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REVIEW

Circadian Rhythm Dysfunction in Neurodegenerative Diseases: A Bidirectional Perspective and Therapeutic Potential

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Abstract: Disruption of circadian rhythms is a recognized hallmark of age-related neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Emerging evidence suggests these disruptions are not merely symptoms but potential causal factors that, in some cases, manifest prior to clinical onset. This points to a bidirectional relationship in which neurodegenerative processes and circadian dysfunction mutually exacerbate each other. Core clock genes, including *BMAL1, PER*, and *CRY*, regulate critical processes such as redox balance, mitochondrial function, and neuroinflammation, which are commonly disrupted in neurodegenerative conditions. Although molecular pathways involving altered protein homeostasis, immune dysregulation, and inflammatory processes are proposed, the precise mechanisms linking circadian rhythm disruptions to neurodegeneration remain unclear. This review provides an integrated overview of shared circadian rhythm disruptions observed in major neurodegenerative diseases and evidence on the underlying molecular mechanisms including oxidative stress and clock gene perturbation, and evaluates the temporal dynamics of circadian disruption relative to disease onset and progression. Furthermore, we discuss the translational potential of circadian-oriented interventions and highlight the limitations of current evidence. Understanding these interactions may help identify novel therapeutic strategies for stabilizing circadian rhythm to mitigate disease progression in neurodegenerative diseases.

Keywords: circadian rhythm, neurodegenerative diseases, suprachiasmatic nucleus, Circadian-oriented interventions

Introduction

The development of public healthcare systems has significantly increased global life expectancy. However, this advancement has coincided with the prevalence of neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and other dementias. These disorders, which primarily affect older adults, are characterized by progressive loss of neuronal structure and function, resulting in cognitive, behavioral, and motor impairments. For instance, AD, the most prevalent form of dementia, is characterized by the accumulation of β-amyloid (Aβ) plaques and tau tangles, which disrupt synaptic function and lead to neuronal death.[1] PD is caused by the degeneration of dopaminergic neurons in the substantia nigra and manifests as motor symptoms such as tremors, bradykinesia (slowness of movement), and muscle stiffness, together with non-motor symptoms like sleep disturbances, mood disorders, and cognitive impairment.[2] HD is linked to a mutation in the HTT gene, which results in abnormal repetition of DNA sequences (CAG repeats). This mutation causes neuronal degeneration in the basal ganglia, leading to involuntary movements, cognitive decline, depression, and anxiety.[3]

Circadian rhythms are intrinsic 24-hour cycles that regulate physiological processes such as sleep-wake cycles, hormone release, body temperature, and cognitive function and are regulated by the suprachiasmatic nucleus (SCN) of the brain. The SCN, located anterior to the hypothalamus and dorsal to the optic chiasm, synchronizes peripheral clocks across the body through synaptic and diffusible signals. Light exposure signals are relayed to the SCN via the retinohypothalamic tract and synchronize the internal circadian rhythm with environmental stimuli.[4–6] This coordination

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is critical for the maintenance of local circadian rhythm in peripheral organs such as the lungs, liver, and heart.[7] Circadian rhythms also play a vital role in sustaining cognitive function and overall brain health. Disruptions in these rhythms, caused by irregular sleep patterns or exposure to artificial light at night, are associated with an increased risk of neurodegenerative diseases, mood disorders, and cognitive decline, particularly in aged populations.[5,8]

At the molecular level, the circadian rhythm is regulated by feedback loops involving core clock genes such as *BMAL1, CLOCK, PERIOD* (*PER*), and *CRYPTOCHROME* (*CRY*). BMAL1 and CLOCK heterodimers promote *CRY* and *PER* transcription, but the resulting PER-CRY complexes inhibit BMAL1-CLOCK activity through a feedback loop. Additional regulation occurs at the post-transcriptional level via kinases such as casein kinase 1ε/δ (CK1ε/δ).[9] Furthermore, other clock genes modulate BMAL1 expression: RORα promotes its expression, while REV-ERBα represses it.[10] The rhythmic expression of these clock genes influences various cellular processes, including cell division, metabolism, and oxidative stress[11,12] (Figure 1).

Disruption of circadian rhythms is linked to many health issues, including cancer, metabolic disorders, and mood disorders like depression and bipolar disorder.[13–15] Many studies also have demonstrated the significant role of circadian disruptions in the development of motor and cognitive symptoms in neurodegenerative diseases.[16–18] Mutations in *Per* and *Bmal1* genes have been shown to accelerate aging and tissue degeneration in mice, resulting in disrupted cognitive behaviors and reduced lifespan,[19,20] while circadian disruption in humans is associated with worsened cognitive and behavioral symptoms.

In this review, we summarize findings on the links between circadian rhythm disruptions and neurodegenerative diseases and explore circadian rhythm-oriented therapies such as bright light therapy, timed melatonin supplementation, time-restricted feeding and scheduled physical activity as promising non-pharmacological strategies to support brain health and delay disease progression.

Methodology

A systematic literature search was conducted in PubMed/MEDLINE, Scopus, Embase, and Web of Science covering studies published on neurodegenerative diseases and circadian rhythm disruptions/dysfunctions between January 2000 and September 2025. Search terms included combinations of circadian rhythm, sleep-wake cycle, clock genes, neurodegeneration, Alzheimer's disease, Parkinson's disease, Huntington's disease, and therapeutics. Inclusion criteria were studies that examined circadian dysfunction in neurodegenerative diseases, described bidirectional mechanisms with disease pathology, or evaluated therapeutic strategies targeting circadian rhythms. Only peer-reviewed, English-language articles were included. Exclusion criteria were studies limited to non-neurodegenerative disorders, conference abstracts, editorials, commentaries, case reports without mechanistic or therapeutic relevance, doctoral dissertations without primary data, and papers lacking direct relevance to circadian biology. The literature selection process involved initial title and abstract screening, followed by full-text evaluation of potentially relevant papers. Disagreements between reviewers during the screening process were resolved through discussion and consensus.

Disrupted Circadian Rhythm in Neurodegenerative Diseases

Circadian rhythms regulate numerous physiological processes, including sleep-wake cycles, core body temperature (CBT), hormone secretion, and blood pressure, oscillating about a 24 hour period. These rhythms often become disrupted in neurodegenerative diseases, significantly impacting patient behavior and physiology.[21] Such circadian disruptions are particularly prevalent in older people, coinciding with the increased incidence of age-related neurodegenerative disorders.[22] While these associations are well documented, many of the underlying studies are based on relatively small cohorts and observational designs, limiting generalizability. In addition, contradictory findings have been reported across patient populations and disease stages, suggesting that circadian disruption may not manifest uniformly in all neurodegenerative conditions.

