Neuroscience 557 (2024) 12–23

Contents lists available at ScienceDirect

Neuroscience

journal homepage: www.elsevier.com/locate/nsc

Review

Alzheimer's disease and sleep disorders: A bidirectional relationship

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ARTICLE INFO

Keywords:
Alzheimer's disease pathogenesis
Circadian rhythm disruption
Neuronal oscillation disturbance
Amyloid beta pathology
Tau pathology
Neuroinflammation

ABSTRACT

Alzheimer's disease (AD) is the most prevalent dementia, pathologically featuring abnormal accumulation of amyloid-β (Aβ) and hyperphosphorylated tau, while sleep, divided into rapid eye movement sleep (REM) and nonrapid eye movement sleep (NREM), plays a key role in consolidating social and spatial memory. Emerging evidence has revealed that sleep disorders such as circadian disturbances and disruption of neuronal rhythm activity are considered as both candidate risks and consequence of AD, suggesting a bidirectional relationship between sleep and AD. This review will firstly grasp basic knowledge of AD pathogenesis, then highlight macrostructural and microstructural alteration of sleep along with AD progression, explain the interaction between accumulation of Aβ and hyperphosphorylated tau, which are two critical neuropathological processes of AD, as well as neuroinflammation and sleep, and finally introduce several methods of sleep enhancement as strategies to reduce AD-associated neuropathology. Although theories about the bidirectional relationship and relevant therapeutic methods in mice have been well developed in recent years, the knowledge in human is still limited. More studies on how to effectively ameliorate AD pathology in patients by sleep enhancement and what specific roles of sleep play in AD are needed.

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disease. It is estimated that around 5.5 million people worldwide suffer from dementia, 80 % of whom are AD patients (Crous-Bou et al., 2017), and there are nearly 10 million new cases each year. Amyloid-β plaques (ABPs) made of extracellularly deposited amyloid-β (Aβ) and neurofibrillary tangles (NFTs) consisting of hyper-phosphorylated tau are the main pathological hallmarks of AD (Goedert, 2009; Vishal et al., 2011). The clinical syndromes of AD include cognitive impairments, language impairment, behavioral abnormalities, mental and emotional disorders (Mucke, 2009), and are often combined with sleep disorders (Peter-Derex et al., 2015). However, it is far from clear how AD influences cognition and sleep as well as how to effectively prevent or cure it. Therefore, thorough and detailed research is needed to elucidate the mechanisms underlying the cognitive impairments and sleep disturbance in AD. Emerging evidence has highlighted the bidirectional relationship between sleep-wake cycle and AD: Neural alterations in specific brain regions are associated with mild cognitive impairment (MCI) and AD and that might lead to disrupted sleep pattern (Stopa et al., 1999; Lim et al., 2014; Braak and Del, 2016); the circadian sleep-wake rhythm disorders in AD patients may contribute to cognitive ability decline, accelerating AD pathology (Feinsilver, 2021; Romanella et al., 2021). This review will highlight the common Aβ-pathology and tau-pathology of AD, summarize the abnormalities of sleep in AD's progression, and discuss the role of sleep disturbance in AD pathogenesis (see Fig. 1).

Sleep is defined as a naturally recurring and reversible state of less perceptual engagement along with reduced consciousness and relatively less mobility, the propensity of which is decided by homeostatic and circadian factors (Grandner and Fernandez, 2021). It is fundamental to animal's life. Typically, sleep is divided into two stages based on the

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https://doi.org/10.1016/j.neuroscience.2024.08.008
Received 16 June 2024; Accepted 7 August 2024
Available online 11 August 2024
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different fluctuations of brain waves measured by electroencephalogram (EEG), eye movement measured with electro-oculograms (EOG) and muscle tone measured by electromyography (EMG) (Danker-Hopfe et al., 2009). One is nonrapid eye movement (NREM) sleep, also known as slow-wave sleep (SWS), and the other is rapid eye movement (REM) sleep (Keene and Duboue, 2018). NREM sleep is characterized by slow waves and slow oscillations present in EEG and local field potential (LFP) as well as strongly reduced cholinergic activity. REM sleep is characterized by theta activity (4–8 Hz) in rodents, a wake-like combination of low-amplitude "desynchronized" EEG oscillation in humans and non-human primates, and minimum noradrenergic activity but wake-like cholinergic activity (Brodt et al., 2023). While EEG patterns in REM sleep is indistinguishable from those in wakefulness, EMG is necessary for differentiation of these two states. Usually, the determination of wakefulness, REM sleep, and NREM sleep in mice is conducted with EEG and EMG but without EOG (Adamantidis et al., 2019; Aime et al., 2022). In human, NREM sleep is further subdivided into N1, N2, and N3, whereas NREM sleep in rats and cats is subdivided into N1 and N2, versus one stage in mice (Adamantidis et al., 2019). At the beginning of a normal night sleep, one experiences a brief period of stage N1 sleep followed by deeper stages N2 and N3. Stage N3 sleep is followed by another stage N2 sleep. Then, it progresses into REM sleep before starting next roughly 90-minute sleep cycle or progresses into wakefulness (Merica and Fortune, 2004; MacDonald and Cote, 2021). Both REM and NREM sleep have been thought to be essential for consolidation of memory, whereas encoding memory primarily takes place during daytime. Sharp wave ripples (SWRs) in hippocampus play key roles in memory consolidation and action planning (Gupta et al., 2010; Xu et al., 2019). They consist of sharp waves, negative polarity deflection in CA1 apical dendritic layer in hippocampus reflecting the magnitude of CA3 inputs, and ripples, fast oscillatory pattern (140–220 Hz) of the LFP in CA1 pyramidal layer. Long-duration CA1 SWRs during NREM sleep improve spatial memory in rats (Fernández-Ruiz et al., 2019), while reactivated CA2 pyramidal neurons in NREM sleep and REM sleep-active neurons projected from supramammillary nucleus to CA2 are crucial for social memory consolidation (Oliva et al., 2020; Qin et al., 2022).

Circadian rhythm refers to cyclic variations in behavior and physiology, including prominent behavioral states such as sleep-wake cycle and a group of less conspicuous oscillations in neurological, metabolic, endocrine, cardiovascular, and immune functions (Patke et al., 2020). It is genetically controlled and undergoes autoregulatory pathways composed of a set of transcription factors (Emery et al., 2000). Once the circadian rhythm is disrupted, disorders such as sleep-wake disturbances may happen, possibly resulting in aberrant accumulation of misfolding and aggregated proteins and subsequently neurodegenerative diseases such as AD (Logan and McClung, 2019). However, the exact mechanism of it is unclear.

