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The Influence of Circadian Rhythm on Mental Disorders

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Abstract: People in modern society are under significant pressure from various aspects, such as the workplace, school, and social expectations. These factors contribute to the development of mental disorders and are often associated with cognitive impairments and disruptions in circadian rhythms. Dysregulation of circadian rhythms can lead to shifts in various mental disorders, including Major Depressive Disorder (MDD), Bipolar Disorder (BD), Schizophrenia (SZ), and other mental diseases. Various factors, including CLOCK genes, related hormones, neurotransmitters, and individual lifestyle, all contribute to this dysregulation. These factors have been thoroughly examined in this study to provide a comprehensive understanding of how they influence circadian rhythms and may contribute to the development of mental disorders. The essay also highlights current treatments, including chronotherapy and pharmacological interventions, which primarily aim to improve mental health symptoms by resetting patients' circadian rhythms. Furthermore, the essay discusses potential future research directions, specifically focusing on epigenetic mechanisms and biomarkers linked to circadian rhythms. As emphasized in the conclusion, it is crucial to refine existing treatment methods by incorporating strategies that target the circadian rhythm, ultimately leading to improved patients' health outcomes and enhancing the well-being of the population.

Keywords: Circadian rhythm, Mental disorders, Clock genes, Hormones

1. Introduction

Circadian rhythm refers to the natural oscillation that occurs approximately every 24 hours, regulating the cycles of wakefulness and sleepiness in many organisms [1]. Disruptions in the circadian cycle are closely associated with various physiological and behavioral disorders. Many individuals with mental disorders, including depression, schizophrenia, and bipolar disorder, frequently exhibit circadian abnormalities, including both phase-advanced and phase-delayed rhythms, compared to healthy controls [2]. The suprachiasmatic nucleus (SCN), located in the hypothalamus, plays a crucial role in maintaining daily physiological functions, acting as the body's primary circadian oscillator. As a biological clock, the SCN regulates the timing of various processes, including sleep-wake cycles [3]. At the molecular level, the circadian rhythms are driven by multiple transcription factors, including BMAL1, CLOCK, PER, and CRY genes, which form autoregulatory transcription-translation feedback loops (TTFLs). These feedback loops play a significant role in controlling the circadian cycle in mammals. Specifically, the CLOCK and BMAL1 genes are essential in regulating gene expression and biological processes at specific times of the day. This mechanism involves CLOCK:BMAL1 binding to nucleosomes and chromatin modifications, such as the incorporation of

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histone variant H2A.Z. PER and CRY proteins act as negative feedback regulators; once their levels accumulate following transcription by CLOCK-BMAL1, they bind to the complex and prevent further transcription of their own genes, thereby halting the activation loop and maintaining the rhythmic cycle of gene expression [4].

Additionally, circadian rhythms are influenced by environmental factors, including light-dark cycles, medication, substance use, stress, and other external stimuli. Among these, the light-dark cycle serves as the primary environmental cue that regulates the circadian rhythm. According to previous studies, exposure to evening light before bed can cause the circadian cycle to be delayed by around two hours, whereas morning light usually causes it to advance by around one hour each day. Bright light exposure, both morning and evening, can increase the intensity needed to alter the circadian pacemaker, but afternoon light has a less significant effect. Conversely, exposure to midday light improves alertness during the day and encourages higher-quality sleep at night [5]. Disruption in sleep patterns, particularly circadian misalignment, leads to destabilization of physiological processes and contributes to the development of various pathologies. Sleep disturbances, including the misalignment of the internal circadian cycle, contribute to both physical and mental health issues. Sleep generation and normal brain function are linked by shared neurotransmitter systems and regulatory mechanisms [6]. Over time, this misalignment may exacerbate symptoms and contribute to the development of severe mental health disorders. Therefore, disruptions in circadian rhythm not only act as a consequence but also play a significant role in their onset and progression.