In mammals, systemic circadian rhythms are regulated by the suprachiasmatic nucleus (SCN), the master clock located in the anterior hypothalamus. At the cellular level, circadian rhythms are generated by transcriptional-translational feedback loops involving core clock genes such as *BMAL1, CLOCK, PERIOD* (*PER*), and *CRYPTOCHROME* (*CRY*). These genes regulate the rhythmic expression of other genes in a tissue-specific manner,

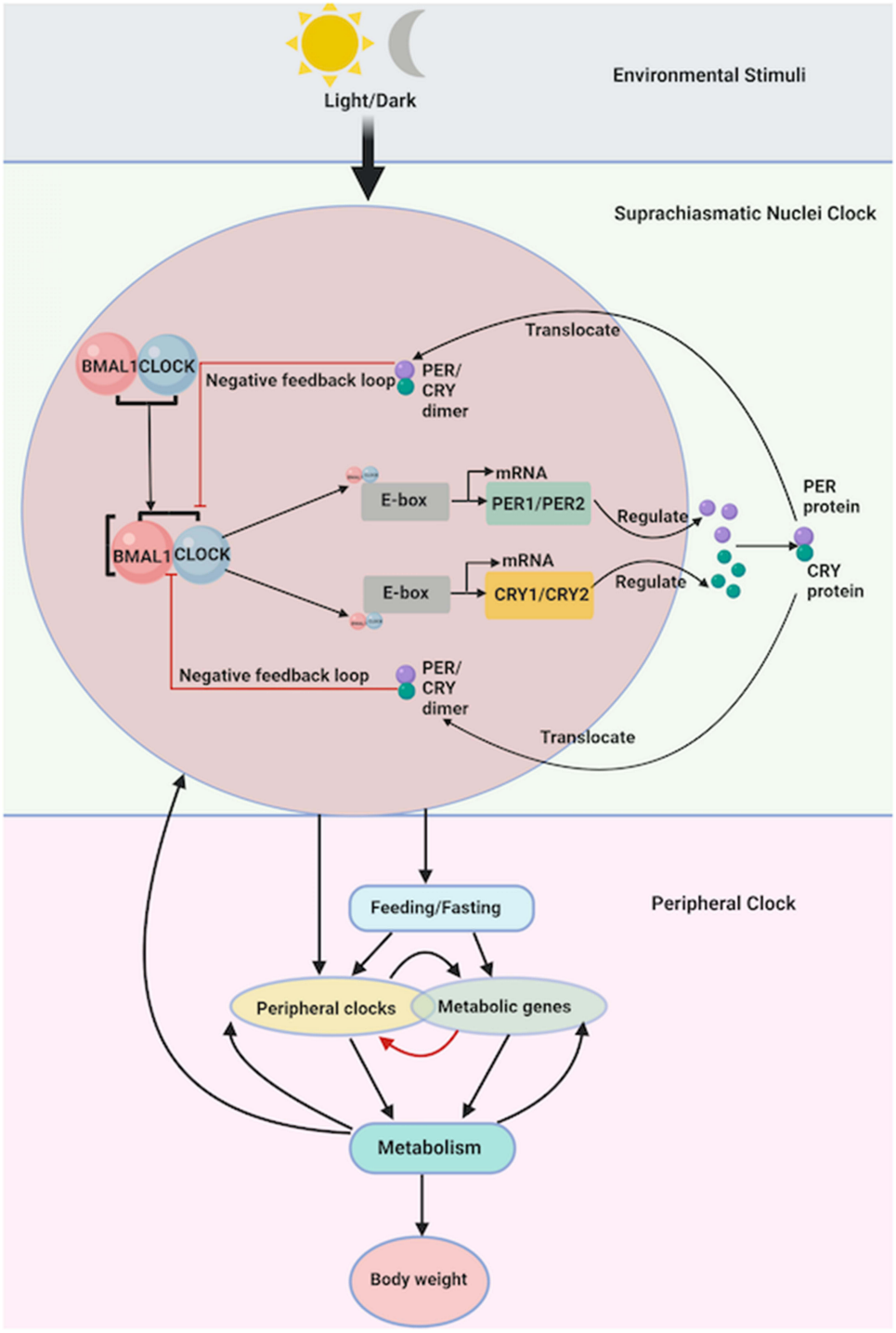

Figure 1 Molecular and systemic regulation of the circadian clock and its impact on metabolism and neurodegenerative disease. The circadian rhythm is orchestrated by the central pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus, which receives environmental light/dark cues via the retinohypothalamic tract. These cues regulate the expression of core clock genes including *BMAL1, CLOCK, PER*, and *CRY* within the SCN. BMAL1 and CLOCK form heterodimers that bind to E-box elements to initiate the transcription of *PER* and *CRY* genes. The translated PER and CRY proteins form dimers that translocate back into the nucleus and inhibit BMAL1/CLOCK activity, forming a transcription-translation feedback loop. This molecular clock drives rhythmic output signals that synchronize peripheral clocks located in organs such as the liver, lungs, and heart. Peripheral clocks are influenced by feeding/fasting cycles and regulate metabolic gene expression, impacting systemic metabolism and ultimately affecting body weight. Created in BioRender. Namgyal, (D) (2025). https://BioRender.com/zjhagzh.

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influencing processes like metabolism, immune function, and cellular repair.[23,24] Neurodegenerative diseases often disrupt this precise regulation, but detailed insights into specific alterations of clock gene and protein expression in these conditions remain incomplete. For example, while some studies in Alzheimer's disease (AD) report loss of rhythmic BMAL1 expression,[25,26] others find preserved but phase-shifted rhythms,[27,28] reflecting heterogeneity and methodological variation across studies.

Given the overlapping features of circadian disruptions and neurodegenerative symptoms, it is essential to distinguish between circadian rhythm disruptions directly contributing to disease progression and those that are secondary outcomes. Failure to separate correlation (circadian disruption occurring alongside disease) from causation (circadian dysfunction actively driving disease pathology) has been a major limitation of much of the existing research. Current evidence remains predominantly correlational, and only a handful of longitudinal or interventional studies support causality. Such differentiation can aid in identifying biomarkers for disease diagnosis and designing therapeutic strategies. Common circadian disruptions in neurodegenerative diseases include severe disruptions in sleep-wake cycles, CBT regulation, hormone secretion, mood, and behavior, as well as aberrations in core clock gene expression.

Dysregulated Sleep-Wake Cycles in Neurodegenerative Diseases

Humans spend approximately one-third of their lives sleeping, yet the importance of sleep for mental and physical health has only recently been widely recognized.[29–31] Sleep can be distinguished from the awake state using electroencephalograms (EEGs), which measure brain activity. Based on these measurements, sleep is categorized into two distinct states: rapid eye movement (REM) sleep and non-rapid eye movement (NREM) sleep. In general, sleep cycles alternate between NREM and REM every 90–120 minutes, with NREM dominating earlier in the night and REM sleep becoming more prominent in the early morning.[29,30]

Disturbances in sleep-wake cycles are prominent circadian symptoms of neurodegenerative diseases.[32,33] These conditions are often associated with fragmented nighttime sleep and increased daytime sleepiness.[27,33–35] As neurodegenerative diseases progress, disruptions in sleep-wake cycles and activity levels between day and night become more pronounced. Sleep disorders in AD, for example, frequently emerge in the early stages of the disease and can be early predictors of β-amyloid (Aβ) plaque formation.[36–39] However, most of these findings are derived from relatively small or cross-sectional studies, and others report inconsistent results,[40,41] which makes it difficult to determine whether disrupted sleep is a causal factor of amyloid pathology or simply an early symptom. In PD, REM sleep behavior disorder and restless leg syndrome are highly prevalent.[32,42] Although these disorders are strongly correlated with underlying α-synuclein pathology, the evidence for a direct causal role remains limited. Many studies lack adequate control for confounding factors such as dopaminergic medication use, disease stage, or comorbid psychiatric conditions,[43–46] which complicates interpretation. Moreover, not all patients with REM sleep behavior disorder (RBD) develop PD,[43,47] underscoring that correlation does not necessarily equal causation.