The two-process model serves as a major conceptual framework in sleep science (Borbély, 2022). This model was first put forward by Borbély in 1979 and is still continuously enriched and developed. It postulates that the interaction of a sleep-wake-dependent homeostatic process (Process S) with a circadian pavemarker-controlled process (Process C) regulates salient aspects of sleep. Process S represents sleep debt, increasing during wakefulness and exponentially declining during sleep. It oscillates between upper and lower thresholds with a periodicity. When S approaches the lower threshold, it triggers awakening; near the upper threshold, it triggers sleep (Borbély et al., 2016). The inverse of C represents the variation of the sleep threshold, defining the time of awakening by interacting with S (Borbély, 2022). NREM sleep EEG slow wave activity and theta activity in waking are principal markers of S, while core body temperature and melatonin rhythm are markers of C (Borbély and Achermann, 1999; Borbély et al., 2016). For decades, the two-process model has sparked a group of human and animal experiments, not only extending the notion of sleep to the realm of invertebrates (Tobler, 1983; Tobler and Neuner-Jehle, 1992) but also leading to the exploration of concomitants of sleep in specific regions and structures of brain (Vyazovskiy et al., 2000; Borbély, 2022).

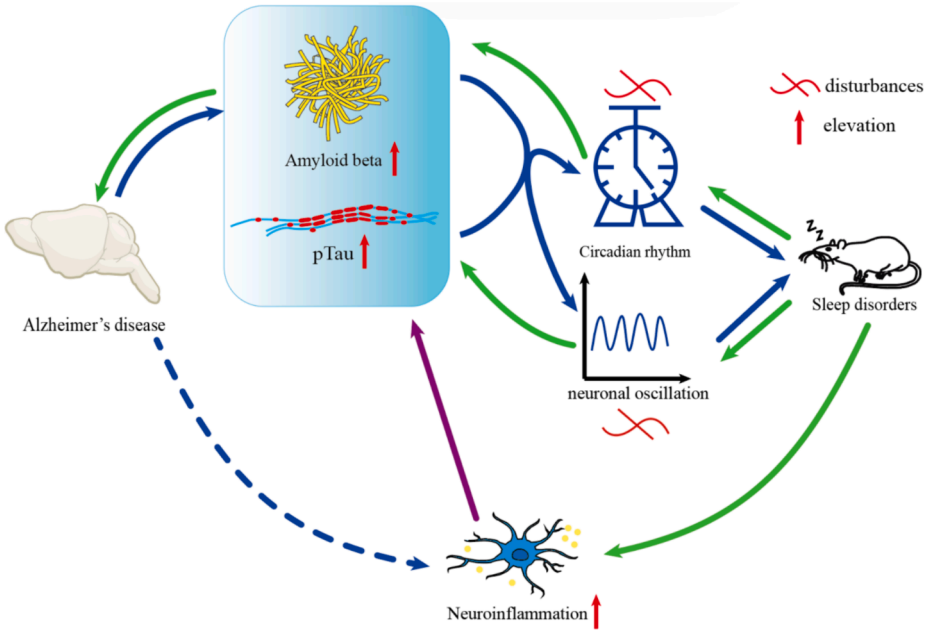

Fig. 1. The bidirectional relationship of sleep disorders and AD. Aberrantly accumulated Aβ and hyperphosphorylated tau are two main hallmarks of AD and profoundly affect AD progression. The biomarkers damage sleep architecture, circadian rhythm and neuronal oscillation, resulting in sleep disorders. Conversely, sleep disorders reduce the clearance and increase the production of Aβ and tau via disrupted circadian rhythm and neuronal rhythmic activity, worsening AD pathology. Neuroinflammation such as activated microglia is another key contributor to both AD and sleep disorders and deserves further investigation. Sleep-regulatory neuropeptides such as neuropeptide Y are associated with AD as well.

Main pathogenesis of AD

Abnormal accumulation of Aβ

Amyloid precursor protein (APP), an integral protein on the plasma membrane, is digested into fragments of different sizes by various secretases, such as α-, β-, γ-, and η-secretase (Harris et al., 2020). In healthy neurons, soluble polypeptides are produced by α-secretase along with γ-secretase cleavage of APP and eventually degraded in cell, which is called the nonamyloidogenic process. However, when the process undergoes with altered β- and γ-secretase, it leads to the production of the Aβ peptides with different numbers of amino acids (Ashrafian et al., 2021). The physiological functions of Aβ remain elusive. Some studies claim that Aβ functions as anti-microbial peptides in the innate immune system and defends against eight clinically relevant microorganisms (Soscia et al., 2010), while other research attributes synaptic depression to excessive Aβ and postulates that endogenous Aβ production modulated by activity may participate in the negative feedback systems which stop neurons from hyperactivity (Kamenetz et al., 2003). Because of its intrinsic tendency to self-assemble into a series of aggregates, Aβ can not only form ABPs that are morphologically detectable in AD, but also form soluble as well as dispersible Aβ oligomers, protofibrils, and mature fibrils which are undetectable with common anti-Aβ immunohistochemistry but can be extracted and measured from brain tissue, and from the hippocampal interstitial in mouse AD models and in human cerebrospinal fluid (Thal et al., 2013). However, late studies reveal that the correlation between ABPs and dementia or other cognitive alterations is poor, either in human or in mice, and soluble Aβ oligomers are of high possibility to directly contribute to the neuronal toxicity (Walsh et al., 2002; Glabe, 2006) and to neuroinflammation (as discussed below).

Why do a large number of Aβ assemble abnormally in AD? On one hand, overexpression or specific mutations of the gene encoding APP shift the quantity of Aβ or the ratio of $A\beta_{40}/A\beta_{42}$. For example, the mutations close to the cleavage site of *β*-secretase (KM670/671NL, Swedish mutation) or γ-secretase (V717F, V717G, V717I, V717L, et al.) are attributed to higher $A\beta_{40,42}$ expression and dramatical $A\beta_{40}/A\beta_{42}$ decline respectively (2023). In addition, in transgenic mice and cultured cells overexpressing mutant PS1, the changed APP proteolytic processing resulted in both enhanced production of $A\beta_{1\text{-}42}$ and lowered level of secreted APP with effects of neuroprotection (Scheuner et al., 1996). On the other hand, reduced expression or activity of Aβ-degrading enzymes and/or dysfunctions of cell clearance pathways such as autophagy failure could contribute the accumulation of Aβ as well (Vekrellis et al., 2000; Lipinski et al., 2010). Moreover, it has been known that neuroinflammation and dysfunction of innate immune system also emerge as significant factors impairing Aβ clearance (Tejera et al., 2019; Roy et al., 2022). Recent studies demonstrate that type I interferon, a typical innate immune cytokine, is activated by Aβ, resulting in increased microgliosis, inflammation, and plaque accumulation (Roy et al., 2022).

