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Neurobehavioral Consequences of Circadian Rhythm Disturbances: Insights into Mood Disorders and Cognitive Decline

Dhanshri B. Pimpalshende, Radha V. Matte, Kshitij U. Lingame, Prajwali V. Shende*

Hi-Tech College of Phamacy, Morwa, Chandrapur (MS) 442406

Corresponding author: Prajwalishende25@gmail.com

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Abstract

Circadian rhythms are endogenous biological oscillations with an approximately 24-hour periodicity that synchronize behavioural and physiological processes with the environmental light–dark cycle. In humans, the circadian timing system regulates sleep-wake behaviour, hormonal secretion, neurotransmission, and higher cognitive functions. This system is hierarchically organised, with the suprachiasmatic nucleus (SCN) acting as the central pacemaker and coordinating peripheral clocks through transcription-translation feedback loops involving core clock genes such as CLOCK, BMAL1, PER, and CRY. Disruption of circadian rhythms, driven by light exposure, shift work, irregular sleep schedules, aging, and chronic stress, has emerged as a major contributor to neurobehavioral dysfunction. Growing evidence links circadian misalignment to mood disorders, including depression, bipolar disorder, and anxiety, as well as to cognitive decline. Mechanistically, circadian disruption impairs sleep-dependent memory consolidation, alters synaptic plasticity, dysregulates neuroendocrine pathways such as the hypothalamic-pituitary–adrenal axis, and disturbs the rhythmic release of neurotransmitters including serotonin, dopamine, glutamate, and GABA. At the molecular level, clock gene dysregulation, neuroinflammation, mitochondrial dysfunction, oxidative stress, and reduced neurogenesis collectively compromise emotional regulation and cognitive resilience. Age-related weakening of circadian rhythmicity further increases vulnerability to mood instability and neurodegenerative processes. This review integrates molecular, neurochemical, behavioural, and clinical evidence linking circadian rhythm disturbances to mood disorders and cognitive decline, and highlights emerging chronotherapeutic, light-based, pharmacological, and lifestyle interventions aimed at restoring circadian alignment and promoting brain health.

Keywords: Circadian rhythm, Clock genes, Mood disorders, Cognitive decline, Depression.

1. Introduction:

Endogenous, self-sustaining biological oscillations with a roughly 24-hour period, circadian rhythms control a variety of physiological and behavioural functions in living things. Because of these rhythms, organisms are able to anticipate and adjust to predictable changes in their environment, especially the daily cycle of light and dark. Human circadian rhythms control vital processes like hormone secretion, body temperature, metabolism, sleep-wake cycles, and cognitive function. It is becoming more widely acknowledged that disruption of these rhythms plays a significant role in neurobehavioral dysfunction and disorders relating to the brain [1]. A central pacemaker and several peripheral clocks make up the hierarchically structured circadian timing system. The hypothalamic SCN synchronizes physiological rhythms throughout the body by acting as the master circadian clock. Through the Retin hypothalamic tract, the SCN receives photic input from the retina, enabling internal circadian rhythms to be synchronized with external light cues. A transcription–translation feedback loop involving core clock genes, such as CLOCK, BMAL1, PER (Period), and CRY (Cryptochrome), controls circadian rhythms at the molecular level [2]. These genes work together in a tightly regulated oscillatory system that controls the expression of rhythmic genes in a variety of tissues, including the brain. Peripheral clocks, which are found in various brain regions and organs in addition to the central clock, regulate regional physiological and cellular processes while staying in sync with the SCN. Physiological homeostasis depends on the exact synchronization of the central and peripheral clocks. Any misalignment of these clocks brought on by behavioural, environmental, or pathological factors can cause disruptions in the circadian rhythm, which can have far-reaching systemic and neurological effects.

Circadian regulation plays a pivotal role in maintaining optimal brain function. Numerous neural processes, including neurotransmitter release, synaptic plasticity, neuronal excitability, and neurogenesis, exhibit circadian variation [3]. Neurotransmitter systems such as serotonin, dopamine, glutamate, and gamma-aminobutyric acid (GABA) are under circadian control and are critically involved in mood regulation, motivation, emotional behaviour, and cognition. Furthermore, circadian rhythms influence higher-order brain functions such as learning, memory consolidation, attention, and emotional processing. The circadian clock tightly regulates sleep, which is necessary for synaptic remodelling and memory formation. Circadian timing disruption can affect executive functions mediated by the prefrontal cortex and hippocampus-dependent learning. Through its interactions with the hypothalamic pituitary–adrenal (HPA) axis, circadian regulation also affects cortisol secretion and emotional resilience, which in turn modulates stress responsiveness. Circadian rhythms and neurobehavioral health are closely related, as evidenced by the association between altered circadian signalling and maladaptive behavioural responses, emotional dysregulation, and increased susceptibility to stress.

