

## REVIEW ARTICLE

## Special Series on Foundations of Circadian Medicine

# 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.<sup>1,2</sup> Disturbances in the circadian clock severely impact on human health and are associated with many

human diseases such as cancer, diabetes, and neurological diseases.<sup>3–6</sup> 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.<sup>7,8</sup> Several

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recent studies suggest that circadian rhythm and sleep disturbances already occur during the pre-symptomatic stages of AD.<sup>6,9,10</sup> 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

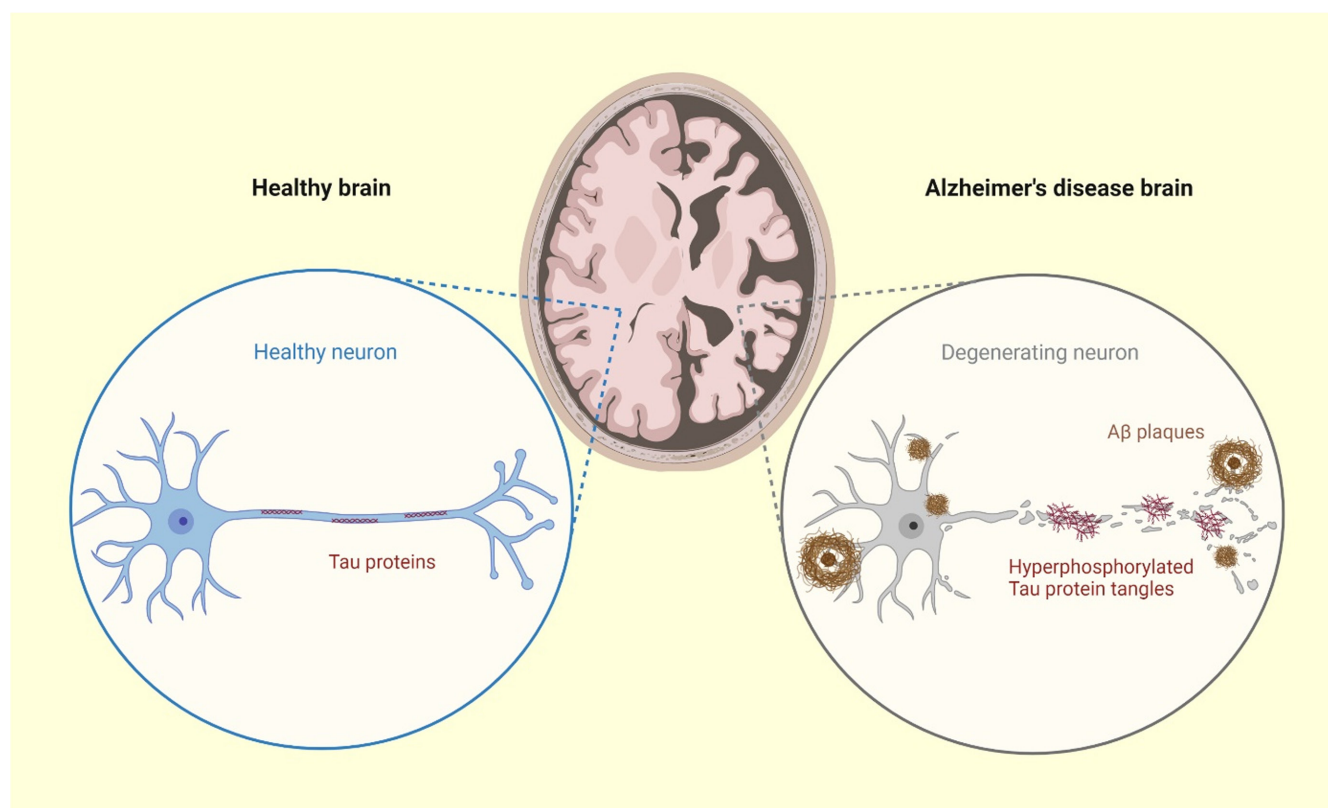
AD is a chronic neurodegenerative disease and the most common cause of dementia worldwide. In 2016, an estimated 40 million people suffered from AD worldwide,<sup>11</sup> a number that is expected to rise to 131 million in 2050.<sup>12</sup>

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 ( $A\beta$ ) and intracellular neurofibrillary tangles composed of hyperphosphorylated tau<sup>11,13</sup> (Figure 1).

