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REVIEW ARTICLE

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Dysfunction of circadian and sleep rhythms in the early stages of Alzheimer's disease

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Abstract

Dysfunction of circadian and sleep rhythms is an early feature of many neurodegenerative diseases. Alzheimer's disease (AD) is a progressive neurodegenerative disorder resulting in cognitive and psychiatric disturbances. Although it is largely unclear whether dysfunctions in sleep and circadian rhythms contribute to the etiology of AD or are a consequence of the disease, there is evidence that these conditions are involved in a complex self-reinforcing bidirectional relationship. According to the recent studies, dysregulation of the circadian clock already occurs during the asymptomatic stage of the disease and could promote neurodegeneration. Thus, restoration of sleep and circadian rhythms in preclinical AD may represent an opportunity for early intervention to slow the disease course.

KEYWORDS

Alzheimer's disease, circadian system, clock, neurodegeneration, sleep

1 | INTRODUCTION

Circadian clocks are fundamental endogenous oscillators that allow essentially all organisms on Earth to adapt and adjust their physiology and behavior to environmental 24-h cycles.[1,2] Disturbances in the circadian clock severely impact on human health and are associated with many human diseases such as cancer, diabetes, and neurological diseases.[3–6] Dysfunctions in the circadian clock are common symptoms of neurodegenerative diseases, including Alzheimer's disease (AD). Alterations in circadian and sleep functions in AD patients include highly fragmented nocturnal sleep patterns, increased arousals and wakefulness, and decreased levels of daytime activity.[7,8] Several

recent studies suggest that circadian rhythm and sleep disturbances already occur during the pre-symptomatic stages of AD.[6,9,10] Thus, circadian clock dysfunction may represent both a marker for pathology and a crucial opportunity for early intervention in AD. Nevertheless, the relationship between circadian dysfunction and neurodegeneration is still poorly understood, and more studies are needed to better understand the pathophysiological role of circadian and sleep dysfunction in AD.

In this review, we focus on recent data exploring the relationship between sleep and circadian rhythm disruption during early stages of AD. We summarize findings from preclinical and clinical studies, and we discuss potential mechanisms involved in the disruption of the circadian system during the early phases of AD.

1.1 | Alzheimer's disease

AD is a chronic neurodegenerative disease and the most common cause of dementia worldwide. In 2016, an estimated 40 million people suffered from AD worldwide,[11] a number that is expected to rise to 131 million in 2050.[12]

AD is characterized by progressive cognitive decline and neuropsychiatric symptoms and, at a cellular level, by neuronal degeneration, microglial activation, and aggregation of misfolded proteins resulting in the accumulation of extracellular amyloid-beta (Aβ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau[11,13] (Figure 1).

The etiology of AD is still unclear. The greatest risk of developing AD is old age,[11] and the risk is estimated to double every 5 years after the age of 65.[14] Only a small portion (1%–5%) of the cases develop the familial form of AD which is caused by autosomal dominant mutations in genes implicated in the generation of Aβ: presenilin1-2 (*PSEN1-2*), and amyloid precursor protein (*APP*).[15] The vast majority of cases are sporadic and are believed to result from a complex interaction between genetic risk and environmental factors.[16] The human *ε4 allele of Apolipoprotein E* (*APOEε4*) *is known to increase susceptibility to AD, and it has been associated with 15%–20% of the cases.*[17]

A key feature of AD is the dysregulation of circadian rhythms reported both in preclinical AD as well as in mid- to late stages of the disease.[6,13] Several studies suggested that circadian rhythm and sleep disturbances, including fragmentation of sleep–wake cycles, long periods of wakefulness during the night and excessive daytime sleepiness,[8,10,18] reduced circadian amplitude and phase

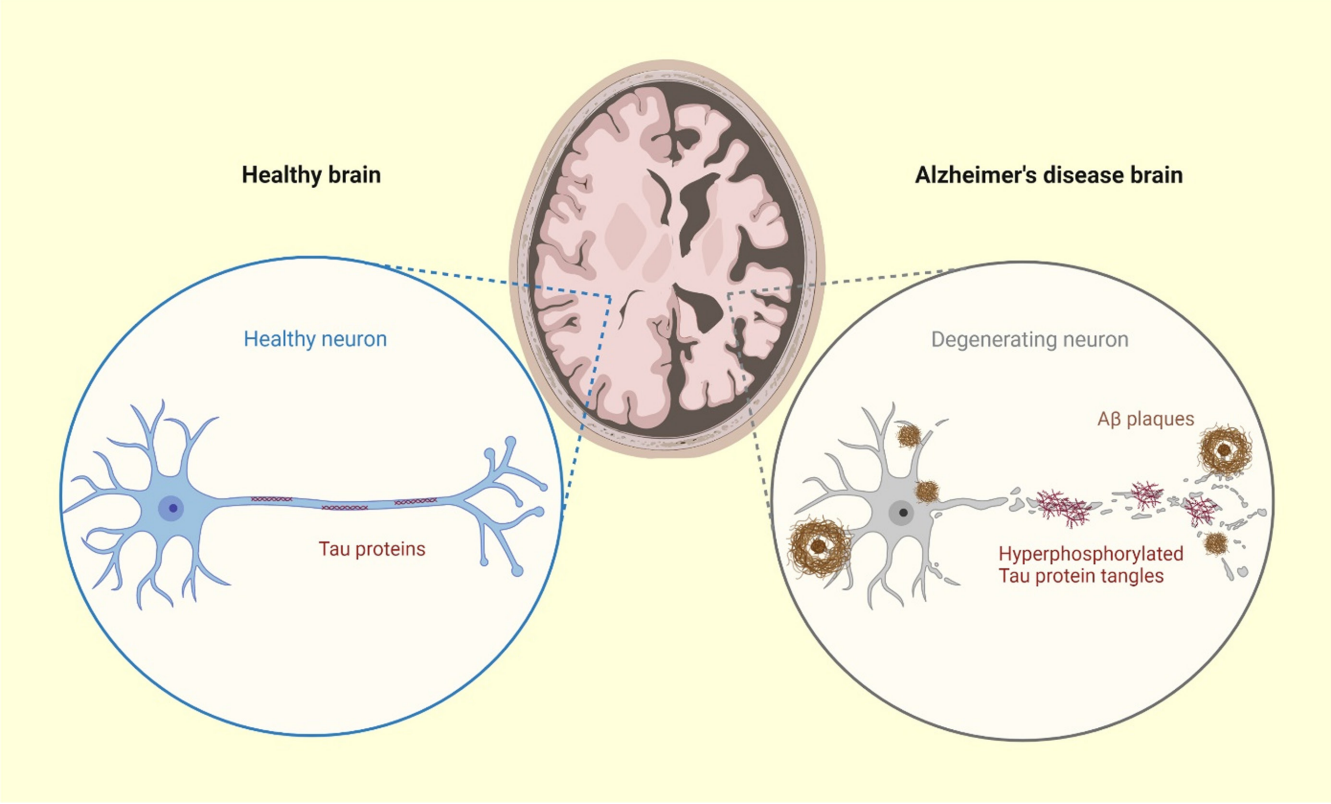

FIGURE 1 Alzheimer's disease pathology: Compared to a normal healthy brain (left), AD is characterized by brain atrophy (top), with neuronal degeneration, aggregation and accumulation of extracellular amyloid-beta (Aβ) plaques and intracellular tau neurofibrillary tangles (right).

delay,[6,19] as well as advanced timing of melatonin secretion onset,[20] can be early manifestations of neurodegeneration and might occur long before AD onset.[6,9,10]

