Chapter 42

Circadian Dysregulation in Brain Aging and Neuropsychiatric Health

Colleen McClung; Aleksandar Videnovic; Erik Musiek

Chapter Highlights

- Circadian rhythm disruption, often accompanied by sleep disturbance, is a common symptom of normal aging and numerous age-related neurodegenerative diseases, including Parkinson disease and Alzheimer disease. Fragmentation of rhythms in activity is the most common finding in aging and these conditions.
- Psychiatric diseases are also associated with prominent circadian disruption. These vary depending on the disease and can be present in patients of all ages.
- Emerging data suggest disruption of the molecular clock in these conditions and implicate circadian dysfunction as a possible contributor to disease pathogenesis.

INTRODUCTION

The circadian system serves to couple cellular function, physiology, and behavior with the light-dark cycles of the earth. Circadian clocks are found in most plants and animals on the earth and allow organisms to predict and adapt to the daily changes in the environment. The circadian system has been proven vital for organismal health. Disruption of circadian function in animals, altered by either light exposure or genetic manipulation of clock gene, can exacerbate a variety of pathologic conditions. Moreover, circadian dysfunction in humans, as can occur in the setting of shift work, sleep disorders, jet lag, or simply the realities of modern life, has been implicated as a risk factor for numerous chronic diseases, ranging from diabetes to cancer.[1] This chapter discusses the evidence supporting a role for circadian rhythm dysfunction in psychiatric and neurodegenerative diseases, conditions that exert enormous burdens on society and for which there are few effective therapies.

The cellular and molecular basis of the circadian clock has been described in other chapters. Briefly, the master circadian clock resides in the suprachiasmatic nucleus (SCN) of the hypothalamus, which receives direct input from the retina to coordinate its activity to the external light-dark cycle. Cells of the SCN, as well as most cells of the body, express a set of conserved circadian clock proteins, which form a transcription-translational feedback loop that can maintain near-24-hour oscillations in transcription and cellular activity.[2] These clock proteins include the positive transcriptional limb consistent of BMAL1 (also known as ARNTL), CLOCK, and NPAS2, and the negative feedback limb consisting of PERIOD1 to PERIOD3, CRYPTOCHROME 1 and 2, and REV-ERBα/β protein.[2] The SCN serves to synchronize cellular peripheral clocks in organs throughout the body (including the rest of the brain) to maintain optimal function.

Circadian behavioral rhythms are commonly assessed by monitoring patterns in movement throughout the course of many days, using either wheel-running caged rodents or wristwatch actigraphy for humans.[3] Circadian rhythms can be quantified in humans and mice by monitoring other parameters, such as temperature, blood pressure, hormone levels (such as cortisol or melatonin), or even clock gene expression in blood samples or other tissues. Because exposure to light can induce changes in behavior in animals independently of the circadian clock, true circadian studies are carried out under constant lighting conditions, usually dim light. While this is feasible with lab animals, it is very difficult with humans, particularly when assessing circadian rhythms in disease populations. Thus a caveat of much of the data pertaining to circadian function in human aging and neuropsychiatric disease is that they are obtained under normal environmental light-dark conditions. It is also notable that the SCN regulates the timing of sleep, with SCN lesioning or BMAL1 deletion in rodents leading to fragmented sleep with no clear night-day differentiation.[4,5] Thus circadian effects on sleep timing and consolidation are difficult to disentangle from effects related to other aspects of clock dysfunction.

CIRCADIAN DYSFUNCTION IN AGING

Aging is well known to impact the circadian system. Fragmentation of circadian activity rhythms is observed in older humans, usually manifested as increases in both daytime napping and nocturnal awakenings.[6,7] There is also a shift in circadian phase in older people, as they tend to go to sleep and awaken earlier.[8] Studies in human postmortem brains find that there is a general loss of normal molecular rhythms in prefrontal cortical regions with aging; however, there appears to be a gain of rhythmicity in a separate set of genes, which may be compensatory.[9] Studies in aged mice show a pronounced loss of amplitude in neuronal firing, as well as more subtle disorganization and blunting of rhythms in clock gene expression, in the SCN.[10,11] Decreased amplitude in clock gene expression

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rhythms is also observed in peripheral organs from aged mice, including heart and liver, although it is unclear if this is due to impaired signals from the SCN or altered local clock function. Secretion of melatonin, a hormone that is directly controlled by the circadian system and regulates sleep timing, also declines with age, which may impact sleep timing in the elderly.[12-14] Other factors, including poor light exposure, cataracts, physical disability limiting activity, and limited social interaction may also contribute to age-related declines in rhythmic activity. Thus disrupted circadian function occurs with aging and may therefore contribute to age-related diseases.

Circadian Dysfunction in Alzheimer Disease

Alzheimer disease (AD) is the most common cause of dementia in older adults and affects more than 10% of the population above the age of 65. AD is characterized clinically by slowly progressive cognitive impairment, which usually begins as short-term memory loss then progresses to involve other domains. The pathologic hallmarks of AD include extracellular amyloid plaques, which accumulate many years before cognitive symptom onset and contain aggregated forms of amyloid-β peptide (Aβ) as well as neurofibrillary tangles, which are intracellular accumulations of aggregated tau protein and more closely correlate temporally and spatially with neurodegeneration and cognitive decline.