Sleep deprivation (SD) and sleep restriction (SR) have been widely studied in animal models, especially in rodents, and show detrimental effects on cognitive function. SD and SR impair various attentional processes, resulting in increased lapses during vigilance tests and slower reaction time.[48,49] In modern society, SR and SD are increasingly common due to the prevalence of night shift work and the impact of artificial light exposure at night on sleep quality. Chronic SR, even at moderate levels, can mimic the cognitive and physiological effects of several days of acute SD, leading to significant consequences.[50,51]

Sleep is also crucial for memory encoding and consolidation.[52] SD and SR, therefore, have profound adverse effects on learning and memory, particularly on emotional memories.[53] Chronic REM sleep deprivation aggravates key pathological processes in neurodegeneration, such as the accumulation of Aβ plaques and tau protein tangles in the brain, which are critical in the pathogenesis of AD.[54,55] These findings underscore the role of sleep disturbances as both contributors to and accelerators of neurodegenerative disease progression.[56,57] Nevertheless, some clinical studies have failed to detect a consistent link between REM sleep disruption and tau accumulation,[58,59] highlighting the importance of distinguishing correlation from causation.

Imbalanced Cortisol and Melatonin Secretion Rhythm in Neurodegenerative Diseases

The sympathetic nervous system (SNS) plays a crucial role in regulating melatonin secretion, a hormone associated with circadian rhythm and widely used to treat sleep disturbances.

Rhythmic melatonin secretion by the pineal gland is regulated by the suprachiasmatic nucleus (SCN) of the anterior hypothalamus. During nighttime, norepinephrine (NE) is released from the postganglionic sympathetic nerve terminals, stimulates arylalkylamine N-acetyltransferase (AANAT), leading to melatonin synthesis.[60,61] Consequently, melatonin levels peak at night and decline in the early morning.[60,62,63] Melatonin shifts endogenous circadian rhythms via a phase-response curve opposite to that of light exposure, promoting sleep, sedation, and the reduction of core body temperature (CBT).[64–67]

Cortisol is a glucocorticoid hormone synthesized by the adrenal glands and essential for maintaining homeostasis and responding to arousal events such as exercise, waking, and acute stress.[68–70] The hypothalamic-pituitary-adrenal (HPA) axis regulates rhythmic cortisol secretion, which typically peaks in the early morning and declines throughout the day.[70] Light exposure profoundly influences melatonin and cortisol levels (Figure 2A).

Internal circadian disruption is more common in elderly individuals due to progressive degeneration of molecular circadian mechanisms with age.[71,72] Among the various circadian rhythms, melatonin and cortisol secretion rhythms exhibit significant changes in older people. Melatonin secretion decreases with age, and its peak shifts later into the night.[73,74] Conversely, basal cortisol release increases, with the maximum secretion occurring earlier at night, contributing to advanced sleep-wake phases often seen in elderly people.[75] Neurodegenerative diseases commonly feature disrupted melatonin secretion rhythms, with a reduced nighttime peak compared to age-matched healthy controls.[76–81] In dementia patients, decreased nighttime melatonin levels correlate with increased daytime sleepiness, too.[77,81,82] However, some small-scale clinical cohorts report preserved melatonin secretion in early Alzheimer's disease (AD) stages,[83,84] suggesting that hormonal disruption may be disease-stage dependent. In addition, variations in assay methods and limited sample sizes across studies may account for inconsistent findings. Alterations in cortisol rhythms vary among neurodegenerative diseases.

In healthy people, cortisol secretion peaks early in the morning and gradually declines toward the evening. While minimal rhythmic changes are observed in AD patients, alterations include increased total daily cortisol levels and altered secretion timing in Huntington's disease (HD) and Parkinson's disease (PD) patients[33,82,85–87] (Figure 2B). Although some AD cohorts report no significant differences compared to controls,[88–90] others find elevated baseline cortisol.[91–93] This variability underscores methodological limitations, including heterogeneous patient populations, differing disease stages, and confounding medication effects.

Overall, most evidence linking melatonin and cortisol disruption with neurodegeneration remains correlational. While reduced melatonin is consistently associated with poor sleep quality and cognitive function, causation has not been definitively established.[94–97] Similarly, altered cortisol patterns may reflect downstream stress responses rather than direct circadian dysfunction. Larger, longitudinal studies are needed to clarify whether these hormonal changes act as drivers, biomarkers, or consequences of neurodegeneration.

Core Body Temperature Rhythm Fluctuation in Neurodegenerative Diseases

Core body temperature (CBT) represents the physiological state at which internal organs and their functions operate optimally, playing a critical role in the body's thermoregulation. Human CBT varies throughout the day, increasing during waking hours and peaking in the evening before declining at night to reach its lowest level in the early morning.[98] These fluctuations are closely related to autonomic nervous system (ANS) activity and are regulated by circadian rhythms governing thermal production and cellular metabolic loss.[99,100] During nighttime, CBT decreases as metabolic activity decreases, with melatonin playing a pivotal role in modulating CBT through the hypothalamic thermoregulatory center.[101]