Numerous studies have established a strong link between circadian rhythm disruptions and mental disorders. For example, Emens et al. demonstrated that the intensity of major depressive symptoms is correlated with the misalignment of circadian rhythms [7]. Specifically, patients with depression exhibited a delayed circadian rhythm relative to the timing of sleep onset when compared to a control group without depression. Interestingly, patients treated with agomelatine, a melatonin agonist with serotonergic activity, showed improvements in both their circadian rhythm and depressive symptoms. Agomelatine is believed to act as a "circadian synchronizer," increasing the amplitude of circadian rhythms, thereby stabilizing mood and alleviating symptoms of depression [8]. This evidence underscores the significant role of circadian rhythm regulation in the treatment of psychiatric disorders and supports the concept that stabilizing circadian rhythms may be a key initial step in managing mental health conditions. This review is Mental health is influenced by various factors, including lifestyle, stress levels, social environment, and diet. For instance, individuals experiencing high levels of stress are more likely to develop mental health issues, as stress accumulation can overwhelm one’s emotional and cognitive functioning. Mental health disorders can vary in severity, with diagnoses made by healthcare professionals based on specific symptoms and behaviors. To prevent the onset of mental illness and to stabilize or improve existing conditions, individuals can benefit from maintaining a consistent sleep schedule, adopting a balanced diet, engaging in stress-reducing activities, and participating in regular physical exercise. These proactive measures contribute to improved mental well-being and help mitigate the risk of developing more severe psychiatric conditions in the future.

2. Neurobiological basis of circadian rhythm in mental health

Circadian rhythms are primarily controlled by the suprachiasmatic nucleus (SCN), which requires neurotransmitters to modulate and transmit signals between the SCN and the rest of the body. Endogenous chemicals known as neurotransmitters are produced by neurons and control a variety of physiological activities, hormone production, sleep-wake cycles, and other biological processes. These neurotransmitters include glutamate, gamma-aminobutyric acid (GABA), glycine, acetylcholine, dopamine (DA), epinephrine, and serotonin [9]. Dopamine is often referred to as the "feel-good" neurotransmitter due to its involvement in the brain's reward system. It plays a significant

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role in memory, movement, motivation, mood, and attention. Abnormal dopamine levels are associated with neurodegenerative and mental disorders, such as Parkinson's disease and depression, respectively [10]. Dopamine also exhibits circadian-like activities in several brain regions, including the retina, olfactory bulb, striatum, midbrain, and hypothalamus. These wide ranges of areas with dopamine positions suggest that it is critical to maintain the rhythmicity of these areas [11]. Retinal dopamine production specifically promotes appropriate light adaptation and light information transfer to the SCN, which aids in synchronizing the body's internal clock. Serotonin, another key neurotransmitter, plays a crucial role in regulating behavior, mood, and physiological functions. It is synthesized in both the brain and other tissues, with high concentrations discovered in the brain's limbic regions, which play a role with regard to how emotions are processed by neurons [12]. Different serotonin levels are linked to various mood states. For instance, normal serotonin levels contribute to emotional stability and focus, while low levels are associated with conditions such as depression and anxiety. Many mental health disorders are characterized by decreased serotonin levels, which is why medications targeting serotonin regulation are commonly used to treat mental illnesses [13].