Circadian Rhythm Disruption in Patients with Alzheimer Disease

Individuals with symptomatic AD dementia exhibit a variety of changes in circadian function, including rhythm fragmentation and phase delay.[15] Rhythm fragmentation, which often manifests as increased napping during the day and restlessness during the night, is commonly observed in both older people and patients with AD dementia. It has also been observed in the presymptomatic phase of the disease, when biomarkers of brain amyloid plaque and neurofibrillary tangle pathology are positive but no cognitive symptoms are yet apparent.[16-19] Thus circadian fragmentation in AD appears very early in the disease course and may represent an exacerbation of a condition that occurs in normal aging. Phase delay, which manifests as a peak in activity later than normal in the day, has only been observed in symptomatic patients with AD and has been hypothesized as a possible contributor to the phenomenon of "sundowning," in which patients with dementia frequently become more confused and agitated in the late afternoon and evening.[20,21] Modest circadian abnormalities can also be observed in some mouse models of AD, in particular those that accumulate both Aβ and tau pathology, although the exact nature of the changes does not seem to be consistent across mouse lines.[22,23]

Mechanism Driving Circadian Dysfunction in Alzheimer Disease

The mechanisms driving circadian dysfunction in aging and AD are not fully understood, although several pathologic studies point to degeneration of the SCN as a possible culprit. Postmortem assessment reveals significantly decreased numbers of two critical neuronal populations, vasoactive intestinal peptide (VIP)–expressing and arginine vasopressin (AVP)–expressing neurons, in the SCN in patients with AD and has associated these changes with accumulation of tau pathology in that region.[15,24-26] Premortem circadian behavioral rhythm changes were correlated with the degree of loss of VIP-ergic neurons in the SCN on postmortem analysis in both aged individuals and patients with AD.[27] Decoupling of SCN input to the pineal gland, which produces melatonin, is also observed in AD, as both pineal gland clock gene expression and melatonin production are dysregulated in the disease.[13,14] Peripheral clock dysfunction may also play a role in AD. A study using fibroblasts derived from patients with AD showed abnormal methylation of the BMAL1 promoter in AD, leading to dysrhythmic clock gene expression, although the upstream causes of these epigenetic changes are unknown.[28] Furthermore, Aβ has been reported to induce the degradation of BMAL1 protein by multiple mechanisms in cells and mice, and incubation of SCN slices with Aβ can alter clock gene rhythms, suggesting a possible direct effect of Aβ on the core clock.[22,29] Finally, patients with AD may have loss of melanopsin-containing retinal ganglion cells, specialized neurons that conduct light information from the retina to the SCN.[30] Loss of these cells could impair the responsiveness of the SCN to changes in environmental light levels. Thus AD appears to disrupt circadian system function at multiple levels, although the exact mechanisms are not fully understood.

The impact of circadian dysfunction on the pathogenesis and symptomatology of AD also is poorly understood. The circadian system regulates sleep timing, and a variety of sleep disturbances, including difficulty sleeping at night with increased daytime sleep, are observed in AD.[31] Sleep deprivation can directly drive both amyloid plaque deposition[32] and tau pathology[33,34] in mouse models and can acutely increase cerebrospinal fluid levels of Aβ and tau in humans,[33,35] suggesting that circadian disruption could exacerbate Aβ and tau pathology through its effect on sleep. Sleep also appears to regulate extracellular fluid flow in the brain, potentially mediating clearance of Aβ and other toxic substances via multiple mechanisms.[36,37] However, core clock genes exert sleep-independent effects on neuroinflammation and oxidative stress in the mouse brain.[38] Accordingly, mice lacking BMAL1, which have fragmented sleep rhythms but no sleep deprivation, exhibit accelerated amyloid plaque deposition.[39] Thus sleep-independent effects of the circadian system on AD pathogenesis are possible and are the topic of ongoing study.

Therapy for Circadian Rhythm Disorders in Alzheimer Disease

Symptomatically, circadian rhythm disruption in patients with AD is a major cause of morbidity and institutionalization and is thus an area of concerted effort for therapy development. Numerous efforts have been made to treat circadian dysfunction in patients with dementia with light therapy, melatonin, or combinations of the two. These studies have yielded mixed results.[40-43] Morning light (2500 lux) and evening melatonin (5 mg) improved circadian function and decreased daytime sleep in patients with AD, with no effect on nighttime sleep.[40] Combined treatment with bright light exposure during the day (1000 lux) and melatonin therapy at bedtime (2.5 mg) yielded slight improvement in measures of cognition and mood, with more substantial improvement in evening agitation.[42] However, melatonin alone worsened mood, suggesting that combination therapy was important.

In summary, considerable human and animal data suggest a bidirectional relationship between circadian function and AD, as AD is associated with significant circadian dysfunction,

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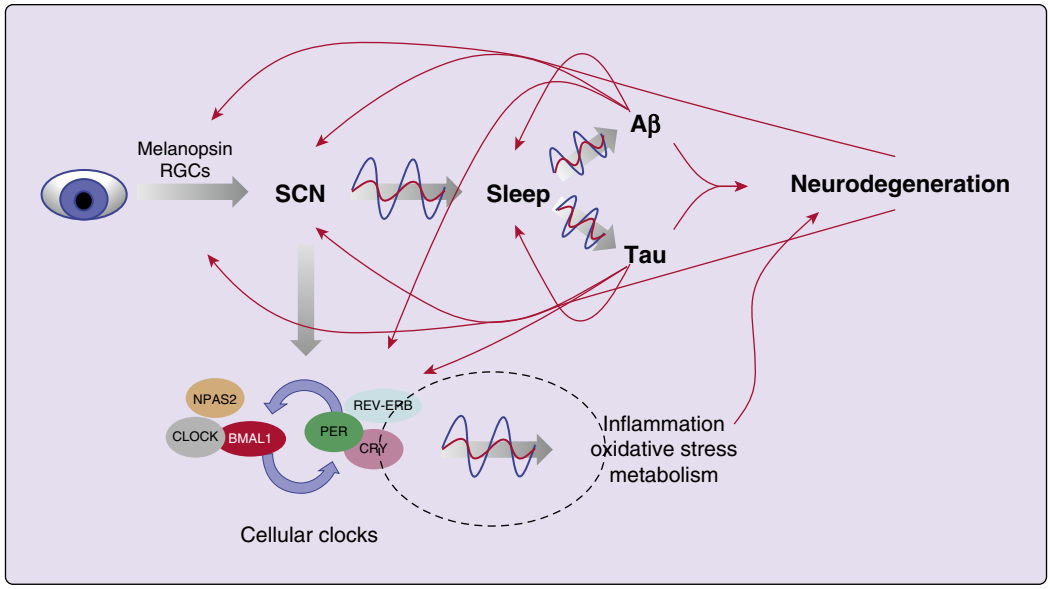