Circadian rhythm disruptions are becoming more common in modern society as a result of exposure to artificial light, erratic sleep patterns, working shifts, and ongoing stress. These disturbances have been closely linked to mood disorders, such as anxiety, bipolar disorder, and depression, as well as neurodegenerative diseases and cognitive decline. The underlying mechanisms are still unclear and complex, despite mounting evidence that links circadian dysfunction to neurobehavioral outcomes [4].

This review's justification is to present a thorough synthesis of the most recent data regarding the role that circadian rhythm disruptions play in neurobehavioral changes, with a focus on mood disorders and cognitive impairment. The objective of this review is to clarify the mechanisms by which circadian dysregulation affects brain function by combining results from molecular, neurochemical, behavioural, and clinical investigations. In addition to outlining potential avenues for future research and treatment, the review aims to highlight the significance of circadian health in preserving emotional stability and cognitive integrity [5].

2. Neurobiological Basis of Circadian Rhythms:

Circadian rhythms are natural biological oscillations that control behaviour and physiological functions in accordance with the 24-hour day-night cycle. An internal time-keeping system that synchronizes cellular, tissue, and organism-level processes produces these rhythms. By maintaining the temporal organization of biological processes, the circadian system enables the best possible response to environmental stimuli. When this system is upset, physiological processes become out of sync, which has a significant impact on behaviour and brain function [6].

2.1 Central and Peripheral Clocks:

The central clock and several peripheral clocks make up the hierarchically structured circadian timing system. The anterior hypothalamic SCN houses the central clock. The SCN coordinates circadian rhythms throughout the body, acting as the body's master pacemaker. The Retin hypothalamic tract allows it to receive direct photic input from intrinsically photosensitive retinal ganglion cells, which allows for precise entrainment of internal rhythms to the external light-dark cycle. The SCN uses behavioural, hormonal, and neural signals to synchronize peripheral clocks. The hippocampus, cortex, amygdala, liver, and adrenal glands are among the organs and parts of the brain that have peripheral clocks. Although autonomous circadian oscillations can be produced by peripheral clocks, the SCN regulates their phase and amplitude to preserve systemic coherence. The brain's peripheral clocks serve specialized purposes in various areas. For example, the amygdala's clocks regulate stress responses and emotional processing, while the hippocampus's circadian regulation influences memory and learning. A disturbance in the communication between the central and peripheral clocks results in circadian misalignment, which is commonly observed in elderly people, shift workers, and patients with neuropsychiatric disorders [7].

2.2 Molecular Architecture of the Circadian Clock

A highly conserved transcription–translation feedback loop (TTFL) involving a collection of key clock genes and proteins produces circadian rhythms at the cellular level. Thousands of clock-controlled genes are driven to express themselves rhythmically by this molecular clock, which functions in almost all cells, including neurons and glial cells. The genes CLOCK, BMAL1, PER (Period), and CRY are the main parts of the molecular clock. The transcription of the PER (PER1, PER2, PER3) and CRY (CRY1, CRY2) genes is started by the transcription factors CLOCK and BMAL1 heterodimerizing and binding to E-box elements in the target gene's promoter regions. After translation in the cytoplasm, the proteins PER and CRY combine to form complexes that return to the nucleus and stop the CLOCK–BMAL1 complex from working [8]. Their own transcription is suppressed by this negative feedback, resulting in a rhythmic oscillation with a periodicity of roughly 24 hours. Additional regulatory loops that involve genes like casein kinase 1 (CK1), RORα, and REV-ERBα regulate the timing, stability, and degradation of clock proteins. The accuracy and resilience of circadian rhythms are improved by these auxiliary loops. The significance of molecular clock integrity for regular neurobehavioral function is highlighted by the correlations found between dysregulation of clock gene expression in the brain and altered synaptic plasticity, impaired neurogenesis, emotional instability, and cognitive dysfunction [8,9].

Table 1: Circadian Clock Genes and Protein — Location and Function

Gene	Chromosomal Location	Major Expression Location	Primary Function	References
CLOCK	Chromosome 5	Suprachiasmatic nucleus (SCN), brain, liver, peripheral tissues	Transcription factor that forms a heterodimer with BMAL1 to activate circadian gene transcription.	[10]
BMAL1 (MOP3)	Chromosome 7	SCN, heart, liver, peripheral tissues	Partners with CLOCK to bind E-box promoter regions and upregulate *Per* and *Cry* genes, driving the molecular circadian clock.	[10]
PER1	Chromosome 11	SCN and peripheral tissues	Interacts with CRY proteins to inhibit CLOCK-BMAL1 activity, forming the negative feedback loop.	[11]
PER2	Chromosome 1	SCN and peripheral tissues	CLOCK-BMAL1 inhibitor that helps regulate circadian period timing.	[11]
PER3	Chromosome 4	SCN and peripheral tissues	Participates in PER/CRY interactions to modulate circadian rhythms.	[12]
CRY1	Chromosome 12q23.3	Highly expressed in liver and testis; also, in SCN and retina	Essential oscillator protein that interacts with PER/BMAL1 to regulate transcriptional feedback.	[13]
CRY2	Chromosome 2	SCN and peripheral tissues	Works with PER proteins to inhibit CLOCK-BMAL1 transcription.	[14]
REV-ERBα (NR1D1)	Chromosome 17	Liver, skeletal muscle, adipose tissue, brain (including SCN)	Nuclear receptor that represses BMAL1 transcription, stabilizing circadian oscillations and linking the clock to metabolism.	[15]
REV-ERBβ (NR1D2	Chromosome 3	Brain, liver, kidney, peripheral tissues	Nuclear receptor that represses BMAL1 transcription, stabilizing circadian oscillations and linking the clock to metabolism.	[16]
RORα (RORA)	Chromosome 15	Brain (notably cerebellum), liver, lung, immune cells	Nuclear receptor that activates BMAL1 transcription, counterbalancing REV-ERB	[17]