1.2 | Circadian rhythms and sleep/wake regulation

The circadian timing system is an evolutionarily conserved program which generates oscillations with a period of approximately 24 h, thereby temporally orchestrating the physiology of essentially all organisms on Earth. Such circadian oscillations enable the organisms to anticipate and adapt physiology to rhythmic external stimuli caused by the Earth's rotation, such as light–dark or temperature cycles.[21–24] Sleep–wake cycle, hormone secretion, body temperature, immune system, motor, and cognitive activities are only some of the many physiological processes that are under direct control of the circadian system. Human cells possess an autonomous internal clock which is controlled and coordinated by the hypothalamic suprachiasmatic nucleus (SCN), known as the "master clock". The SCN, which is composed of two clusters of approximately 100 000 specialized neurons in humans,[25] receives direct photic input, known as "zeitgeber" (German for "time giver"), from the external world via the retino-hypothalamic tract. In addition, dietary input, motor activity and social cues can also act as zeitgebers and synchronize the endogenous rhythms of each cell with the environment, a process called "entrainment"[24] (Figure 2). The most important zeitgeber is light.[26–29] Light is perceived by specific cells in the retina of the eye, the intrinsically photosensitive retinal ganglionic cells (ipRGCs), which express the photopigment melanopsin (Opn4), a G-protein coupled receptor (GPCR) leading to action potential generation and calcium influx upon activation.[28] The ipRGCs project to the SCN where the light signal activates a wide range of kinases, which eventually result in transcriptional activation via CREB (cAMP response element binding protein) of several clock genes, such as *PERIOD 1-2* (*PER1* and *PER2*). Other zeitgebers, such as exercise, mealtime and social contact are integrated within the thalamic intergeniculate leaflet and brain stem serotonergic raphe magnus nuclei, which then project to the SCN.[30] Dietary zeitgebers can act

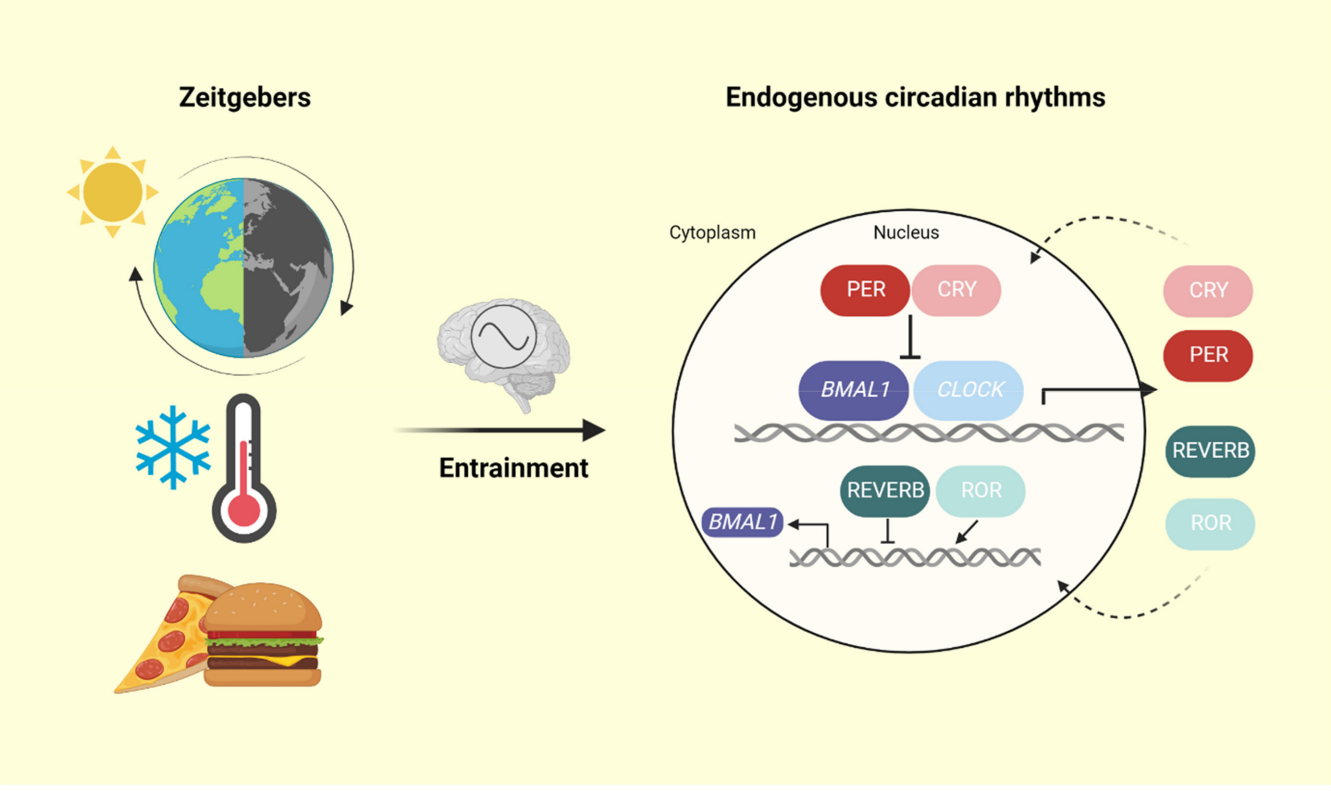

FIGURE 2 Circadian rhythms: Endogenous circadian rhythms are entrained by external stimuli called "zeitgebers". The most important zeitgeber is light and together with other zeitgebers such as visual, dietary, motor activity and social cues synchronize the circadian clock to temporally coordinate physiology and behavior to environmental cycles. At the cellular level, the circadian rhythms are generated by molecular oscillators with clock genes expressing transcriptional activators (BMAL1, CLOCK, ROR) and repressors (PER1/2, CRY, REV-ERB).

independently of the SCN and directly entrain clocks in peripheral tissues.[31,32]

At the molecular level, circadian rhythms are generated by fine-tuned transcriptional and translational feedback loops or TTFL.[21–23,33,34] In human TTFL, at the beginning of the day, the first loop begins in the cell nucleus with the dimerization of BMAL1 (brain and muscle Arnt-like protein-1) and CLOCK (circadian locomotor output cycles kaput) proteins.[35,36] This complex works as a transcriptional activator of the *PER* and *CRYPTOCHROME (CRY)* genes. The inhibitory action of PER/CRY on BMAL1/CLOCK is controlled by progressive phosphorylation and ubiquitin-targeted degradation of PER1/2 by casein kinases (CK) 1ε and δ,[37,38] and by CRY1/2 protein degradation by the SCF/Fbxl3 ubiquitin ligase complex.[39,40]

In the late afternoon, the proteins PER and CRY accumulate in the cytoplasm where CK1ε/δ regulates their stability. Together with CK1 proteins, PER and CRY enter the nucleus and form a large multi-protein complex with other transcriptional repressor complexes, comprising chromatin modifiers and remodelers.[41] Integrated within this large repressor complex, PERs and CRYs interact with the heterodimer BMAL1/CLOCK[36] and negatively regulate the activity of BMAL1/CLOCK by promoting the dissociation of the heterodimer from DNA.[42] There is also an additional feedback loop incorporating nuclear receptors (REV-ERB) and receptor-related orphan receptors (ROR). The BMAL1/CLOCK heterodimer activates the expression of its own activator genes, *ROR*,[43] and also of *NR1D1* (nuclear receptor subfamily 1, group D, member 1, also known as *REV-ERBα*) and *NR1D2* (nuclear receptor subfamily 1, group D, member, also known as *REV-ERBβ*), whose protein products in return suppress *BMAL1* expression.[44,45]

Sleep and wakefulness are complex behaviors, regulated by both the circadian clock and homeostasis. Sleep/wake states are characterized by specific physiological, behavioral, and electrophysiological parameters.

Wake and alertness are characterized by consciousness and high muscle tone, which are controlled by wake-promoting areas in the brain that use different neurotransmitters, namely monoaminergic wake-promoting neuronal populations in basal forebrain (acetylcholine), dorsal and median raphe nuclei (dopamine and serotonin), locus coeruleus (noradrenaline), tuberomamillary nucleus (histamine), and ventral tegmental area (dopamine).[46] Other wake-promoting modulators emerge from glutamatergic neurons in the parabrachial area, from cholinergic neurons (basal forebrain lateral and pedunculopontine and laterodorsal tegmental nuclei) and from orexinergic neurons (lateral hypothalamus). Orexin is particularly important to maintain wakefulness in challenging environments or conditions.[47]

Non-rapid eye movements (NREM) sleep is characterized by both reduced consciousness and muscle tone. NREM sleep is controlled mainly by GABAergic neurons in the ventrolateral preoptic area and median preoptic nucleus that will inhibit the activity of the wake-promoting neurons in the brainstem and posterior hypothalamus. GABAergic neurons in the parafacial zone and cortex are also thought to be sleep-active neurons.