The etiology of AD is still unclear. The greatest risk of developing AD is old age,<sup>11</sup> and the risk is estimated to double every 5 years after the age of 65.<sup>14</sup> 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  $A\beta$ : presenilin-1-2 (*PSEN1-2*), and amyloid precursor protein (*APP*).<sup>15</sup> The vast majority of cases are sporadic and are believed to result from a complex interaction between genetic risk and environmental factors.<sup>16</sup> The human  $\epsilon 4$  allele of Apolipoprotein E (*APOE* $\epsilon 4$ ) is known to increase susceptibility to AD, and it has been associated with 15%–20% of the cases.<sup>17</sup>

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.<sup>6,13</sup> 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,<sup>8,10,18</sup> reduced circadian amplitude and phase



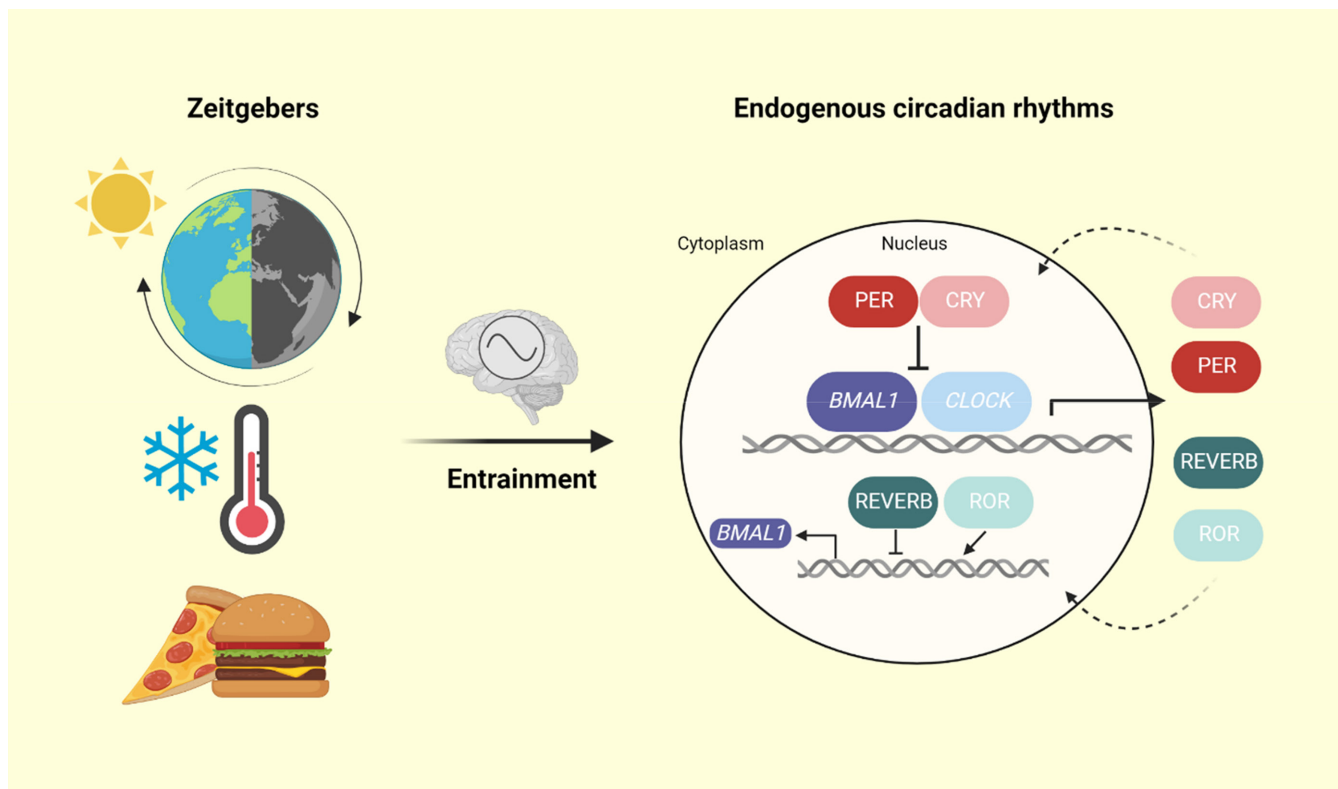
**FIGURE 1** Alzheimer's disease pathology: Compared to a normal healthy brain (left), AD is characterized by brain atrophy (top), with neuronal degeneration, aggregation and accumulation of extracellular amyloid-beta ( $A\beta$ ) plaques and intracellular tau neurofibrillary tangles (right).