			repression and maintaining rhythmic gene expression.	

2.3 Regulation of Circadian Rhythm

Both internal physiological signals and external environmental cues, or zeitgebers, control circadian rhythms. Among these, hormone secretion, sleep-wake patterns, and light exposure are crucial for preserving circadian synchrony.

Light-Dark Cycle

The most powerful zeitgeber for the circadian system is light. Melanopsin-containing photoreceptive retinal ganglion cells sense surrounding light and send signals to the SCN. While exposure to artificial light at night can result in phase delays or advances in circadian rhythms, exposure to light during the day strengthens circadian alignment. SCN signalling is disrupted and clock gene expression is changed by prolonged exposure to erratic light-dark cycles, such as working shifts or using screens at night. Cognitive impairments, mood dysregulation, and sleep disorders have all been linked to these disruptions [18].

Sleep-Wake Cycle

Circadian timing and homeostatic sleep drive interact to control the sleep-wake cycle, one of the circadian clock's primary behavioural outputs. For restorative sleep and the best possible brain function, sleep must be properly synchronized with the circadian phase. Sleep fragmentation and decreased sleep quality are caused by circadian misalignment, which is typified by sleeping at inappropriate biological times. This contributes to neurobehavioral disorders by negatively affecting executive functioning, attention, memory consolidation, and Hormonal emotional regulation [19].

Hormonal Control (Melatonin and Cortisol)

Melatonin and cortisol are the two most important circadian hormones, and hormonal rhythms are essential to circadian regulation. The pineal gland secretes melatonin, which has a strong circadian rhythm and peaks in secretion at night. It synchronizes peripheral clocks and promotes the onset of sleep by acting as a signalling molecule of darkness. Melatonin suppression brought on by exposure to nighttime light throws off circadian rhythms and has been connected to mood disorders and cognitive decline. HPA axis controls cortisol, which has a circadian pattern with high levels in the morning and low levels at night. Energy metabolism, stress response, and alertness are all impacted by cortisol rhythms. Impaired cognitive function, elevated stress sensitivity, and emotional dysregulation are all consequences of cortisol rhythmicity disruption [20,21].

3. Circadian Rhythm and Brain Function

The circadian timing system is crucial for regulating brain activity because it synchronizes synaptic plasticity, neurotransmitter release, neural activity, and cognitive processes with the time of day. Nearly every region of the brain expresses genes related to the circadian clock, which allows neuronal circuits to synchronize their activity with environmental cycles. Proper circadian regulation is essential for maintaining emotional stability, cognitive function, and adaptive behaviour, whereas disruption of the circadian rhythm leads to widespread neurobehavioral dysfunction [22].

3.1 Circadian Control of Neurotransmission

Serotonin

In the brain, serotonin signalling has a clear circadian rhythm and is crucial for controlling mood, emotional behaviour, and sleep patterns. Time-of-day-dependent firing is exhibited by neurons originating in the dorsal raphe nucleus, which are most active during wakefulness and suppressed during nocturnal sleep. Genes related to the circadian clock control important enzymes that produce serotonin and affect receptor sensitivity and expression. According to experimental research, circadian misalignment can result in a 40–60% decrease in nocturnal melatonin synthesis, which is indicative of a compromised serotonin-to-melatonin conversion. These changes are closely linked to the depressive symptoms, anxiety-like conduct, and poor emotional control seen in people who experience ongoing circadian disruption [23].