The central nervous system (CNS) is the primary location for the inhibitory neurotransmitter GABA (gamma-aminobutyric acid), where it is widely distributed across various brain regions. It functions to reduce neuronal excitability by inhibiting nerve transmission [14]. In contrast, glutamate is a major excitatory neurotransmitter that plays an essential role in brain functions such as memory, learning, and neurotransmission. Glutamate receptors are found throughout the spinal cord and brain in both neurons and glial cells [15]. The balance between GABA-mediated inhibition and glutamate-mediated excitation is crucial for maintaining proper brain function and neural homeostasis. Disruptions of this balance can lead to mental disorders like epilepsy, schizophrenia, depression, and bipolar disorder, as well as problems such as excitotoxicity, seizures, and neuronal cell death, often due to increased extracellular glutamate and reduced GABA concentrations [16]. An important hormone involved in the body's reaction to stress, cortisol, is secreted by a set of organs called the hypothalamus-pituitary-adrenal (HPA) axis [17]. Cortisol is produced by the adrenal glands, and its levels increase in response to stress, which is why it is often referred to as the "stress hormone." Cortisol plays a crucial role in boosting metabolism, regulating blood pressure, and promoting alertness. Its levels follow a daily rhythm, peaking in the morning and gradually declining throughout the day, reaching their lowest levels at night to create a restful internal environment. Disruption of this rhythm can lead to sleep disorders and, in more severe cases, contribute to mental health issues such as depression, anxiety, and post-traumatic stress disorder (PTSD). For instance, individuals with depression often exhibit low cortisol levels due to dysfunction in the HPA axis. This dysregulation may manifest as symptoms such as fatigue and an inability to engage in daily and social activities. In addition, cortisol levels can fluctuate unpredictably during stress, and erratic cortisol secretion resulting from HPA axis dysregulation may significantly result in the development of cognitive abnormalities and mental illnesses. Furthermore, those CLOCK genes, which are crucial in regulating circadian rhythms, also influence mood regulation, psychological functions, hormone secretion, and metabolism. It is becoming more well acknowledged that genetic variations in these clock genes are linked to mental illnesses, especially when it comes to bipolar disorder, schizophrenia, and depression. Changes in clock genes have been linked to disruptions in circadian rhythm, including sleep cycle disturbances (such as insomnia, hypersomnia, or shifts in the circadian cycle) and mood instability, which can increase the likelihood of developing mental health disorders [18].

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3. Circadian dysregulation in mental disorders

3.1. Major Depressive Disorder (MDD)

All mental and psychotic disorders, including Major Depressive Disorder (MDD), Bipolar Disorder, and Schizophrenia, are strongly associated with abnormalities in circadian rhythm. The illness known as major depressive disorder (MDD) is typified by a persistently low mood and a loss of interest in activities. Patients with MDD often exhibit abnormalities in their sleep-wake cycles, including insomnia, hypersomnia, and early morning awakening. Disruptions in circadian rhythms and the underregulation of the suprachiasmatic nucleus (SCN) closely link these phenomena. The altered secretion of cortisol and melatonin is considered a major contributing factor. Melatonin, a hormone crucial for regulating circadian rhythms, is synthesized from serotonin through the actions of serotonin N-acetyltransferase (SNAT) and hydroxyindole-O-methyltransferase (HIOMT) [19]. MDD patients frequently demonstrate altered melatonin secretion patterns and disrupted cortisol rhythms, which can either be advanced or delayed. The biological etiology of MDD is closely related to deficiencies in monoamine neurotransmitters, such as norepinephrine (NE) and dopamine (DA). The hypoactivity of these neurotransmitters in the prefrontal cortex is thought to underline the lack of energy, feelings of depression, and fatigue commonly observed in MDD patients [20].

3.2. Bipolar Disorder (BD)

Bipolar disorder is another mental health condition that is closely linked with disruptions in circadian rhythms. Patients with bipolar disorder often experience mood dysregulation and sleep disturbances, including both depressive and manic episodes. During depressive episodes, patients may experience hypersomnia and insomnia, and their sleep phases may become delayed. In contrast, during manic episodes, patients tend to experience reduced sleep needs (hyposomnia) alongside heightened energy levels. Disruptions in circadian rhythms in bipolar disorder are attributed to dysregulation of biological markers, including melatonin, cortisol, and abnormalities in clock gene expression. During manic episodes, melatonin levels are frequently delayed and misaligned with the natural light-dark cycle. Additionally, elevated cortisol levels, particularly during manic episodes, exacerbate symptoms and contribute to sleep disturbances. Lithium is commonly used to synchronize circadian rhythms by modulating clock gene expression. Research has shown that lithium can correct behavioral changes in models of mania induced by sleep deprivation. Patients with bipolar disorder who do not respond to lithium exhibit significantly elevated GSK3β activity and reduced expression of genes associated with the circadian clock [21].