Rapid eye movement (REM) sleep is characterized by muscle atonia and reduced consciousness and is mainly generated by neuronal populations located in the pons and adjacent portions of the midbrain involving neurons called REM-on (expressing GABA, acetycholine, glutamate, or glycine) and REM-off (expressing noradrenaline, adrenalin, acetylcholine, histamine, or GABA), depending on their activation during that sleep state.[48]

The different wake–sleep states can also be distinguished based on their respective electroencephalogram (EEG) characteristics. The wake EEG shows low-voltage fast-activity, dominated by beta (16–32 Hz) and gamma (>32 Hz) waves. During NREM sleep, the EEG shows slower waves (12–15 Hz) called sleep spindles, and even slower waves of large amplitude (delta). REM sleep shares some EEG characteristics with the tonically activated wake EEG with beta (16–32 Hz) and gamma (>32 Hz) waves[49] but can be differentiated from the wake EEG by the higher presence of theta waves (4–8 Hz) and the occurrence of phasic events (e.g. rapid eye movements).[48]

Sleep regulation has been conceptualized under a model describing the interaction between a homeostatic process (process S) and a process involving the circadian clock (process C).[50] The homeostatic control of sleep ensures that prolonged bouts of wakefulness are followed by proportionally longer bouts of deep non-REM sleep, which are in part mediated by the secretion of somnogens, including adenosine and prostaglandin D2 that will stimulate sleep-promoting neurons when sleep pressure increases. A small subset of GABAergic neurons expressing nitric oxide synthase has also been shown to be responsible for the coupling between homeostatic sleep drive and EEG parameters characteristic of slow wave sleep.[51]

The circadian regulation of sleep is ensured by indirect inputs of the SCN on wake centres (lateral hypothalamus, orexinergic neurons) and sleep centres (ventrolateral preoptic area, GABAergic neurons) in the brain. The SCN also activates in a time-of-day dependent manner the dorsomedial hypothalamus (DMH) via a direct input. The DMH regulates wake/sleep states by activating the lateral hypothalamus and by inhibiting the ventrolateral preoptic area. In humans, sleep is

also regulated by the SCN via the secretion of melatonin that occurs in the evening (in the absence of light) and is reduced at dawn. Melatonin plays a role as a mediator between thermoregulation and the arousal systems in humans by regulating core body temperature in the evening and inducing sleep.[52]

Circadian clocks control the daily variations of physiology, however, it has been proven difficult to dissociate the circadian components from contributions of periodic changes in the environment or in behaviors (sleep–wake states, posture, eating, social interactions).[53] To remediate this, protocols using either forced desynchrony (FD) or free-running protocols (without environmental time cues) were designed. The FD protocols require placing the subjects under a non-24 h light/dark cycle to which the SCN cannot entrain resulting in a free-run of the endogenous rhythm (on average 24.15 h in humans). The pioneering experiment of Kleitman revealed that, when sleep–wake cycles are forced to adjust to a 28 h-day routine, although circadian parameters are maintained at cycles of around 24 h, the rise of body temperature in the morning is due to an endogenous circadian rhythm and not due to the increase of activity after wakefulness or food intake.[54] The historic free-running protocols (with no environmental time cues) sometimes induce a spontaneous internal desynchronization leading to the uncoupling between the sleep/wake timing (then unstable and running at much shorter or longer cycles than 24 h) and the circadian endogenous rhythms that are maintained close to 24 h (body temperature, cortisol and melatonin secretion, urine parameters).[55]

1.3 | Circadian and sleep dysregulation in neurodegeneration

Sleep and circadian rhythm alterations have long been associated with neurodegenerative diseases, including Parkinson's disease (PD), Huntington's disease (HD), and AD. Familial and sporadic fatal insomnia (FFI) are prion diseases with disrupted slow-wave and REM sleep and severe neuronal loss in the thalamus, inferior olives, cerebral cortex, and cerebellum.[56] Mutations in the human *RORA* gene have been associated with ataxia and cerebellar atrophy.[57] Patients with neurodegenerative disorders often present with a dysregulated 24-h rest-activity cycle with increased arousals and wakefulness, frequent daytime naps, altered phase angles (shifts in bed-time and wake-time), and reduced amplitudes.[6,58] Furthermore, people affected with AD, PD and HD show alterations in the circadian amplitudes of cortisol and melatonin release, impaired body temperature, variability in blood pressure, and heart rate as well as dysregulation of the diurnal pattern of urine excretion.[58] In particular, individuals with HD show a delayed sleep phase associated with worse cognitive performance and greater symptoms of depression and anxiety.[59,60] Interestingly, 27 genes related to HD were found to be expressed in a circadian manner in colorectal cancer cell lines (including *HTT*), with some involved in processes such as cell survival (*CASP3*, *TP53*, *CYSC*) and mitochondrial metabolism (*SOD2, SDHD, NDUFA2, NDUFA4, NDUFA4L2, NDUFAB1, NDUFS3, UQCR10*, and *UQCRHL*), shedding new light on an association between cancer and HD.[61] In people with PD, fragmented sleep is the most common sleep problem, affecting up to 80% of the individuals.[62] A comprehensive review of sleep and circadian rhythms in PD, isolated REM sleep behavior disorder, Lewy body dementia, and multiple system atrophy is provided in the accompanying manuscript of Kunz et al.[63] The roles of circadian and sleep dysregulation in the mechanisms underlying neurodegeneration are still unclear. Among the proposed mechanisms, circadian dysfunction could promote neurodegeneration by influencing the timing of sleep and by promoting sleep deprivation, which can have an impact on the diurnal clearance of misfolded proteins from the brain, increase inflammatory responses and affect synaptic and neuronal homeostasis.[6,64] Moreover, circadian and sleep dysfunction can disturb protein homeostasis and protein quality control, thereby promoting protein aggregation.[65–67] Importantly, they also increase oxidative stress which is key driver of neurodegeneration.[68]

1.4 | Sleep and circadian rhythm dysfunction in early stages of AD

Disruption of circadian rhythms can be the consequence of several factors such as age, impaired eyesight, malnutrition, stress, reduced social and physical activity.[69] It is, therefore, often difficult to attribute them directly to the neurodegenerative process. Sleep–wake cycle and rest-activity rhythms are under the direct control of the circadian clock and are the most direct behavioral outputs.[6] Individuals suffering from AD develop circadian and sleep–wake cycle disruptions, including highly fragmented nocturnal sleep patterns, increased arousals and wakefulness, and decreased levels of daytime activity.[7,8]

Although it is unclear whether sleep and circadian rhythm disruption contributes to the etiology of AD or is a consequence of it, several lines of evidence suggest that the two not only overlap pathophysiologically but also are in a complex, self-reinforcing bidirectional relationship in which disruption of the biological clock increases the risk of developing AD, which in turn amplifies circadian rhythm disruption.[10,13,70,71] Notably, studies suggest that

sleep and circadian rhythm disruptions occur long before the onset of dementia and likely contribute to the pathogenesis of AD.[71,72]

A survey using questionnaires to qualitatively assess sleep revealed that 24.5% of people with early AD suffered from sleep disruption.[73] However, due to the cognitive impairments in AD, this proportion may be underestimated according to more recent studies.[74] Polysomnography (PSG) is a useful objective technique to assess sleep parameters in preclinical AD. PSG studies revealed prolonged sleep latencies, sleep fragmentation, and decreased duration of REM sleep and deep sleep stages (N3) in early AD.[75] Individuals with probable AD had less Stage 3 sleep, no Stage 4 sleep, very little REM sleep, and experienced fragmentation of their sleep with frequent awakenings.[76] Interestingly, a correlation was found between the extent of sleep structure abnormalities and the severity of cognitive impairment in AD.[77] Actigraphy allows for the assessment of sleep quality by recording rest-activity rhythms. In individuals with early AD, actigraphy over several weeks revealed that sleep fragmentation was the predominant sleep disorder,[78] which is also associated with an increased risk of future dementia.[78–80] Recently, dysregulation of the homeostatic sleep drive in people with early AD has been correlated to the neurodegeneration of wake-promoting neurons in the locus coeruleus (noradrenalin), tuberomamillary nucleus (histamine), and lateral hypothalamus (orexin).[81,82]

Importantly, circadian dysfunction is already present in the stage of mild cognitive impairment (MCI). In a study of 30 patients with MCI (mean age, 50 years) and matched controls who were assessed by overnight PSG and measurement of salivary melatonin levels, the MCI group showed disturbed sleep with more nocturnal awakenings, increased REM latency and advanced melatonin rhythms, but no difference in melatonin concentration.[20] In 2018, a cross-sectional study assessed circadian rest-activity rhythms and AD biomarkers in 189 cognitively healthy adults (mean age, 66.6 years), 50 of which showed amyloid pathology by positron emission tomography (PET) imaging.[10] Fragmented circadian rhythms were associated with preclinical amyloid plaque pathology and disrupted daily rest-activity patterns, indicating that circadian dysfunction already appears in the preclinical phase of AD and precedes cognitive impairment.[10] More recently, Alfini et al.[83] collected actigraphy records from 179 older individuals (mean age, 72.6 years) with normal cognition ($n = 153$) and MCI ($n = 26$) and found that the MCI group had altered circadian rest-activity cycles, including more night-time activity and less activity in the morning, which are significantly associated with cognitive performance.