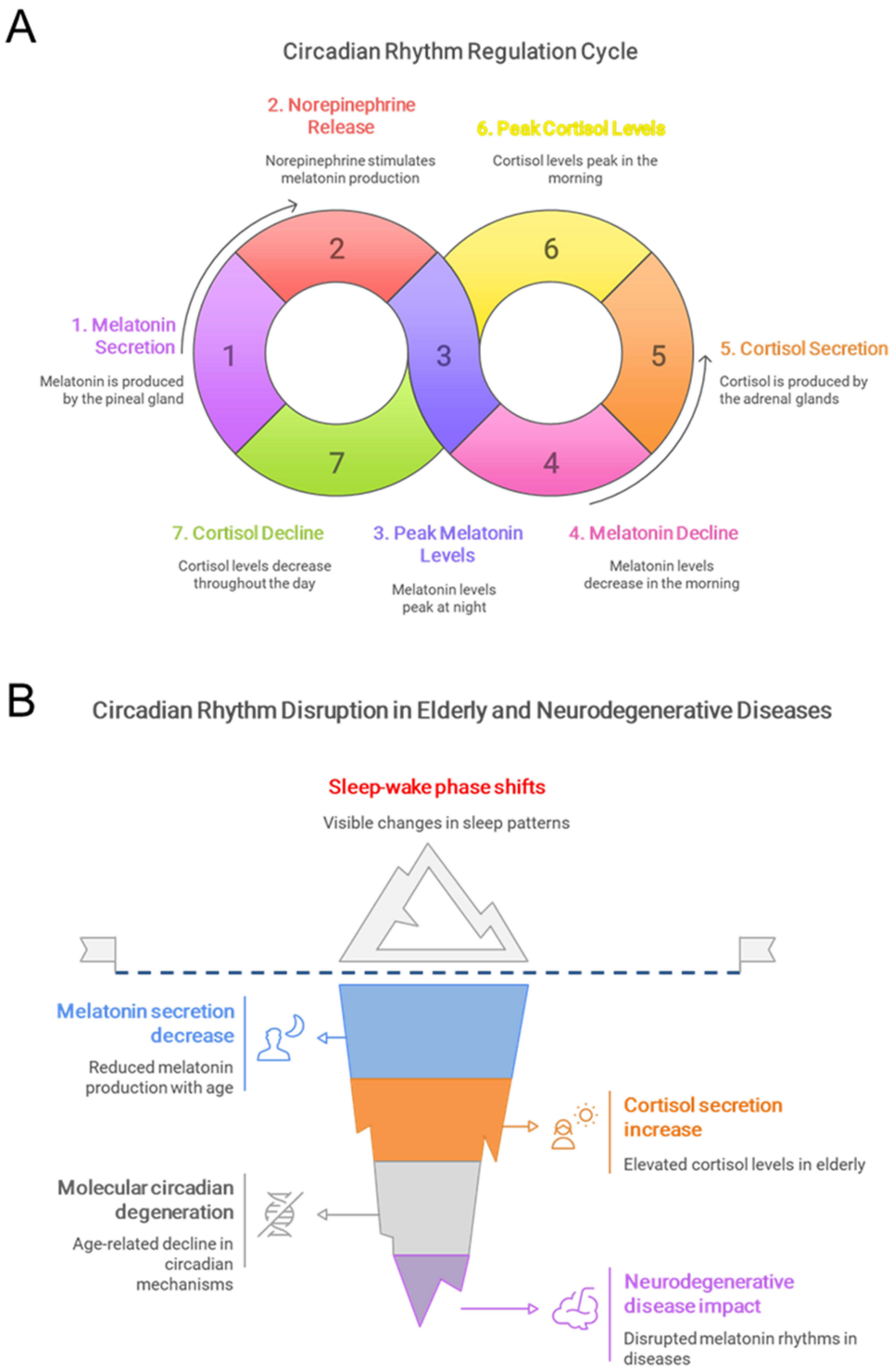

Figure 2 Age- and disease-related alterations in circadian hormone rhythms. (**A**) Normal circadian rhythm of melatonin and cortisol secretion. In healthy individuals, melatonin levels rise at night, peaking during the dark phase under the control of the suprachiasmatic nucleus (SCN) and sympathetic nervous system via norepinephrine stimulation of the pineal gland. In contrast, cortisol levels—regulated by the hypothalamic-pituitary-adrenal (HPA) axis—peak in the early morning and gradually decline throughout the day. These opposing rhythms help maintain physiological homeostasis and sleep-wake regulation. (**B**) Disruption of circadian rhythms in aging and neurodegenerative diseases. With aging, melatonin secretion decreases and shifts to later hours, while basal cortisol levels increase and peak earlier, contributing to sleep-wake phase advances. In neurodegenerative diseases, melatonin rhythms are further dampened, and cortisol secretion becomes dysregulated. These changes exacerbate sleep disturbances and reflect broader circadian rhythm degeneration in these conditions.

CBT within the brain is homeostatically regulated and buffered against environmental heat fluxes by the skull, but it remains influenced by external conditions. This regulation is mediated through systematically organized neuronal mechanisms.[102] In addition, projections from the rostral suprachiasmatic nucleus (SCN) circadian pacemaker to the preoptic area facilitate the modulation of CBT circadian rhythms.[103] The SCN coordinates the daily light-dark cycle, influencing CBT rhythms.[104] Light stimuli entering the retina relay information to the SCN, which transforms it into neuronal pulses to regulate CBT. These daily CBT fluctuations help synchronize cell metabolism and determine organ activity states.[105]

Many studies have shown the role of CBT in regulating three primary mechanisms of cellular damage: oxidative stress,[106] oxygen demand overload,[107] and inflammation.[108] Oxidative stress is a leading cause of neurodegeneration and cellular injury.[109] Notably, reduced CBT has been linked to anti-aging effects and extended lifespan, as demonstrated in caloric restricted rodent models.[110] Lowering CBT may have protective effects against neurodegeneration.[110] However, most of these findings stem from animal studies, often with small sample sizes and tightly controlled laboratory conditions. Whether similar protective effects apply to human populations remains unclear, and caution must be exercised when extrapolating these results.

In patients with Alzheimer's disease (AD), a significant delay in peak CBT and reduced CBT amplitude are observed, distinguishing them from healthy age-matched controls.[111,112] Parkinson's disease (PD) patients also show reduced CBT amplitude, though the peak timing remains unaffected.[113,114] Similarly, significant reductions in CBT amplitude are shown in Huntington's disease (HD) rodent models compared to controls.[115,116] However, it remains uncertain whether CBT alterations directly drive neurodegenerative processes or are secondary consequences of neuronal loss and circadian disruption. At present, evidence linking CBT fluctuations to neurodegeneration is predominantly correlational, and interventional studies directly testing whether CBT manipulation alters disease progression are lacking.

Dysregulation of Mood and Behavioral Rhythm in Neurodegenerative Diseases

From a psychological perspective, mood can be defined as an emotional state with a positive or negative valence. Mood disorders are characterized by significant fluctuations in an individual's mood, which can adversely impact daily life activities. These disorders are primarily classified into three categories: major depressive disorder, manic disorder, and bipolar disorder.[117,118] Major depressive disorder is marked by a persistently depressed mood, manic disorder by an elevated mood, and bipolar disorder by cycles of both depressive and manic states.