3.3. Schizophrenia

Schizophrenia is a psychotic disorder characterized by symptoms such as hallucinations, delusions, and disorganized thinking. Patients with schizophrenia often experience sleep disturbances and irregular sleep patterns, which may exacerbate the severity of their symptoms. Circadian rhythm dysregulation in schizophrenia is thought to result from impairments in clock genes, leading to disruptions in the rhythm and underlying neurobiological mechanisms [22]. A major factor contributing to schizophrenia is the dysregulation of the dopamine system. Hyperactivity of dopamine is associated with positive symptoms, such as hallucinations and paranoia, whereas hypoactivity of dopamine is linked to negative symptoms, including social withdrawal and cognitive impairments. Another critical system involved in schizophrenia is the glutamate system [23]. Dysregulation of glutamate activity, particularly hyperactivity of NMDA receptors, has been implicated in the disorder. Regions of the prefrontal cortex, hippocampus, and thalamus, which are associated with negative symptoms and cognitive deficits, show reduced NMDA receptor activity. The imbalance between

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dopamine and glutamate systems contributes to the pathology of schizophrenia, as glutamate activates neurons and signaling pathways, while dopamine regulates mood and emotional responses. Disruption in the balance between these two systems is an important factor in the beginning stages of the growth of mental or psychotic disorders when they reach a certain severity. Antipsychotic medications are commonly used to treat psychotic disorders, including schizophrenia, bipolar disorders, and delusional disorders. It has been discovered that some antipsychotic medications, like olanzapine and clozapine, raise melatonin levels, considering melatonin is essential for controlling circadian rhythms. This effect helps patients reset their sleep-wake cycles and improves sleep quality. However, long-term use of antipsychotic medications can impact on the pineal gland, where melatonin is synthesized and released. As a result, patients may experience difficulty sleeping once they discontinue their medication, as their melatonin levels may become dysregulated again [24].

4. Impact of modern lifestyles on circadian-mental health interactions

4.1. Shift work and irregular sleep schedules

Today, individuals are often overwhelmed by their busy lifestyles, which are typically occupied by work, school, social events, and other responsibilities. While these situations can sometimes be unavoidable, other factors, particularly disruptions to the circadian rhythm, can significantly impact one's health. One example of such circumstances is shifting work, which can profoundly affect the body's internal clock. Since the circadian rhythm is heavily influenced by light and darkness, misalignment between the internal clock and the external environment is common in shift workers. This misalignment can lead to various health issues, including sleep disorders, mood disturbances, and metabolic dysfunction, which may, over time, develop into more severe mental health conditions such as depression, bipolar disorder, anxiety, and schizophrenia. The hypothalamic-pituitary-adrenal (HPA) axis, which regulates the synthesis of cortisol, a crucial stress hormone that is particularly dependent on light-darkness, can also be disrupted by shift work. Under normal circumstances, cortisol levels peak in the early morning and gradually decline throughout the day. However, the misalignment of internal clocks caused by shift work interferes with the actual natural timing, leading to abnormal cortisol production. This disruption can result in consistently elevated cortisol levels, which significantly raises the chance of developing mental disorders as well as cognitive impairments.

4.2. Artificial light exposure

Another significant factor contributing to circadian rhythm disruption is artificial light exposure, particularly blue light emitted by digital devices. It is nearly impossible to avoid the use of such devices in today’s technology-driven society. The retinal ganglion cells in the eyes are highly sensitive to blue light, and when exposed, they send signals to the suprachiasmatic nucleus (SCN) in the brain. This, in turn, suppresses melatonin secretion, which negatively affects sleep patterns. The consequences include a disrupted sleep-wake cycle, misalignment of the circadian rhythm, and poor sleep quality. Over time, the cumulative impact of this disruption can lead to more severe health problems, as previously discussed [25].

