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The effect of reduced activity of prefrontal cortex neurons on sleep rhythm

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Abstract. The etiology of depression, a prevalent psychiatric disorder, remains elusive. Depression often manifests as a sleep disturbance. A significant proportion of individuals suffering from depression exhibit various sleep rhythm problems. There occurs a well-established and intricate bidirectional association between sleep rhythm abnormalities and depression. The prefrontal cortex (PFC) has been demonstrated to have a crucial role in the development of depression in recent years. The PFC plays a crucial role in the regulation of several cognitive, emotional, behavioral, and other significant activities. The atypical functioning of the PFC might result in the disruption of the sleep cycle. Unusual neuronal activity in the PFC could play a crucial role in controlling both sleep problems and depression. This paper presents a comprehensive overview of the research methods employed in studying the PFC in animal models. It also investigates the potential neural mechanism by which reduced PFC neuron activity may impact sleep rhythm via the PFC-LH-HPA loop. By doing so, this study offers novel insights and concepts that contribute to a deeper comprehension of the underlying causes of depression. Furthermore, this research introduces a prospective approach for addressing depression and sleep disorders through the manipulation of PFC neuron activity, while also highlighting its medical implications and obstacles.

Keywords: PFC, Neuronal activity, Sleep rhythm, Depression

1. Introduction

Depression is classified as a persistent, recurrent, and possibly perilous psychiatric disorder [1]. Depression ranks among the top 10 causes of illness and death globally, as reported by the World Health Organization (WHO). Over 350 million individuals are afflicted by depression. Depression has emerged as the fourth most prevalent global ailment, with a continuous and significant increase in the number of those affected. It is noteworthy that an annual number exceeding 700,000 individuals succumb to suicide as a result of despair. Despite significant advancements in the field of depression research, the precise underlying mechanism of depression remains incompletely understood. There is currently a lack of comprehensive therapy modalities for depression. The pathophysiology and treatment techniques of this condition have consistently been a focus of extensive research. Depression is characterized by symptoms such as a persistent poor mood, lack of interest, weariness, sleep disturbances, along with cognitive deterioration and decreased volitional activity.

Significant symptoms, such as sleep difficulties, not only contribute to the psychological load experienced by patients, but also have a profound impact on their social functioning and overall

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quality of life. As per available statistics, a significant proportion of individuals diagnosed with depression exhibit varying levels of sleep disturbances [2]. Several studies have identified variations in circadian rhythms across depressive mouse models, including psychosocial stress-induced depression-like animals [3]. Furthermore, certain investigations have demonstrated that sleep rhythm abnormalities might disrupt molecular expression in the prefrontal cortex (PFC), specifically in relation to other brain regions associated with emotions. This disruption may explain the potential link between sleep disorders and mood disorders [4]. The findings of this study indicate that sleep disturbances are not solely indicative of depression, but rather might play a significant role in its development. There is likely an intricate and reciprocal connection between sleep disturbances and depression.

The PFC plays a crucial role in various cognitive and emotional regulatory processes. Cheng et al. have demonstrated that the PFC plays a significant role in modulating the association between depressive symptoms and sleep quality [5]. This observation implies a potential association between the aberrant functioning of PFC neurons and the development of sleep problems and depression. Hence, the objective of this paper is to examine the impact of diminished PFC neuron activity on sleep patterns and its involvement in the development of depression. Additionally, it aims to suggest potential approaches for managing depression and sleep disorders by modulating PFC neuron activity, while also highlighting its medical implications and obstacles.

2. Sleep disorders and depression

Several psychiatric disorders often coincide with disruptions in sleep and circadian rhythm, leading to significant harm. Sleep has a crucial role in sustaining human existence. Optimal sleep is essential for safeguarding cognitive functions, including learning and memory, as well as for preserving the equilibrium of the body's immune system and metabolism. Issues pertaining to sleep patterns are frequently denoted as sleep disorders.

Depression is commonly associated with atypical sleep patterns, such as early awakening and difficulty initiating sleep. Additionally, patients with depression often experience notable alterations in their overall sleep pattern, including accelerated initiation of the first rapid eye movement (REM) sleep stage and an increase in the duration of total REM sleep [6]. Anomalous sleep patterns have been found to be correlated with heightened levels of despair and anxiety, while extended periods of sleep deprivation have been linked to increased mood fluctuations and suicidal ideation. Do sleep disturbances arise as a consequence of depression or as a contributing factor to it? The feasibility of achieving antidepressant effects in the treatment of sleep disturbances warrants further investigation. Abnormal rapid eye movement (REM) sleep does not directly cause depression. However, the disruption of the sleep structure's homeostasis during non-rapid eye movement (NREM) sleep can lead to abnormal growth of the REM sleep structure, ultimately leading in a decrease in happy feelings. REM sleep inhibition is a mechanism by which certain antidepressant medications exert their effects. According to certain research, sleep deprivation has been found to impair the connectivity between the medial prefrontal cortex (mPFC) and the amygdala, a brain region often involved in emotional processing. In contrast, following emotional stimulation, the activity and connectivity of the mPFC decreased, while the activity in the dorsal ACC and amygdala increased. In addition, the amygdala controls associated functions in the hypothalamus, which is closely linked to the sleep-wake cycle [7].