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

## 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.<sup>21–24</sup> 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,<sup>25</sup> 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”<sup>24</sup> (Figure 2). The most important zeitgeber is light.<sup>26–29</sup> 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.<sup>28</sup> 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.<sup>30</sup> 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.<sup>31,32</sup>

At the molecular level, circadian rhythms are generated by fine-tuned transcriptional and translational feedback loops or TTFL.<sup>21–23,33,34</sup> 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.<sup>35,36</sup> 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) 1 $\epsilon$  and  $\delta$ ,<sup>37,38</sup> and by CRY1/2 protein degradation by the SCF/Fbx13 ubiquitin ligase complex.<sup>39,40</sup>

In the late afternoon, the proteins PER and CRY accumulate in the cytoplasm where CK1 $\epsilon$ / $\delta$  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.<sup>41</sup> Integrated within this large repressor complex, PERs and CRYs interact with the heterodimer BMAL1/CLOCK<sup>36</sup> and negatively regulate the activity of BMAL1/CLOCK by promoting the dissociation of the heterodimer from DNA.<sup>42</sup> 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*,<sup>43</sup> and also of *NR1D1* (nuclear receptor subfamily 1, group D, member 1, also known as *REV-ERB $\alpha$* ) and *NR1D2* (nuclear receptor subfamily 1, group D, member, also known as *REV-ERB $\beta$* ), whose protein products in return suppress *BMAL1* expression.<sup>44,45</sup>

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), tuberomammillary nucleus (histamine), and ventral tegmental area (dopamine).<sup>46</sup> 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.<sup>47</sup>

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, acetylcholine, glutamate, or glycine) and REM-off (expressing noradrenaline, adrenalin, acetylcholine, histamine, or GABA), depending on their activation during that sleep state.<sup>48</sup>

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<sup>49</sup> 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).<sup>48</sup>

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).<sup>50</sup> 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.<sup>51</sup>

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.<sup>52</sup>

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).<sup>53</sup> 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.<sup>54</sup> 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).<sup>55</sup>

### 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.<sup>56</sup> Mutations in the human *RORA* gene have been associated with ataxia and cerebellar atrophy.<sup>57</sup> 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.<sup>6,58</sup> 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.<sup>58</sup> In particular, individuals with HD show a delayed sleep phase associated with worse cognitive performance and greater symptoms of depression and anxiety.<sup>59,60</sup> 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*, *UQCRI0*, and *UQCRL*), shedding new light on an association between cancer and HD.<sup>61</sup> In people with PD, fragmented sleep is the most common sleep problem, affecting up to 80% of the individuals.<sup>62</sup> 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.<sup>63</sup> 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.<sup>6,64</sup> Moreover, circadian and sleep dysfunction can disturb protein homeostasis and protein quality control, thereby promoting protein aggregation.<sup>65–67</sup> Importantly, they also increase oxidative stress which is key driver of neurodegeneration.<sup>68</sup>

### 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.<sup>69</sup> 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.<sup>6</sup> 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.<sup>7,8</sup>

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.<sup>10,13,70,71</sup> Notably, studies suggest that

sleep and circadian rhythm disruptions occur long before the onset of dementia and likely contribute to the pathogenesis of AD.<sup>71,72</sup>

A survey using questionnaires to qualitatively assess sleep revealed that 24.5% of people with early AD suffered from sleep disruption.<sup>73</sup> However, due to the cognitive impairments in AD, this proportion may be underestimated according to more recent studies.<sup>74</sup> 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.<sup>75</sup> 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.<sup>76</sup> Interestingly, a correlation was found between the extent of sleep structure abnormalities and the severity of cognitive impairment in AD.<sup>77</sup> 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,<sup>78</sup> which is also associated with an increased risk of future dementia.<sup>78–80</sup> 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), tuberomammillary nucleus (histamine), and lateral hypothalamus (orexin).<sup>81,82</sup>

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.<sup>20</sup> 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.<sup>10</sup> 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.<sup>10</sup> More recently, Alfini et al.<sup>83</sup> 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 A $\beta$  deposition in the brain followed by tau phosphorylation

