

Association between circadian rhythms and neurodegenerative diseases

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Dysfunction in 24-h circadian rhythms is a common occurrence in ageing adults; however, circadian rhythm disruptions are more severe in people with age-related neurodegenerative diseases, including Alzheimer's disease and related dementias, and Parkinson's disease. Manifestations of circadian rhythm disruptions differ according to the type and severity of neurodegenerative disease and, for some patients, occur before the onset of typical clinical symptoms of neurodegeneration. Evidence from preliminary studies suggest that circadian rhythm disruptions, in addition to being a symptom of neurodegeneration, might also be a potential risk factor for developing Alzheimer's disease and related dementias, and Parkinson's disease, although large, longitudinal studies are needed to confirm this relationship. The mechanistic link between circadian rhythms and neurodegeneration is still not fully understood, although proposed underlying pathways include alterations of protein homeostasis and immune and inflammatory function. While preliminary clinical studies are promising, more studies of circadian rhythm disruptions and its mechanisms are required. Furthermore, clinical trials are needed to determine whether circadian interventions could prevent or delay the onset of neurodegenerative diseases.

Introduction

Circadian rhythm activities change markedly as people age, and these changes might further accelerate the ageing process.¹ Although it is recognised that circadian dysfunction in older adults can be partly attributed to the degeneration of the suprachiasmatic nucleus (SCN), known as the master circadian clock in mammals, the link between circadian rhythms and neurodegeneration is not fully understood. Patients with neurodegenerative diseases frequently experience circadian rhythm disruptions in a much more severe form than typical age-related disruptions.²⁻⁴ For example, these patients become more active during the night, less active during the day, and sometimes have complete reversal or loss of the 24-h rest-activity pattern. For example, the observed 24-h rest-activity pattern in healthy individuals (who are less active during the night and more active during the day) is lost or even reversed in these patients (who become more active during the night and less active during the day).^{5,6} Importantly, evidence⁷⁻⁹ suggests that disruptions of circadian functions could be early manifestations of neurodegeneration, and might even be a risk factor for the development of neurodegenerative diseases in healthy adults older than 60 years. A greater understanding of the relationship between circadian rhythms and neurodegeneration could be key to enabling the early identification and management of neurodegenerative diseases.

This Review discusses the association between circadian rhythms and neurodegenerative diseases by summarising evidence from both human and animal studies. We focus on Alzheimer's disease and related dementias and Parkinson's disease as these are the most common neurodegenerative diseases that have been studied in relation to circadian rhythms. We present both behavioural and biological circadian features in patients with Alzheimer's disease and related dementias, and Parkinson's disease. We also summarise findings from

clinical and longitudinal epidemiological studies of the effects of circadian rhythm disruption on the development of Alzheimer's disease and related dementias, and Parkinson's disease, discussing potential underlying mechanisms. Finally, we describe the results of different circadian interventions. For a detailed discussion of studies published before 2013, we refer readers to previous reviews.¹⁰⁻¹³

Circadian rhythms

Circadian rhythm patterns can be measured with both biological and behavioural markers (panel 1). Landmark experiments by Czeisler and colleagues¹⁷ in the 1990s identified core body temperature, as well as melatonin and cortisol secretions, as circadian biomarkers, oscillations of which are controlled by the SCN. In normally entrained individuals, core body temperature has a rhythm that falls during the night and rises in the early hours of the morning; cortisol concentration peaks in blood and saliva early in the morning and gradually decreases throughout late morning and afternoon, to reach low values during evening and night, thereby aiding sleep. Melatonin, another key circadian biomarker, is generated by the pineal gland, with its onset near sunset, peak during the nighttime hours, and offset after sunrise, thereby stimulating wakefulness. The circadian rhythm of melatonin in saliva or plasma is one of the most commonly used circadian phase biomarkers in human beings.¹⁸ The onset time of melatonin secretion under dim light conditions, known as the dim light melatonin onset, has been suggested as the most accurate circadian phase marker in humans.¹⁹

Behavioural markers of circadian rhythm include sleep-wake cycles and rest-activity rhythms. The circadian system has a powerful influence over the sleep cycle and wake cycle, making it difficult to distinguish the effect of circadian disruption from those caused by sleep disturbance. The circadian clock regulates the timing of sleep. Mutations in the core circadian clock genes in mice

Lancet Neurol 2019; 18: 307-18

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Panel 1: Basics of the circadian rhythm

A circadian rhythm is an approximately 24-h cycle in the physiological processes of most organisms that is endogenously generated and can be modulated by external cues.¹⁴ A circadian cycle is characterised by several features. It is self-sustained as the rhythm persists in the absence of any exogenous time signals (known as zeitgebers), including dark–light cycles, which indicate the presence of an intrinsic time-keeping mechanism (ie, biological clock). Circadian cycles show rhythmicity, as they persist with a cycle of approximately 24 h. Circadian cycles also show the ability to be synchronised by external cues, such as the dark–light cycle or other social and environmental modulators, such as physical activity and temperature. The circadian rhythmicity is typically measured by three parameters: amplitude, phase, and period. Amplitude is defined as the magnitude of a cycle, or the difference between crest and trough values. In relation to a hormonal cycle, for example, amplitude would be the difference in the levels of the hormone from the trough to the peak within a time period (ie, 24 h). Phase (advanced or delayed) is defined as the timing of a reference point in the cycle relative to a fixed event. In relation to a sleep–wake cycle, for example, a phase advance would mean that sleep timing moves earlier. A phase delay, conversely, describes a later sleeping time. Period is the time interval between two reference points within a rhythm or recurring wave (for example, between two hormonal peaks).

