuron density in the locus coeruleus after extended wakefulness in wild-type mice [139]. Critically, chronic sleep restriction in mice leads to neuronal loss in the locus coeruleus that could not be compensated for after a 6 month recovery period in normal sleep conditions [140].

Normal aging is also associated with structural changes in sleep–wake regulating structures [141]. The locus coeruleus shows a limited decline in neuron number with age and undergoes a marked reduction in the number of its projections to the cortex and particularly to the prefrontal cortex [6, 142]. The basal forebrain, and especially the cholinergic neurons of the nucleus of Meynert [143], the suprachiasmatic nucleus corresponding to the master circadian clock [144], and the lateral hypothalamus secreting orexin and melanin-concentrating hormone [145], also exhibit a decrease in neuron and/or axonal density in aging. These deficits are further aggravated in AD [146–148]. However, the functional consequences of the changes in sleep–wake regulating subcortical structures are mostly unassessed. It is therefore unclear whether they directly contribute to the well-characterized degradation in sleep quality and sleep–wake regulation associated with aging [149].

Hence, age-related neurodegeneration must undoubtedly contribute to changes in sleep and wakefulness, but direct evidence remains scarce. How neurodegeneration contributes to AD through sleep remains therefore unclear. In turn, how sleep–wake dysfunction affects AD through neurodegeneration is not known. Addressing these issues is complicated notably because quantifying changes in brain structure in vivo is far from trivial. Although the first demonstrations of age-related changes in MRI data were interpreted as indications of neurodegeneration, recent research showed that these changes may reflect modifications in neuronal iron or axonal myelin content rather

than reflecting a mere loss of neurons [150, 151]. Crucially, the development of unbiased quantitative MRI [152] will provide important tools to address the link between sleep–wake quality and brain structure and microstructure.

Conclusions

We reviewed findings indicating that disruption of sleep–wake regulation is linked to the hallmarks of AD pathogenesis in the preclinical stages of the disease, that is, many years before the cognitive symptoms emerge. Evidence for bidirectional relationships between sleep–wake regulation and the three hallmarks of AD pathophysiology has accumulated, albeit more convincingly with Aβ. Recent technical developments in MRI and PET in vivo measures of brain structure will help establishing these relationships [130]. Yet, research is still limited by the sensitivity of current techniques. Indeed, PET imaging does not allow to quantify the earliest tau (e.g. in the brainstem) or Aβ deposits. Besides, soluble forms of misfolded Aβ and tau proteins may be more involved in AD progression and neuronal death compared with their aggregates [23, 153]. However, these soluble forms remain mostly undetectable in vivo and their impact on sleep–wake regulation is unknown. One could also consider that the locations of protein aggregates and of their soluble precursors are important, but this remains largely unexplored (see Mander et al. [77] for the importance of medial prefrontal Aβ deposits for SWS).

The large time-window of AD pathophysiological progression is a great opportunity for preventive interventions. However, it also means that curative or preventive interventions may be applied too late in the process to be efficient, i.e. when irreversible damage has occurred [1]. Thus, the earliest aspects associated with AD pathogenesis need to be established. Factors related to sleep–wake regulation are, in our view, excellent candidates based on the findings reviewed here, but also given the fact that the first signs of tau deposition are detected, post mortem, in the locus coeruleus. However, these first deposits are undetectable in vivo, and their functional consequences are unknown [6]. In addition, tau accumulation may primarily represent age-related modifications, i.e. brain changes that are normal over the lifespan [154]. This does not preclude these protein accumulations, variable across individuals [64], to contribute to the observed variability in age-related changes in sleep–wake regulation, or to be caused by the latter variability. It is therefore highly needed, and yet highly challenging, to separate what constitutes normal neurodegeneration, protein accumulations, and sleep–wake changes from what will contribute to AD pathology decades later.

The definite proofs that improving sleep and wakefulness in the preclinical stages of the disease causally slows down the AD neuropathological processes over decades still need to be provided. Conversely, whether hindering tau and Aβ accumulation as well as neurodegeneration may improve sleep has to be demonstrated. Longitudinal studies in interventional designs are of particular interest to provide these proofs, but they may not be available before long. Even in the absence of such evidence, one could consider applying cognitive behavioral therapy [155] or increasing the amplitude of the rest-activity cycle with light [156] and/or physical activity [157] to modulate AD neuropathological processes through improved sleep and wakefulness quality. Given the high prevalence of sleep–wake complaints in our 24–7 society, these appear as useful examples of reasonable and easy strategies to improve brain function in the short term, and to decrease the odds of developing AD, particularly in those individuals that are more at risk.

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