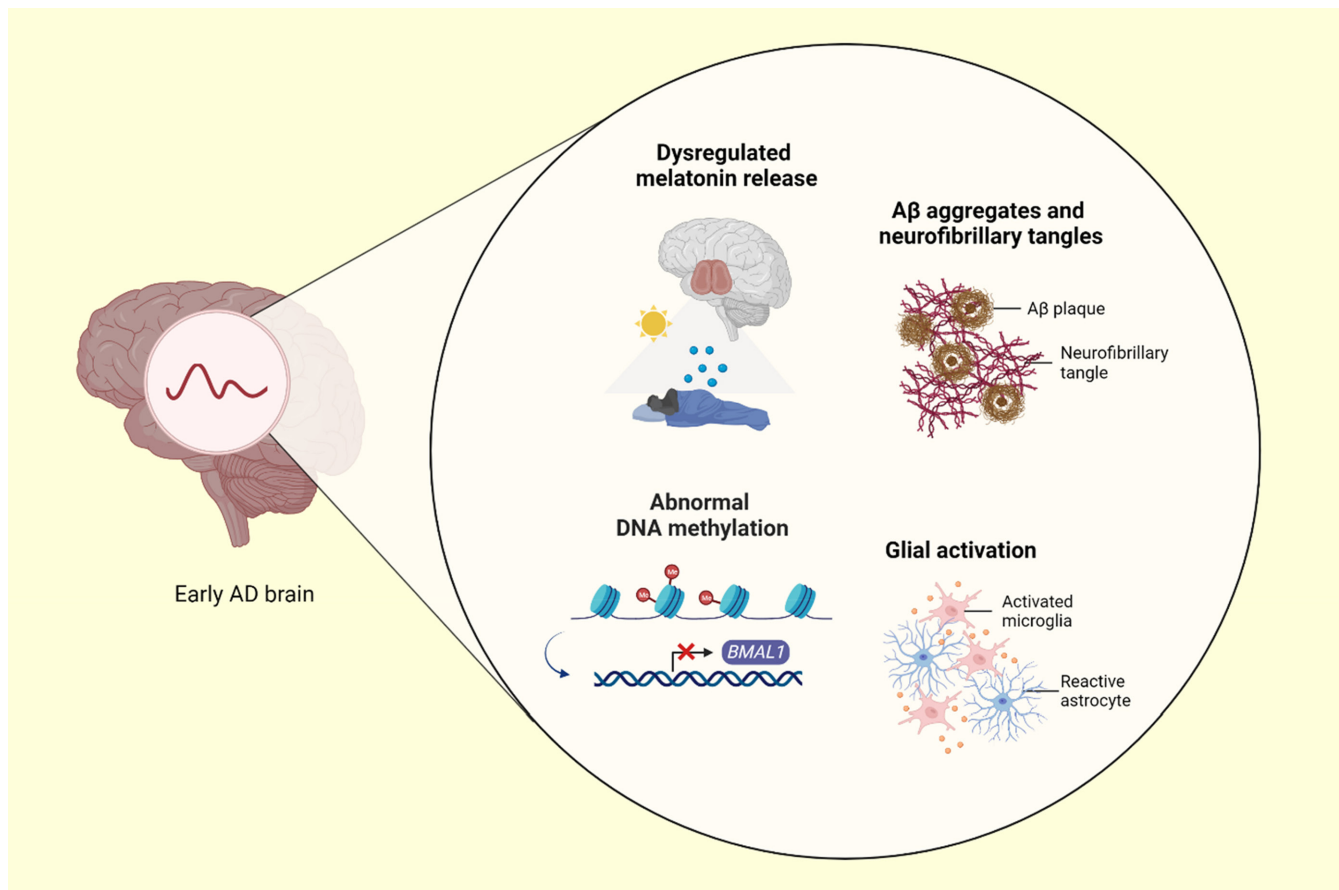
and aggregation.<sup>84</sup> A $\beta$  peptide is constantly produced in the brain. When it aggregates, it forms insoluble amyloid plaques which sequester soluble A $\beta$ 42, the major component of amyloid plaques in the brain. A decline of soluble A $\beta$ 42 levels in the cerebrospinal fluid (CSF) and interstitial fluid (ISF) correlates with the formation of amyloid plaques in transgenic mice.<sup>85</sup> Longitudinal studies in humans showed that a decrease of CSF A $\beta$ 42 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.<sup>86–89</sup> In the APPSwe/PS1dE9 mouse model of amyloid pathology, sleep–wake abnormalities appear and develop in parallel with A $\beta$  aggregation.<sup>85</sup>