Circadian rhythms are generated in highly specialised cells of specific structures of the brain that control a complex network of coupled self-sustained clocks in the brain and in the peripheral organs. In mammals, the central or master clock of the circadian network is located in two groups of neurons called the suprachiasmatic nucleus (SCN), in the anterior hypothalamus. The SCN consists of approximately 20 000 specialised neurons that receive direct synaptic input from the retina, synchronising activity to the external light–dark cycle.¹⁵ Light input serves to synchronise the core cellular clock machinery in SCN neurons, which keeps 24-h time and in turn synchronises cellular clocks throughout the body via neurohormonal modulation. At the molecular level, the properties of circadian clocks are based on changes in the expression of certain genes and consist of proteins that form a transcriptional–translation feedback loop that is tuned to a 24-h period.¹⁶ The clock proteins BMAL1 and Clock interact to drive transcription of clock-controlled genes, including their own negative feedback repressors, which include PERIOD, CRYPTOCHROME, and REV-ERB proteins.¹⁷ This transcriptional feedback loop maintains 24-h rhythms in gene expression, which are required for behavioural and physiological rhythmicity at the organismal level. While light is the primary circadian cue, resetting the circadian cycle in synchrony with the daily environmental and behavioural cycle (entrainment) is achieved through the 24-h cycle of light input (photic synchroniser) to the SCN and neurohormonal modulations (non-photic synchronisers — eg, temperature, food availability, and social interactions) for the peripheral ones. Importantly, in the absence of external cues, such as in constant darkness, the circadian system retains a near 24-h rhythm, while light cues that are out of phase with the SCN cause a gradual resetting of the clock to entrain to the new rhythm.

and humans manifest as abnormal sleep patterns, including short sleep time, early or late sleep phase, or unstable and fragmented sleep–wake rhythms.^{20,21} Moreover, clock gene expression can be influenced by sleep deprivation, emphasising that these systems are inter-related.²² While specific circadian analyses (such as cosinor analysis) can be used to distinguish aspects of circadian rhythm disruption from behavioural data, total movement must be monitored around the clock for several days. Some circadian biomarkers, such as the timing of melatonin secretion or oscillation of expression of selected clock genes in blood, maintain their 24-h oscillations even in the event of sleep deprivation.^{23,24}

Therefore, studies need to include both behavioural and biological markers of circadian rhythms to more robustly identify circadian rhythm disruption. Given the scope of this Review, we included studies if they presented information on biological markers or behavioural markers related to sleep timing, daytime sleep or sleepiness, and rest–activity rhythm. Studies that only presented nocturnal sleep disruptions were excluded.

Age-related changes in any of the structures or processes involved in generating or entraining circadian rhythms may modify circadian rhythmicity. Circadian phase has been shown, in a study²⁵ comparing 48 older adults (aged 77–89 years) with 36 younger adults (aged 20–52 years), to move earlier in the day, or advance, with age. Furthermore, the amplitude of the rhythms tended to decrease, meaning individuals might become more active during the night and less active during the day as they age.²⁶ For example, adults older than 60 years have decreased peaks of melatonin, an elevated minimum core body temperature, and a phase advance (earlier onset) in the peak of these rhythms compared with adults younger than 60 years.^{1,27,28} Age-related changes in sleep–wake cycles may be related to circadian dysfunction and result in earlier bedtimes and waking times, increased sleep fragmentation, and increased daytime sleepiness.^{29,30} Evidence indicates that these features might serve as early indicators of declining health in adults older than 60 years.^{29,30} Adults older than 60 years are also more prone to several circadian rhythm sleep–wake disorders.^{31,32} These disorders are characterised by the inability to fall asleep, remain asleep, or wake at the desired time, and also include advanced sleep–wake phase disorders, jet lag disorder, and shift-work disorder.^{31,32} The circadian system is paramount for maintaining synchrony between internal physiology, behaviour, and external environmental cues (such as sunlight). When this synchrony is lost (eg, due to jet lag, shift work, or chronic sleep deprivation) a circadian misalignment occurs, leading to substantial health consequences.^{33–35} These health consequences affect cardiovascular, metabolic, cognitive, immunological, and oncogenic processes. Furthermore, circadian misalignment also affects safety, performance, and productivity in the workplace.^{33–35}

Circadian disruption in neurodegeneration Alzheimer's disease and related dementias

Compared with healthy adults of the same age, patients with moderate to severe Alzheimer's disease have been considered to have much more severe circadian disruptions,⁵ including higher levels of sleep fragmentation, reduced amplitude of circadian rhythmicity, and shifts in both bedtime and wake times to later in the day (known as a “phase delay”).⁵ Sundowning, a term describing the increased behavioural and neuropsychiatric symptoms in patients with Alzheimer's disease around the time of sunset, might also partly be attributed to the phase delay of temperature and hormone rhythms in such patients.^{36,37} The most common circadian rhythm sleep–wake disorders

	Participants	Type of circadian markers	Measure of circadian markers	Results
Musiek et al (2018) ⁷	189 cognitively healthy older adults (mean age 66.6 years, 50 with preclinical amyloid pathology and 139 amyloid negative)	Rest-activity rhythm	7 to 14-day actigraphy	Those with preclinical AD had increased rest-activity rhythm fragmentation (p=0.008) but no significant difference in the amplitude (p=0.89) or phase (p=0.12), after adjusting for age and sex, compared with healthy controls
Weissova et al (2016) ²	13 patients with mild AD (mean age 78.9 years) and 13 age-matched controls	Rest-activity rhythm; melatonin rhythm; peripheral clock gene expression	21-day actigraphy; sleep diary; saliva melatonin assay; real-time PCR	The mean number of daytime naps was higher among patients with AD than controls (p=0.04); patients with AD had dampened melatonin profiles and non-significantly reduced amplitude of melatonin rhythm (p=0.59); expression of PER1 (p=0.47) and BMAL1 (p=0.21) was not significantly different between AD patients and controls
La Morgia et al (2016) ⁴²	16 patients with mild to moderate AD and 10 age-matched controls (mean age 70.3 years)	Rest-activity rhythm	7-day actigraphy	Patients with AD had a reduced rhythm amplitude (p=0.04), were less active during the wake period (p=0.04) but more active during the night (p=0.12) compared with controls; there were large individual variabilities among patients with AD
Wang et al (2015) ⁴⁴	Seven patients with AD and ten age-matched controls (mean age 90.5 years at death)	Rest-activity rhythm	≥7-day actigraphy within the 18 months before death	Patients with AD had a phase delay (activity nadirs and acrophases occurred 2.9 h later than in controls; p=0.002); there was no significant difference in rhythm amplitude (p=0.88)
Hooghiemstra et al (2015) ³	61 patients with EOD and 67 controls (mean age 61.9 years)	Rest-activity rhythm	7-day actigraphy	Patients with EOD had increased rest-activity rhythm fragmentation (p=0.03) but no significant difference in the amplitude or regularity
Liguori et al (2014) ⁴³	48 drug-naive patients with AD (mean age 70.6 years; 21 mild and 27 moderate to severe) and 29 controls	Sleep timing	Polysomnography	Those who had AD had earlier bedtimes, especially for patients with moderate (2215 h) to severe (2145 h) AD, compared with controls (2330 h, p<0.01) and patients with mild AD (2245 h, p=0.04); there was no difference in rise times
Naismith et al (2014) ⁴⁰	26 patients with MCI (mean age 65.9 years) and 26 age-matched controls	Sleep timing; melatonin rhythm	14-day actigraphy; saliva melatonin assay	Patients with MCI had earlier melatonin peaks (p=0.001) and sleep onset (p=0.01) compared with controls; there was no significant difference in melatonin levels
Ortiz-Tudela et al (2014) ⁴¹	21 patients with MCI (mean age 74.1 years) and 19 age-matched controls	Rest-activity rhythm; temperature rhythm	7-day actimeter; wrist temperature sensor	Patients with MCI showed a phase advance in both activity rhythm (p=0.04) and temperature (p=0.01)