Figure 42.1 Schematic of circadian mechanisms in neurodegenerative diseases. The suprachiasmatic nucleus (SCN) integrates light input from the retina and then generates circadian rhythms in sleep-wake and other physiologic processes, as well as synchronizing cellular clocks. Sleep-wake rhythms regulate levels of Aβ and tau proteins. In the setting of aging or neurodegenerative diseases (*red lines*), blunting of SCN-generated rhythms could disrupt Aβ and tau metabolism and disrupt cellular clocks, which promote inflammation and oxidative stress. RGCs, Retinal ganglion cells.

whereas circadian and sleep disruption appear to drive pathology in early AD (Figure 42.1). Further study is needed to understand how to better optimize circadian function to alleviate symptoms of AD and to potentially reduce AD risk.

Circadian Dysfunction in Parkinson Disease

Parkinson disease (PD) is the second most common neurodegenerative disorder. Nonmotor symptoms (NMSs) affect up to 98% of patients with PD.[44] Disruption of the sleep-wake cycle is among the most common NMS in PD.[45] Alterations of the circadian system are increasingly being recognized as an etiology for disrupted sleep, alertness, and other manifestations of PD.

Dopamine and the Circadian System

Dopaminergic neurotransmission lies at the core of PD and is relevant in all three major components of the circadian system: its input, the pacemaker (SCN), and the output. The existence of diurnal variation in dopamine (DA) and some of its metabolites has been known for many years.[46,47] Striatal DA levels[48-50] and clock genes[51,52] also exhibit periodic variations. In the retina DA plays an important role in the modulation of circadian retinal input.[53] Specifically, DA is involved in light adaptation and the rhythmic expression of melanopsin and clock genes. DA also modulates light input to the SCN from the retina.[53] Further, rhythmic dopaminergic activity may also regulate the activity of the SCN.[54,55] Dopaminergic activity can also be considered an output of the SCN, since evidence points to the primary role of SCN in circadian variations of DA.[54] Dopaminergic input is required for proper modulation of the clock gene *PER2* in the dorsal striatum.[50] Moreover, functional loss of rhythmicity induced by bright constant light[51] or SCN lesions[55] disrupts DA and tyrosine hydroxylase rhythms and reward-related behaviors such as interval timing. Circadian genes within dopaminergic neurons also directly regulate DA synthesis and DA neuron activity.[56-58] Within striatal regions, circadian transcription factors (NPAS2 in particular) also directly regulate expression of DA receptors.[59] In summary, DA exhibits a two-way interaction with the circadian system at several levels.

Circadian Disruption in Parkinsonism: Lessons from Animal Models

Disruption of circadian rhythms has been well documented in animal models of parkinsonism.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated dogs exhibit blunted circadian oscillations in renal parameters, including urine volume, creatinine, and several hormones.[60-62] The 6-hydroxy dopamine (6-OHDA) models exhibit disruptions in circadian rhythms of locomotion, temperature, and heart rate.[63] Some of these abnormalities are partially reversible by levodopa (L-DOPA) administration.[63] Circadian changes have been also documented in rotenone-induced neurodegeneration, including changes in serotonergic transmission and clock genes expression.[64] α-Synuclein transgenic mice exhibit accelerated fragmentation of rest-activity and reductions in neuronal activity in the SCN.[65] In a mouse model of parkinsonism that involves deactivation of a mitochondrial transcription factor, MitoPark, diurnal patterns of rest/activity rhythms are altered.[66] Collectively, these basic investigations provide support for the concept of alterations of the circadian system in parkinsonism.

Neurodegenerative processes intrinsic to PD contribute to the disruption of sleep-wake and circadian rhythms, as major anatomic networks that regulate these rhythms become affected as the neurodegeneration progresses. Conversely, emerging studies suggest that circadian disruption may influence this neurodegenerative process as well, although the evidence supporting this relationship is less clear at this point. Preexposure to circadian disruption in mice treated with MPTP results in an exacerbation of motor deficits and a significant reduction in the capability of acquiring motor skills.[67] These changes are associated with a greater loss of

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tyrosine hydroxylase cell content and intense neuroinflammation. These findings point to the potential role that circadian disruption may have as an environmental risk factor for developing PD. Further research is needed to test this interesting hypothesis, which has significant translational and therapeutic implications.

Circadian Rhythms in Patients with Parkinson Disease

Many signs and symptoms associated with PD demonstrate diurnal variations in intensity and frequency. These include fluctuations of motor function in PD,[68-71] autonomic and sensory functions,[72-77] mood and cognitive performance,[78,79] and sleep and alertness.[80-83] Unstable day-to-day rest-activity rhythms predict cognitive dysfunction in patients with early PD.[84] NMSs fluctuate throughout the year, with worsening of symptoms in the winter months.[85] Whether these variations in physiologic functions are influenced by circadian oscillations remains to be investigated, as studies conducted so far have not employed experimental circadian protocols.

Several recent investigations have started to provide insight into the neuropathology that may underlie circadian symptoms in patients with PD. Retinal neuropathology in PD encompasses degeneration of dopaminergic amacrine cells and retinal ganglion cells.[86] The number of melanopsin-containing retinal ganglion cells as well as their branches and terminals is significantly reduced in patients with PD compared with controls.[87,88] Further, α-synuclein deposition is present in the retina of patients with PD.[88,89] Similarly, postmortem examination of the pineal gland and the SCN in patients who suffered from PD reveals deposits of α-synuclein.[90] Further studies are needed for understanding the neuroanatomic basis of circadian dysregulation in PD.