The neurotoxicity of Aβ manifests in various aspects, such as disruption of intercellular balance of calcium, loss of mitochondrial proteostasis, loss of neurons, and alteration of synaptic plasticity, which are all associated with AD (Resende et al., 2008; Shankar et al., 2008; Umeda et al., 2011; Companys-Alemany et al., 2022). Severe or prolonged endoplasmic reticulum (ER) stress is one of the triggers that induce apoptosis (Resende et al., 2008). It is reported that the accumulation of Aβ oligomers in COS-7 cells gives rise to calcium dyshomeostasis-induced ER stress that leads to cell death, because of the activation of apoptotic pathway involving activated caspase-3 and-4 (Resende et al., 2008; Umeda et al., 2011). Similarly, when treated with fresh $A\beta_{1\text{-}42}$ peptides, cortical neurons show less dendritic complexity and notably increased ER stress-induced intercellular concentration of calcium, due to the activated phospholipase C (Resende et al., 2008). Besides, mitochondrial dysfunction is thought to be another adverse effect of accumulated *Aβ* peptides. Oligomeric Aβ is attributed to the aberrant depolarization of mitochondrial membranes that is a crucial reason for the release of cytochrome *c*, a sign of server mitochondrial damage (Umeda et al., 2011). In addition, the Aβ-mediated inhibition of Cym1, a metallopeptidase taking part in mitochondrial processing peptidase (MPP) degradation, is proved to impair presequence cleavage activity of MPP, preventing preprotein from maturation and causing mitochondrial dysfunction (Mossmann et al., 2014). Aβ also has an influence on synaptic plasticity through various receptors including N-methyl-D-aspartate receptors (NMDARs), nicotinic acetylcholine receptors, and metabotropic glutamate receptors (mGluR) (Shankar et al., 2008; Companys-Alemany et al., 2022). For example, Aβ can induce synaptic depression that shares mechanisms and second messenger pathways with mGluR LTD, supported respectively by occlusion experiments and inhibition of p38 MAPK and calcineurin. That synaptic depression is responsible for Aβ-mediated reduced pyramidal neuron spine loss (Hsieh et al., 2006) and the onset of AD (Shankar et al., 2008).

Tau hyperphosphorylation

Tau is a microtubule-binding protein normally located in axons of neurons, helping assemble and maintain the microtube as well as transport axonal substance. There are six subtypes of tau in human including 0N4R, 1N4R, 2N4R, 0N3R, 1N3R, and 2N3R. Physiologically, tau is neither folded nor polymerized but soluble and has strong potential for phosphate group binding (Wang and Mandelkow, 2016; Stefanoska et al., 2022). However, tau assembly, mainly referring to neurofibrillary tangles (NFTs), is found in neurons of AD patients. Hyperphosphorylated tau can be dissociated from microtube and be transported to soma as well as dendrites, forming protofibrils and subsequently NFTs (Leuzy et al., 2019). Clinically, AD patients are categorized into different Braak Stages from I to VI according to how severe the NFTs are and where they aggregate (Braak and Braak, 1991). It is worthwhile to mention that hyperphosphorylated tau itself cannot form NFTs directly, as supported by non-NFTs neurons with hyperphosphorylated tau in hibernating animals (Härtig et al., 2007).

Emerging evidence has demonstrated that phosphorylated tau can be both neurotoxic and neuroprotective. It is believed that Aβ toxicity is tau dependent and tau-dependent loss of microtubule integrity is initiated by diffusible Aβ (King et al., 2006; Ittner et al., 2010). Mechanistically, Aβ contributes to tau phosphorylation (King et al., 2006). Then, hyperphosphorylated tau is transported to dendrites where it recruits Fyn to NMDAR/PSD-95 complex, resulting in the phosphorylation of NR2 on NMDAR and subsequently excitotoxicity (Ittner et al., 2010). Moreover, it can cause loss of neurons and synapse. In addition to Aβ-mediated pathways, accumulated senescent cells, increased DOPA decarboxylase and Aβ-induced CDK/pRB/E2F1 signaling pathways are also responsible for the progression of tauopathies (Bussian et al., 2018; Kow et al., 2018; Zhang et al., 2021). Interestingly, there is evidence that phosphorylation on particular residue of tau can protect neurons from excitotoxicity and spine loss in a mouse model of AD. Ittner and his colleagues reveal that p38γ-dependent phosphorylation of T205 on tau markedly inhibits Aβ toxicity via disruption of PSD-95/tau/Fyn complexes (Ittner et al., 2016; Ittner et al., 2020). However, no such protective phosphorylation site of tau has been found in human.

The bidirectional relationship between sleep and AD

Alteration in circadian rhythm associated with AD

Normal aging can change sleep pattern, worsening quality of life, whereas dementia contributes to further degeneration. As people aging, their sleep becomes more fragmented with increased latency, advanced sleep timing, excessive daytime napping, reduced SWS, and changes in REM sleep stages (Scullin and Bliwise, 2015; Li et al., 2023). A report analyzing 65 studies representing participants aged 5–102 has shown that percentage of SWS linearly decreased at a rate of about 2 % per

decade of age and a 3 % decrease in sleep efficiency per decade of age can happen until very old age (Ohayon et al., 2004). Although efforts have been made to reveal the potential relationship between sleep alteration and normative aging, what effectively regulatory factors are needed in the process and how they modulate it remains unknown.

AD patients suffer from more disrupted nocturnal sleep than the age-matched normal elderly. Alteration of sleep pattern occurs a decade or more earlier than diagnosis of AD, suggesting that sleep disruption happens in an early prodromal state of the disease and could contribute to AD development and progression (Vitiello and Borson, 2001). More than 80 % patients with AD complain about poor circadian rhythmicity, such as sundowning, excessive daytime sleepiness, and insomnia (Colwell, 2021). Sundowning refers to aggressive behaviors mainly occurring after the sun goes down, including being violent, yelling, and wandering around (Khachiyants et al., 2011). Fragmentation of daily sleep-wake cycle has been shown to be statistically correlated with subsequent AD development (Lim et al., 2013; Musiek et al., 2018; Li et al., 2020). Musiek ES et al. provided evidence that independent of age and sex, preclinical AD is associated with rest-activity rhythm fragmentation, supporting the contribution of circadian dysfunction to early disease pathogenesis (Musiek et al., 2018). In addition, fragmented daily sleep-wake rhythm also stimulates AD-like neuropathology in mouse models of AD (Minakawa et al., 2017; Duncan et al., 2022). It is demonstrated that despite the maintained circadian activity-rest rhythm, AD patients experience significantly longer inactivity interval during 24 h but poorer sleep quality than healthy subjects in similar ages (Khachiyants et al., 2011; Weissová et al., 2016). The circadian disorders syndromes develop into worse stages as the disease becomes severer. The relative proportion of daytime sleepiness in patients with severe AD is 14 %, higher than ones in moderate stage (5 %) and mild stage (2 %) (Vitiello et al., 1992). Obstructive sleep apnea (OSA) is the most common form of sleep disorders, leading to intermittent hypoxia and sleep fragmentation (Gottesman et al., 2024). It has been linked to a 34 % increased risk of all-cause dementia, 28 % increased risk of AD (Guay-Gagnon et al., 2022), subsequent diagnoses of MCI and all-cause dementia (Yaffe et al., 2011), and alteration of Aβ and tau (Baril et al., 2018). In addition, insomnia has been also associated with a 53 % increased risk of dementia (de Almondes et al., 2016).