AD=Alzheimer's disease. EOD=early-onset dementia. MCI=mild cognitive impairment. PCR=polymerase chain reaction.

Table 1: Case-control studies of circadian rhythm disruptions in patients with dementia or mild cognitive impairment

seen in patients with Alzheimer's disease is irregular sleep-wake rhythm disorder, in contrast to advanced sleep-wake phase disorders commonly observed in healthy older adults. Irregular sleep-wake rhythm disorder is defined as a lack of clear 24-h sleep-wake pattern, usually with long periods of wakefulness during the night and irregular bouts of sleep throughout the day, which might deteriorate further for patients with severe Alzheimer's disease.^{38,39}

Over the past 5 years, a growing number of studies observed patients with various levels of cognitive impairment and found that their circadian patterns differed from findings reported in previous studies that focused on moderate to severe Alzheimer's disease.^{5,7,40} These conflicting results could be due to the different type or severity of cognitive impairment reported in the studies. These studies^{2,3,7,40,41-44} included patients with preclinical Alzheimer's disease (those with amyloid plaque pathology, but no cognitive symptoms),⁷ mild cognitive impairment,^{40,41} mild Alzheimer's disease,^{2,42,43} moderate to severe Alzheimer's disease,⁴³ Alzheimer's disease of any severity,⁴⁴ as well as early-onset dementia.³ Furthermore, these studies also reported behavioural markers of circadian rhythm disruption, including disruptions of rest-activity rhythms and sleep timing (table 1). Overall, studies have

found high rest-activity rhythm fragmentation (meaning physical activity is scattered across the 24-h day)^{3,7} but only a slight reduction or no change in the amplitude of rest-activity or melatonin rhythms, regardless of the severity of cognitive impairment.^{2,3,7,42,44} One US study⁷ of 189 cognitively healthy older adults (mean age 66.6 years, 50 of whom had preclinical Alzheimer's disease pathology as measured by PET) showed decreased rhythm amplitude associated with ageing, but not with Alzheimer's disease pathology. Another study⁴² in 16 patients with mild-to-moderate Alzheimer's disease (mean age 70.3 years) from Italy found large variability among individual actigraphic profiles compared with ten age-matched neurologically healthy controls, which could have also contributed to the overall minor changes in the amplitude of rhythms in these patients. There are mixed findings in published studies with regard to changes in circadian phases. Data from the ongoing Rush University Memory and Aging Project⁴⁴ suggested a significant phase delay in rest-activity rhythm among seven patients with Alzheimer's disease (mean age 90.5 years) compared with ten age-matched controls without Alzheimer's disease, whereas a study⁴³ of 48 patients with Alzheimer's disease (mean age 70.6 years) from Italy and 29 age-matched controls without dementia showed an advanced bedtime in patients with Alzheimer's

disease, especially for moderate to severe cases. Meanwhile, two studies of patients with mild cognitive impairment both found a phase advance. One study⁴⁰ analysed melatonin levels and sleep onset in 30 patients (mean age 65.9 years) with mild cognitive impairment compared with 28 healthy age-matched controls; the other study⁴¹ analysed core body temperature and activity rhythm in 21 patients (mean age 74.1 years) with mild cognitive impairment compared with 19 healthy age-matched controls. The differences among these findings could be caused by differences in the baseline characteristics of the participants in both studies, including age and severity of cognitive impairment.

In general, studies that focused on severe Alzheimer's disease found more circadian disruptions, while studies in patients with mild cognitive impairment, preclinical Alzheimer's disease, and mild Alzheimer's disease suggested only moderate circadian changes.^{2,7,40} However, a study⁴² in 16 patients with mild to moderate Alzheimer's disease (mean age 70.3 years) compared with ten age-matched neurologically healthy controls, identified no correlation between circadian features and severity measures of Alzheimer's disease. However, this result might be explained by the small sample size and relatively small range of Alzheimer's disease severity between participants in this single study. No study to date has prospectively examined the changes in circadian rhythms that occur with the progression of Alzheimer's disease symptoms. Few studies have examined molecular perturbations in circadian clock oscillations in Alzheimer's disease and related dementias, although alteration in clock gene methylation and expression have been described in fibroblast cultures from post-mortem tissue,⁴⁵ and altered clock gene expression has been observed in varying brain regions of post-mortem tissue.⁴⁶ Furthermore, evidence specifically pertaining to circadian disruptions among patients with non-Alzheimer's disease dementia is sparse. Larger and longitudinal studies are needed to determine the correlation between both behavioural and biological markers of circadian rhythm disruption and severity or progression of Alzheimer's disease. Additional studies designed to establish circadian markers and features specific to each type of dementia might help with the differential diagnosis of the disease.