Markers of endogenous circadian rhythmicity, such as melatonin, cortisol, and core body temperature, have been investigated in the PD population. The amplitude of melatonin rhythm is significantly lower in patients with moderate PD compared with age-matched controls.[91] Those patients with excessive daytime sleepiness have significantly lower amplitudes of their melatonin rhythm compared to those with good alertness (Figure 42.2). This low amplitude of melatonin rhythms points to a weak alerting circadian signal, which may contribute to the excessive daytime sleepiness frequently reported by patients with PD. Similar changes in the amplitude of melatonin rhythms have been observed in early stages of PD.[92] Bolitho and colleagues demonstrated prolongation of the phase angle of entrainment of melatonin rhythm in medicated patients with PD compared to the unmedicated group and controls with PD.[93] These observations provide the rationale to suggest an uncoupling of circadian timing and sleep-wake regulation, possibly related to dopaminergic therapy.

Time-related variations in the expression of core clock genes in patients with PD have been reported. The relative abundance of the clock gene *Bmal1* is significantly lower during the night in a small group of patients with PD. Expression levels of *Bmal1* in patients correlate with PD severity as assessed by the Unified Parkinson Disease Rating Scale (UPDRS).[94] A lack of time-dependent variation in *Bmal1* expression in patients with PD was recently confirmed in another study.[92] These studies have laid out the groundwork for future clinical investigations related to molecular regulation of circadian timekeeping in PD and other neurodegenerative disorders.

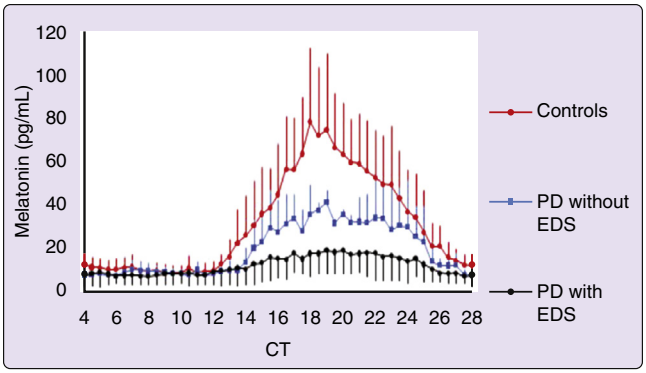

Figure 42.2 The amplitude of daily melatonin release is decreased in Parkinson disease (PD) compared with controls, and a greater decrease is seen in individuals with PD with excessive daytime sleepiness (EDS) compared with those without EDS. CT, Circadian time.

Cortisol rhythm also appears to be impaired in PD. While patients with PD exhibit a preserved circadian rhythm of cortisol, the amount of cortisol secreted is elevated in early PD.[92] However, somatotrophic, thyrotrophic, and lactotrophic axes appear to be intact in early stage PD.[95] Adipokines are endocrine factors released by fat cells and have an important role in feeding, body weight regulation, and metabolism. Because patients with PD frequently experience weight loss, a recent study by Aziz and colleagues focused on the circadian aspects of adipokines in PD, specifically leptin, adiponectin, and resistin, revealing no differences in the levels between patients with PD and controls.[96] A significant decrease in the core body temperature mesor and amplitude has been reported in PD.[97]

Circadian-Based Treatment Approaches in Parkinson Disease

As a consequence of their overall sedentary lifestyle, patients with PD are likely to be exposed to lower intensities of bright light, the most potent synchronizer of the circadian system. Age-related changes may further limit retinal light exposure. Degeneration and impairment of retinal ganglion cells in PD may contribute to decreased sensitivity to light and consequently aberrant melanopsin-mediated responses. Collectively, these factors strongly point to the possibility that patients with PD may benefit from light therapy. Several studies have assessed the safety and therapeutic efficacy of light therapy in patients with PD.[98-103] Results of these investigations revealed benefits to sleep, other nonmotor manifestations, and even some motor symptoms such as rigidity and bradykinesia. Several unresolved questions related to the utility of light therapy in PD remain. These include the optimization of several aspects related to the dose of light therapy and its mechanism of action in PD.

Regular physical activity has been accepted as an important lifestyle modification that reduces the burden of PD symptoms and perhaps may influence the biology of PD-specific neurodegeneration. The use of timed physical activity as a nonphotic zeitgeber that may improve synchronization of circadian system, however, has not been systematically examined in patients with PD. Another chronotherapeutic, melatonin, has a potential role in alleviating sleep-wake cycle disturbances in PD,[104,105] although its effects as a modulator of the circadian system have not been explored in studies published to date. Future studies should focus on optimizing

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the protocols as well as the parameters of light exposure and other circadian-based approaches geared toward improving symptoms and quality of life and even slowing down disease progression in patients with PD.[106]

CIRCADIAN RHYTHMS, SLEEP, AND PSYCHIATRIC DISEASE

Disruptions to the sleep-wake cycle are a cardinal feature of nearly all psychiatric disorders and are typically one of the core diagnostic criteria used by psychiatrists for diagnosis. The exact phenotype can be variable: for example, some subjects with depression experience insomnia, early morning awakening, and too little sleep, whereas others sleep too much, often missing work or other activities. Fragmented or disrupted circadian rhythm and sleep patterns are also common in psychiatric disorders as is a late or delayed chronotype (i.e., preference for activity during the night). Moreover, environmentally induced changes to the normal sleep-wake schedule can exacerbate symptoms and precipitate episodes. In later sections we highlight some of the associations between circadian phenotypes and specific psychiatric disorders, as well as chronobiology-based treatments.