The preclinical phases of AD are characterized by Aβ deposition in the brain followed by tau phosphorylation and aggregation.[84] Aβ peptide is constantly produced in the brain. When it aggregates, it forms insoluble amyloid plaques which sequester soluble Aβ42, the major component of amyloid plaques in the brain. A decline of soluble Aβ42 levels in the cerebrospinal fluid (CSF) and interstitial fluid (ISF) correlates with the formation of amyloid plaques in transgenic mice.[85] Longitudinal studies in humans showed that a decrease of CSF Aβ42 levels occurs 25 years before the expected symptom onset while amyloid plaque pathology, measured by CSF biomarkers and amyloid PET, was detected 15 to 20 years before the onset of cognitive impairment.[86–89] In the APPSwe/PS1dE9 mouse model of amyloid pathology, sleep–wake abnormalities appear and develop in parallel with Aβ aggregation.[85]

In humans, sleep and circadian fragmentations have been associated with a higher risk of Aβ aggregation and the formation of amyloid plaques. Interestingly, the clearance of Aβ peptide follows a diurnal pattern in both CSF and ISF which is regulated by the sleep–wake cycle: the Aβ concentration increases during time awake and decreases during sleep in transgenic mice.[90] The association between Aβ deposition and fragmented sleep–wake cycle has also been well documented for the preclinical stages of AD. In a study of 145 cognitively normal, middle-aged individuals (mean age, 65.6 years), amyloid deposition was associated with worse sleep quality but not duration.[78] In contrast, a recent cross-sectional study of 4425 healthy, cognitively unimpaired adults (mean age, 71.3 years) found that longer night-time sleep duration was associated with lower levels of Aβ deposition.[91] In fact, each additional hour of sleep was associated with a reduction in the Aβ accumulation, while daytime sleep was associated with increased accumulation of Aβ.[91]

1.5 | Pathophysiological role of circadian disruption in early AD

Several events such as dysregulation of clock genes by Aβ, aberrant DNA methylation, degeneration of the SCN and subsequent changes in melatonin release, as well as neuroinflammation may provide mechanistic links between the disruption of circadian rhythms and the neurodegenerative process during the early phases of AD[9] (Figure 3).

Experimental studies in mice provided evidence that amyloid pathology induces a dysregulation of clock genes. Indeed, Aβ accumulation was shown to contribute to circadian disruption by interfering with the expression of clock genes such as *BMAL1*, CREB-binding protein (*CBP*) and *PER1*.[92,93] In the 5xFAD mouse model, Aβ induces BMAL1 degradation by promoting BMAL1 sumoylation, while degradation of CBP was mediated by N-cadherin cleavage products.[93] The degradation of BMAL1 and CBP

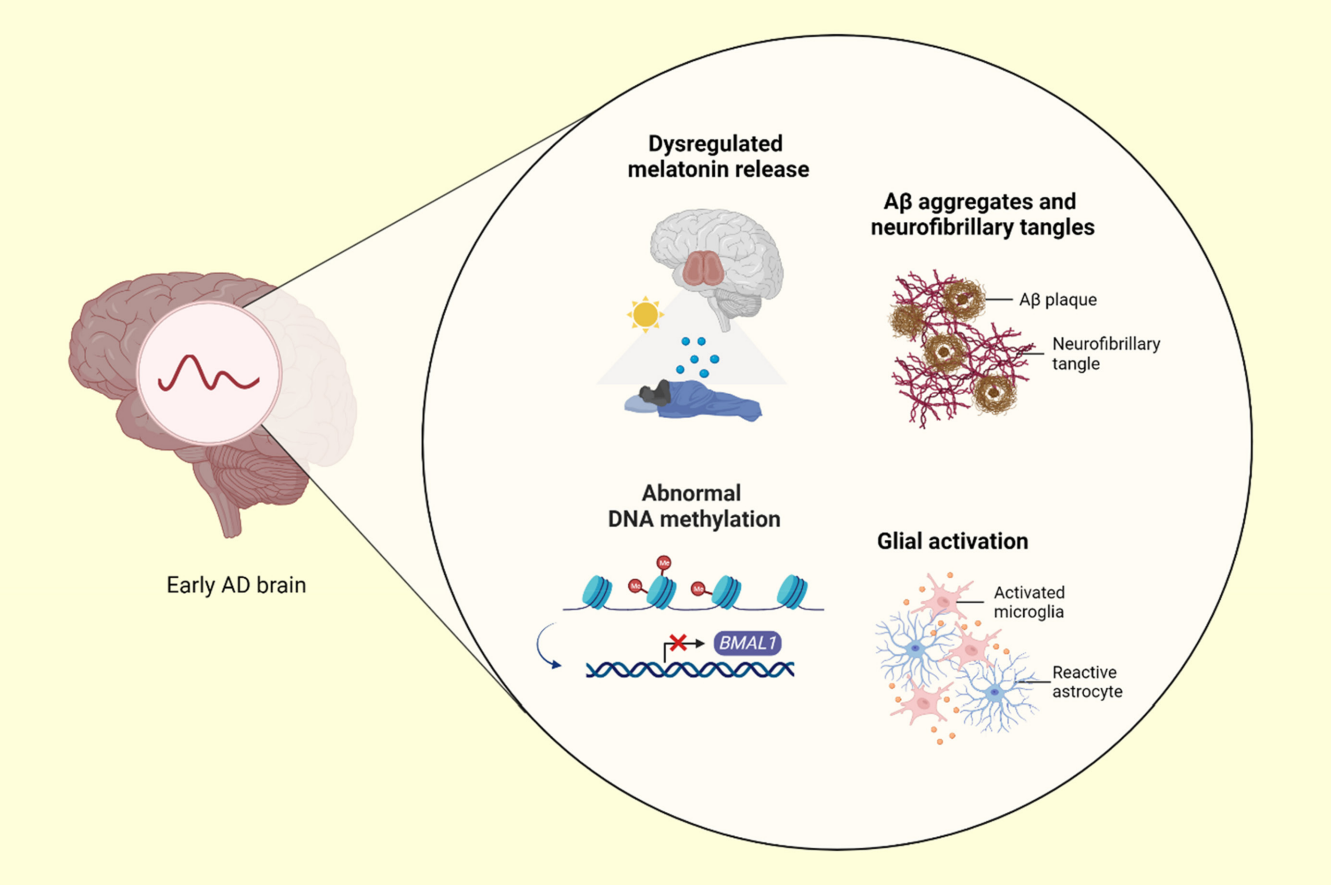

FIGURE 3 Pathophysiological events in the early stages of AD: The disruption of circadian rhythms is associated with dysregulation of clock genes, aberrant DNA methylation, degeneration of the SCN and the resulting changes in melatonin release, formation of Aβ plaques and neurofibrillary tangles, and neuroinflammation.

in turn causes PER2 dysregulation and circadian rhythm disruption.[93] Since BMAL1 is an essential clock component, its absence dysregulates the entire circadian molecular clock in all bodily tissues, including the SCN. Mice with a global deletion of *BMAL1* show circadian disruption, including motor and temperature dysregulation,[94] and neuroinflammation.[68,95]

During early AD, alterations in epigenetic mechanisms could also contribute to disease progression through dysregulation of the circadian system. In human brain samples and fibroblasts from people with early AD, aberrant brain DNA methylation patterns correlated with abnormalities in *BMAL1* expression.[96] In mice, specific deletion of *BMAL1* in neurons and glia induced oxidative damage and degeneration of synaptic terminals.[68] Moreover, *BMAL1* methylation is associated with tau pathology, night-waking and depression but not with speed and memory tests, or sleep duration in humans.[97]