In humans, sleep and circadian fragmentations have been associated with a higher risk of A $\beta$  aggregation and the formation of amyloid plaques. Interestingly, the clearance of A $\beta$  peptide follows a diurnal pattern in both CSF and ISF which is regulated by the sleep–wake cycle: the A $\beta$  concentration increases during time awake and decreases during sleep in transgenic mice.<sup>90</sup> The association between A $\beta$  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.<sup>78</sup> 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 A $\beta$  deposition.<sup>91</sup> In fact, each additional hour of sleep was associated with a reduction in the A $\beta$  accumulation, while daytime sleep was associated with increased accumulation of A $\beta$ .<sup>91</sup>

## 1.5 | Pathophysiological role of circadian disruption in early AD

Several events such as dysregulation of clock genes by A $\beta$ , 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<sup>9</sup> (Figure 3).

Experimental studies in mice provided evidence that amyloid pathology induces a dysregulation of clock genes. Indeed, A $\beta$  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*.<sup>92,93</sup> In the 5xFAD mouse model, A $\beta$  induces *BMAL1* degradation by promoting *BMAL1* sumoylation, while degradation of *CBP* was mediated by N-cadherin cleavage products.<sup>93</sup> 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 A $\beta$  plaques and neurofibrillary tangles, and neuroinflammation.

in turn causes PER2 dysregulation and circadian rhythm disruption.<sup>93</sup> 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,<sup>94</sup> and neuroinflammation.<sup>68,95</sup>

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.<sup>96</sup> In mice, specific deletion of *BMAL1* in neurons and glia induced oxidative damage and degeneration of synaptic terminals.<sup>68</sup> Moreover, *BMAL1* methylation is associated with tau pathology, night-waking and depression but not with speed and memory tests, or sleep duration in humans.<sup>97</sup>

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.<sup>9</sup>

Melatonin has a neuroprotective effect in animal models of AD.<sup>98</sup> It ameliorates cognitive functions by decreasing A $\beta$  accumulation and by preventing hyperphosphorylation of tau through inhibition of glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ) and stimulation of protein phosphatase-2A (PPP2A).<sup>98</sup> Furthermore, melatonin promotes A $\beta$  clearance and ameliorates A $\beta$  neurotoxicity.<sup>99</sup> 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.<sup>100</sup>

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.<sup>101,102</sup> 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.<sup>102</sup> 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 A $\beta$  accumulation in mouse models of AD.<sup>103,104</sup> BMAL1 is a key mediator of the circadian control of the immune system and has anti-inflammatory effects.<sup>105</sup> In APP-KI mice, reducing BMAL1 levels promoted an inflammatory phenotype of microglia through increased NF- $\kappa$ B and decreased I $\kappa$ B $\alpha$  activity.<sup>102</sup> 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 A $\beta$  and phagocytosis is circadian-regulated.<sup>106–108</sup> Recently, Clark et al.<sup>106</sup> showed in vitro that diurnal oscillations of A $\beta$ 42 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 A $\beta$ 42 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 pre-clinical phase of AD, even before cognitive impairment.<sup>10</sup> Quality of sleep was also associated with the risk of A $\beta$  deposition,<sup>78</sup> and sleep fragmentation in older adults was correlated with incident AD and cognitive decline.<sup>79</sup>

## 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.<sup>5,109</sup>

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.<sup>109</sup> Light therapy, for example, is widely used in psychiatric and neurological diseases.<sup>110–112</sup> Bright light in AD has been shown to improve sleep efficacy during the night, decrease napping during the day, improve cognition, and reduce depression.<sup>113–115</sup> Moreover, light exposure during evening hours is effective in inducing more solid sleep during the night and more stable rest/activity rhythms.<sup>116,117</sup> 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.<sup>118,119</sup> In addition to AD, therapeutic strategies that

target the clock have shown promise in other neurodegenerative diseases such as PD and HD.<sup>112,120–122</sup> 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.<sup>121</sup> 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.<sup>122</sup> 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.<sup>123</sup>

Importantly, an increasing number of pharmacological studies are exploiting the knowledge of circadian rhythmicity for more accurate treatments.<sup>124</sup> Indeed, the pharmacokinetics and pharmacodynamics of most drugs follow circadian fluctuations, and thus, efficacy and toxicity are influenced by the time of administration.<sup>5,124</sup> Likewise, many surgical interventions can benefit from chronobiological optimization.<sup>5</sup> 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.<sup>5,125</sup> 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.<sup>113,114,126</sup> 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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