Development and Childhood: Focus on Autism Spectrum Disorders

Sleep disturbances and circadian disruptions are associated with several neurodevelopmental disorders, including autism spectrum disorders (ASDs). Sleep problems are very often found in children diagnosed with ASD. The most common complaints are delay in sleep onset (insomnia) and issues with sleep maintenance, resulting in overall reduced sleep duration.[107] Night wakings of 2 to 3 hours are common in children with ASD.[108,109] While some of these sleep problems could be behavioral, circadian rhythm abnormalities have also been measured in children with ASD. These include irregular sleep-wake patterns, early morning wakening or sleep-onset delay, and free-running rhythms.[110] Genetic studies have suggested an association between polymorphisms in several core circadian genes with ASD.[111-113] Several studies have also found abnormalities in the regulation of melatonin levels in children with ASD. The most consistent finding in ASD is significantly lower levels of evening melatonin.[114-117] Importantly, low levels of melatonin correlate with severity of autism symptoms.[114] Moreover, studies have found that unaffected parents of children with ASD also have lower melatonin levels, suggesting that this effect may be genetic.[117] One hypothesis is that circadian rhythm disruptions in children with ASD are the result of mutations in genes involved in melatonin synthesis *(ASMT)*[117] and that melatonin, along with the clock genes, are important in the underlying changes in synaptic transmission seen in ASD.[118] In addition to its role as a circadian entraining molecule, melatonin acts as a potent antioxidant. One possibility is that a reduction of melatonin during development leads to a buildup of oxidative stress, which is harmful to the developing nervous system.[119] This would increase the risk for ASD and other neurodevelopmental disorders.

Melatonin therapy is often used by clinicians to treat the sleep disturbances seen in children with ASD. A recent study assessed the impact of prolonged-release melatonin (2 to 5 mg) on 125 children with ASD in whom sleep failed to improve with behavioral interventions alone.[120] The authors found that, after 13 weeks of this double-blind study, the melatonin treatment was associated with an increase in sleep by nearly 1 hour (57.5 minutes) compared to only 9 minutes with placebo. They also found that sleep latency decreased by 40 minutes and that 68.9% of participants had a clinically meaningful response with very few side effects. It will be interesting in future studies to determine if other chronotherapies are affective in managing the symptoms of ASD.

Other genetic studies have found significant associations between ASD and synaptic proteins in the SHANK family, which act as scaffold-organizing factors in the postsynaptic density of excitatory synapses.[122] Furthermore, SHANK3 protein levels in mice oscillate in the hippocampus and striatum over the light-dark cycle and correlate with changes in serum melatonin.[123] In addition, levels of SHANK3α expression show patterns in the thalamus, cortex, and striatum that associate with diurnal rhythms in activity levels.[123] These studies suggest that there may be an association between deficits in circadian rhythms and changes in synaptic proteins that are strongly linked to ASD.

Adolescence: A Time of Developmental and Environmental Risk

Adolescence is a particularly vulnerable time for the emergence of psychiatric and addictive disorders. In addition to the neurobiologic changes occurring during adolescence, hormonal and other biologic changes associated with puberty lead to an evolutionarily conserved shift in circadian rhythms in which preferred sleep and wake times become later. This shift is more prominent in boys than in girls, but it occurs in both sexes.[124] This shift in rhythms is also seen in measures of melatonin onset, which gradually become later during puberty.[125,126] During adulthood, most people show a shift back toward the earlier chronotypes observed in childhood, making adolescence a unique time in which the late chronotype prevails. Teenagers are exposed to a number of social and environmental factors that weaken, shift, or misalign their natural rhythms. These include very early high school start times, increased social interactions with peers, highly caffeinated energy drink consumption, nicotine exposure, and the use of electronic devices at night. To compound these effects, prepubertal and midpubertal kids are biologically more sensitive to the melatonin-suppressing effects of light at night than older adolescents or adults are.[127] Thus the current lifestyle of many teenagers creates a perpetual state of circadian misalignment known as "social jet lag": they wake up for school early 5 days a week but stay up late, often using illuminated electronic devices, and then sleep in on weekends.[128,129] The shift to later sleep times on weekends is equivalent in some teens to traveling from San Francisco to New York City—and back again—each week, significantly disrupting normal biologic rhythms throughout the brain and body. Because of these changes and other factors, the typical adolescent is chronically sleep deprived.[130] A recent study published by the Centers for Disease Control and Prevention[130a] showed that less than 10% of teenagers get the 8 to 10 hours of sleep a night recommended by the American Academy of Pediatrics. In fact, the American Academy of Pediatrics has labeled insufficient sleep in this population as a public health epidemic that increases risk for substance abuse, along with other problems such as depression, obesity, and suicide.[131-133] Studies have found that even a single night of sleep deprivation in healthy adolescents leads

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to an increase in activity in the ventral striatum and reduced deactivation in the medial prefrontal cortex during the receipt of monetary reward relative to the same task after normal sleep conditions.[134] However, this response is variable, and although most adolescents experience some form of sleep/circadian disruption, not all go on to have psychiatric disorders. This raises the possibility that individual, biologically driven sleep/circadian phenotypes, or gene-by-environment interactions, mediate increased susceptibility to these diseases.