Parkinson's disease

Both motor and non-motor manifestations of Parkinson's disease can have a circadian rhythm that is susceptible to disruption. Unlike patients with Alzheimer's disease and related dementias, circadian rhythm disruption in patients with Parkinson's disease is characterised by a reduction in the amplitude of the circadian rhythm, but no significant shift in circadian phases.^{4,47-51} Sleep-wake disturbances as a whole are the most common non-motor symptom in patients with Parkinson's disease, affecting up to 80%.⁵² Indeed, five of the six studies that examined circadian features in patients with Parkinson's

disease reported either excessive daytime sleepiness^{4,47,48} or changes in sleep timing (table 2).^{48,49,51} Studies have shown that patients with Parkinson's disease are at least twice as likely to experience excessive daytime sleepiness compared with healthy adults older than 60 years.^{4,47} Only one study reported slightly later sleep onset time in 30 patients (mean age at diagnosis 68.0 years) compared with 15 healthy age-matched controls from England,⁵³ while the other studies did not find significant differences in sleep timing.^{49,51} One Australian study⁴⁹ found a significant reduction in the mean core temperature rhythm oscillation value (known as the mesor) and amplitude of their core body temperature rhythm value among 12 patients (mean age 62.2 years) with Parkinson's disease, compared with 11 healthy age-matched controls. Three additional studies examined rhythms of melatonin secretion, using plasma,⁴ serum,⁴⁸ and saliva melatonin.⁵¹ Although none of these studies found a difference in the timing of melatonin onset, most found significantly reduced circulating melatonin levels among patients with Parkinson's disease compared with age-matched healthy controls.^{4,48} Importantly, the occurrence of a circadian dip in blood pressure usually noted during the night may be lost in Parkinson's disease, putting patients with Parkinson's disease at substantially higher risk for cardiovascular complications, including nocturnal hypertension.⁵⁰ For example, a study⁵⁰ of 111 patients with Parkinson's disease (mean age 67.8 years) from Spain reported that 71% of patients did not experience a dip in blood pressure, as measured by 24-h ambulatory blood pressure monitoring.

Despite the consistently reported circadian rhythm disruption among patients with Parkinson's disease, it remains unclear whether these circadian changes result from dopaminergic treatment or from Parkinson's disease progression itself. Studies^{54,55} have reported that dopaminergic treatment might lead to phase advance of the melatonin rhythm. However, a study⁵¹ including 29 patients with Parkinson's disease (mean age 64.2 years; 16 medicated and 13 non-medicated) and 28 healthy age-matched controls from Australia found more than double the melatonin secretion and uncoupling of circadian and sleep-wake regulations in the group receiving dopamine treatment compared with no treatment. Excessive daytime sleepiness is another potential consequence of dopaminergic treatment.⁴⁷ One study in Norway observed a doubled frequency of excessive daytime sleepiness among 153 untreated patients with early Parkinson's disease (mean age 66.3 years), compared with 169 age-matched and sex-matched healthy controls at baseline, and a tripled frequency of excessive daytime sleepiness among these patients after 5 years of dopaminergic treatment compared to the controls.⁴⁷ Larger studies with other circadian markers (eg, cortisol secretion and core body temperature) are needed to help clarify the effects of dopaminergic treatment on circadian rhythms, relative to neurodegeneration.

	Participants	Type of circadian markers	Measure of circadian markers	Results
Tholfsen et al (2015) ⁴⁷	153 drug-naive patients with PD (mean age 66.3 years) and 169 age-matched and sex-matched controls	EDS	ESS	12% patients with PD and 5% controls had EDS at baseline; after 5 years on PD medication, 23% of patients with PD and 8% of controls had EDS
Videnovic et al (2014) ⁴	20 patients with PD and 15 age-matched controls (mean age 64.1 years)	Melatonin rhythm; EDS	Plasma melatonin by 24-h repeated blood sampling; ESS	Patients with PD had reduced melatonin rhythm amplitude ($p<0.001$) and four-fold decrease in 24-h AUC for circulating melatonin levels compared with controls; there was no significant difference in DLMO. 60% patients with PD and 27% controls had EDS ($p<0.01$)
Breen et al (2014) ⁴⁸	30 patients with PD (mean age at diagnosis 68.0 years) and 15 age-matched and sex-matched controls	Sleep timing; EDS; melatonin rhythm; cortisol rhythm; peripheral clock gene expression	14-day actigraphy; ESS; serum melatonin and cortisol by 24-h repeated blood sampling	Patients with PD had more fragmented motor activity during 24-h ($p=0.01$) and later sleep onset time ($p=0.04$); they had reduced circulating melatonin levels ($p=0.05$), increased cortisol levels ($p<0.001$), and altered <i>Bmal1</i> expression ($p=0.04$) compared with controls; the timing of melatonin or cortisol onset or offset did not differ
Bolitho et al (2014) ⁵¹	29 patients with PD (mean age 64.2 years; 16 medicated and 13 non-medicated) and 28 age-matched controls	Sleep timing; melatonin rhythm; phase angle of entrainment	14-day actigraphy and saliva melatonin assay	There were no differences in sleep timing or DLMO; dopaminergic treatment more than doubled ($p=0.001$) the melatonin secretion and the phase angle of entrainment in patients with PD compared with control
Zhong et al (2013) ⁴⁹	12 patients with PD (mean age 62.2 years) and 11 age-matched controls	Sleep timing; core-body temperature profiling	14-day actigraphy; temperature profile recorded by 24-h ingestible capsule sensor	There was no significant difference in sleep timing; patients with PD had lower temperature mesor ($p=0.02$) and reduced nocturnal temperature amplitude ($p=0.04$) compared with controls
Berganzo et al (2013) ⁵⁰	111 patients with PD (mean age 67.8 years)	Blood pressure	24-h ambulatory blood pressure monitoring	71% of patients with PD had no usual dip in nocturnal blood pressure; patients with PD had a high burden of nocturnal hypertension

AUC=area under the curve. DLMO=dim light melatonin onset. EDS=excessive daytime sleepiness. ESS=Epworth Sleepiness Scale. PD=Parkinson's disease. Meso=mean value around which the rhythm oscillates.