Dopamine

Dopamine (DA) is a critical neuromodulator involved in the regulation of both central and peripheral circadian rhythms, while dopaminergic neurotransmission itself is under strong circadian control. DA synthesis, release, and receptor signalling are regulated by circadian processes, and mounting data suggests a reciprocal relationship between dopaminergic pathways and molecular clock elements. The retina, olfactory bulb, striatum, midbrain, and hypothalamus are the five main brain regions where this interaction is most noticeable. Circadian DA release in the retina is crucial for both light adaptation and the transmission of photic information to the SCN via intrinsically photosensitive retinal ganglion cells that express melanopsin [23]. Dopaminergic interneurons in the olfactory bulb exhibit diurnal variations in DA release, indicating circadian regulation of olfactory processing DA receptors have a direct impact on circadian gene expression, whereas DA signalling controls PER2 clock gene rhythms in the striatum. Tyrosine hydroxylase, an enzyme that synthesizes DA, is controlled by core clock genes and displays circadian oscillations in the striatum and midbrain, establishing a connection between DA availability and circadian timing. Prolactin secretion is one of the homeostatic processes that are rhythmically regulated in the hypothalamus by circadian dopaminergic activity. Attenuated dopaminergic signalling, decreased reward sensitivity, and compromised cognitive function are the outcomes of circadian rhythm disruption. Circadian misalignment has been shown in preclinical and clinical studies to lower striatal DA levels by roughly 20–30%, which can lead to anhedonia, motivational problems, and heightened susceptibility to mood and neurodegenerative diseases [24].

GABA & Glutamate

Neuronal stability and synchronized brain activity depend on the balance between excitatory glutamatergic and inhibitory GABAergic neurotransmission, which is largely controlled by the circadian system. While glutamate transmits photic information from the retina to the SCN via the Retin hypothalamic tract, allowing light-dependent entrainment of the circadian clock, GABA serves as the main neurotransmitter in the SCN, coordinating interneuron communication and ensuring phase coherence among circadian oscillators. At the molecular level, GABA receptors, glutamate transporters, and NMDA and AMPA receptor subunits are all influenced by circadian clock genes in a way that varies with the time of day. This excitatory–inhibitory balance is altered by circadian rhythm disruption, which is typified by increased glutamatergic excitation and decreased GABAergic inhibitory tone [23,25]. After chronic circadian misalignment or sleep deprivation, experimental studies have shown a 25–40% increase in extracellular glutamate levels and a 20–30% decrease in GABA release. Mechanistically, increased neuronal firing and network hyperexcitability are caused by dysregulation of core clock genes like BMAL1 and PER2, which modifies synaptic vesicle trafficking, calcium homeostasis, and receptor phosphorylation. Overactive NMDA receptors are further encouraged by excessive glutamatergic signalling, which results in increased intracellular calcium, oxidative stress, and synaptic dysfunction. These neurochemical changes impair synaptic plasticity and interfere with limbic and cortical circuit communication. Functionally, this imbalance leads to sleep fragmentation, elevated anxiety, cognitive impairments, and hyperreactivity to stress; circadian rhythm disturbances are frequently associated with increased amygdala activity and decreased prefrontal inhibitory control [26].

3.2 Circadian Regulation of Neuroplasticity

A key modulator of neuroplasticity, circadian timing influences adult neurogenesis, dendritic remodelling, and synaptic strength in a time-dependent fashion. Learning and memory are supported by plasticity-related proteins, especially in the hippocampus and prefrontal cortex, whose rhythmic expression is regulated by core clock genes. When endogenous circadian rhythms and sleep-wake behaviour are in sync, synaptic efficiency and cognitive performance reach their maximum. A healthy circadian rhythm promotes memory consolidation while you sleep and improves long-term potentiation. Circadian organization disruption reduces synaptic adaptability and hinders hippocampus neurogenesis. Modified CLOCK–BMAL1 signalling disrupts the transcriptional regulation of synaptic proteins at the molecular level [21]. Additionally, brain-derived neurotrophic factor is suppressed by circadian dysregulation, which lowers dendritic growth and synaptic stability. Additionally, sleep fragmentation disrupts neural network reorganization and synaptic downscaling. Neuronal vulnerability is increased by hormonal imbalance, which includes decreased melatonin and increased nocturnal cortisol. The proper energy supply for synaptic remodelling is guaranteed by the circadian regulation of mitochondrial metabolism. When these cycles are disturbed, oxidative stress and neuroinflammation are encouraged. Together, these processes reduce executive function and learning effectiveness. Age-related cognitive decline is accelerated by prolonged circadian misalignment. Increased susceptibility to disturbed circadian–plasticity coupling is seen in neuropsychiatric disorders. Therefore, maintaining cognitive resilience and adaptive brain function requires intact circadian regulation [27].