Melatonin is a circadian clock-regulated hormone secreted by the pineal gland under the control of the SCN as a biological signal for darkness; it has sleep-promoting properties in humans and regulates body temperature.[9] Melatonin has a neuroprotective effect in animal models of AD.[98] It ameliorates cognitive functions by decreasing Aβ accumulation and by preventing hyperphosphorylation of tau through inhibition of glycogen synthase kinase-3β (GSK-3β) and stimulation of protein phosphatase-2A (PPP2A).[98] Furthermore, melatonin promotes Aβ clearance and ameliorates Aβ neurotoxicity.[99] In humans, melatonin levels decrease with disease progression in AD. Notably, the loss of melatonin rhythms in preclinical AD is associated with a dysfunction of the noradrenergic system and the depletion of serotonin, the precursor of melatonin.[100]

Another important contributor to AD pathophysiology is microglial activation. It was suggested that glial cells, such as microglia and astrocytes, possess intrinsic molecular clocks that temporally regulate their functions.[101,102] In APP knock-in (APP-KI) mice, microglial clock gene expression is altered which has been suggested to contribute to disease by promoting chronic neuroinflammation.[102] Inhibition of microglia proliferation by colony-stimulating factor 1 receptor (CSF1R) inhibitors rescued the inflammatory state, improved performance in

memory and behavioral tasks, but did not affect Aβ accumulation in mouse models of AD.[103,104] BMAL1 is a key mediator of the circadian control of the immune system and has anti-inflammatory effects.[105] In APP-KI mice, reducing BMAL1 levels promoted an inflammatory phenotype of microglia through increased NF-kB and decreased IκBα activity.[102] Thus, an impaired microglial clock induces chronic immune activation and may contribute to cognitive impairment during the early stages of AD.

Glial cells also play an important role in the clearance of Aβ and phagocytosis is circadian-regulated.[106–108] Recently, Clark et al.[106] showed in vitro that diurnal oscillations of Aβ42 clearance, which are lost in cells with disrupted circadian rhythms, are regulated by heparan sulfate proteoglycans (HSPGs) on the cell surface. The presence of HSPGs suppresses the glial-mediated phagocytosis of Aβ42 and modulation of HSPGs may thus help to prevent amyloid plaque formation.

Finally, several human studies confirmed an association between circadian disruption and the development of AD. Fragmented circadian rhythms were reported to be associated with preclinical amyloid plaque pathology, suggesting that circadian dysfunctions appear early in the preclinical phase of AD, even before cognitive impairment.[10] Quality of sleep was also associated with the risk of Aβ deposition,[78] and sleep fragmentation in older adults was correlated with incident AD and cognitive decline.[79]

1.6 | Circadian medicine approaches

As described in this review, a large body of evidence suggests that the circadian clock is disrupted in preclinical AD. For this reason, the identification of mechanisms involved in the interaction between sleep and circadian rhythms and the neurodegenerative process may benefit the prevention, treatment, and diagnosis of clock-related diseases.[5,109]

Improvement or resynchronization of the dysregulated clock may slow disease progression or even prevent its initiation. Targeting the clock using zeitgebers such as light, food, and exercise can be used for this purpose.[109] Light therapy, for example, is widely used in psychiatric and neurological diseases.[110–112] Bright light in AD has been shown to improve sleep efficacy during the night, decrease napping during the day, improve cognition, and reduce depression.[113–115] Moreover, light exposure during evening hours is effective in inducing more solid sleep during the night and more stable rest/activity rhythms.[116,117] Time-restricted eating has been shown to improve blood pressure and glucose regulation, while exercise can shift the phase of the circadian clock similarly to light.[118,119] In addition to AD, therapeutic strategies that target the clock have shown promise in other neurodegenerative diseases such as PD and HD.[112,120–122] For example, bright light therapy was administered for 14 days to 31 individuals with PD (mean age 63.2 years), which resulted in improved daily activity rhythms and reduced daytime sleepiness.[121] In two mouse models of HD (BACHD and Q175), treatments with blue light for 6 h at the beginning of the daily light cycle over 3 months improved locomotor activity rhythms but did not change sleep behavior.[122] Notably, new pharmacological molecules targeting the circadian system are being developed and tested in animals such as stabilizers of CRY to improve glucose tolerance in obese mice.[123]

Importantly, an increasing number of pharmacological studies are exploiting the knowledge of circadian rhythmicity for more accurate treatments.[124] Indeed, the pharmacokinetics and pharmacodynamics of most drugs follow circadian fluctuations, and thus, efficacy and toxicity are influenced by the time of administration.[5,124] Likewise, many surgical interventions can benefit from chronobiological optimization.[5] Finally, knowledge of individual chronotypes, defined as the interaction between genetic disposition, age, sex, environment, and light exposure, should be integrated into the new emerging field of precision medicine.[5,125] Interventions tailored to the individual chronotype may also improve individualized treatments in the preclinical stages of AD.

2 | CONCLUSIONS

Many studies suggest that sleep and circadian rhythm disruptions occur in the early stages of AD, which offers a good opportunity for intervention. Sleep and circadian rhythm disruptions at this stage could be an indicator of disease development, and early treatment could potentially prevent or slow the disease. Notably, strengthening circadian rhythms with combined light therapy and melatonin supplementation, but not alone, was shown to improve sleep disturbances and cognition in AD.[113,114,126] However, our understanding of the pathophysiological roles of sleep and circadian rhythm disruptions in the process of neurodegeneration is still incomplete, and further studies are required in order to develop novel chronotherapies for AD.

2.1 | Search strategy

For this review, we focused on references published within the past 5 years by searching PubMed entries between January 1, 2017 and May 30, 2022. We used the Mesh terms: “Alzheimer disease” (MeSH Unique ID:

D000544), "early onset Alzheimer disease" (MeSH Unique ID: D000544), "neurodegeneration" (MeSH Unique ID: D009410), "cognition" (MeSH Unique ID: D003071), "cognitive decline" (MeSH Unique ID: D060825), "circadian rhythm" (MeSH Unique ID: D002940), "circadian clock" (MeSH Unique ID: D057906)," biological clock" (MeSH Unique ID: D001683), "sleep–wake disorder" (MeSH Unique ID: D012893), "twenty-four-hour rhythm" (MeSH Unique ID: D002940). The Boolean factor OR was used to link similar keywords while the factor AND was used to link different Mesh terms and to find all of the terms in the search. No language restriction was applied. All species were included in the search, but human studies were the main focus of the search strategy. The final reference list was made based on relevance to this review and selection of key studies in the field.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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REFERENCES