3. Effects of reduced activity of PFC neurons on sleep rhythm and depression

The PFC is a significant area within the cerebral cortex, located in the anterior portion of the frontal lobe. It can be further split into three subregions: the dorsolateral (dlPFC), ventrolateral (vlPFC), and medial (mPFC) prefrontal cortex. Within the mPFC, it is possible to further categorize it into several regions, including the anterior cingulate cortex, anterior limbic cortex (PrL), and inferior limbic cortex (IL). The PFC is intricately linked to regulatory processes, cognitive decision-making, social interactions, and various other functions.

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Studies conducted on patients with depression have demonstrated a general decrease in activity of PFC neurons, as evidenced by basic, clinical, and neuroimaging research [8]. The following aspects mostly demonstrate this phenomenon. In animal models of depression, there is a decrease in the PFC, which leads to neuronal development issues like as synaptic reduction, axon reduction, synaptic density reduction, and neuron reduction in the chronic unforeseeable stress model (CUMS model) [9]. The chronic binding stress model (CRS model) is associated with a decrease in both the length and number of dendritic spines, as well as a reduction in the expression of glutamate receptors [10]. In addition, electron microscopy revealed a decrease in the number of synapses in the dorsolateral prefrontal cortex (dlPFC) among patients with depression [11]. The dlPFC is strongly associated with mood. Furthermore, post-mortem brain study of individuals with depression revealed a substantial reduction in the quantity of neurons and glial cells [12]. The findings indicate that depressed patients exhibit reduced neuronal activity in the PFC, which may be attributed to diminished neuronal function, decreased neuronal firing activity, and reduced synaptic transmission efficiency. The PFC primarily consists of a neuronal network made of Glu ergic pyramidal neurons and GABA ergic pyramidal neurons, which exhibit an excitation-inhibition balance. They disrupt the equilibrium and induce a shift towards inhibition. Furthermore, the cerebral cortex of depressed patients exhibits a notable suppression of Glu signaling, potentially linked to a downward mood. This inhibition is particularly evident in the chronic stress stress model, as chronic stress diminishes the excitability of PFC (particularly mPFC) projection neurons, leading to decreased neuronal firing and compromised neuronal connections. The chronic stress model has the potential to induce depression as a result of the activation of the NLRP3 inflammasome signaling pathway in the PFC [13]. Furthermore, research has demonstrated that stress might interfere with the BDNF-TrkB signaling pathway, leading to a weakness in the subsequent ERK-Akt signaling pathway [14]. Brain-derived neurotrophic factor (BDNF) is a crucial component in the processes of synapse development, neuronal maturation, and synaptic plasticity. Dysfunction of associated pathways results in impairments in the synthesis of proteins at the postsynaptic level, hence exerting a detrimental impact on the maturation and stability of synapses.

EEG investigations conducted on the frontal lobe of mice with CRS depression model demonstrated a significant decrease in the power of all brain waves [15]. The delta, alpha, beta, and other waves exhibit a strong correlation with sleep, and there is a notable alteration in the magnitude of their transmission. The diminished activity of PFC neurons will also impact the sleep rhythm and is intricately linked to the sleep-wake cycle. Furthermore, atypical functioning of PFC neurons can impact neurotransmitters associated with sleep chronology, such as dopamine and norepinephrine. In contrast, an irregular sleep pattern can disturb the properties of PFC neurons, leading to aberrant production of clock molecules and IEG genes in the PFC [16], and reducing the excitability of two thirds of the spinal neurons in the plPFC [17]. The findings revealed a reciprocal relationship between disruptions in sleep patterns and the PFC.