Alterations in circadian rhythmicity are consistently observed in mood disorders. Patients with major depressive disorder and bipolar disorder exhibit significant alterations in core body temperature (CBT), behavioral activity, and hormone secretion rhythms.[118] Environmental factors such as jet lag, shift work, and seasonal changes in day length can contribute to mood disturbances.[119,120] Many core clock genes are implicated in mood disorders. Treatments targeting these disorders, including social rhythm therapy, light/dark exposure therapy, and advanced sleep phase therapy, have shown effectiveness in managing symptoms.[121,122] Consequently, addressing circadian disruptions may represent a crucial therapeutic approach for mood disorders.[123,124] However, much of the available evidence comes from small or heterogeneous patient cohorts, and contradictory results have been reported regarding whether circadian rhythm interventions directly improve mood symptoms or act indirectly by stabilizing sleep.[125,126] Furthermore, causal relationships remain unclear, as mood instability itself may disrupt circadian rhythms.[118,127]

As neurodegenerative diseases progress, significant mood changes and heightened emotional volatility often emerge. This phenomenon, referred to as "sundown syndrome", is characterized by increased levels of agitation, aggression, and emotional instability, peaking in the late afternoon or early evening.[128,129] Sundown syndrome is not yet formally recognized as a clinical mood disorder due to uncertainties about which behavioral features qualify and whether these disturbances occur consistently at specific times of day.[130,131] Nonetheless, predictable daily patterns of behavioral and emotional disturbances have been reported in elderly people with dementia.[132,133] While the underlying causes of sundown syndrome remain unclear, these emotional disturbances are not solely linked to sleep loss.[134] Further investigation is required to elucidate the factors contributing to this phenomenon and to differentiate it from conventional mood

disorders. Some studies attribute sundown syndrome primarily to circadian disruption,[129,134,135] whereas others suggest environmental stressors, caregiver fatigue, or disease severity play larger roles.[129,136,137] These contradictions emphasize the multifactorial nature of mood and behavioral dysregulation in dementia. Importantly, it remains unresolved whether circadian dysfunction causally drives sundowning, or whether both phenomena stem from advancing neurodegenerative pathology.

Molecular Mechanisms Linking Circadian Rhythms to Neurodegenerative Disease Progression

Disturbances in circadian rhythm are widely recognized in aging and across neurodegenerative disorders. However, the mechanisms linking these disturbances to disease progression remain incompletely understood. In *Drosophila*, the antioxidant glutathione exhibits circadian-like oscillations regulated by the *Period* (*Per*) gene. Loss of Per aggravates oxidative stress-induced damage, accelerates neurodegeneration, and shortens lifespan.[138,139] Similarly, age-related reductions in *Cryptochrome* (*Cry*) gene expression, which modulates the light response, have been observed in *Drosophila*,[140] suggesting that core clock genes like *Per* and *Cry* influence age-related neurodegenerative processes.[21] Although these animal studies provide mechanistic insight, their applicability to human disease remains limited due to species-specific differences in circadian regulation. Larger comparative and translational studies are required to validate these mechanisms (Table 1).

Table 1 Molecular Mechanisms Linking Circadian Disruption to Neurodegeneration

Molecular Mechanism	Species / Model	Pathological Consequences	Evidence Quality & Notes	Reference(s)
Loss of *Per* gene	Drosophila	Accelerated neurodegeneration, reduced lifespan	Strong mechanistic evidence in flies, but human translation uncertain	[138,139]
Age-related Cry expression decline	Drosophila	Increased light sensitivity, circadian impairment	Robust in animal models, limited direct human evidence	[140]
Altered light/dark cycle	Mammalian models (Rodents)	Impaired hippocampal neurogenesis and cognition	Experimental, small sample studies; correlation, not causation	[141,142]
Disrupted BMAL1, PER1, CRY1 rhythms	Human (AD)	Desynchronized circadian control in tissues	Human postmortem and peripheral tissue; results heterogeneous across cohorts	[28,143]
Reduced BMAL1/PER2	Human (PD, HD), rodent models	Reduced dopamine, motor and cognitive decline	Correlational; some studies show preservation of rhythms; stage dependent	[79,144,145]
Clock gene dysregulation	Dementia patients	Fragmented sleep wake cycles, memory issues	Clinical evidence, often small samples; confounding comorbidities common	[146,147]
SCN neuron loss and MT1 receptor reduction	Human postmortem (AD)	Impaired circadian control of peripheral clocks	Limited sample sizes; correlation only; stage specific changes possible	[148,149]
Oxidative stress via Bmal1 and Per loss	Rodent models	Cellular oxidative damage, mitochondrial stress	Strong mechanistic evidence; causality in humans not confirmed	[19,150]
Melatonin deficiency and ROS buildup	Human & rodent	Reduced antioxidant defense, DNA vulnerability	Correlation stronger than causation; contradictory outcomes in clinical trials	[87,151]
Clock gene mediated neuroinflammation	Rodent & Cellular models	Autophagy disruption, β-amyloid/α-synuclein buildup	Mechanistic support in preclinical models; human validation lacking	[152,153]

In mammalian models, environmental perturbations such as altered light/dark cycles impair hippocampal neurogenesis and cognitive behaviors.[141,142] Despite these insights, the precise pathways through which circadian dysfunction drives neurodegeneration remain to be elucidated.[21,87]

Clock gene abnormalities have been documented in patients with neurodegenerative diseases. For instance, in Alzheimer's disease (AD), BMAL1 expression remains rhythmic in both brain and peripheral tissues but exhibits altered phase relationships.[27,28] In the pineal gland of AD patients, the rhythmic expression of BMAL1, PER1, and CRY1 is absent.[143] Peripheral BMAL1 transcript levels are significantly reduced,[79,144] and Per2 expression is disrupted in brain areas such as the striatum, correlating with dopamine depletion[145,154] in Parkinson's disease (PD). Likewise, Huntington's disease (HD) mouse models show disturbed Per2 expression across both the central and peripheral nervous systems.[34,155] However, these findings are not entirely consistent; some studies report preserved or only mildly altered rhythmicity,[156–158] suggesting that clock gene disruption may be stage-dependent or influenced by methodological variability such as tissue source, detection methods, and cohort characteristics.

Patients with dementia and neurodegenerative diseases often display excessive daytime sleepiness, fragmented activity patterns, and sleep behavior disorders.[146,147,159–164] Clock genes such as *BMAL1* and *PER1* directly influence neurodegenerative processes, and their altered expression increases PD risk.[165] Presenilin-2, which exhibits circadian rhythmicity, regulates intracellular β-amyloid levels, and disruptions in its expression are linked to AD pathology.[166–168] Yet, much of this evidence remains correlational, and it is unclear whether gene disruptions are causal in driving pathology or represent downstream consequences of neurodegenerative processes.

Postmortem studies show loss of suprachiasmatic nucleus (SCN) neurons and reduced MT1 melatonin receptor expression in AD brains.[148,149,169,170] In animal models, SCN dysfunction corresponds with reduced neuronal firing and impaired circadian control.[115,171,172] As the SCN orchestrates circadian rhythms throughout the body, its degeneration may exacerbate neurodegenerative progression via downstream effects on peripheral oscillators.[87,173] Nevertheless, postmortem studies are limited by small sample sizes and variability in disease staging, which restricts definitive conclusions about causality.

Oxidative stress—a central mechanism in neurodegeneration—is tightly coupled to circadian regulation. Core clock genes modulate intracellular levels of reactive oxygen species (ROS). For instance, Bmal1 controls antioxidant responses by transcriptional regulation of genes containing antioxidant response elements.[19,152,153] Mouse models lacking Bmal1 or Per exhibit heightened oxidative damage and reduced resistance to ROS-induced stress.[19,150] Melatonin, a circadian output with potent antioxidant properties, also plays a protective role by reducing free radicals and supporting mitochondrial integrity[151] (Table 1). However, while animal and cellular studies strongly support this role, clinical evidence in patients remains sparse and sometimes contradictory, with trials on antioxidant benefits showing inconsistent outcomes.