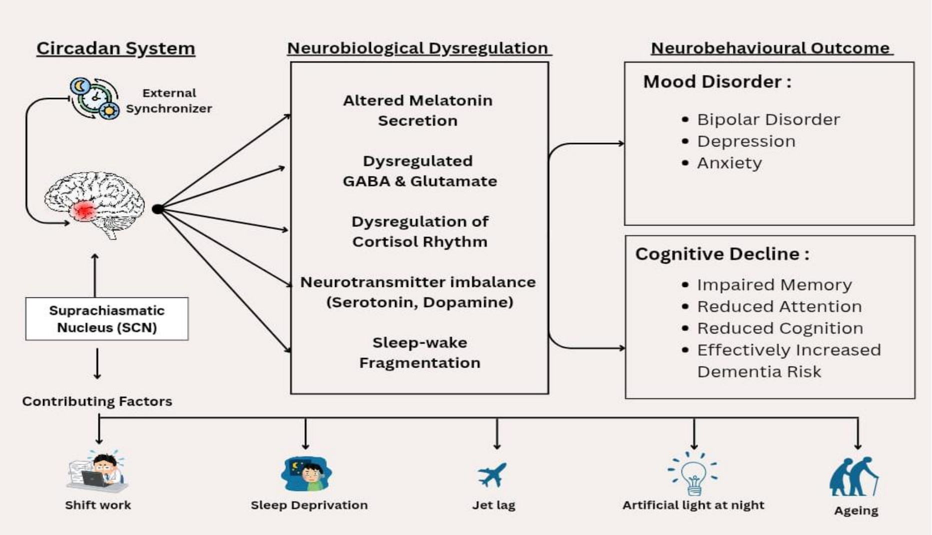

Fig 1: Neurobehavioral Consequences of Circadian Rhythm Disturbances

4. Causes of Circadian Disruption

A number of physiological and environmental factors that interfere with the regular sleep-wake cycle can cause disruptions to the circadian rhythm. Shift work, fast trans meridian travel that causes jet lag, lack of sleep, aging, and unhealthy lifestyle choices are common causes. By requiring activity during the biological night and sleep during the day, shift work causes circadian misalignment. This impairs sleep quality, cognition, and emotional regulation by suppressing melatonin secretion, altering cortisol rhythms, and disrupting clock gene expression [28]. Rapid time zone changes that surpass the circadian system's ability to adapt result in jet lag, which desynchronizes central and peripheral clocks and causes mood swings, cognitive impairments, and sleep disturbances. By changing hormonal cycles and impairing the relationship between sleep homeostasis and the circadian clock, sleep deprivation further disrupts circadian timing. Circadian rhythms are gradually weakened by aging and lifestyle factors such as decreased melatonin production, diminished light sensitivity, excessive nighttime light exposure, irregular meal timing, and sedentary behaviour. This makes people more susceptible to mood disorders, sleep disorders, and cognitive decline [29].

5. Circadian Rhythm Disturbances and Mood Disorders

An important factor in the onset and progression of mood disorders is disruptions of the circadian rhythm. Hormonal secretion, neurotransmitter activity, and sleep-wake cycles are all regulated by the circadian system, which is crucial for controlling emotions. Internal biological clocks and environmental cues become out of sync when this system is disturbed. This kind of circadian misalignment is frequently seen in bipolar disorder and depression, and it is linked to mood instability and changed sleep patterns. There is growing evidence that the pathophysiology of mood disorders involves circadian dysfunction as both a contributing mechanism and a consequence [8,30].

5.1 Depression

Disturbances in circadian rhythms, which control hormone release, body temperature, sleep-wake cycles, and emotional behaviour, are closely linked to depression. Rather than being incidental symptoms of major depressive disorder (MDD), circadian disruptions are the direct cause of the onset, intensity, and recurrence of depressive episodes. Insomnia, hypersomnia, early morning awakening, and diurnal mood fluctuations are common signs of circadian misalignment, with morning symptoms typically being more severe. These characteristics, which include phase advances or delays, decreased circadian rhythm amplitude, and changed core body temperature patterns, are indicative of anomalies in internal biological timing that impair cognitive and emotional control [31,32]. Melatonin dysregulation is a significant neuroendocrine marker of circadian disruption linked to depression. People who are depressed often have delayed, blunted, or phase-shifted melatonin secretion, which disrupts circadian synchronization and results in restless nights. Serotonin, an essential neurotransmitter and the building block for the production of melatonin, further links mood regulation and circadian rhythms. Impaired serotonergic signalling makes circadian misalignment worse by reducing SCN sensitivity to light stimuli. Antidepressants—specifically, selective serotonin reuptake inhibitors—help to partially restore mood by enhancing serotonergic transmission and controlling circadian rhythms. Circadian dysfunction, altered melatonin secretion, serotonergic imbalance, and aberrant cortisol rhythms create a bidirectional feedback loop that makes depression patients more emotionally vulnerable and sensitive to stress [23,33]

5.2 Dipolar Disorder

One of the mental illnesses most closely linked to dysregulation of the circadian rhythm is bipolar disorder (BD). Now regarded as essential elements of bipolar pathophysiology, disturbances in sleep-wake cycles, daily activity patterns, hormonal rhythms, and molecular clock function are crucial for mood episode initiation, mood switching, and relapse susceptibility. Even during euthymic phases, clinical research shows that over 90% of people with BD have significant circadian and sleep disturbances, which frequently precede mood episodes and may be causal. Circadian phase shifts are closely associated with mood states in BD [34]. While depressive episodes are typified by phase advances, dampened circadian rhythms, hypersomnia, and decreased daytime activity, manic and hypomanic episodes are generally linked to circadian phase delays, decreased sleep need, and increased circadian instability. Circadian instability is especially severe in BD that cycles quickly. Strong mania triggers include sleep deprivation and circadian misalignment; experimental data indicates that up to 30–50% of susceptible patients experience manic episodes as a result of sleep deprivation. The dysregulation of core clock genes, such as CLOCK, BMAL1, PER, and CRY, is linked to BD at the molecular level. This results in changes to neuronal excitability and neurotransmission. Dopaminergic, serotonergic, and melatonergic signalling are also impacted by circadian disruption, which leads to mood instability, impulsivity, and poor mood regulation [23,35].