Table 2: Case-control studies of circadian rhythm disruptions in patients with Parkinson's disease

Circadian disruption and risk of neurodegeneration

A crucial question is whether neurodegeneration is caused by, or is a consequence of, circadian rhythm disruption, or both. If circadian rhythm disruption were contributing to neurodegeneration, it would be expected to occur early in the disease course (or even preceding disease onset), and would increase the risk of disease or speed of disease progression. While this question is still unanswered, growing evidence suggests that circadian rhythm disruption might precede the development of clinical symptoms of neurodegenerative diseases. One study⁷ of 189 cognitively healthy older adults (mean age 66.6 years; 50 with preclinical Alzheimer's disease pathology as measured by PET) reported that circadian rest-activity rhythm fragmentation appeared very early on in the preclinical phase of Alzheimer's disease (compared with healthy controls) and correlated with Alzheimer's disease-related pathology as assessed with PET imaging and CSF phosphorylated tau to amyloid beta ($A\beta$)₄₂ ratio. Several studies^{9,56,57} have found a correlation between sleep-wake disturbances and increased levels of Alzheimer's disease-related biomarkers or brain structural changes in cognitively healthy adults aged 60 years and older, although other biological markers of circadian rhythm disruption (such as core body temperature or cortisol rhythm) were not specifically examined. Alterations in circadian melatonin rhythm measured in saliva

were also found in 26 men (mean age 57.3 years) who were cognitively impaired compared with 24 age-matched cognitively healthy men.⁵⁸ These cross-sectional findings suggested that circadian rhythm disruption could be a result of preclinical Alzheimer's disease pathology and might be a prodromal symptom.

Several longitudinal studies with long follow-up periods (5–41 years) have also reported greater cognitive decline, increased risk of all-cause dementia, and increased risk of Parkinson's disease among individuals with circadian rhythm disruptions, such as shift workers, compared with those without circadian rhythm disruptions.^{59–63} Several longitudinal studies have been published in the past 5 years investigating circadian rhythm disruption and risk of developing Alzheimer's disease and related dementias, or Parkinson's disease (table 3). These studies all examined behavioural indicators of circadian rhythm disruption, including actigraphy-measured rest-activity rhythm and short durations of daytime sleeping^{8,61,64} as well as self-reported sleep timing.⁶⁵ Two studies found an association between lower baseline circadian amplitude and greater cognitive decline at 3–5 years-follow-up in 2754 cognitively healthy men (mean age 76.0 years)⁶⁴ and 1287 cognitively healthy women (mean age 82.8 years)⁶¹ from the USA. A study of 11247 individuals (mean age 72.5 years at baseline) from the Swedish Twin Registry provided evidence that delayed rising time predicted dementia incidence after 17 years of follow up.⁶⁵ Another

	Participants	Length of follow-up (mean or maximum)	Type of circadian marker	Measure of circadian marker	Primary outcome	Results
Rogers-Soeder et al (2018) ⁶⁴	2754 men with CI* (mean age 76.0 years)	3.4 years (mean)	Rest-activity rhythm	Actigraphy	Cognitive decline by tests of global cognition (3MS) and executive function (Trails B)	Lower circadian amplitude (p<0.001) and phase advance was associated with greater cognitive decline
Bokenberger et al (2017) ⁶⁵	11 247 adults with CI* (mean age 72.5 years)	17 years (max)	Sleep timing	Karolinska Sleep Questionnaire	Incident dementia by ICD-10 codes	Delayed rising time was associated with increased dementia risk
Walsh et al (2014) ⁶¹	1287 women with CI* (mean age 82.8 years)	5 years (max)	Rest-activity rhythm	Actigraphy	Cognitive decline by tests of global cognition (3MS), memory (CVLT-II recall, Digits Span Backward), and executive function (Trails B, categorical Fluency, and Letter Fluency)	Lower circadian amplitude was associated with worse cognitive function, especially executive function (p<0.05)
Leng et al (2018) ⁸	2920 men with PD (mean age 76.3 years)	11 years (max)	Daytime sleepiness and napping	Actigraphy	Incident PD defined by self-report or PD medication use	Long daytime sleeping was associated with increased risk of PD (p=0.001)

3MS=Modified Mini-Mental State Examination. AD=Alzheimer's disease. CI=cognitive impairment. CVLT-II= California Verbal Learning Test-II. ICD-10= International Statistical Classification of Diseases and Related Health Problems (10th revision). PD=Parkinson's disease. Trails B=Trail Making Test, part B. *including Alzheimer's disease and related dementias.

Table 3: Longitudinal studies on circadian rhythm disruptions and subsequent risk of neurodegenerative diseases

study⁸ of 2920 men (mean age 76.0 years) from the USA suggested that those who napped for at least 1-h per day were twice as likely to develop Parkinson's disease after 11 years of follow-up, compared with those who napped for less than 1-h per day. Although together these studies suggest that reduced circadian amplitude and circadian phase shifts precede the risk of Alzheimer's disease and related dementias, and that daytime inactivity precedes the risk of Parkinson's disease in healthy older adults, the number of published studies is relatively small, especially studies examining Parkinson's disease. A recent study showed that less stable day-to-day rest-activity rhythm in patients with mild to moderate Parkinson's disease was associated with cognitive impairment, independent of sleep.⁶⁶ This finding supports the concept that circadian dysfunction could be one of the common physiological pathways in different neurodegenerative diseases leading to cognitive decline. Additional confirmatory studies with a long follow-up period are needed to determine whether circadian rhythm disruption is a risk factor for these diseases. Comprehensive and repeated measures of circadian rhythm disruption with simultaneous assessment of preclinical disease biomarkers (such as amyloid and tau pathology) will also help us to understand the nature of this association.