Aberrant Aβ accumulation is associated with sleep-wake cycle disturbances. Studies in *trans*-genic mice expressing mutated APP or PSEN1 found that high neuronal activity was associated with high interstitial fluid (ISF) Aβ concentration, which predicts the high level of Aβ aggregation reliably, and ISF Aβ concentration shows diurnal fluctuations (Bero et al., 2011). Besides, mice with more soluble Aβ manifest increased sleep fragmentation (Sethi et al., 2015), supporting that sleep disturbances may be attributed to Aβ accumulation. You et al. demonstrated that Aβ deposition in precuneus, the strongest one among other brain regions, has a positive association with the number of nocturnal awakenings (You et al., 2019). Accompanied with the finding that precuneus is vulnerable to Aβ accumulation and plays a role in modulating slow-wave sleep (Murphy et al., 2009; Matsuoka et al., 2018), this result indicates an unrevealed link among Aβ aggregation, sleep disorders and cognitive impairment. In addition, different sizes of Aβ oligomers in zebrafish modifies sleep in different ways. The lower Aβ oligomers increase waking activity of zebrafish via intact adrenergic receptor β_2 (Adrb2) and Progesterone Membrane Receptor Component 1 (Pgrmc1), while the higher ones induce sleep via Prion Protein (PrP) signaling cascade (Özcan et al., 2020). However, it is unknown whether there are similar receptors or signaling cascade in human. Moreover, lack of studies in the roles of pathways involved in deposited Aβ-induced sleep alteration play in further sleep pattern degeneration in AD pathology hinder a profounder discussion on this aspect.

Except for studies on Aβ-driven sleep disorders, tau-dependent sleep changes attract much attention. Sleep-wake cycle disorders often start in preclinical stage of AD, overlapping with the tauopathy when hyperphosphorylated tau aggregates and spreads before Aβ forms plaques (Braak and Del, 2011). Similar with the studies mentioned above, ISF tau experiences diurnal fluctuation consistent with sleep-wake cycle, whose amplitude is greater than ISF Aβ's (Bero et al., 2011; Roh et al., 2012). Moreover, both ISF and CSF tau are regulated by sleep-wake cycle and chronic sleep deprivation exacerbates tau spreading and aggregation (Holth et al., 2019). These findings suggest that tauopathy is potentially relevant to circadian rhythm and optimal circadian cycle makes contribution to the prevention of AD. A number of wake-promoting neurons are severely affected by NFTs in AD. For example, locus coeruleus (LC) composed of neurons containing neuromelanin is a major source of norepinephrine (NE) in brain, with wide-ranging projection modulating the sleep-wake cycle (Berridge et al., 2012). LC NE neurons are wake-promoting but suffer from an abundance of NFTs and tremendous neuron loss in early stage of AD (Takahashi et al., 2010), supported by the study that abnormal tau most often (38 in 42 cases) affects LC throughout the brainstem (Braak and Del, 2011). Furthermore, the accumulation of NFTs and neuron loss have a positive correlation with AD progression (Ehrenberg et al., 2017, Theofilas et al., 2017). These early changes in LC may lead to sleep disruption preceding cognitive and behavioral changes in AD (Lucey et al., 2019). Other neurons such as dorsal raphe nucleus and parabrachial nucleus manifest different degrees of NFTs burden and neuronal loss (Grinberg et al., 2009; Eser et al., 2018). However, the molecular mechanisms of mentioned neurons influencing sleep and subsequently the disease progression still need further investigation.

Additionally, damage of suprachiasmatic nucleus (Harper et al., 2008) and low level of melatonin in brain (Prodhan et al., 2021) may also contribute to sleep-wake disturbances in AD but concise evidence is limited. A high level of orexin decreases Aβ clearance via inhibition of PI3K-Akt-p38 mitogen activated protein kinase (p38MAPK) signaling pathway as well as the suppression of phagocytosis in microglia and regulates the circadian oscillation from hippocampus (Ma et al., 2016; An et al., 2017). More specific effects of orexin need to be confirmed.

Alteration in neuronal rhythmic activity associated with AD

Scientists have recognized that the rhythmic activity in brain plays a significant role in orchestrating neuronal spiking in response to internal and external stimuli and underlies complex brain function through the inter-regional communication of cortical networks (Kopell et al., 2014; Zhang et al., 2018). Based on different frequency bands shown by EEG, these oscillations are classified into five types, including delta (δ: <4 Hz), theta (θ: 4–7 Hz), alpha (α: 8–12 Hz), beta (β: 15–30 Hz), and gamma (γ: 30–90 Hz) (Chan et al., 2021). It is well demonstrated that the rhythmic activity is crucial for acquisition and maintenance of information in working memory (Baddeley, 2012). For instance, compared to control and MCI groups, the band frequency of alpha, beta, and gamma slow down along with reduced power (Osipova et al., 2005; Poza et al., 2007), whereas the one of delta and theta bands are with enhanced power in AD patients (Jafari et al., 2020). More importantly, theta and gamma oscillations as well as their cross-frequency coupling are regarded as key factors in memory processing. Specifically, theta oscillation contributes to the consolidation and retrieval of episode and spatial memory (Rajji et al., 2017; Kim et al., 2019), while gamma oscillation is associated with higher brain function, such as temporal signals processing (Buzsáki and Chrobak, 1995), perception of sensory features (Martorell et al., 2019), and information recalling. It has been revealed that a specific 40-Hz sensory stimuli, termed gamma entrainment using sensory stimuli (GENUS), effectively reduced amyloid load, inducing a protective molecular response of 5 × FAD mice (Iaccarino et al., 2016). During exploration or REM/NREM sleep (Canolty and Knight, 2010; Hammer et al., 2021), temporal coupling between theta and gamma oscillations is established in various manners, among which phase-amplitude coupling is linked to neuronal computation, communication (Canolty and Knight, 2010), and plenty of cognitive process such as learning (Axmacher et al., 2010). Apart from two oscillations

mentioned, the others including delta and alpha bands are generally associated with sleep-related memory-enhancing process.

Studies have revealed that theta and gamma oscillations are predominant in REM sleep, whereas NREM sleep is characterized by slow oscillations (<1.25 Hz), delta waves, spindles, and SWRs (Adamantidis et al., 2019). Theta rhythm occurs in NREM N1 as a transition period and is followed by spindles burst from CA3 and κ-complexes defined by alternating negative high-voltage peak and positive high-voltage deflection in N2. During stage N3, the oscillation slows down and delta rhythm dominates, resulting in SWS for spatial memory consolidation. At the end of the sleep cycle, desynchronized sleep with theta and gamma oscillations leads to REM sleep (Wang and Holtzman, 2020). As mentioned above, disruption of SWRs-associated structures causes drastic spatial memory impairment due to disability of consolidation of spatial maps and memory maintenance (Girardeau et al., 2009; van de Ven et al., 2016). Reduced amplitude and changed temporal structure of SWRs were observed in a transgenic mouse model overexpressing tau protein (Witton et al., 2016). Accompanied with evidence that reduced SWR abundance and associated CA3 slow gamma were shown in mouse models of AD (Jones et al., 2019), these results indicate that damage of spatial memory can be attributed to the reduction of SWRs and consequently SWRs may serve as potential biomarkers of AD. Moreover, studies in 5 × FAD mice uncovered potential relationship between shorter and fewer SWRs and inhibitory synaptic deficits during spatial navigation (Prince et al., 2021). Parvalbumin-expressing basket cells and Apolipoprotein E4-induced GABAergic interneurons degeneration are responsible for this alteration, supported by further investigation (Gillespie et al., 2016; Caccavano et al., 2020). Although lists of conclusions have been drawn from studies in rodent, it is unclear that whether the alteration of SWRs in AD patients as well as the pathology it undergoes is as the same as the one in mice or not.