5.3 Anxiety Disorders

Anxiety disorders are increasingly recognized as conditions in which circadian rhythm disruption plays a significant modulatory role. Normal circadian regulation is essential for optimal functioning of neural circuits involved in fear processing, stress response, emotional regulation, and arousal. Disruption of circadian timing alters these systems, contributing to persistent anxiety, hypervigilance, and impaired stress adaptation. Sleep and circadian disturbances are highly prevalent across anxiety disorders, including generalized anxiety disorder, panic disorder, social anxiety disorder, and post-traumatic stress disorder, with 60–80% of patients reporting chronic sleep disruption and increased variability in sleep–wake timing [23,32]. Circadian rhythms strongly regulate fear and stress circuits within the amygdala, hippocampus, and prefrontal cortex. The HPA axis is also under circadian control, and anxiety disorders frequently exhibit abnormal cortisol rhythms, including elevated nocturnal cortisol and flattened diurnal slopes, which promote hyperarousal and insomnia. Neurochemical systems involved in anxiety, including serotonin, GABA, and norepinephrine, display circadian fluctuations. Circadian disruption reduces GABAergic inhibition and impairs serotonergic signalling, increasing neuronal excitability and anxiety. Reduced melatonin secretion and dysregulation of clock genes further exacerbate stress sensitivity and anxiety vulnerability [31].

6. Circadian Rhythm Disruption and Cognitive Decline

Circadian misalignment, in which internal biological timing desynchronizes from environmental cues, is caused by disruption of the circadian rhythm brought on by aging, irregular sleep patterns, altered light exposure, or neurodegenerative pathology. Due to its negative impacts on sleep quality, synaptic plasticity, neurotransmitter balance, and neuroprotective mechanisms, there is mounting evidence that circadian dysregulation contributes to cognitive decline. The rhythmic release of important hormones and neurotransmitters, such as DA, acetylcholine, cortisol, and melatonin, which are all necessary for memory and learning, is changed by circadian disruption. Decreased melatonin levels and irregular cortisol cycles increase vulnerability to cognitive decline and neurodegenerative processes by fostering oxidative stress, neuroinflammation, and hippocampus dysfunction [36].

6.1 Impact on Learning and Memory

The precise circadian regulation of hormones and neurotransmitters that control network stability, synaptic plasticity, and neuronal excitability is essential for learning and memory. By controlling sleep architecture, especially slow-wave and REM sleep, and by protecting hippocampus neurons with its anti-inflammatory and antioxidant properties, melatonin promotes memory consolidation. Circadian disruption lowers nocturnal melatonin, which compromises long-term potentiation (LTP). Cortisol has a strong circadian rhythm and influences how memories are formed in the hippocampus and prefrontal cortex through glucocorticoid receptor signalling [37]. While flattened or elevated rhythms hinder LTP, decrease neurogenesis, and encourage hippocampal atrophy, optimal rhythmic levels support attention and encoding. With circadian regulation supporting encoding during wakefulness and consolidation during sleep, acetylcholine improves attention and hippocampus plasticity. Disruption of cholinergic rhythms results in impaired synaptic transmission and cognitive decline. DA regulates working memory and reward-based learning through circadian modulation of prefrontal and striatal signalling; circadian misalignment reduces dopamine rhythmicity, which in turn reduces memory function and cognitive flexibility. Memory and learning deficits result from the circadian disruption of these neurochemical systems, which also affects cortical and hippocampus plasticity [38].

6.2 Circadian Dysfunction in Aging

The core molecular clock is not the primary cause of circadian dysfunction in aging; rather, it is a result of compromised network properties of the SCN. As we age, the amplitude and synchrony of circadian oscillations across SCN neurons decrease, despite the transcription–translation feedback loops involving CLOCK, BMAL1, PER, and CRY remaining nearly intact. Decreased expression of important neuropeptides like arginine vasopressin (AVP) and vasoactive intestinal peptide (VIP), which are essential for coherent circadian signalling, as well as weaker intercellular coupling and neuronal firing rhythms are the causes of this desynchronization [39]. As a result, SCN output signals deteriorate in strength and stability, which affects the entrainment of peripheral and downstream neural clocks. The expression of rhythmic genes is dampened and phase variability is increased in peripheral tissues, such as muscle, adipose tissue, and liver. Due to changes in retinal input and SCN photic signalling, aging also lessens sensitivity to zeitgebers, especially light. When taken as a whole, these central and peripheral changes cause hormonal and metabolic dysregulation, blunted melatonin rhythms, disrupted sleep-wake cycles, and impaired cognitive and physiological homeostasis, all of which contribute to age-related functional decline [40].