5. Therapeutic Interventions targeting circadian rhythm in mental disorders

5.1. Chronotherapy

Various treatments have been developed to target circadian rhythm abnormalities specifically in mental disorders. Chronotherapy has been widely utilized as a primary approach, aiming to restore

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the circadian rhythm through practices such as maintaining proper sleep hygiene, administering medications, and controlling light exposure. This approach has a generally positive effect on the internal clock. Chronotherapy is frequently used in two different ways: first, to improve the symptoms of specific pathologies through modifying the patients' sleep-wake rhythm; and second, to improve therapeutic outcomes by taking the patients' circadian rhythms into account [26]. Light therapy is a non-pharmacological treatment. A non-pharmacological treatment known as light therapy has demonstrated significant improvements in various mental illnesses, including depression and bipolar disorder. In order to synchronize the circadian rhythm and alleviate symptoms, this therapy requires exposing patients to light sources at specific times, particularly in the morning, to reset and realign the body's internal clock. Bright light therapy is especially effective for patients with seasonal depression, as their symptoms are primarily triggered by changes in natural light. Therefore, light therapy addresses the root cause of the disorder.

5.2. Pharmacological treatment

Individuals with bipolar disorder often experience depressive episodes similar to major depressive disorder (MDD). Light therapy can alleviate these symptoms primarily by resetting the patient's circadian rhythm and inducing appropriate changes in hormone levels. However, light therapy has to be applied with caution in patients with bipolar disorder, especially with regard to the timing of its application. During manic episodes, exposure to light may exacerbate symptoms by increasing energy levels, leading to heightened impulsivity and irritability. Consequently, careful monitoring and precise timing of light therapy are essential to avoid triggering or worsening manic symptoms. There are also alternative approaches, such as pharmacological treatments. Melatonin has been found to be effective when used in combination with antidepressant medications targeting mental symptoms. It has a supportive effect on depressive symptoms, particularly when these symptoms are associated with circadian disturbances. Some depressive patients have been found to have low melatonin levels, which disrupt the sleep-wake cycle. As a result, melatonin supplementation is often used to improve sleep quality and reset the circadian cycle, potentially stabilizing and modulating mood. However, there are potential risks and adverse effects associated with long-term melatonin use. Prolonged intake of melatonin may lead to imbalances in the natural production of hormones, which could have long-term implications for the body’s hormonal regulation. In particular, it may affect the menstrual cycle in females and disrupt the system for producing sex hormones. Therefore, it is important to consider the duration of melatonin use and monitor its potential side effects [27]. In addition to melatonin, individuals with bipolar disorder are often treated with lithium due to its positive effects on circadian rhythm regulation. Lithium significantly increases the expression of PER2 and CRY1, particularly through the inhibition of GSK-3β. PER2 plays a vital part in controlling the circadian cycle, while CRY1 works in conjunction with PER proteins to stabilize the clock mechanism. GSK-3β is an enzyme that destabilizes circadian proteins, and lithium’s inhibition of this enzyme leads to greater stability in the circadian rhythm. As a result, lithium's modulation of the circadian system may contribute to improved circadian rhythm regulation and increased mood stability, which could alleviate symptoms in the long term [28].

6. Conclusion

Mental disorders, such as Major Depressive Disorder (MDD), Bipolar Disorder (BD), Schizophrenia (SZ), and others, are often linked with disruptions in their circadian rhythms. Various factors, including CLOCK genes, hormone levels, neurotransmitters, light exposure, lifestyle, and sleep schedules, play a pivotal part in circadian rhythm regulation. Dysregulation of these factors can directly shift an individual's circadian rhythm and potentially contribute to cognitive impairments and

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the development of mental disorders. Based on this mechanism, several treatments have emerged that specifically target circadian rhythm dysregulation to improve general mental health symptoms. One such treatment is bright light therapy in chronotherapy, along with medications designed to target circadian rhythms. However, many areas remain unexplored, and there are significant shortcomings that require further investigation and improvement. For example, further research is needed to explore the various factors that may lead to epigenetic modifications of genes and to understand how these modifications are linked to circadian rhythms and psychiatric disorders. Using longitudinal studies on circadian markers, like gene expression markers (clock genes), hormonal levels, sleep-wake patterns, and other signs of circadian rhythm activity, could also help predict and maybe even stop mental illness before it starts. Thus, it is essential to further develop potential biomarkers related to circadian rhythms. Such discoveries would enable a more comprehensive assessment of mental disorders and drive innovation in treatment methods, making them more well-rounded and effective.

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