The transiently increased frequency and power of theta waves during REM sleep correlate with spiking rate and coordination throughout the hippocampus (Drieu et al., 2018). In addition, theta oscillations-dependent fine timing of hippocampus activity is crucial for memory encoding and consolidation during NREM sleep ripples (Montgomery et al., 2008). These findings show the significant physiological function of theta oscillations both in REM and NREM sleep. There is evidence that hippocampus-dependent contextual memory is impaired by optogenetically inhibition of theta oscillation in medial septum (Boyce et al., 2016) or alternating the activity of adult-born hippocampus neurons in dentate gyrus during REM (Kumar et al., 2020), indicating the causal role of theta oscillation in contextual memory processing. In APP/PS1 mouse model of AD, severe Aβ accumulation not only causes theta-gamma phase-amplitude coupling impairment, but also worsens theta-involved neuronal synchronization (Zhou et al., 2022). This is found in human via EEG as well (Stomrud et al., 2010; Legaz et al., 2023). However, the molecular mechanism lacks detailed studies.

Slow oscillations and delta rhythm are believed to improve memory-enhancing properties of sleep (Kjaerby et al., 2022). Slow oscillations are characterized by the membrane potential alternation between depolarized and hyperpolarized states (Crunelli and Hughes, 2010). The depolarized state is shown to participate in the coordination of the coupling between hippocampus high frequency oscillations and scalp spindles (Clemens et al., 2007; Clemens et al., 2011). Evidence is emerging that normal aging is accompanied with reduction of the density, amplitude, slope, and frequency of slow oscillations, while such situation in AD is worse (Carrier et al., 2011; Mander et al., 2017), suggesting that disruption of slow oscillations damages memory consolidation during NREM sleep in AD. Moreover, it is demonstrated that enhancing slow oscillation is beneficial to patients with early AD (Ladenbauer et al., 2017). While exerting optogenetic stimulation to increase cortical excitatory activity do rescue slow waves power at the normal frequency of 0.6 Hz and subsequently stop plaque deposition in a mouse model of amyloidosis (APP mice) (Kastanenka et al., 2017), Ksenia Kastanenka and her colleagues demonstrated that doubling the frequency of slow waves by optogenetic stimulation exacerbates Aβ-dependent neuronal calcium overload and loss of synaptic spines in the same mouse model (Kastanenka et al., 2019). These results suggest that the frequency is a defining factor. Furthermore, the inactivity of GABAergic interneurons may explain the occurrence of decreased delta power and SWS in APP-GAD-Cre mice (Zhao et al., 2023), supported by the sleep restoration through optogenetic stimulation. Of note, APP-GAD-Cre mice refer to the mice which co-express the Swedish mutation of APP and a deltaE$_9$ mutation in presenilin 1 and can target GABAergic neuronal population in presence of amyloidosis (Zhao et al., 2023). Additionally, the disturbances in slow oscillations and SWS profoundly affect metabolic clearance of tau and Aβ and sequentially cognitive function (Varga et al., 2016; Ju et al., 2017; Winer et al., 2019), indicating a bidirectional relationship between sleep and dementia. Efforts remain to be made because of the insufficient studies that reveal the relationship between GABAergic interneurons and slow oscillations in human, particularly in AD, which may provide a novel therapeutic strategy for the disease.

Influence of sleep disorders on Aβ pathology

Sleep disorders start in the preclinical stage of AD and Aβ deposition is observed about 15–20 years before cognitive decline occurs (Holtzman et al., 2011), indicating that Aβ deposition is temporally linked to sleep disturbances. It is also supported by evidence that deprived sleep was linearly associated with high ABPs and decreased cognitive function in a 4417 participants-involved clinical study (Winer et al., 2021). Additionally, increased plasma Aβ levels may be attributed to SWS disruption, resulting in loss of gray matter in posterior cingulate and sequentially shortened REM sleep in MCI patients (Sanchez-Espinosa et al., 2014). Even conducted in heathy adults without sleep disorders, acute sleep deprivation, particularly disruption of slow wave activity, markedly increases CSF Aβ $_{40}$ levels (Ju et al., 2017; Lucey et al., 2018). Chronic poor sleep quality leads to higher CSF Aβ$_{40}$/ Aβ$_{42}$, t-tau/Aβ$_{42}$, p-tau/Aβ$_{42}$ (Sprecher et al., 2017). It is generally believed that severer the sleep disorders are, more Aβ deposition, measured by positron emission computed tomography (PET) scanning, patients have. Shorter sleep duration contributes to greater Aβ burden in AD-sensitive brain regions, such as angular gyrus, frontal medial orbital cortex, cingulate gyrus, and precuneus (Sprecher et al., 2015). Longer sleep latency is associated with greater Aβ burden in prefrontal areas and more nocturnal awakenings is linked to less gray matter volume in insular region as well as increased ISF/CSF Aβ levels (Kang et al., 2009; Roh et al., 2012; Ooms et al., 2014).

Mechanisms have been continuously proposed to explain the relationship among sleep, Aβ, and sequentially AD so far but most of the studies focus on how sleep disturbance affects Aβ clearance. Since ISF and CSF Aβ both manifest diurnal fluctuation (Holth et al., 2019), it is reasonable that genes controlling circadian rhythm are associated with Aβ production or clearance. In vitro, microglia express higher level of BMAL1, a master clock protein that directly drives transcription of another clock proteins REV-ERBs, at circadian time (CT) 4 than at CT 12, in parallel with which is more phagocytosed fibrillary Aβ$_{1\text{-}42}$ at CT4 than at CT12. Moreover, inhibition of REV-ERBs as well as genetic knockdown of *Rev-erbs* in microglia from 5 × FAD mouse model in vitro can accelerate microglial uptake of fibrillary Aβ$_{1\text{-}42}$. REV-ERBα deficiency also leads to reduction of amyloid plaque and plaque-associated synaptic loss (Lee et al., 2020). Additionally, deficiency of clock genes that implicate loss of central circadian rhythm such as global *Bmal1* deletion and lack of *Per1*, hinders the oscillation of Aβ and/or accelerates its accumulation in mice (Kress et al., 2018; Börner et al., 2021). These results uncover a promising strategy to alleviate Aβ deposition as well as AD pathogenesis through restoration of the central circadian rhythm. However, lack of studies that demonstrate the link between clock gene and Aβ in human hinders its clinical practice.