Underlying mechanisms

The mechanisms by which neurodegenerative pathology affects circadian function probably vary by specific disease. In Alzheimer's disease, human post-mortem neuropathological studies have demonstrated loss of critical neuronal populations in the SCN, including those expressing arginine vasopressin or vasoactive intestinal peptide (VIP).^{44,67} Both age-associated and Alzheimer's disease-associated loss of VIP-expressing neurons in

the SCN were correlated with pre-mortem circadian dysfunction (figure).⁴⁴ However, the mechanisms driving SCN neuronal loss are unclear, as it is not a major site of amyloid plaque or neurofibrillary pathology.⁷⁸ Circadian abnormalities are observed in transgenic mouse models of Alzheimer's disease, including those expressing human mutant amyloid precursor protein, tau, or both.⁷⁹⁻⁸¹ However, there is great heterogeneity across mouse models, and little correlation with pathology, obscuring any definitive mechanistic conclusions.⁷⁹⁻⁸¹ The A β peptide has been implicated as a mediator of circadian dysfunction, and in cultured cells it can induce degradation of the master clock protein BMAL1.^{82,83} However, this direct interaction between A β and the circadian clock has not been demonstrated in vivo in animals, or in humans. Altered methylation of the *BMAL1* promoter, leading to altered BMAL1 expression and disrupted circadian rhythms, was demonstrated in fibroblasts from patients with Alzheimer's disease and in post-mortem brain samples taken from patients with Alzheimer's disease, suggesting an underlying epigenetic mechanism of circadian disruption (figure).⁴⁵

Conversely, several mechanisms have been proposed by which the circadian clock influences neurodegenerative disease (figure). Circadian dysfunction could promote neurodegeneration by altering sleep timing, leading to less consolidated night-time sleep and increased daytime napping. Sleep deprivation causes altered A β dynamics in humans⁸⁴ and increased A β and tau pathology in mouse models^{85,86} and can increase inflammatory and neuronal injury markers in human CSF.⁸⁷ Sleep deprivation has also been shown in mouse models to affect other aspects of neurodegeneration, including protein clearance from the brain, inflammation, and synaptic homeostasis.^{88,89} In this case, intervention to promote sleep should

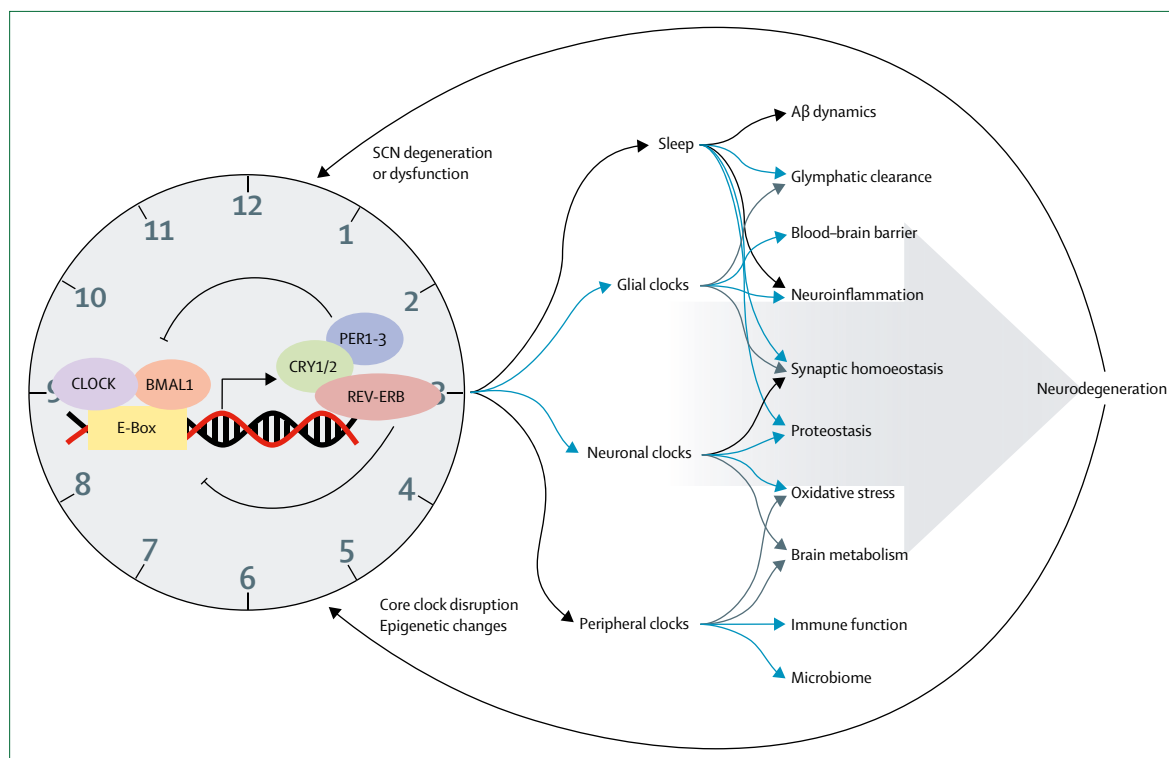


Figure: Proposed bidirectional relationship between circadian rhythm disruption and neurodegeneration

The core circadian clock is present in most cells, including those of the central circadian pacemaker in the SCN, and consists of a transcriptional-translational feedback loop involving the positive transcriptional regulators CLOCK and BMAL1 bound to E-box 1, and their negative feedback inhibitors PER1-3, CRY1/2, and REV-ERB proteins. The circadian clock influences sleep timing, which has been shown to directly control A β dynamics (in humans⁶⁸ and mice^{69,70}) and glymphatic clearance of toxic proteins (in animals⁷¹). Sleep disruption also alters a host of other factors, from synaptic homeostasis to inflammation. Circadian clocks in microglia and astrocytes (glial clocks) might regulate the blood-brain barrier, inflammation, and synaptic function,⁷²⁻⁷⁶ although the evidence is too preliminary to draw a strong conclusion. Animal studies suggest that circadian clocks in neurons influence brain oxidative stress,⁷² and could affect brain metabolic function and synaptic homeostasis.⁷⁷ Finally, peripheral clocks in organs such as the gut, liver, and immune tissue impact peripheral metabolism, the microbiome, and immune function.⁷⁷ This multi-system perturbation could promote toxic protein aggregation and neurodegeneration, which in turn could disrupt circadian clocks in the SCN and periphery. Black arrows=supported by human data. Blue arrows=supported by animal data. Grey arrows=data are suggestive but too preliminary to draw firm conclusions. SCN=suprachiasmatic nucleus.

overcome any effect of circadian disruption. However, in mouse models, clock gene deletion in the brain can cause neuropathology (such as astrogliosis) without altering sleep, suggesting that altered sleep patterns alone may not explain the brain effects of circadian disruption.⁷²

Circadian regulation of immune responses may also contribute to the effects of circadian dysfunction on neurodegeneration. The circadian system strongly modulates the peripheral immune response to inflammogens in mice, because the degree of inflammation is highly dependent on the time-of-day that exposure occurs.^{77,89} In a mouse model of experimental autoimmune encephalitis, the time of day of immunisation had a striking impact on disease severity weeks later, while deletion of *Bmal1* in myeloid cells exacerbated pathology.^{90,91} Microglia and astrocytes represent the primary innate immune cells in the brain, and in rodents both cell types possess functional circadian clocks that regulate inflammatory activation.^{73,92} Deletion of *Bmal1* in the mouse brain disrupts all circadian clock function and causes widespread astrocyte activation and synaptic degeneration, emphasising the importance

of core clock function in maintaining innate immune homeostasis in the brain.⁷² In mouse models of amyotrophic lateral sclerosis and Parkinson's disease, circadian disruption using non-24-h light dark cycles led to increased glial activation and neuroinflammation and significantly exacerbated neuropathology.^{93,94} Therefore, circadian dysfunction appears to promote aspects of neuroinflammation which could, in turn, influence neurodegeneration in many disease states.