1. Finger AM, Dibner C, Kramer A. Coupled network of the circadian clocks: a driving force of rhythmic physiology. *FEBS Lett*. 2020;594(17):2734-2769. doi:10.1002/1873-3468.13898
2. Finger AM, Kramer A. Mammalian circadian systems: organization and modern life challenges. *Acta Physiol (Oxf)*. 2021;231(3):e13548. doi:10.1111/apha.13548
3. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*. 2001;93(20):1557-1562. doi:10.1093/jnci/93.20.1557
4. Knutsson A, Kempe A. Shift work and diabetes—a systematic review. *Chronobiol Int*. 2014;31(10):1146-1151. doi:10.3109/07420528.2014.957308
5. Kramer A, Lange T, Spies C, Finger AM, Berg D, Oster H. Foundations of circadian medicine. *PLoS Biol*. 2022;20(3):e3001567. doi:10.1371/journal.pbio.3001567
6. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. *Lancet Neurol*. 2019;18(3):307-318. doi:10.1016/S1474-4422(18)30461-7
7. van Someren EJ, Hagebeuk EE, Lijzenga C, et al. Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biol Psychiatry*. 1996;40(4):259-270. doi:10.1016/0006-3223(95)00370-3
8. Vitiello MV, Prinz PN. Alzheimer's disease. Sleep and sleep/wake patterns. *Clin Geriatr Med*. 1989;5(2):289-299.
9. Lananna BV, Musiek ES. The wrinkling of time: aging, inflammation, oxidative stress, and the circadian clock in neurodegeneration. *Neurobiol Dis*. 2020;139:104832. doi:10.1016/j.nbd.2020.104832
10. Musiek ES, Bhimasani M, Zangrilli MA, Morris JC, Holtzman DM, Ju YS. Circadian rest-activity pattern changes in aging and preclinical Alzheimer disease. *JAMA Neurol*. 2018;75(5):582-590. doi:10.1001/jamaneurol.2017.4719
11. Scheltens P, Blennow K, Breteler MM, et al. Alzheimer's disease. *Lancet*. 2016;388(10043):505-517. doi:10.1016/s0140-6736(15)01124-1
12. Prince MJ, Comas-Herrera A, Knapp M, Guerchet M, Karagiannidou M. *World Alzheimer Report 2016 - Improving Healthcare for People Living with Dementia: Coverage, Quality and Costs Now and in the Future*. London: Alzheimer's Disease International; 2016, 131 p.
13. Lucey BP. It's complicated: the relationship between sleep and Alzheimer's disease in humans. *Neurobiol Dis*. 2020;144:105031. doi:10.1016/j.nbd.2020.105031
14. Jorm AF, Jolley D. The incidence of dementia: a meta-analysis. *Neurology*. 1998;51(3):728-733. doi:10.1212/wnl.51.3.728
15. Mayeux R, Stern Y. Epidemiology of Alzheimer disease. *Cold Spring Harb Perspect Med*. 2012;2(8):a006239. doi:10.1101/cshperspect.a006239
16. Swerdlow RH. Pathogenesis of Alzheimer's disease. *Clin Interv Aging*. 2007;2(3):347-359.
17. Homolak J, Mudrovčić M, Vukić B, Toljan K. Circadian rhythm and Alzheimer's disease. *Med Sci (Basel)*. 2018;6(3):52. doi:10.3390/medsci6030052
18. Ju YE, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology—a bidirectional relationship. *Nat Rev Neurol*. 2014;10(2):115-119. doi:10.1038/nrneurol.2013.269
19. Videnovic A, Lazar AS, Barker RA, Overeem S. 'The clocks that time us'—circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol*. 2014;10(12):683-693. doi:10.1038/nrneurol.2014.206
20. Naismith SL, Hickie IB, Terpening Z, et al. Circadian misalignment and sleep disruption in mild cognitive impairment. *J Alzheimers Dis*. 2014;38(4):857-866. doi:10.3233/jad-131217
21. Bass J, Lazar MA. Circadian time signatures of fitness and disease. *Science*. 2016;354(6315):994-999. doi:10.1126/science.aah4965
22. Crane BR, Young MW. Interactive features of proteins composing eukaryotic circadian clocks. *Annu Rev Biochem*. 2014;83:191-219. doi:10.1146/annurev-biochem-060713-035644
23. Reddy AB, Rey G. Metabolic and nontranscriptional circadian clocks: eukaryotes. *Annu Rev Biochem*. 2014;83:165-189. doi:10.1146/annurev-biochem-060713-035623
24. Welsh DK, Takahashi JS, Kay SA. Suprachiasmatic nucleus: cell autonomy and network properties. *Annu Rev Physiol*. 2010;72:551-577. doi:10.1146/annurev-physiol-021909-135919
25. Bollinger T, Schibler U. Circadian rhythms—from genes to physiology and disease. *Swiss Med Wkly*. 2014;144:w13984. doi:10.4414/smw.2014.13984
26. Blume C, Garbazza C, Spitschan M. Effects of light on human circadian rhythms, sleep and mood. *Somnologie (Berl)*. 2019;23(3):147-156. doi:10.1007/s11818-019-00215-x

27. Hendrickson AE, Wagoner N, Cowan WM. An autoradiographic and electron microscopic study of retino-hypothalamic connections. *Z Zellforsch Mikrosk Anat*. 1972;135(1):1-26. doi:10.1007/bf00307084
28. Hughes S, Jagannath A, Hankins MW, Foster RG, Peirson SN. Chapter six—photic regulation of clock systems. In: Sehgal A, ed. *Methods in Enzymology*. Vol 552. Academic Press; 2015:125-143. doi:10.1016/bs.mie.2014.10.018
29. Moore RY, Eichler VB. Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res*. 1972;42(1):201-206. doi:10.1016/0006-8993(72)90054-6
30. Mistlberger RE, Skene DJ. Nonphotic entrainment in humans? *J Biol Rhythms*. 2005;20(4):339-352. doi:10.1177/0748730405277982
31. Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U. Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev*. 2000;14(23):2950-2961. doi:10.1101/gad.183500
32. Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M. Entrainment of the circadian clock in the liver by feeding. *Science*. 2001;291(5503):490-493. doi:10.1126/science.291.5503.490
33. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*. 2008;9(10):764-775. doi:10.1038/nrg2430
34. Yamazaki S, Numano R, Abe M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. *Science*. 2000;288(5466):682-685. doi:10.1126/science.288.5466.682
35. Gekakis N, Staknis D, Nguyen HB, et al. Role of the CLOCK protein in the mammalian circadian mechanism. *Science*. 1998;280(5369):1564-1569. doi:10.1126/science.280.5369.1564
36. Landgraf D, Shostak A, Oster H. Clock genes and sleep. *Pflugers Arch*. 2012;463(1):3-14. doi:10.1007/s00424-011-1003-9
37. Eide EJ, Woolf MF, Kang H, et al. Control of mammalian circadian rhythm by CKIepsilon-regulated proteasome-mediated PER2 degradation. *Mol Cell Biol*. 2005;25(7):2795-2807. doi:10.1128/mcb.25.7.2795-2807.2005
38. Lowrey PL, Shimomura K, Antoch MP, et al. Positional syntenic cloning and functional characterization of the mammalian circadian mutation tau. *Science*. 2000;288(5465):483-492. doi:10.1126/science.288.5465.483
39. Busino L, Bassermann F, Maiolica A, et al. SCFFbxl3 controls the oscillation of the circadian clock by directing the degradation of cryptochrome proteins. *Science*. 2007;316(5826):900-904. doi:10.1126/science.1141194
40. Siepka SM, Yoo SH, Park J, et al. Circadian mutant overtime reveals F-box protein FBXL3 regulation of cryptochrome and period gene expression. *Cell*. 2007;129(5):1011-1023. doi:10.1016/j.cell.2007.04.030
41. Aryal RP, Kwak PB, Tamayo AG, et al. Macromolecular assemblies of the mammalian circadian clock. *Mol Cell*. 2017;67(5):770-782.e776. doi:10.1016/j.molcel.2017.07.017
42. Chiou YY, Yang Y, Rashid N, Ye R, Selby CP, Sancar A. Mammalian period represses and de-represses transcription by displacing CLOCK-BMAL1 from promoters in a cryptochrome-dependent manner. *Proc Natl Acad Sci U S A*. 2016;113(41):E6072-E6079. doi:10.1073/pnas.1612917113
43. Guillaumond F, Dardente H, Giguère V, Cermakian N. Differential control of Bmal1 circadian transcription by REV-ERB and ROR nuclear receptors. *J Biol Rhythms*. 2005;20(5):391-403. doi:10.1177/0748730405277232
44. Bugge A, Feng D, Everett LJ, et al. Rev-erbα and rev-erbβ coordinately protect the circadian clock and normal metabolic function. *Genes Dev*. 2012;26(7):657-667. doi:10.1101/gad.186858.112
45. Cho H, Zhao X, Hatori M, et al. Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature*. 2012;485(7396):123-127. doi:10.1038/nature11048
46. Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. *Neuron*. 2017;93(4):747-765. doi:10.1016/j.neuron.2017.01.014
47. Mahler SV, Moorman DE, Smith RJ, James MH, Aston-Jones G. Motivational activation: a unifying hypothesis of orexin/hypocretin function. *Nat Neurosci*. 2014;17(10):1298-1303. doi:10.1038/nn.3810
48. Siegel JM. Sleep function: an evolutionary perspective. *Lancet Neurol*. 2022;21(10):937-946. doi:10.1016/s1474-4422(22)00210-1
49. Merica H, Blois R. Relationship between the time courses of power in the frequency bands of human sleep EEG. *Clin Neurophysiol*. 1997;27(2):116-128. doi:10.1016/S0987-7053(97)85664-X
50. Borbély AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. *J Sleep Res*. 2016;25(2):131-143. doi:10.1111/jsr.12371
51. Morairty SR, Dittrich L, Pasumarthi RK, et al. A role for cortical nNOS/NK1 neurons in coupling homeostatic sleep drive to EEG slow wave activity. *Proc Natl Acad Sci U S A*. 2013;110(50):20272-20277. doi:10.1073/pnas.1314762110
52. Kräuchi K, Cajochen C, Pache M, Flammer J, Wirz-Justice A. Thermoregulatory effects of melatonin in relation to sleepiness. *Chronobiol Int*. 2006;23(1–2):475-484. doi:10.1080/07420520500545854
53. Wang W, Yuan RK, Mitchell JF, et al. Desynchronizing the sleep—wake cycle from circadian timing to assess their separate contributions to physiology and behaviour and to estimate intrinsic circadian period. *Nat Protoc*. 2022;18:579-603. doi:10.1038/s41596-022-00746-y
54. Kleitman N. *Sleep and Wakefulness*. University of Chicago Press; 1939.
55. Aschoff J, Gerecke U, Wever R. Desynchronization of human circadian rhythms. *Jpn J Physiol*. 1967;17(4):450-457. doi:10.2170/jjphysiol.17.450
56. Montagna P, Gambetti P, Cortelli P, Lugaresi E. Familial and sporadic fatal insomnia. *Lancet Neurol*. 2003;2(3):167-176. doi:10.1016/s1474-4422(03)00323-5
57. Guissart C, Latypova X, Rollier P, et al. Dual molecular effects of dominant RORA mutations cause two variants of syndromic intellectual disability with either autism or cerebellar ataxia. *Am J Hum Genet*. 2018;102(5):744-759. doi:10.1016/j.ajhg.2018.02.021
58. Fifel K, Videnovic A. Circadian and sleep dysfunctions in neurodegenerative disorders-an update. *Front Neurosci*. 2020;14:627330. doi:10.3389/fnins.2020.627330
59. Diago EB, Martínez-Horta S, Lasaosa SS, et al. Circadian rhythm, cognition, and mood disorders in Huntington's disease. *J Huntingtons Dis*. 2018;7(2):193-198. doi:10.3233/jhd-180291