Glymphatic system (GS) has been described as an important

perivascular network taking part in interstitial Aβ clearance (Iliff et al., 2012). During sleep, CSF along with harmful waste products such as Aβ is propelled inflow along periarterial spaces by lots of physiological drivers such as respiration, slow vasomotion, and cardiac cycle. Consequently, waste transported to peripheral tissues is removed by lymphatic system, leading to peripheral clearance of Aβ (Alhola and Polo-Kantola, 2007; Rasmussen et al., 2022). Compared to the awaken brain, the perivascular exchange between ISF and CSF markedly increases in the asleep brain, supported by experiment measuring and comparing CSF tracer flux as well as Aβ clearance rate in sleeping state and in waking state (Xie et al., 2013). Insufficient sleep or prolonged deprived sleep inevitably break the homeostasis of central and peripheral Aβ clearance and sequentially cause neurological damage in healthy individuals, a risk factor of AD (Wiig and Swartz, 2012). Other studies also strived to link reduced CSF clearance in AD patients with increased grey-matter concentrations of Aβ in human that is consistent with findings in mice that decreased glymphatic function results in Aβ accumulation (Iliff et al., 2012; Xu et al., 2015), supporting that the damaged glymphatic system probably attributed to poor sleep contributes to AD pathology via CSF Aβ clearance dysfunction. However, the link is not causal. Studies so far have not focused on similar factors propelling glymphatic flow in human and revealed the relationship between neurodegeneration disease and perivascular ISF-CSF solute exchange. In addition, genetic regulation of this system is still unclear (see Fig. 2).

Influence of sleep disorders on tau pathology

Similar with the findings about Aβ in mouse, ISF tau and CSF tau in human manifest diurnal fluctuation too. Chronic sleep deprivation makes its amplitude higher than in normal circumstance. Holth et al. showed that ISF tau in mice was increased about 90 % during normal wakefulness versus sleep and about 100 % during sleep deprivation, whereas CSF tau in human was increased more than 50 % during sleep deprivation (Holth et al., 2019). Specifically, the mean concentration of unphosphorylated tau all increased above baseline levels in healthy subjects after sleep deprivation. The phosphorylated occupancy of different sites, assessed by the ratio of phosphorylated to unphosphorylated tau, differed during sleep deprivation (Liu et al., 2023). Furthermore, chronic sleep deprivation profoundly increased tau spreading (Holth et al., 2019). Additionally, poor in-home sleep quality before sleep deprivation is significantly linked to high CSF tau (Ju et al., 2017). Studies on AD patients also show that longer total sleep time due to AD worsens tau pathology and predicts AD progression as well as memory deficits (Yoon et al., 2023). Obstructive sleep apnea (OSA), a common cause of sleep disturbances and also a typical risk for AD, induces elevated tau in the brain of young individuals, while the level of total tau in brain-derived exosomes is higher in young individuals with OSA and MCI (Motamedi et al., 2018; Sun et al., 2022). These findings suggest that tau pathology correlates with sleep disorders and AD bidirectionally. Spatially, abnormal tau phosphorylation is found in parts of ascending arousal system, including hypothalamic tuberomammillary nucleus, lateral hypothalamus, and the basal forebrain, resulting in sleep disorders during normal aging (Braak and Del, 2011). Moreover, laterodorsal tegmental nucleus and the listed regions above are vulnerable to NFT pathology in AD (Parvizi et al., 2001; Holth et al., 2017), suggesting that regions undergoing tau pathology are overlapped with those damaged by sleep disorders.

Recently, more and more studies have tried to demonstrated how sleep disorders affect tau pathology. Extracellular tau is modulated by neuronal activity, in particular excitatory neuronal activity. When observed via in vivo microdialysis, presynaptic glutamate release, implicating activated excitatory neurons, drove tau release, resulting in significantly increased ISF tau in healthy individuals (Yamada et al., 2014). Based on the results, it is possible that altered activity of excitatory neurons during sleep-wake cycle contributes to ISF/CSF tau fluctuation. Whether excitatory neurons play a similar role in extracellular tau accumulation in AD remains to be investigated. Reduced NREM slow wave activity also causes enhanced tau pathology. Subsequent statistics analysis attributed it to race, ApoE4 status, and sleep medications (Lucey et al., 2019). Other studies pointed out that disrupted NREM spindle-slow oscillation coupling was not associated with Aβ burden but tau accumulation in medial temporal lobe (Winer et al., 2019), whereas reduced NREM N2 spindle density and duration were inversely linked to all AD biomarkers (Kam et al., 2019). For intervention, chronic GENUS in visual cortex, hippocampus, and prefrontal cortex of Tau P301S and CK-p25 mice significantly preserved neuronal as well as synaptic density in many brain regions and improved cognitive function in their early

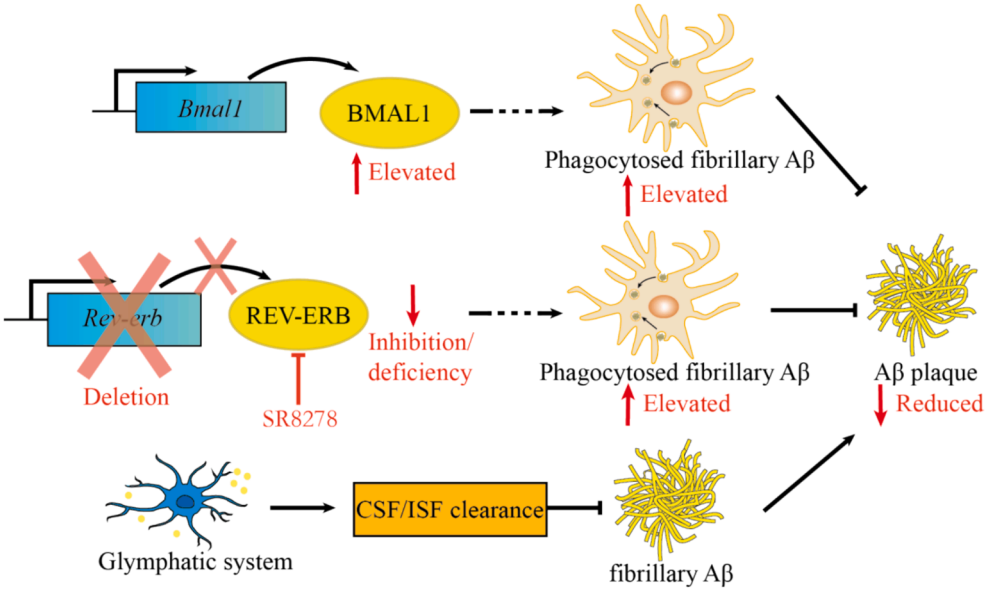

Fig. 2. The mechanisms of sleep-dependent regulation of fibrillary Aβ's deposition. Many central circadian rhythm-related proteins can contribute to or prevent the deposition of fibrillary Aβ via different pathways. Increased BMAL1 in microglia from 5 × FAD mouse model in vitro is parallel with increased phagocytosed fibrillary Aβ. Deletion of *Rev-evb* and inhibition of REV-ERB by SR8278 inhibitor are associated with increased phagocytosed fibrillary Aβ too. These all lead to reduced Aβ plaque accumulation. Glymphatic system-dependent CSF/ISF Aβ clearance is also suggested to participating in the regulation but stronger evidence is needed.

stage of neurodegeneration (Adaikkan et al., 2019). All these findings support the view that oscillation stimuli from surroundings can work as a promising therapeutic intervention of early stages of AD but the specific mechanisms need to be clarified.