Mood and Anxiety Disorders

Depression, bipolar disorder, and anxiety disorders are associated with very disrupted sleep-wake cycles. Symptoms often become worse with environmental sleep-wake or light disruption. In fact, one of the most common mood disorders affecting approximately 2% to 5% of the population in temperate climates is seasonal affective disorder (SAD), a syndrome in which depressive symptoms occur only in the winter months when there are shorter days and a later dawn.[135,136] Delayed rhythms during adolescence and early adulthood strongly associate with depression and severity of mood symptoms.[137,138] Furthermore, more recent work has found that circadian rhythm disruptions in high-risk adolescents predict worse prognosis and symptoms in several longitudinal studies.[139,140] Together, these findings suggest that sleep and circadian disruptions (both biologic and environmental) have a role in the precipitation of disorder symptoms and vulnerability to mood disorders. Biologic circadian rhythm and sleep abnormalities have been described for decades in patients with mood disorders.[141,142] These include disrupted rhythms in sleep/activity, body temperature, plasma cortisol, norepinephrine, thyroid-stimulating hormone, melatonin, pulse, and blood pressure.[143] Interestingly, these rhythms usually return to normal with antidepressant or mood stabilizer treatment and patient recovery. A study of the human postmortem brain[144] found that the amplitude in diurnal rhythms in a number of rhythmic mRNA transcripts was significantly altered in several brain regions from individuals with major depression when compared to healthy controls. The abnormalities in the brains of subjects with depression included shifted gene expression peak timing and disrupted phase relationships between individual circadian genes in several reward-related brain regions, including the hippocampus, amygdala, and ventral striatum.[144] This suggests that there are fundamental molecular rhythm disruptions across brain regions that contribute to depression. Furthermore, genetic circadian disorders such as familial advanced sleep-wake phase disorder or delayed sleep-wake phase disorder are both often comorbid with depression and anxiety.[145-147] As with other psychiatric disorders, individuals who are genetically predisposed toward an evening chronotype are more likely to develop mood disorders.[148-150]

Multiple human genetic studies (including some genome-wide association studies) have identified single-nucleotide polymorphisms or other disruptions in core circadian genes that associate significantly with mood disorders, in particular SAD and bipolar disorder.[151-153] Polymorphisms in *ARNTL* (i.e., *BMAL1*) have been linked to bipolar disorder through convergent functional genomic approaches and are suggested by the International Society for Bipolar Disorders Biomarkers Task Force to be one of four genes with variants that serve as potential biomarkers for the disease.[154] In addition to the effects on sleep, recent studies have determined that the circadian system is intricately involved in the molecular and cellular control of virtually all processes that are hypothesized to underlie mood disorders.[155]

Multiple theories have been put forth over the years to try to explain the development of mood disorders which involve multiple systems and regions of the brain. These include (but are not limited to) mitochondrial or metabolic dysfunction, neuroinflammation, monoamine imbalance, disrupted neurogenesis, and hypothalamic-pituitary-adrenal axis dysregulation, all of which are regulated by the molecular clock. Furthermore, animal studies find that the circadian genes contribute in a fundamental way to neuronal synchronization across multiple brain regions and to the regulation of neuronal circuitry that controls mood and anxiety.[156-159] It seems clear that a combination of biologic and environmental factors contribute to changes in mood, and the diagnosis of mood disorders continues to grow. One contributing factor is likely to be our modern lifestyle, which includes increased exposure to artificial light at night, shift work, less sleep or fragmented sleep patterns, travel across time zones, and reduced exposure to daytime sunlight. These environmental disruptions to the biologic clock are particularly deleterious for vulnerable individuals (i.e., those with mutations in one or more clock-associated genes). Animal studies have also found that exposure to chronic stress disrupts the circadian clock in the SCN and that the severity of disruption correlates directly with increased anxiety- and depression-related behavior.[160] Light exposure at night, constant light, or constant dark also increases depressive and anxiety-like behavior in rodent models.[161]

Given the cyclic nature of bipolar disorder with extreme changes in sleep-wake patterns, many researchers have speculated that circadian abnormalities underlie its development and are a core component of the disorder.[162-164] Furthermore, it is common for symptoms to be seasonal, in that subjects are more likely to have depressive symptoms in the winter and manic symptoms during the summer.[163,165,166] In many subjects with bipolar disorder, manic or depressive episodes are precipitated by disruptions to their normal sleep-wake cycle.[167] For these subjects, shift work or jobs with erratic work schedules can be severely detrimental. Mood episodes can also be brought on by periods of stress, which disrupt natural sleep-wake rhythms. The social zeitgeber theory[168] proposes that in vulnerable individuals, life stress affects sleep-wake and social rhythms, leading to circadian clock disruption and subsequent depressive or manic episodes.[169] It has been hypothesized that many individuals with bipolar disorder have a molecular clock that is unable to properly adapt to changes in the environment, and this underlies the precipitation of these episodes.[169] Dramatic mood-stabilizing effects in patients with bipolar disorder can be obtained through strict regulation of the sleep-wake cycle via a cognitive behavioral approach known as interpersonal and social rhythm therapy (IPSRT).[167] This therapy allows patients to track their time awake, time to first interactions, meals, and sleep with the goal of maintaining a very rigid and regular sleep-wake and social schedule. Other treatments for depression, SAD, and bipolar disorders in adults have been developed to amplify, phase advance, or delay circadian rhythms. These include bright light therapy for depression, acute sleep deprivation, dark therapy for mania, and therapeutic melatonin agonists (such as agomelatine).[170-173] Moreover, antidepressant and mood-stabilizing medications

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such as lithium, valproic acid, and selective serotonin reuptake inhibitors have dramatic effects on the amplification and timing of gene expression rhythms that may, at least in part, underlie their therapeutic efficacy.[174-176] Furthermore, a recent study found that the rapid and lasting antidepressant effects of low-dose ketamine can be predicted based on circadian rhythm measures prior to treatment and on how well ketamine strengthens low-amplitude rhythms, suggesting that the therapeutic effects are directly related to the strengthening of the circadian system.[177] Thus rhythm alignment and amplification is emerging as an important therapeutic approach to helping prevent or treat psychiatric disorders.