Ultimately, clock gene disruption accelerates neurodegenerative pathology through interconnected pathways involving mitochondrial dysfunction, impaired autophagy, and neuroinflammation. Clock gene dysregulation disrupts redox homeostasis, leading to oxidative damage and pathological accumulation of misfolded proteins such as β-amyloid and α-synuclein.[152,164] Neuroinflammatory processes, mediated by PARP1 hyperactivity and microglial activation, further exacerbate damage.[138,153] Melatonin deficiency worsens this cycle by compromising antioxidant gene regulation and enhancing DNA vulnerability.[87,151] These processes form a self-reinforcing feedback loop in which neurodegeneration further disrupts circadian rhythm, accelerating disease progression. While this bidirectional model is compelling, it remains largely theoretical, and empirical evidence to confirm causation in humans is limited. Novel mechanistic frameworks and integrative longitudinal studies are necessary to validate these pathways.

Circadian-Oriented Interventions in Neurodegenerative Diseases

Circadian-oriented interventions offer promising, non-invasive strategies for alleviating symptoms of neurodegenerative diseases. Approaches like bright light therapy, timed melatonin supplementation, time-restricted feeding, and scheduled physical activity have shown therapeutic potential[87,155,174,175] (Figure 3 and Table 2).

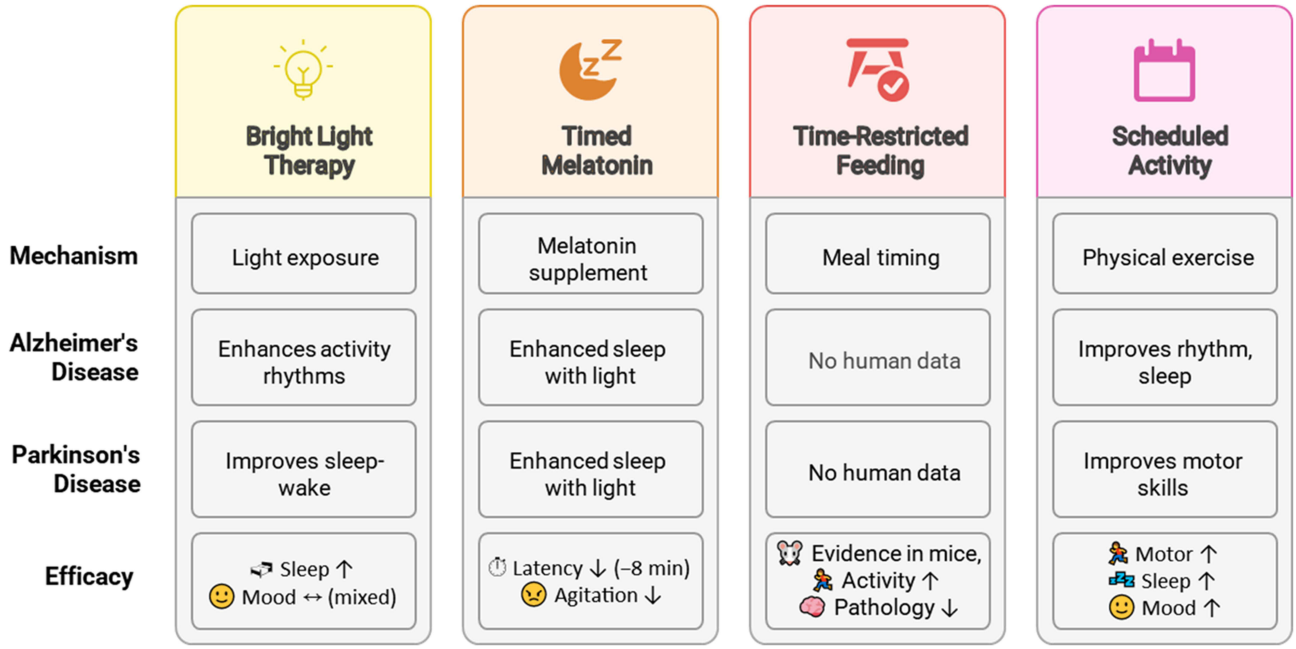

Figure 3 Circadian-based interventions for neurodegenerative diseases. This illustration summarizes four non-invasive strategies to improve circadian rhythm and alleviate symptoms in neurodegenerative diseases. Bright light therapy (BLT) improves daily activity rhythms in Alzheimer's disease (AD) and stabilizes sleep-wake cycles in Parkinson's disease (PD), with modest gains in cognition, mood, and agitation reduction, though results remain heterogeneous. Timed melatonin supplementation reduces sleep latency (−8 minutes), improves sleep efficiency, and alleviates sundowning symptoms, particularly when combined with BLT, but findings remain inconsistent across trials. Time-restricted feeding (TRF) shows benefits in Huntington's disease (HD) mouse models by improving locomotor activity and clock gene expression yet lack human data. Scheduled physical activity functions as a non-photic zeitgeber, improving circadian amplitude, sleep quality, mood and motor performance in both animal models and PD patients. Each intervention's effectiveness varies, and further research is needed to standardize protocols, validate long-term outcomes and clarify causal mechanisms.

Bright Light Therapy

Bright light therapy is a commonly used circadian intervention for neurodegenerative diseases. Timed exposure to bright light has been shown to improve circadian rhythm regulation in patients.[175] In AD patients, daily bright light therapy enhances the consolidation of daily activity rhythms,[183,184] while in PD patients, it improves daily sleep-wake cycles.[185] However, many studies are limited by small sample sizes, short follow-up periods, and variability in light intensity, duration, and timing.[175,186,187] Some trials report significant improvements in sleep consolidation and mood, while others find no clear benefit, reflecting contradictory outcomes. Standardizing variables such as light intensity and timing could help establish the effectiveness of bright light therapy for neurodegenerative diseases.

Table 2 Evidence Summary of Circadian-Oriented Interventions in Neurodegenerative Diseases

Intervention	Disease/ Population	Study Design	Sample Size (n)	Effect (MD/SMD, 95% CI)	Clinical Significance	Reference(s)
Bright Light Therapy (BLT)	Dementia (primarily AD; nursing home residents)	RCT, factorial (light ± melatonin)	189	MMSE: MD +0.9 (95% CI, 0.04–1.71); Cornell Depression: MD −1.5 (95% CI, −2.70 to −0.24); ADL decline: MD −1.8/year (95% CI, −2.92 to −0.61); Sleep efficiency (with melatonin): +3.5% (95% CI, 0.8–6.1)	Small but significant improvements in cognition, mood, and daily function; modest sleep benefit	[176]

(*Continued*)

Table 2 (Continued).