The circadian clock could directly regulate protein homeostasis and quality control, thereby influencing protein aggregation in neurodegenerative diseases.⁶⁹ In a mouse model of Alzheimer's disease, levels of interstitial fluid A β peptide in the hippocampus show clear diurnal oscillation, which require an intact circadian system.^{70,95} Similar diurnal oscillations in A β are observed in human CSF.⁶⁸ Moreover, disruption of the circadian clock in a mouse β -amyloidosis model of Alzheimer's disease leads to accelerated amyloid plaque deposition.⁷⁰ Circadian regulation in protein quality control systems, such as autophagy, might contribute to the circadian influence

on protein aggregation in general.^{74,96} Bulk removal of aggregated proteins from the brain by the glymphatic system, a glia-mediated perivascular fluid flow, has been associated with longer durations of sleep, but its relation to the circadian system and the role of glial clocks in the process are still unclear.⁷¹ Animal studies demonstrating the regulatory role of the circadian clock in blood-brain barrier permeability may also have implications for clearance of protein aggregates from the brain.^{75,97} Finally, several mouse studies reveal a complex, bidirectional relationship between the circadian clock and oxidative stress, a key pathogenic process in neurodegeneration.^{72,98–101} Thus, a number of identified mechanisms, as well as those which are not yet known, could provide a greater understanding of the potential link between the circadian clock and neurodegenerative diseases.

Circadian Interventions

If circadian dysfunction is a risk factor contributing to the development of neurodegenerative diseases, an appealing and testable hypothesis is that restoring regular circadian rhythms might prevent or halt the progress of these diseases as well as mitigate their related symptoms. Several studies have tested this hypothesis using timed light or melatonin treatments, or both, and have yielded inconsistent results.¹⁰² For instance, a double-blind, placebo-controlled, randomised trial¹⁰³ of 189 residents of group care facilities in the Netherlands (mean age 85·8 years; 164 [87%] had dementia) examined the effects of daily treatment with whole-day bright light (1000 lux) compared with dim light (300 lux), and daily evening melatonin treatment compared with placebo. This study found that the long-term light treatment (up to 3·5 years) attenuated cognitive decline with ageing by 5% and significantly improved depressive symptoms.¹⁰³ However, another randomised controlled trial¹⁰⁴ of 48 patients (mean age 83·4 years) in two nursing homes in the UK with diagnosed dementia, sleep disruption, and agitated behaviour did not report a similar cognitive benefit of bright light. This discrepancy may be attributed to differences in treatment dose, such as exposure duration and intensity of light, which are especially important for older adults who have reduced circadian system response to light exposure.¹⁰⁵ Further studies are warranted to study the effects of bright light on depressive symptoms in these populations.

In the past 5 years, only two published circadian intervention studies examined patients with Alzheimer's disease and related dementias, or Parkinson's disease.^{106,107} In a multicentre (one in the UK and four in the USA), double-blinded, parallel-group study,¹⁰⁶ 80 patients diagnosed with mild to moderate Alzheimer's disease dementia (mean age 75·3 years; 13 patients had insomnia) were randomised to receive daily treatment of a prolonged-release melatonin formulation for 24 weeks or placebo. In the 60 participants that completed the trial, there was a positive effect of melatonin treatment

on cognitive performance, especially for those with insomnia, compared with placebo. Another study¹⁰⁷ was done in two Parkinson's disease centres in the USA, where 31 patients (mean age 63·2 years) with Parkinson's disease and coexistent excessive daytime sleepiness who received stable dopaminergic therapy underwent a 14-day light intervention with 1-h exposure to bright (10000 lux) or dim (<300 lux) light twice each day. The light intervention improved daily activity rhythms and reduced daytime sleepiness, and the effects were stronger with bright light than with dim light.

The application of circadian interventions in neurodegenerative diseases is a promising but relatively new field. Many questions and concerns remain to be addressed. For example, circadian rhythms can also be entrained or shifted by many other non-photoc time cues or zeitgebers,¹⁰⁸ including food,¹⁰⁹ caffeine consumption,¹¹⁰ and exercise.¹¹¹ These zeitgebers probably affect circadian rhythms through direct influences on the peripheral clocks and their feedback to the central circadian clock.¹¹² How to appropriately implement these time cues in circadian interventions requires a better understanding of the interactions between the central and peripheral clocks. Additionally, the intrinsic properties of the circadian clock can be different between individuals, leading to different chronotypes (ie, evening and morning types) and variation in circadian timings (relative to time of day) of behaviour and physiological functions (including melatonin secretion). As a result, individuals with different chronotypes have different responses even when light exposure and melatonin are scheduled at the same time of day.¹¹³ However, no clinical trials to date have incorporated chronotype into personalised circadian interventions. Furthermore, although circadian control and sleep regulation are tightly coupled, they have different underlying mechanisms. Understanding these specific mechanistic pathways, in addition to distinguishing whether the observed beneficial effects of interventions result from the influences on the circadian clocks or directly on the neural circuitry of sleep homeostasis, might improve strategies for future drug and therapeutic design. Despite the association between circadian rhythm disruption and cognitive impairment, more evidence for the effects of circadian interventions on cognitive decline and the progression of neurodegenerations over a long time (eg, over more than 5 years), especially after the intervention period, is required. Additionally, no circadian intervention study has yet considered neuropathological biomarkers. Using structural MRI or PET scans of the brain to examine longitudinal changes in A β and tau levels in CSF will help clarify the contributions of circadian rhythm disruption to neuropathological and anatomical changes in the brain. Last, previous studies have exclusively focused on the stages of neurodegenerative diseases after the clinical onset of a disease. It will be important to test the benefits of circadian therapies for the prevention of the diseases and related symptoms at preclinical stages.