The International Society on Bipolar Disorders recently published a systematic review of and practice recommendations for chronotherapy and chronobiology.[178] This task force generally concluded that (1) the acute antidepressant efficacy of bright light therapy was supported; (2) adjunctive dark therapy for bipolar mania is also generally supported as was IPSRT for mood stabilization and improved sleep; (3) data on melatonergic agonists were limited and showed some conflicting evidence. Overall, chronotherapies were generally safe and well tolerated. Such chronotherapy for these disorders, however, must be personalized based on the particular needs of the individual. For example, subjects with depression are more responsive to morning light therapy combined with wake therapy and sleep-time stabilization if they are evening chronotypes and have a positive diurnal variation in mood with the best mood in the evening.[179] In contrast, subjects with bipolar depression respond best to midday light therapy, as morning light therapy can induce manic episodes.[180] In addition to amplifying rhythms, lithium treatments lengthen the period in *Drosophila* spp., nonhuman primates, rodents, and humans.[181-185] Interestingly, patients with bipolar disorder who have an abnormally fast clock respond positively to lithium treatment, whereas the patients who begin with an abnormally slow clock generally do not respond favorably to lithium treatment.[148,162,186] These actions of lithium on the free-running period appear to be SCN dependent[187] and again suggest a personalized medicine approach to chronotherapy is needed.

Schizophrenia

Schizophrenia (SCZ) is a psychiatric disease associated with positive (i.e., psychosis-related symptoms), negative (i.e., affect-related symptoms), and cognitive symptoms. Significant disruptions in diurnal rhythmicity of activity patterns, cortisol and melatonin profiles, and body temperature rhythms are commonly associated with SCZ. For example, actigraphy measurements in subjects with SCZ found that a subset of subjects with SCZ free run, similar to people who are completely blind with non-24-hour disorder, suggesting their rhythms are not able to entrain to the light-dark cycle, while other subjects showed highly disorganized and fragmented rhythms.[188] Furthermore, a study that measured circadian gene expression in blood samples and cultured fibroblasts from subjects with SCZ found a loss of rhythmicity and decreased expression of circadian genes compared to controls.[189] Several studies have identified differential gene expression in numerous transcripts in human cortical regions in the postmortem brains of subjects with SCZ. The most consistent results include reduced expression of genes associated with GABAergic transmission and mitochondrial function and increased expression of transcripts associated with neuroimmune function.[190-194] Using a time-of-death analysis similar to the depression study discussed previously, researchers discovered that subjects with SCZ not only have a loss in rhythmicity in most normally rhythmic transcripts but also have a very different set of transcripts with 24-hour rhythmicity in the dorsolateral prefrontal cortex compared with control subjects.[195] The top pathways identified in transcripts that have 24-hour rhythms only in subjects with SCZ are associated with mitochondrial function, and nearly all of them appear to peak during the day and trough during the night. Interestingly, these novel rhythms drive differential expression patterns of many genes that have long been implicated in SCZ (i.e., *BDNF* and GABAergic-related transcripts), suggesting that the change in molecular rhythmicity is responsible for the difference in expression of these genes. These altered rhythms in neurotransmission and mitochondrial-related transcripts may either drive, or be a marker of, significant diurnal differences in neuronal activity in the prefrontal cortex in subjects with SCZ.

Human genetic studies (mostly candidate gene studies) have identified variants in circadian genes that associate with SCZ; however, these have not been identified in more recent, large-scale studies performed by groups such as the Psychiatric Genomics Consortium. An analysis of 21 different circadian genes in 1527 subjects identified an association between *NPAS2* and SCZ.[196] In a genome-wide association study analysis of a United Kingdom biobank, a genetic correlation was also found between longer sleep duration and SCZ risk.[197] Therefore circadian and sleep gene variation may be important in SCZ but are only one contribution; there are hundreds of genes that contribute small amounts of risk.

Both human and animal experimental work suggest that the interplay between sleep and circadian function and DA is important in the generation and maintenance of psychosis.[198] In particular, both animal and human data suggest that sleep disruption increases DA release and sensitivity. Furthermore, elevated DA disrupts sleep and circadian rhythms.[198] Thus the current literature suggests that circadian rhythms, DA dysregulation, and psychosis are intricately linked, and, as already mentioned, several animal studies have found that circadian genes directly control nearly all aspects of dopaminergic transmission, including DA synthesis, uptake, and receptor activity.[199,200] More work must be done, however, to determine if specific chronobiologic approaches will be useful in the treatment of SCZ.

CONCLUSIONS

Circadian rhythm and sleep disruption are key features of several neurodegenerative diseases, including AD and PD, as well as many psychiatric disorders. The exact mechanisms underlying these phenotypes remain uncertain; however, they likely involve a combination of genetic disruptions to molecular pathways regulating rhythms and sleep, paired with environmental sleep-wake disruption (Figure 42.3). Disruption of the circadian clock exerts a wide array of effects on different aspects of disease pathogenesis, and preclinical data suggest that clock disruption could contribute to disease pathogenesis through multiple pathways. The molecular clock is thus a potential therapeutic target for these disorders. Although existing therapeutic strategies have largely involved light exposure, melatonin, or sleep-inducing agents, future treatments will have to be tailored to the specific disease process and individual patient, as