Intervention	Disease/ Population	Study Design	Sample Size (n)	Effect (MD/SMD, 95% CI)	Clinical Significance	Reference(s)
BLT (Metaanalysis)	Dementia (mixed, mostly AD)	Meta-analysis of 15 RCTs	~598	Sleep efficiency: MD −2.42 (95% CI, −3.37 to −1.48); Interdaily stability: MD −0.04 (95% CI, −0.05 to −0.03); Intradaily variability: MD −0.07 (95% CI, −0.10 to −0.05); Cornell Depression: MD −2.55 (95% CI, −2.98 to −2.12); CMAI: MD −3.97 (95% CI, −5.09 to −2.84); NPI: MD −3.07 (95% CI, −4.14 to −2.00); MMSE: NS (MD 0.44; 95% CI, −0.71 to 1.59)	Improves sleep rhythm and behavioral symptoms; inconsistent cognitive effects	[177]
Melatonin Supplementat -ion (Metaanalysis)	Dementia/ AD with sleep disturbance	Meta-analysis of RCTs	>200	Sleep efficiency: SMD 0.41 (95% CI, 0.08–0.74); Sleep latency: MD −8.3 min (95% CI, −12.6 to −4.0); Sundowning/agitation (CMAI): SMD −0.34 (95% CI, −0.59 to −0.09)	Modest benefits on sleep initiation and agitation; inconsistent cognitive effects	[178]
Time-Restricted Feeding (TRF)	HD and AD mouse models	Preclinical TRF vs ad libitum feeding	6–12 mice/ group	Locomotor activity amplitude ↑ ~30–40%; Core body temperature ↑ 0.3°C; Pathology markers (Aβ, huntingtin aggregates) ↓ 20–30% (no CI reported)	Robust preclinical benefits; no human trial data	[179,180]
Scheduled Physical Activity	PD patients	RCT (structured exercise, 16 weeks)	45	ESS: MD −2.82 (p<0.01); Sleep quality (PSQI): SMD −0.40 (95% CI, −0.72 to −0.08); UPDRS motor: SMD −0.35 (95% CI, −0.68 to −0.02)	Structured exercise improves subjective sleep and motor symptoms; objective sleep results inconsistent	[181]
BLT (Metaanalysis)	PD patients (mixed trials)	Meta-analysis of 5 RCTs	173	Depression: SMD 0.34 (95% CI, 0.06–0.61); Insomnia: SMD 1.15 (95% CI, 0.71–1.60)	Significant effect on mood and sleep, moderate effect size	[182]

Abbreviations: AD, Alzheimer's disease; ADL, Activities of Daily Living; BLT, Bright Light Therapy; CBT, Core Body Temperature; CMAI, Cohen-Mansfield Agitation Inventory; ESS, Epworth Sleepiness Scale; HD, Huntington's disease; MD, Mean Difference; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory; NS, Not Significant; PD, Parkinson's disease; PSQI, Pittsburgh Sleep Quality Index; RCT, Randomized Controlled Trial; REM, Rapid Eye Movement; SMD, Standardized Mean Difference; TRF, Time-Restricted Feeding; UPDRS, Unified Parkinson's Disease Rating Scale.

Timed Melatonin Supplementation

Melatonin supplementation is another circadian therapeutic approach. Daily administration of melatonin improves sleep quality, reduces latency, and alleviates behavioral impairments in patients with sundown syndrome.[174,176] Combining melatonin supplementation with bright light therapy shows even better results, significantly enhancing sleep quality and total sleep time.[176,188–190] Nonetheless, outcomes across clinical trials remain inconsistent. Some randomized controlled trials report clear improvements in sleep efficiency and reduced nighttime agitation, while others find minimal or no benefit.[87,191] These discrepancies may stem from differences in dosage, timing of administration, patient age, or disease stage. Current evidence supports melatonin as a potentially useful adjunct but not a definitive standalone therapy.

Time-Restricted Feeding

Time-restricted feeding (TRF) has shown therapeutic promise in mouse models of neurodegenerative diseases. Meal restriction during the light phase improves locomotor activity and core clock gene expression in Huntington's disease (HD) mouse models.[155] Similarly, restricting meals during the dark phase delays the onset of HD phenotypes and increases core body temperature (CBT) in HD mice.[87,192] While these findings are robust in animal models, human clinical validation is lacking. No large-scale trials in neurodegenerative patients have yet confirmed the benefit of TRF, and translation from rodent models to human care should be cautiously approached.

Scheduled Physical Activity

Scheduled physical activity is also recognized as a circadian-aligned intervention with therapeutic potential for neurodegenerative diseases. Exercise serves as a potent non-photic zeitgeber, which is able to reinforce and realign disrupted circadian rhythms. When performed consistently at fixed times of day, physical activity can restore behavioral and physiological cycles in both animal models and humans.[193–196] In rodent models of Alzheimer's disease (AD), long-term physical activity has been shown to improve circadian rhythm amplitude and sleep quality, likely through enhanced hippocampal neurogenesis and synaptic plasticity. Similar effects were found in Parkinson's disease (PD) models, where scheduled treadmill exercise normalized circadian locomotor activity and improved motor performance.[72,196–200]

In clinical studies, PD patients participating in structured exercise programs experienced improved motor performance, better sleep quality, and reduced depressive symptoms.[200,201] These benefits are likely mediated by increased brain-derived neurotrophic factor (BDNF) levels, improved mitochondrial dynamics, and reduced neuroinflammatory cytokine expression-all of which intersect with circadian regulation pathways.[194–196,198,202,203]

While the optimal parameters-such as time of day, intensity, and duration of exercise for maximum circadian benefit-remain to be standardized, the cumulative evidence supports the role of scheduled physical activity as a cost-effective, non-invasive, and accessible therapeutic strategy. Tailoring exercise timing to individual chronotype–people's tendencies to wake up and fall asleep at certain times of the day or disease stage may further enhance its efficacy in supporting circadian health and mitigating neurodegenerative progression.[194,202]

In summary, circadian-oriented interventions show promise but remain preliminary. Current evidence is often correlational, and while short-term improvements in sleep and behavior are reported, definitive proof of disease-modifying effects is lacking. Well-designed, large-scale randomized controlled trials are essential before these therapies can be considered reliable clinical strategies.

Some circadian-oriented interventions were summarized in Table 2. Across randomized controlled trials (RCTs) of bright light therapy and timed melatonin supplementation, benefits on sleep consolidation were small-to-moderate and inconsistent across cognition and motor outcomes. Scheduled physical activity appears to act as a robust non-photic zeitgeber, improving circadian amplitude and motor performance in PD, while evidence for time-restricted feeding (TRF) is strong in animal models but remains preliminary in humans. These findings highlight both the translational potential and the methodological weaknesses of current studies, underscoring the need for adequately powered, standardized RCTs with harmonized outcome measures.

A Bidirectional Model of Circadian–Neurodegeneration

Circadian disruption and neurodegenerative pathology appear to reinforce one another in a reciprocal cycle, as mentioned in the "Molecular Mechanisms" section. Loss of suprachiasmatic nucleus (SCN) neurons, reduced clock gene expression, and peripheral desynchrony can heighten oxidative stress, mitochondrial dysfunction, impaired autophagy, and neuroinflammation, thereby accelerating protein aggregation. Conversely, early pathological changes–including SCN degeneration, and downregulation of melatonin signaling–further weaken circadian amplitude and stability. This reciprocal deterioration contributes to sleep fragmentation, sundowning, REM sleep behavior disorder, and mood disturbances (Figure 4A).