Conclusions and future directions

People with Alzheimer's disease and related dementias, or Parkinson's disease, frequently experience disruptions in both behavioural and biological markers of circadian rhythm disruption, including disrupted sleep-wake cycles, impaired hormonal and body temperature rhythms, and dysregulation of the autonomic system. Circadian rhythm disruption is associated with neurodegeneration often presents in a much more severe form than that typically observed with age. Unlike healthy older adults who usually have reduced circadian amplitude and advanced circadian phase, patients with Alzheimer's disease and related dementias tend to have high fragmentation and slightly reduced amplitude of circadian rhythms. Findings are mixed regarding phase shift among these patients, and they are likely to have irregular sleep-wake patterns. Patients with Parkinson's disease tend to have reduced circadian amplitude but no change in circadian phases. In general, behavioural circadian rhythm disruption markers, such as sleep timing, daytime sleepiness, and rest-activity rhythms, have been examined more often than biological markers, such as core body temperature and melatonin or cortisol secretion rhythms. Evidence has also suggested that circadian rhythm disruption varies depending on the stage and severity of neurodegenerative diseases, as well as the treatment that patients receive. Large longitudinal clinical studies are needed to examine the change in circadian rhythms associated with the progression of neurodegeneration, including non-Alzheimer's disease dementias, and to separate the potentially interacting effects of disease progression and dopaminergic treatment on circadian rhythms in patients with Parkinson's disease. The integration of non-behavioural circadian biomarkers into these studies would help disentangle circadian rhythm disruption from sleep and behavioural confounding factors (panel 2). Such insights might help identify circadian features that are important for differentiating various types and stages of neurodegenerative diseases, and are important for the management of circadian symptoms in these diseases.

Several epidemiological studies suggested the presence of circadian rhythm disruption at the preclinical stage of Alzheimer's disease and related dementias. Therefore, circadian rhythm disruption might be considered a useful preclinical marker or prodrome for neurodegenerative diseases. Emerging evidence from longitudinal studies has also showed that circadian rhythm disruption precedes the development of these diseases. Additional confirmatory studies with longer follow-up periods are needed to examine the relationship between different circadian markers and subsequent risk of developing neurodegenerative diseases and should consider the use of biomarkers to help understand potential mechanisms. For example, using structural MRI or PET scans of the brain and examining longitudinal changes in

Panel 2: Directions for future research

- Studies of circadian rhythm disruption in neurodegeneration should incorporate the assessment of both biological (eg, core body temperature, melatonin and cortisol rhythms) and behavioural (eg, rest-activity rhythms) markers of circadian rhythm disruption
- Large, longitudinal studies are needed to determine circadian features for different types and severities of Alzheimer's disease and related dementias, and clarify the link between the progression of these conditions and change in circadian rhythm disruptions
- The interaction between Parkinson's disease progression, dopaminergic treatment, and circadian changes should be clarified
- Additional studies with long-term (eg, over 20–30 years) follow-up periods are needed to confirm the effects of circadian rhythm disruption on subsequent cognitive decline and risk of developing Alzheimer's disease and related dementias, or Parkinson's disease
- Underlying mechanisms for the bidirectional relationship between circadian rhythms and neurodegeneration need to be understood to help draw causal inference and inform therapeutic targets
- The use of circadian interventions in patients with neurodegenerative diseases should be further explored, and personalised circadian treatment should be explored, taking the large between-individual differences (ie, differing chronotypes) into consideration
- Randomised controlled trials of individuals at preclinical stages are needed to test the benefits of circadian therapies for the prevention of neurodegenerative diseases

Search strategy and selection criteria

We identified relevant articles in English for this Review by searching PubMed with no language restrictions for articles published between Jan 1, 2013, and Oct 31, 2018, and reference lists from relevant articles. We used the search terms: "dementia", "Alzheimer's disease", "cognitive function", "cognitive decline", "cognition", "Parkinson disease", "neurodegeneration" and "circadian rhythm", "circadian clock", "twenty-four-hour rhythm", "sleep-wake", "melatonin", or "chronotherapy". We included only references published within the past 5 years, except for key or landmark studies in the field. The final reference list was made on the basis of relevance to the theme of this Review.

A β and tau levels in CSF might clarify whether circadian rhythm disruption contributes to Alzheimer's disease pathology or structural change in the brain. Studies of biological mechanisms and intervention trials are required to determine whether circadian rhythm disruption is a cause of neurodegenerative disease.

Finally, personalised multicomponent circadian interventions should be developed and tested for benefits on circadian synchronisation as well as symptom management in these disease. Additionally, large longitudinal clinical trials with long follow-up periods are needed to examine the long-term benefits of these interventions, and especially to determine whether these interventions might help prevent or delay the onset of neurodegenerative diseases among healthy older adults. In this way, circadian rhythm disruption might be a promising therapeutic target for the prevention and management of neurodegenerative diseases.

Contributors

YL and KY conceived the Review and developed the outline of this Review. All authors contributed to the writing and revision of the manuscript.

Declaration of interests

ESM receives personal fees from Eisai Pharmaceuticals and GLG Consulting. FPC receives book royalties from Oxford University Press. KY serves on Data Safety and Monitoring Boards for Takeda, Eli Lilly, and an National Institutes of Health sponsored study and is a member of the Beeson Scholars in Aging Scientific Advisory Board and a Senate member of the German Center for Neurodegenerative Diseases. All other authors declare no competing interests.

Acknowledgments

YL is supported by National Institute on Aging (NIA) 1K99AG056598–01. ESM is supported by NIA R01AG054517 and the Coins for Alzheimer's Research Trust Fund. KH is supported by NIA R01AG048108 and NIA R01AG059867. KY is supported in part by NIA K24AG031155 and NIA R01AG026720. These organisations had no direct input on any aspect of the paper.

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