7. Molecular Pathways Linking Circadian Disruption to Neurobehavioral Change

Circadian rhythms control a variety of molecular functions that are necessary for healthy brain activity and behaviour. Circadian timing disruption affects immunological responses, cellular metabolism, neuroendocrine signalling, gene expression, and results in quantifiable neurobehavioral changes. More and more data points to circadian disruption as a common upstream mechanism underlying the behavioural abnormalities, emotional dysregulation, and cognitive impairment seen in mood and anxiety disorders.

7.1 Clock Gene Dysregulation

Clock genes, which produce self-sustaining molecular oscillations via transcription–translation feedback loops, are central to circadian regulation. Around 24-hour rhythmic cycles are produced when CLOCK and BMAL1 trigger the transcription of the PER and CRY genes, whose protein products then suppress their own expression. These oscillations' amplitude, phase, or stability are all changed by circadian disruption [8]. About 30 to 50 percent of people with mood disorders have abnormal clock gene expression, especially in CLOCK, PER1, and PER2, according to human post-mortem and peripheral blood studies. Animal models with clock gene mutations or deletions exhibit marked neurobehavioral abnormalities, including anxiety- and depressive-like behaviours, impulsivity, and altered reward processing. When clock genes are dysregulated, dopaminergic, serotonergic, and glutamatergic signalling are disrupted. Clock genes are essential for controlling neuronal excitability, synaptic plasticity, and neurotransmitter release. As a result, emotional control, cognitive flexibility, and adaptive reactions to environmental stressors are all compromised by compromised clock gene function [41].

7.2 HPA Axis and Stress Pathways

Strong circadian regulation governs the hypothalamic-pituitary-adrenal (HPA) axis, which is crucial for adaptive stress reactions. Cortisol typically has a strong diurnal cycle, reaching its peak early in the morning and falling throughout the day. This rhythmicity is changed by circadian disruption, which can result in flattened cortisol slopes, increased cortisol levels at night, or heightened stress reactions. According to clinical data, aberrant cortisol rhythms are present in between 50 and 70 percent of people with mood and anxiety disorders. Chronic glucocorticoid exposure is caused by persistent HPA axis activation, which also impairs negative feedback and increases glucocorticoid receptor resistance. The hippocampus, prefrontal cortex, and amygdala are all negatively impacted by excessive glucocorticoids, which compromises memory, emotional control, and stress tolerance. Therefore, a crucial molecular pathway connecting circadian disruption to maladaptive neurobehavioral disorders is long-term HPA axis dysregulation [41].

7.3 Neuroinflammatory Signalling

Circadian rhythms closely control inflammatory signalling and immune response. Immune dysregulation and an increase in pro-inflammatory cytokine production result from circadian timing disruption. Increased levels of C-reactive protein (CRP), tumour necrosis factor-α (TNF-α), and interleukin-6 (IL-6) are linked to circadian misalignment. According to meta-analyses, between 40 and 60 percent of people with mood disorders have elevated inflammatory markers, especially when they are sleep deprived or experiencing circadian disruption. Neuroinflammation disrupts synaptic plasticity, decreases neurogenesis, and affects the metabolism of neurotransmitters. Pro-inflammatory cytokines increase glutamatergic excitotoxicity and disrupt the synthesis of DA and serotonin. Consequently, clock gene expression is suppressed by inflammatory signalling, which further disrupts circadian rhythms and starts a vicious cycle of inflammation and behavioural dysregulation [42].

7.4 Mitochondrial Dysfunction and Oxidative Stress

Reactive oxygen species (ROS) control, calcium homeostasis, and cellular energy production all depend on mitochondria. Antioxidant defences, oxidative phosphorylation, and mitochondrial dynamics are all influenced by circadian rhythms. Reduced ATP production and increased ROS generation are the results of circadian disruption, which affects mitochondrial function. Clock gene disruption reduces mitochondrial respiratory efficiency by 20–40%, according to experimental studies. Lipids, proteins, and DNA are all oxidatively damaged by excessive ROS, especially in metabolically active neurons. Anxiety, mood swings, cognitive decline, and exhaustion are among the neurobehavioral disorders that are closely linked to mitochondrial oxidative stress. According to clinical data, between 50 and 65 percent of people with mood disorders have decreased antioxidant capacity and elevated oxidative stress markers. Moreover, emotional and behavioural dysregulation are exacerbated by mitochondrial dysfunction, which also interferes with neurotransmitter synthesis and increases neuroinflammation [43].

8.Therapeutic and Preventive Strategies

Interventions to restore biological timing have been developed in response to mounting evidence linking disruptions in the circadian rhythm to mental and cognitive disorders. Circadian-based treatments enhance emotional and cognitive functioning, normalize hormone and neurotransmitter rhythms, and stabilize sleep-wake cycles. For both therapeutic and preventative reasons, these tactics are being employed more frequently in conjunction with traditional pharmaceutical and psychological therapies.