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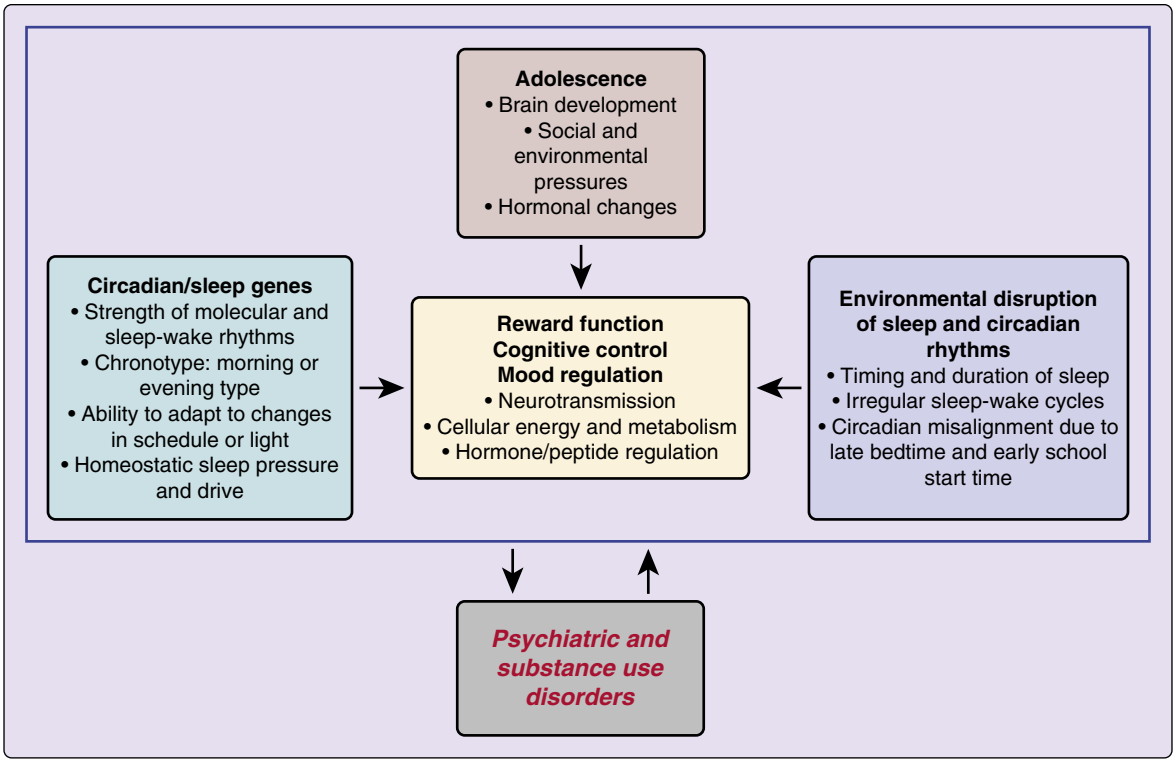

Figure 42.3 Circadian mechanisms in psychiatric disorders. Circadian clock genes/proteins, environmental clock disturbance, and adolescent brain development all interact with reward, cognitive, and mood centers to influence psychiatric disease.

there is a large degree of variability between diseases and within patient groups in terms of phase advances, phase delays, insomnia, fragmentation, and so on. As more specific biomarkers are developed to pinpoint specific sleep and circadian abnormalities within patient populations with neurodegenerative diseases and psychiatric disorders, this will provide better guidance regarding the appropriate treatment options.

CLINICAL PEARL

Screening for sleep disturbances and circadian disruption in patients with neurodegenerative and psychiatric conditions in the clinic is important: treatment of these symptoms may improve function. Treatment of sleep and circadian disturbances in older adults and in patients with dementia is difficult and must rely on nonsedating medications.

SUMMARY

Disruption of circadian rhythms and the molecular circadian clock is a hallmark of many neurodegenerative disorders and psychiatric diseases. Emerging evidence suggests that impaired circadian function occurs early in many of these diseases and may contribute to disease pathogenesis. Degeneration of the master clock in the SCN may drive rhythm fragmentation in AD, which may in turn promote protein aggregation and inflammation. Dopaminergic neurodegeneration in PD may lead to circadian disturbances, causing sleep-wake and behavioral disturbances. Circadian disruption can be both a cause and an effect in several psychiatric disorders, emphasizing the bidirectional relationship between circadian disturbance and brain dysfunction.

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REVIEW QUESTIONS

1. An 82-year-old man with Alzheimer disease (AD) dementia exhibits clear worsening of cognitive function, increased confusion, and combative behavior each day in the evening. This is an example of:
   A. Circadian fragmentation
   B. Sundowning
   C. Non-24-hour syndrome
   D. Amyloid angiopathy

2. In older adults, fragmented rest-activity rhythms have been thought to be caused by degeneration of which cells in the brain?
   A. Dopaminergic neurons in the substantia nigra
   B. Medium spiny neurons in the striatum
   C. Serotonergic neurons in the raphe nucleus
   D. Vasoactive intestinal peptide (VIP)-ergic neurons in the suprachiasmatic nucleus

3. The social zeitgeber theory proposes what?
   A. Stressful life events in vulnerable individuals alter the sleep-wake cycle, leading to changes in molecular rhythms and the precipitation of mood-related episodes.
   B. Social contact with individuals at specific times of day can enhance clock function.
   C. Depression and mania become apparent at different times of the year.
   D. Depression and mania can be treated via increased social interaction.

4. The commonly used mood-stabilizing medication, lithium, does what to molecular rhythms?
   A. Shortens the period and enhances amplitude
   B. Lengthens the period and enhances amplitude
   C. Shortens the period and reduces amplitude
   D. Lengthens the period and reduces amplitude

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ANSWERS

1. **B.** Sundowning is a syndrome in which cognition and behavior decline in dementia patients in the evening. It is thought to be related to abnormal circadian phase.

2. **D.** VIP-expressing neurons in the suprachiasmatic nucleus are important for circadian timekeeping and are lost in elderly people and AD patients with fragmented rhythms.

3. **A.** The social zeitgeber theory postulates that stressful life events in vulnerable individuals alter the sleep-wake cycle, leading to changes in molecular rhythms and the precipitation of mood-related episodes. It is the basis for interpersonal and social rhythm therapy commonly used for the treatment of bipolar disorder.

4. **B.** Lithium lengthens the period and enhances molecular rhythm amplitude. Thus its effects may be more efficacious in those with abnormally short and flattened rhythms.

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