4. Decreased activity of PFC neurons may affect sleep rhythm and lead to depression

The medial prefrontal cortex (mPFC) is a cerebral superior region that governs cognitive processes, attentional processes, and emotional regulation. It extends its neural connections to the hypothalamus brainstem and other brain regions associated with sleep and alertness. The organization mostly consists of Gluergic neurons and GABAergic neurons. mPFC and hippocampus play crucial roles in the development of depression. The involvement of the PFC in the mechanism of consciousness has been a subject of ongoing debate. Its significance extends beyond cognitive and affective activities, as it also seems to play a role in regulating total alertness within the brain. Despite the absence of a universally agreed-upon definition of the PFC across different ethnic groups, it is noteworthy that the mPFC, which encompasses the anterior cingulate gyrus, prelimbic region, and posterior limbic region, has substantial anatomical and functional similarities between rodents and primates. It has been postulated that the involvement of functionally and structurally identical MPFCS in the wakefulness

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loop may be attributed to the fact that PFCS project to numerous sleep-related nuclei across various species [18].

The typical sleep cycle consists of two phases: rapid eye movement sleep (REM) and non-REM sleep (NREM). During REM, the activity of the hippocampus theta oscillations is intensified. Research has demonstrated that suppressing pyramidal excitatory neurons in the mPFC brain area can effectively decrease theta oscillation activity during REM sleep and decrease the length of REM sleep [19]. This indicates that inhibitory neurons in the mPFC brain area suppress the incidence of REM. Furthermore, the study observed that excitatory neurons in the mPFC connect to many regions, including the basolateral amygdala, lateral hypothalamus (LH), thalamic nucleus, and lateral tegmental nucleus. Upon the activation of the aforementioned circuits by light, it is seen that only the MPFC-LH loop may facilitate the onset of REM. This suggests that the regulation of sleep-wake by the mPFC is achieved by this particular loop. Moreover, research conducted on rats has demonstrated that injury to the mPFC impacts REM sleep and exacerbates depressive-like behavior [7]. These findings align with prior research indicating that activation of the mPFC facilitates REM sleep, perhaps elucidating the underlying mechanism of sleep rhythm disruption in individuals diagnosed with depression. Nevertheless, these investigations have shown divergent findings, potentially attributable to variations in the precise position of the mPFC.

Several ideas have been proposed to explain the primary causes of depression, such as the monoamine theory, neurotrophic factor hypothesis, HPA axis (hypothalamic-pituitary-adrenal) hypothesis, and neuroinflammation hypothesis, among others. Depression can be attributed to dysfunction in the GABA and Glu transmitter systems. Numerous studies have demonstrated alterations in network functionality inside the brains of individuals diagnosed with depression, with particular emphasis on excitatory Glu neurons and inhibitory GABA interneurons [20]. This phenomenon has the potential to result in diminished signal integrity within the cerebral cortex and hippocampus; however, the precise biochemical pathways behind this phenomenon remain unidentified. Moreover, stress constitutes a significant risk factor for the development of depression, with numerous symptoms of depression being linked to prolonged exposure to stress. In the endocrine system, the HPA axis plays a crucial role. This pathway can be significantly activated by environmental stress and stress events. Research has indicated that individuals diagnosed with depression exhibit heightened activity of the hypothalamic-pituitary-adrenal (HPA) axis. Additionally, a significant proportion of depressed patients experience elevated levels of cortisol, an endogenous glucocorticoid. This heightened cortisol concentration subsequently binds to the intracellular receptor known as GR. However, excessive activation of GR may result in detrimental effects on associated regions [21].

One may hypothesize that the occurrence of chronic stress initially diminishes the functioning of prefrontal cortex (PFC) neurons, resulting in impaired excitatory and inhibitory neurons within the PFC. This disruption of the excitation-inhibition equilibrium, alteration of neurotransmitter levels, and subsequent impact on downstream neurons are potential consequences. The atypical functioning of prefrontal cortex (PFC) neurons will initially impact the mPFC-LH sleep regulation circuit, subsequently influencing the disruption of REM and NREM sleep rhythms. Crucially, neurons in the PFC have the ability to directly or indirectly influence hypothalamic (LH) neurons responsible for generating corticotrophin releasing factor (CRF) via projecting onto LH neurons. The CRF gland plays a significant role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Its primary function is to promote the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. This, in turn, triggers the release of stress hormones, including cortisol, from the adrenal cortex. The persistent secretion of stress hormones can subsequently impact the quality and dynamics of sleep. Conversely, the operational status of the hypothalamic-pituitary-adrenal (HPA) axis can also impact the functionality of the PFC, and an excessively active HPA axis can influence cognitive processes, emotional state, and behavioral patterns. An essential loop for comprehending emergency response and emotional regulation is the neuronal connection between the PFC and the hypothalamic-pituitary-adrenal (HPA) axis. The diminished functioning of PFC neurons impacts the

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sleep cycle via the PFC-LH-HPA loop. Prolonged disruption of sleep patterns and anxiety levels additionally impact emotional control, resulting in further disruption of neurotransmitter levels, neuroinflammation, and the release of numerous inflammatory markers. Emotional pathways, such as the prefrontal cortex-amygdala, experience disruption, while the HPA axis becomes excessively stimulated, hence impacting physiological processes related to immunity and metabolism, hormone levels, and finally culminating in the manifestation of depression. Furthermore, the disruption of sleep patterns can also impact cognitive function, resulting in memory and concentration impairments, exacerbating emotional irritation, and intensifying the onset of depression. It is imperative to acknowledge that there could potentially exist additional brain regions or circuits implicated in this hypothesized pathway.