Interestingly, glymphatic clearance is also regulated by neuronal activity and enhanced during SWS (Iliff et al., 2012; Xie et al., 2013), suggesting that tau release, spreading, and subsequent clearance are associated with glymphatic system. It is supported by the evidence that ISF tau was increased 90–100 % accompanied with reduced glymphatic function during sleep deprivation or wakefulness (Holth et al., 2019). Acute SWS disruption impairs glymphatic-mediated clearance of tau, which can chronically lead to enlarged perivascular spaces, reduced blood flow and subsequently further glymphatic impairment and increased extracellular tau level (Horsburgh et al., 2018; Morrone et al., 2020).

Genetic factors attract much attention too. Dong et al. demonstrated that DEC2-P384R, Npsr1-Y206H, and Adrb1-A189V mutations of familial natural short sleep were strongly associated with alleviated tau pathology in PS19 mice (Dong et al., 2022; Dong et al., 2023). In specific, although mutant NPSR1 receptor was more active than wild type (Xing et al., 2019) and tau release was only increased in Npsr1-Y206H PS19 mice compared to PS19 mice after NPS treatment, total CSF tau in mice with mutations was lower (Dong et al., 2022), implicating that other systems such as activated clearance system may be responsible for the reduction. In PS19 mice with Adrb1-A189V mutation, neurons with mutant Adrb1 in central amygdala failed to propagate tau to locus coeruleus, resulting in restored REM sleep and attenuated tau pathology (Dong et al., 2023). However, whether such mutations in human affect sleep quality and tau pathology in a similar way remains unclear. Studies are not sufficient enough to expound the relationship between adrenergic receptors and sleep as well as AD pathogenesis.

Influence of sleep disorders on neuroinflammation

Apart from Aβ and tau, neuroinflammation also bridges sleep disorders and AD. Various studies show that glia cells as well as glia-derived neuropeptides are modulated by sleep-wake cycle and affect AD progression (Nadjar et al., 2013; Bellesi et al., 2017). Microglia are known to play a role in eliminating weak synapses and remodeling synapses during sleep (Choudhury et al., 2020). Reduced dendritic spine number and increased synapses formation were observed with the help of two-photon in vivo imaging (Maret et al., 2011), supporting the diurnal fluctuation of synaptic network. The phenomenon was mitigated by deletion of gene for microglia lysosomal protease (Hayashi et al., 2013), indicating the direct involvement of microglia in pruning synapses during sleep. Moreover, failure of clock genes derived transcriptional control induces chronic neuroinflammation before onset of AD (Ni et al., 2019), suggesting that immunocompetent cells such as microglia and astrocytes may be regulated by upstream clock genes and then contribute to AD. Transient stimuli activates microglia that produce pro-inflammatory cytokines such as interleukin-1β (IL-1β), IL-6. These cytokines are secreted to microenvironment, interacting with other neurons as well as astrocytes and subsequently causing inflammation. However, when overactivated, microglia may exacerbate neuronal damage and synaptic loss, resulting in neurodegenerative diseases such as AD (Yong, 2022). Studies have demonstrated that chronic sleep deprivation markedly increases inflammation through abnormal microglia activation, contributing to increased IL-1β, IL-6, and TNF-α and decreased anti-inflammatory cytokines in hippocampus. It leads to destroyed spatial memory and synaptic loss, whereas microglia inhibition can mitigate those negative effects (Wadhwa et al., 2017a, 2017b). In addition, microglia and various cytokines such as TNF-β, IL-6 are found to get accumulated around ABPs in humans and mice overexpressing mutant APP, resulting in inflammatory response that accelerates AD development (Serrano-Pozo et al., 2013). These findings reveal that typical AD biomarkers may act as triggers or targets of inflammatory factors. Further studies demonstrated that the level of CSF myeloid cells type 2 (TREM2), an innate immune receptor, was higher in AD patients than in control group and increased with the disease stage (Piccio et al., 2016; Suárez-Calvet et al., 2016; Liu et al., 2018). Loss of functional TREM2 increases ABP-dependent toxicity (Jay et al., 2017). Additionally, chronic sleep deprivation exacerbates TREM2-dependent microglia reactivity but the hyperreactive microglia are inefficient in removing Aβ deposition (Parhizkar et al., 2023). These studies indicate that immune receptors may be targets of immunosuppression for the treatment of AD. However, to set up a novel therapeutic strategy, more specific studies are needed to uncover how sleep disorders-induced alteration of immune cells influences AD progression.

Neuropeptide Y (NPY) is one of the sleep-regulatory neuropeptides that are associated with AD. It is widely distributed in many brain regions but expressed higher in hippocampus, LC, and cerebral cortex et al., many of which are associated with sleep-wake regulation (Lynch et al., 1989; Dumont et al., 1992). NPY signaling from intergeniculate leaflet (IGL) to suprachiasmatic nucleus (SCN) serves as an essential component of the neuronal pathways that regulate circadian synchronization to light–dark cycle (Morin and Allen, 2006; Glass et al., 2010). The daily rhythm of its release in depends on the 14-hour light: 10-hour darkness photocycle and may be modulated by serotonergic activation of NPY units in IGL (Glass et al., 2010). Earlier studies reported that the expression of NPY in human astrocytes involved forskolin, basic fibroblast growth factor, protein kinases C, cFos, and JunB pathways (Barnea et al., 1998; Barnea et al., 2001) and it was crucial for against neurovascular dysfunction and microgliosis through the activation of Y2 receptors (Gonçalves et al., 2012; Ventura et al., 2020). Additionally, findings showed that microglia dysfunction-induced neurotoxicity exacerbated AD pathology (Hansen et al., 2018) and decreased NPY was observed in AD patients (Li and Larsen, 2023) as well as patients with primary insomnia (Huang et al., 2015). Moreover, NPY administration to healthy subjects prolonged total sleep time and reduced sleep latency (Antonijevic et al., 2000). Administration of NPY receptor agonist increased the duration of NREM sleep in rats (Akanmu et al., 2006). Therefore, it is reasonable that activation of the mentioned pathways above may induce higher expression of NPY so that it can increase sleep quality of AD patients as well as mitigate microglia-induced neurotoxicity, alleviating the disease progression. To date, studies have demonstrated the protective effects of NPY against AD. Treatment of NPY can prevent Aβ-induced neurotoxicity, cognitive impairment, and depression-like symptoms and ER stress-mediated neuronal loss via activation of Y2 receptors and increased nerve growth factors and brain-derived neurotrophic factors (Croce et al., 2012; Dos Santos et al., 2013; Lee et al., 2018). However, studies in human are insufficient. Other small peptides such as somatostatin (Song et al., 2021; Li and Larsen, 2023) and orexin (Kang et al., 2009; An et al., 2017) also take part in neuroinflammation-regulated AD pathology but lack of studies on their effectiveness on AD patients limits their clinical application.