From this conceptual framework, several testable predictions emerge (Figure 4B):

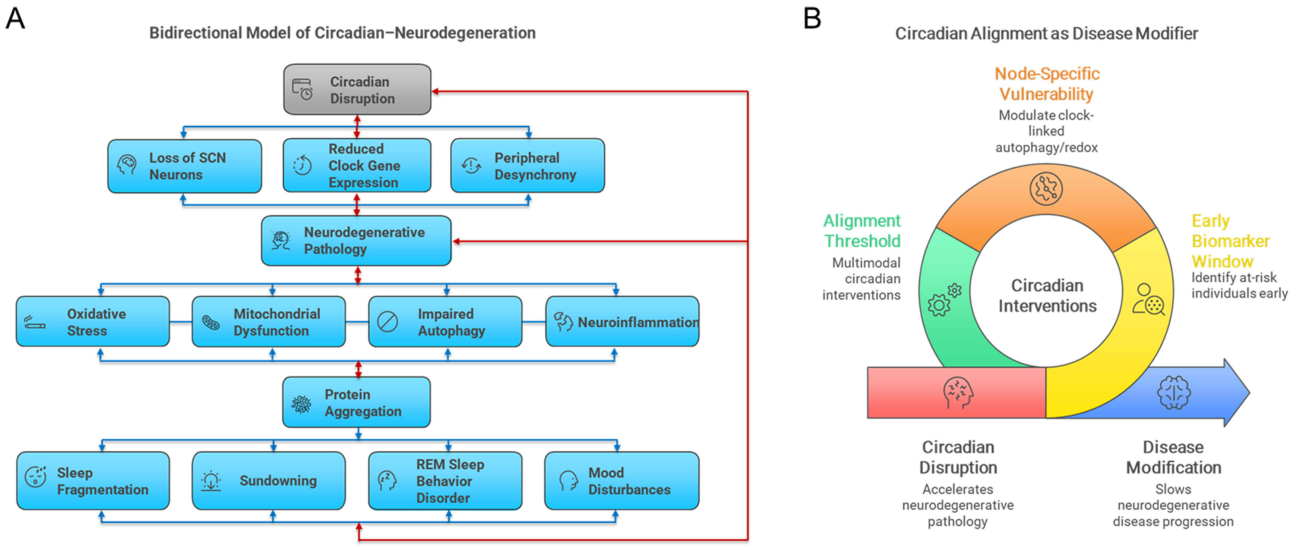

Figure 4 A bidirectional model of circadian–neurodegeneration. (**A**) Circadian disruption accelerates neurodegenerative pathology via suprachiasmatic nucleus (SCN) neuronal loss, weakened clock gene expression, and peripheral desynchrony, which heightens oxidative stress, mitochondrial dysfunction, impaired autophagy, and neuroinflammation, leading to pathological protein aggregation. In turn, early pathological changes–including SCN degeneration and impaired melatonin signaling–further weaken circadian amplitude and stability, creating a reciprocal cycle that contributes to sleep fragmentation, sundowning, REM sleep behavior disorder, and mood disturbances. (**B**) The model also highlights three testable predictions: (1) reduced circadian amplitude as an early biomarker window; (2) node-specific vulnerability through modulation of clock-linked autophagy and redox genes; and (3) an alignment threshold whereby multimodal interventions (light, activity, feeding) may exert supra-additive benefits. Together, panels A and B underscore circadian alignment as both a symptomatic and potentially disease-modifying strategy.

1. Early biomarker window–Reduced circadian amplitude (via actigraphy or melatonin profiles) may precede clinical symptom onset in at-risk individuals.

1. Node-specific vulnerability–Genetic or pharmacologic modulation of clock-linked autophagy and redox pathways could alter protein aggregation burden.

1. Alignment threshold–Multimodal circadian interventions (light, activity, feeding) may produce greater benefits than single approaches.

This model highlights circadian alignment not only as a symptomatic treatment but also as a potential disease-modifying strategy, warranting further validation in larger, standardized clinical studies.

Conclusion and Perspectives

An expanding body of evidence underscores the connection between circadian rhythm disruption and the pathogenesis of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD). Although circadian dysregulation is frequently reported in neurodegenerative diseases, whether it represents a driver or a consequence of pathology is still uncertain. In some cases, circadian disturbances may precede clinical manifestations, implying a contributory role.[21,87] However, current findings are largely associative, and inconsistent outcomes across cohorts underscore the need for cautious interpretation. Recent studies point toward a reciprocal relationship between circadian dysfunction and neurodegeneration, suggesting that each can amplify the other's progression. This bidirectional model, while conceptually strong, requires further mechanistic and clinical validation to establish its predictive and therapeutic value.

From a clinical perspective, circadian-oriented interventions, including bright light therapy, melatonin supplementation, time-restricted feeding, and scheduled physical activity, offer noninvasive therapeutic avenues for improving

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circadian rhythm and potentially delaying symptom progression in neurodegenerative diseases.[163,175,176] However, claims regarding their disease-modifying potential must be moderated. Effect sizes across trials are often small, contradictory results have been reported, and methodological limitations (sample size, follow up duration, intervention protocols) constrain firm conclusions.

Practice Points

1. Circadian-oriented interventions (bright light therapy, melatonin, time-restricted feeding, scheduled exercise) can support management of sleep, mood, and behavioral symptoms in neurodegenerative diseases.
2. Simple clinical tools such as actigraphy, sleep diaries, and core body temperature monitoring can be used to assess circadian health and guide personalized care.
3. Incorporating circadian strategies into routine neurology and sleep practice should emphasize individualized schedules aligned with patient chronotypes.

Future Directions

1. Large, rigorously designed clinical trials are required to define optimal timing, intensity, and multimodal combinations of circadian interventions.
2. Development of circadian biomarkers (eg, melatonin, cortisol, clock gene expression) may enable earlier diagnosis and more precise monitoring of treatment response.
3. Mechanistic studies, including genetic, molecular, and metabolic approaches, are essential to establish causal pathways linking circadian disruption and neurodegeneration.
4. Personalized circadian therapies should consider genetic variation, chronotype, and lifestyle factors to maximize efficacy and disease-modifying potential.

Abbreviations

AD, Alzheimer's disease; PD, Parkinson's disease; HD, Huntington's disease; SCN, Suprachiasmatic nucleus; BMAL1, Brain and muscle ARNT-like protein 1; PER, Period gene; CRY, Cryptochrome; CLOCK, Circadian locomotor output cycles kaput; REM, Rapid eye movement; NREM, Non-rapid eye movement; ROS, Reactive oxygen species; BDNF, Brain-derived neurotrophic factor; Aβ, Amyloid beta.

Data Sharing Statement

Data sharing is not applicable to this article as no data was created or analyzed in this study.

Author Contributions

Dhondup Namgyal: conceptualization, investigation, writing - original draft; Chae-Seok Lim: conceptualization, investigation, writing - review and editing, supervision. All authors have reviewed and approved the final version of the paper; agreed on the journal this paper was submitted; and agree to be responsible for the contents of this paper.

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