5. Regulation of PFC neuronal activity to achieve antidepressant treatment strategies and challenges

Research has demonstrated that depressed patients exhibit distinct discharge activity in the PFC during acute stress [22]. The discharge activity in the PFC varies between depressed patients during acute stress. This phenomenon may give rise to various therapeutic approaches. The earliest animal trials revealed varying impacts of different depression models, with CUMS models demonstrating a reduction in PFC neuronal activity. In CUMS, sleep patterns are also impacted by exposure to light during the overnight period. Other models of depression, such as the learned helplessness model, exhibit shorter durations. The social failure stress model, which is associated with social disorder, possesses gender and anxiety characteristics that often lead to confusion with depression. The pathological process of the riscepin-induced model is incongruous with depression, as human depression is primarily triggered by prolonged stress and mental burden. Consequently, this model is somewhat less dependable [23]. These depression models fail to account for the transient nature of depression. Attempting to modulate the functioning of PFC neurons to combat depression can only be initiated from the chronic stress model. However, it is not feasible to treat all patients without a more comprehensive and effective depression model, as well as a more pragmatic depression assessment strategy.

The existing experimental technology exhibits limitations in its ability to regulate PFC neuronal activity. Various methods, including electrophysiology, transcranial magnetic stimulation (TMS), optogenetics, and transgenic technology, are unable to effectively augment neuronal activity in specific brain regions. Several studies have provided evidence that the introduction of light-activated channel proteins in the mPFC can lead to an optogenetic stimulation of mPFC discharge. This optogenetic intervention has been shown to have a significant antidepressant effect, while not compromising general motor activities, anxious behaviors, social memory, and other related functions. These findings highlight the potential of optogenetics as a viable approach for enhancing neuronal activity as a treatment strategy for depression [24]. While the current research is mostly centered in optogenetics, its applicability in clinical trials has yet to be evaluated. The utilization of transcranial magnetic stimulation (TMS) has demonstrated enhanced efficacy in promoting neuronal activity, particularly in the context of clinical application for depression treatment. Specific brain regions are stimulated in order to reduce symptoms of depression. This approach is currently regarded as a generally safe strategy with little side effects. However, the therapeutic efficacy of this strategy is not readily apparent [25]. Depending on the specific circumstances, the current utilization of monoamines remains higher. Overall, TMS exhibits superior research value. Furthermore, at present, there are no pharmaceutical substances that facilitate neuronal stimulation in certain areas of the brain, and medications are more susceptible to adverse reactions and long-term reliance. Regardless of the methodology employed, it is imperative to consider the disparities in the kinds, arrangement, and composition of PFC neurons between the human PFC and those of mice or other animals when converting animal investigations into clinical applications. The mPFC, which encompasses a significant amount of the brain's PFC area, has a greater abundance of neuronal subtypes and synaptic connections. It assumes a crucial function in higher cognitive processes and emotional regulation,

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hence proportionally enhancing its significance [26]. Due to its inherent complexity, the application of this concept necessitates a more cautious approach.

6. Conclusions

All things considered, there is strong evidence that aberrant PFC neuronal activity is important for the circuits linked to depression and sleep patterns, probably in both directions. This paper examines the correlation between sleep and depression, as well as the impact of abnormalities in PFC neurons on sleep and performance resembling depression. Based on a synthesis of existing data, it is hypothesized that prolonged stress leads to a reduction in the functioning of PFC neurons. This drop in activity subsequently impacts the PFC-LH-HPA circuit, resulting in an irregular sleep pattern and ultimately causing depression. Indeed, additional investigation is required in order to elucidate the sequence, such as to what extent does stress contribute to diminished neural activity? What is the initial pathway that becomes activated? What are the other behaviors that are influenced by PFC projection? Furthermore, it is imperative to take into account the impact of additional neural circuits, such as the amygdala and the hippocampus, on behavior, cognition, and emotion. These studies aim to elucidate the atypical functioning of PFC neurons in mood disorders and its association with the sleep circuitry. This will facilitate the advancement of therapeutic procedures and strategies that are more efficacious, secure, and tailored to specific needs.

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