Therapeutic methods of sleep enhancement

Based on the bidirectional relationship between sleep disorders and AD as discussed above, more and more studies try to develop new pharmacological and non-pharmacological methods of sleep enhancement to ameliorate AD pathology. Melatonin, lemborexant, suvorexant, galantamine, eszopiclone, sedative hypnotics, trazodone, and donepezil are popular pharmacological interventions studied in the last two decades (Blackman et al., 2021; Bedward et al., 2024), while phase locked loop acoustic stimulation, transcranial magnetic stimulation, low-intensity transcranial electrical stimulation, transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and probiotic supplements are promising non-pharmacological interventions (Menardi et al., 2022; Fei et al., 2023; Lu et al., 2023). Non-pharmacological interventions are typically the beginning treatment for sleep disturbances in patients with AD. When pharmacological

treatments are necessary, sleep medications reducing the incidence of sleep disturbances are commonly prescribed (Bedward et al., 2024).

Melatonin is a significant physiological sleep regulator in diurnal species including humans and is the most studied medication (Zisapel, 2018; Bedward et al., 2024). Due to its roles in attenuating the wake-promoting signal of circadian clock (Liu et al., 1997) and promoting fatigue and sleep-like changes in activation of precuneus (Gorfine et al., 2006), melatonin is regarded as an important component in the treatment for sleep disorders. It is demonstrated that immediate release melatonin cannot result in statistically significant differences in objective sleep measures compared to a placebo in patients with AD with sleep disturbances (McCleery et al., 2016), probably because of rapid absorption and first-pass hepatic metabolism (Zisapel, 2018). However, prolonged-release melatonin (PRM) not only improves subjectively-perceived sleep quality, shortens sleep latency, but also improves morning alertness and quality of life while preserving physiological sleep structure (Lemoine and Zisapel, 2012). PRM helps maintain or improve cognitive function versus placebo in mile or moderate AD patients (Wade et al., 2014). Orexin antagonists are also prescribed for people with AD with sleep disturbances but less commonly used due to its relatively short history and uncertain impact of the orexin system on AD progression (Gao et al., 2021; Bedward et al., 2024). Sedative hypnotics are usually prescribed for short-term treatment for sleep disorders but its risk of dependence, mental confusion, and potential for rebound issues (Lader, 1997) limit its use in long-term sleep enhancement in AD patients. Other medications such as trazodone and galantamine are shown to have favorable outcomes and mild side effects on sleep disorders such as obstructive sleep apnea in patients with AD (Bedward et al., 2024).

As discussed above, slow oscillations stimulation is beneficial to patients with early AD, supporting by the fact that slow oscillatory tDCS (so-tDCS) increased slow wave activity and spindle synchronization of MCI patients, leading to enhanced visual memory performance (Ladenbauer et al., 2017). However, studies on so-tDCS in MCI patients as well as healthy elderly manifest conflicting results (Romanella et al., 2020), hindering its clinical practice. Close-loop tACS is shown to entrain slow wave activity in healthy young individuals, resulting in improved long-term memory, but its application on MCI or AD patients is still largely unexplored (Xu et al., 2019; Romanella et al., 2020). There are several studies trying to develop new and promising methods of sleep enhancement on mice models of AD. Ksenia Kastanenka et al showed that the activation of channelrhodopsin-2 (Kastanenka et al., 2017), astrocytes (Lee et al., 2023), and GABAergic interneurons (Zhao et al., 2023) by optogenetic stimulation rescues the slow wave activity of mouse model of AD, ameliorating AD pathology. What's more, low-frequency visual stimulation also enhances slow wave activity without disrupting sleep pattern (Thankachan et al., 2022). Interestingly, thermoneutral temperature exposure of a mouse model of AD leads to improvement of slow wave sleep and reduction of diethylamine-soluble $A\beta_{40}$ and $A\beta_{42}$ in hippocampus, revealed by Wang et al. Of note, thermoneutral temperature refers to the temperature gradually increasing, from ambient temperature at zeitgeber time (ZT) 0–8 °C higher than ambient temperature at ZT8, and then gradually falling back to ambient temperature by ZT14 (Wang et al., 2024). More similar studies about the mentioned methods above in human are needed and their safety as well as efficiency needs further evaluation.

Conclusion and future perspectives

Although many factors have been proved to contribute to AD pathogenesis, aberrant Aβ and tau accumulation are still the "golden standards" for diagnose of AD. Recent studies have elucidated that both ISF and CSF Aβ and tau manifest diurnal fluctuation in healthy individuals, whereas the two aberrantly increased biomarkers have been found in AD mouse models and patients, linking AD pathology to circadian rhythm disorder potentially. AD is associated with poor sleep quality, reduced SWS, and excessive day napping. Conversely, sleep deprivation induces markedly increased Aβ, tau, and neuroinflammation in brain. Acutely, it causes transient change of the two biomarkers as well as the brain immune cells, while it chronically leads to acceleration of Aβ deposition and tau accumulation as well as spreading. With the help of EEG and PET, electrophysiological effects of oscillations explain the microscopic mechanisms that NREM and REM sleep affects episodic and contextual memory respectively during normal and disrupted sleeping state. Glymphatic system including microglia, astrocytes, and their secreted neuropeptides, which are key to the clearance of the biomarkers, is found to be disrupted during AD and sleep-wake disturbances, contributing to exacerbated Aβ and tau pathology. Currently, studies have demonstrated the bidirectional relationship of AD and sleep disorder but the understanding of it is still immature. Although several pharmacological and non-pharmacological methods have been proposed, further studies are needed to reveal whether the dynamic alteration of Aβ and tau in human is modulated by the similar components of sleep uncovered in rodent, for better treatment in AD patients. Moreover, it is worthwhile to find out whether neuronal oscillations take part in the regulation of AD pathology or not when patients and experimental mice suffer from sleep disorder, and how they affect the dynamics of AD biomarkers.

Funding

This research is supported by National Natural Science Foundation of China (Grant No. 32271028, No. 32071031).

CRediT authorship contribution statement

Junhua Chen: Writing – review & editing, Writing – original draft, Visualization, Project administration, Conceptualization. **Guoping Peng:** Writing – review & editing, Supervision, Project administration, Conceptualization. **Binggui Sun:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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