60. Tanigaki WK, Rossetti MA, Rocha NP, Stimming EF. Sleep dysfunction in Huntington's disease: perspectives from patients. *J Huntingtons Dis*. 2020;9(4):345-352. doi:10.3233/jhd-200434
61. Yalçin M, El-Athman R, Ouk K, Priller J, Relógio A. Analysis of the circadian regulation of cancer hallmarks by a cross-platform study of colorectal cancer time-series data reveals an association with genes involved in Huntington's disease. *Cancers (Basel)*. 2020;12(4):963. doi:10.3390/cancers12040963
62. Chahine LM, Amara AW, Videnovic A. A systematic review of the literature on disorders of sleep and wakefulness in Parkinson's disease from 2005 to 2015. *Sleep Med Rev*. 2017;35:33-50. doi:10.1016/j.smrv.2016.08.001
63. Kunz D, Oster H, Rawashdeh O, Neumann J, Münte T, Berg D. Sleep and circadian rhythms in α-synucleinopathies—perspectives for disease modification. *Acta Physiol*. 2023;in press;e13966.
64. Xie L, Kang H, Xu Q, et al. Sleep drives metabolite clearance from the adult brain. *Science*. 2013;342(6156):373-377. doi:10.1126/science.1241224
65. Curtis AM, Bellet MM, Sassone-Corsi P, O'Neill LA. Circadian clock proteins and immunity. *Immunity*. 2014;40(2):178-186. doi:10.1016/j.immuni.2014.02.002
66. Hastings MH, Goedert M. Circadian clocks and neurodegenerative diseases: time to aggregate? *Curr Opin Neurobiol*. 2013;23(5):880-887. doi:10.1016/j.conb.2013.05.004
67. Huang G, Zhang F, Ye Q, Wang H. The circadian clock regulates autophagy directly through the nuclear hormone receptor Nr1d1/rev-erbα and indirectly via Cebpb/(C/ebpβ) in zebrafish. *Autophagy*. 2016;12(8):1292-1309. doi:10.1080/15548627.2016.1183843
68. Musiek ES, Lim MM, Yang G, et al. Circadian clock proteins regulate neuronal redox homeostasis and neurodegeneration. *J Clin Invest*. 2013;123(12):5389-5400. doi:10.1172/jci70317
69. Walker WH 2nd, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. *Transl Psychiatry*. 2020;10(1):28. doi:10.1038/s41398-020-0694-0
70. Hoyt KR, Obrietan K. Circadian clocks, cognition, and Alzheimer's disease: synaptic mechanisms, signaling effectors, and chronotherapeutics. *Mol Neurodegener*. 2022;17(1):35. doi:10.1186/s13024-022-00537-9
71. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. *Science*. 2016;354(6315):1004-1008. doi:10.1126/science.aah4968
72. Wang C, Holtzman DM. Bidirectional relationship between sleep and Alzheimer's disease: role of amyloid, tau, and other factors. *Neuropsychopharmacology*. 2020;45(1):104-120. doi:10.1038/s41386-019-0478-5
73. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med*. 2005;6(4):347-352. doi:10.1016/j.sleep.2004.12.005
74. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. *J Affect Disord*. 2016;190:264-271. doi:10.1016/j.jad.2015.09.069
75. McCurry SM, Ancoli-Israel S. Sleep dysfunction in Alzheimer's disease and other dementias. *Curr Treat Options Neurol*. 2003;5(3):261-272. doi:10.1007/s11940-003-0017-9
76. Prinz PN, Peskind ER, Vitaliano PP, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *J Am Geriatr Soc*. 1982;30(2):86-93. doi:10.1111/j.1532-5415.1982.tb01279.x
77. Liguori C, Romigi A, Nuccetelli M, et al. Orexinergic system dysregulation, sleep impairment, and cognitive decline in Alzheimer disease. *JAMA Neurol*. 2014;71(12):1498-1505. doi:10.1001/jamaneurol.2014.2510
78. Ju YE, McLeland JS, Toedebusch CD, et al. Sleep quality and preclinical Alzheimer disease. *JAMA Neurol*. 2013;70(5):587-593. doi:10.1001/jamaneurol.2013.2334
79. Lim AS, Kowgier M, Yu L, Buchman AS, Bennett DA. Sleep fragmentation and the risk of incident Alzheimer's disease and cognitive decline in older persons. *Sleep*. 2013;36(7):1027-1032. doi:10.5665/sleep.2802
80. Tranah GJ, Blackwell T, Stone KL, et al. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. *Ann Neurol*. 2011;70(5):722-732. doi:10.1002/ana.22468
81. Havekes R, Heckman PRA, Wams EJ, Stasiukonyte N, Meerlo P, Eisel ULM. Alzheimer's disease pathogenesis: the role of disturbed sleep in attenuated brain plasticity and neurodegenerative processes. *Cell Signal*. 2019;64:109420. doi:10.1016/j.cellsig.2019.109420
82. Oh JY, Walsh CM, Ranasinghe K, et al. Subcortical neuronal correlates of sleep in neurodegenerative diseases. *JAMA Neurol*. 2022;79(5):498-508. doi:10.1001/jamaneurol.2022.0429
83. Alfini A, Albert M, Faria AV, et al. Associations of actigraphic sleep and circadian rest/activity rhythms with cognition in the early phase of Alzheimer's disease. *Sleep Adv*. 2021;2(1):zpab007. doi:10.1093/sleepadvances/zpab007
84. Lucey BP, Bateman RJ. Amyloid-β diurnal pattern: possible role of sleep in Alzheimer's disease pathogenesis. *Neurobiol Aging*. 2014;35(suppl. 2):S29-S34. doi:10.1016/j.neurobiolaging.2014.03.035
85. Roh JH, Huang Y, Bero AW, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of β-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med*. 2012;4(150):150ra122. doi:10.1126/scitranslmed.3004291
86. Bateman RJ, Xiong C, Benzinger TL, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med*. 2012;367(9):795-804. doi:10.1056/NEJMoa1202753
87. Jansen WJ, Ossenkoppele R, Knol DL, et al. Prevalence of cerebral amyloid pathology in persons without dementia: a meta-analysis. *JAMA*. 2015;313(19):1924-1938. doi:10.1001/jama.2015.4668
88. Roe CM, Fagan AM, Grant EA, et al. Amyloid imaging and CSF biomarkers in predicting cognitive impairment up to 7.5 years later. *Neurology*. 2013;80(19):1784-1791. doi:10.1212/WNL.0b013e3182918ca6
89. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: a prospective cohort study. *Lancet Neurol*. 2013;12(4):357-367. doi:10.1016/s1474-4422(13)70044-9
90. Kang JE, Lim MM, Bateman RJ, et al. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science*. 2009;326(5955):1005-1007. doi:10.1126/science.1180962
91. Insel PS, Mohlenhoff BS, Neylan TC, Krystal AD, Mackin RS. Association of sleep and β-amyloid pathology among older cognitively unimpaired adults. *JAMA Netw Open*. 2021;4(7):e2117573. doi:10.1001/jamanetworkopen.2021.17573