8.1 Chronotherapy

The purpose of chronotherapy is to realign circadian rhythms by purposefully adjusting sleep, wakefulness, and the timing of daily activities. Methods include stabilizing social rhythms, controlled sleep deprivation, and sleep phase advance or delay. For mood disorders like depression and BD, chronotherapy works especially well. Although sleep deprivation has quick antidepressant effects, rhythm-stabilizing therapies must be used in conjunction for long-lasting benefits. Through the reinforcement of consistent daily routines and the improvement of synchronization between central and peripheral clocks, interpersonal and social rhythm therapy (IPSRT) lowers the risk of relapse [44].

8.2 Light Therapy

By supplying the central clock with retinal input, light is a powerful circadian timing regulator. The circadian phase is reset and the rhythm amplitude is strengthened by timed exposure to bright light. While evening light can postpone phase when necessary, morning light promotes circadian timing, enhancing mood and alertness. Light therapy helps with depression, sleep-wake irregularities, and age-related circadian weakening. It also improves cognitive function and daytime functioning [45].

8.3 Melatonin and Circadian-Targeted Pharmacotherapy

A key component of circadian synchronization is melatonin signalling. Melatonin receptor agonists and exogenous melatonin improve sleep initiation, stabilize circadian rhythms, and correct phase misalignment. A number of psychotropic substances, such as mood stabilizers like lithium and antidepressants, work therapeutically in part by altering molecular clock mechanisms [46].

8.4 Lifestyle and Behavioural Interventions

Maintaining circadian stability and avoiding relapses require lifestyle changes. Regular daylight exposure, decreased nighttime light exposure, regular sleep-wake cycles, planned meal timing, physical activity, and stress reduction are important tactics. By strengthening circadian amplitude and enhancing resilience against age- and stress-related circadian disruption, these interventions strengthen environmental time cues (zeitgebers) [47].

9. Future Perspectives and Research Gaps

9.1 Need for translational and longitudinal studies

To link molecular circadian processes to clinical outcomes like mood, sleep, and cognition, translational research is required. Even with well-characterized clock genes, polypharmacy, comorbidities, and lifestyle factors limit their applicability to humans. Clinical applicability is diminished by this gap. Furthermore, understanding causality is limited by the absence of longitudinal studies. In order to find early biomarkers and direct chronotherapeutic interventions, long-term, multimodal approaches are crucial [48].

9.2 Biomarkers of circadian disruption

Sleep-wake patterns, peripheral clock gene expression, and melatonin and cortisol rhythms are biomarkers of circadian disruption. Their unclear connections to the central clock, high variability, and inadequate standardization restrict their clinical use. Future research will concentrate on non-invasive, integrated panels that combine wearable and multi-omics data. Limited testing across aging and disease populations and the absence of validated longitudinal markers are important gaps [49].

9.3 Personalized circadian-based interventions

Personalized circadian-based interventions match therapies to a patient's biological clock in an effort to maximize treatment. With the help of new wearable-based circadian monitoring, strategies like chronotype-specific light therapy, timed melatonin, and chrono pharmacology appear promising. Yet, the dependence on set treatment regimens and the absence of standardized biomarkers continue to be significant drawbacks, highlighting the necessity of long-term, individualized research [50].

10. Conclusion

The preservation of neurobehavioral health, emotional stability, and cognitive integrity is largely dependent on circadian rhythms that function on a strictly controlled 24-hour cycle. The evidence compiled in this review shows that disruption of circadian timing, whether caused by disease, aging, lifestyle choices, or environmental factors, has a broad impact on brain function. Circadian misalignment increases susceptibility to mood disorders and cognitive decline by changing the rhythmicity of neurotransmitters, compromising synaptic plasticity, interfering with sleep-dependent memory consolidation, and dysregulating neuroendocrine, inflammatory, and metabolic pathways. Crucially, circadian dysfunction is a primary mechanistic factor in the onset, progression, and recurrence of neuropsychiatric illness rather than just a secondary effect. According to developments in molecular chronobiology, neurobehavioral pathology is caused by a complex network of interrelated factors, including dysregulation of core clock genes, altered hypothalamic-pituitary-adrenal axis activity, neuroinflammation, and mitochondrial dysfunction. These discoveries demonstrate that the circadian system is an important and reversible therapeutic target. Novel approaches that aim to improve clinical outcomes and restore 24-hour biological synchrony include chronotherapy, light-based therapies, melatonin and circadian-targeted medications, and lifestyle-based rhythm stabilization. Major gaps still exist despite tremendous progress, especially in the application of mechanistic findings to clinical practice. Longitudinal and multimodal studies, easily accessible and standardized biomarkers of circadian disruption, and customized circadian-based interventions catered to individual chronotypes must be the top priorities of future research. One effective way to prevent mood disorders, slow cognitive decline, and improve overall brain resilience may be to strengthen circadian health throughout life.

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