92. Schmitt K, Grimm A, Eckert A. Amyloid-β-induced changes in molecular clock properties and cellular bioenergetics. *Front Neurosci*. 2017;11:124. doi:10.3389/fnins.2017.00124
93. Song H, Moon M, Choe HK, et al. Aβ-induced degradation of BMAL1 and CBP leads to circadian rhythm disruption in Alzheimer's disease. *Mol Neurodegener*. 2015;10:13. doi:10.1186/s13024-015-0007-x
94. Kress GJ, Liao F, Dimitry J, et al. Regulation of amyloid-beta dynamics and pathology by the circadian clock. *J Exp Med*. 2018;215(4):1059-1068. doi:10.1084/jem.20172347
95. Kondratov RV, Kondratova AA, Gorbacheva VY, Vykhovanets OV, Antoch MP. Early aging and age-related pathologies in mice deficient in BMAL1, the core componentof the circadian clock. *Genes Dev*. 2006;20(14):1868-1873. doi:10.1101/gad.1432206
96. Cronin P, McCarthy MJ, Lim ASP, et al. Circadian alterations during early stages of Alzheimer's disease are associated with aberrant cycles of DNA methylation in BMAL1. *Alzheimers Dement*. 2017;13(6):689-700. doi:10.1016/j.jalz.2016.10.003
97. Hulme B, Didikoglu A, Bradburn S, et al. Epigenetic regulation of BMAL1 with sleep disturbances and Alzheimer's disease. *J Alzheimers Dis*. 2020;77(4):1783-1792. doi:10.3233/jad-200634
98. Gong YH, Hua N, Zang X, Huang T, He L. Melatonin ameliorates Aβ(1–42) induced Alzheimer's cognitive deficits in mouse model. *J Pharm Pharmacol*. 2018;70(1):70-80. doi:10.1111/jphp.12830
99. Li Y, Zhang J, Wan J, Liu A, Sun J. Melatonin regulates Aβ production/clearance balance and Aβ neurotoxicity: a potential therapeutic molecule for Alzheimer's disease. *Biomed Pharmacother*. 2020;132:110887. doi:10.1016/j.biopha.2020.110887
100. Wu YH, Feenstra MG, Zhou JN, et al. Molecular changes underlying reduced pineal melatonin levels in Alzheimer disease: alterations in preclinical and clinical stages. *J Clin Endocrinol Metab*. 2003;88(12):5898-5906. doi:10.1210/jc.2003-030833
101. Hayashi Y, Koyanagi S, Kusunose N, et al. The intrinsic microglial molecular clock controls synaptic strength via the circadian expression of cathepsin S. *Sci Rep*. 2013;3:2744. doi:10.1038/srep02744
102. Ni J, Wu Z, Meng J, et al. An impaired intrinsic microglial clock system induces neuroinflammatory alterations in the early stage of amyloid precursor protein knock-in mouse brain. *J Neuroinflammation*. 2019;16(1):173. doi:10.1186/s12974-019-1562-9
103. Olmos-Alonso A, Schetters ST, Sri S, et al. Pharmacological targeting of CSF1R inhibits microglial proliferation and prevents the progression of Alzheimer's-like pathology. *Brain*. 2016;139(Pt 3):891-907. doi:10.1093/brain/awv379
104. Spangenberg EE, Lee RJ, Najafi AR, et al. Eliminating microglia in Alzheimer's mice prevents neuronal loss without modulating amyloid-β pathology. *Brain*. 2016;139(Pt 4):1265-1281. doi:10.1093/brain/aww016
105. Uddin MS, Sumsuzzman DM, Jeandet P, et al. Deciphering the interacting mechanisms of circadian disruption and Alzheimer's disease. *Neurochem Res*. 2021;46(7):1603-1617. doi:10.1007/s11064-021-03325-x
106. Clark GT, Yu Y, Urban CA, et al. Circadian control of heparan sulfate levels times phagocytosis of amyloid beta aggregates. *PLoS Genet*. 2022;18(2):e1009994. doi:10.1371/journal.pgen.1009994
107. Fiala M, Zhang L, Gan X, et al. Amyloid-beta induces chemokine secretion and monocyte migration across a human blood–brain barrier model. *Mol Med*. 1998;4(7):480-489.
108. Zhang R, Miller RG, Madison C, et al. Systemic immune system alterations in early stages of Alzheimer's disease. *J Neuroimmunol*. 2013;256(1–2):38-42. doi:10.1016/j.jneuroim.2013.01.002
109. Panda S. The arrival of circadian medicine. *Nat Rev Endocrinol*. 2019;15(2):67-69. doi:10.1038/s41574-018-0142-x
110. Bais B, Hoogendijk WJG, Lambregtse-van den Berg MP. Light therapy for mood disorders. *Handb Clin Neurol*. 2021;182:49-61. doi:10.1016/b978-0-12-819973-2.00004-6
111. Liu CR, Liou YM, Jou JH. Ambient bright lighting in the morning improves sleep disturbances of older adults with dementia. *Sleep Med*. 2022;89:1-9. doi:10.1016/j.sleep.2021.10.011
112. Liu YL, Gong SY, Xia ST, et al. Light therapy: a new option for neurodegenerative diseases. *Chin Med J (Engl)*. 2020;134(6):634-645. doi:10.1097/cm9.0000000000001301
113. Dowling GA, Burr RL, Van Someren EJ, et al. Melatonin and bright-light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. *J Am Geriatr Soc*. 2008;56(2):239-246. doi:10.1111/j.1532-5415.2007.01543.x
114. Riemersma-van der Lek RF, Swaab DF, Twisk J, Hol EM, Hoogendijk WJ, Van Someren EJ. Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial. *JAMA*. 2008;299(22):2642-2655. doi:10.1001/jama.299.22.2642
115. Sloane PD, Williams CS, Mitchell CM, et al. High-intensity environmental light in dementia: effect on sleep and activity. *J Am Geriatr Soc*. 2007;55(10):1524-1533. doi:10.1111/j.1532-5415.2007.01358.x
116. Ancoli-Israel S, Gehrman P, Martin JL, et al. Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients. *Behav Sleep Med*. 2003;1(1):22-36. doi:10.1207/s15402010bsm0101_4
117. Hanford N, Figueiro M. Light therapy and Alzheimer's disease and related dementia: past, present, and future. *J Alzheimers Dis*. 2013;33(4):913-922. doi:10.3233/jad-2012-121645
118. Adafer R, Messaadi W, Meddahi M, et al. Food timing, circadian rhythm and chrononutrition: a systematic review of time-restricted eating's effects on human health. *Nutrients*. 2020;12(12):3770. doi:10.3390/nu12123770
119. Lewis P, Korf HW, Kuffer L, Groß JV, Erren TC. Exercise time cues (zeitgebers) for human circadian systems can foster health and improve performance: a systematic review. *BMJ Open Sport Exerc Med*. 2018;4(1):e000443. doi:10.1136/bmjsem-2018-000443
120. Endo T, Matsumura R, Tokuda IT, et al. Bright light improves sleep in patients with Parkinson's disease: possible role of circadian restoration. *Sci Rep*. 2020;10(1):7982. doi:10.1038/s41598-020-64645-6
121. Videnovic A, Klerman EB, Wang W, Marconi A, Kuhta T, Zee PC. Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease: a randomized clinical trial. *JAMA Neurol*. 2017;74(4):411-418. doi:10.1001/jamaneurol.2016.5192
122. Wang HB, Whittaker DS, Truong D, et al. Blue light therapy improves circadian dysfunction as well as motor symptoms in two mouse models of Huntington's disease. *Neurobiol Sleep Circadian Rhythms*. 2017;2:39-52. doi:10.1016/j.nbscr.2016.12.002
123. Hirota T, Lee JW, St John PC, et al. Identification of small molecule activators of cryptochrome. *Science*. 2012;337(6098):1094-1097. doi:10.1126/science.1223710
124. Ruben MD, Smith DF, FitzGerald GA, Hogenesch JB. Dosing time matters. *Science*. 2019;365(6453):547-549. doi:10.1126/science.aax7621

125. Roenneberg T, Kuehnle T, Juda M, et al. Epidemiology of the human circadian clock. *Sleep Med Rev*. 2007;11(6):429-438. doi:10.1016/j.smrv.2007.07.005
126. Singer C, Tractenberg RE, Kaye J, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*. 2003;26(7):893-901. doi:10.1093/sleep/26.7.893

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