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Review

Sleep Disruption During Adolescence: Effects on BMAL1 Gene Expression and Psychiatric Vulnerability

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Abstract: Sleep disruption (SD) is an increasingly alarming public health crisis with profound implications for psychiatric disorders. Particularly vulnerable are adolescents, who are in a critical period for brain development; insufficient sleep exacerbates neuro-developmental risks and predisposes to long-term cognitive and emotional deficits. A growing population with insomnia and other sleep disorders worldwide indicates the importance of understanding the underlying molecular mechanisms to develop targeted interventions. This study integrates clinical data, neurological studies, and molecular evidence from animal models to investigate the topic. Our analysis shows how the impacts of SD on circadian regulator BMAL1 impair prefrontal cortex (PFC) and hippocampus development, and how they are linked to common mood disorders such as depression and anxiety. Notably, key findings from the previous studies demonstrate that circadian misalignment in mice disrupts BMAL1 rhythms in prefrontal and hippocampal regions; in particular, it suppresses oligodendrocyte maturation genes and reduces myelination. Human clinical studies consistently link SD to mood disorders, while neurobiological evidence reveals the adolescent brain's heightened vulnerability--a consequence of the ongoing maturation of the PFC, which governs emotional regulation and cognitive control. This developmental immaturity explains why teenagers are uniquely susceptible to sleep-related disruptions, often manifesting as heightened emotional reactivity and increased risk of mood disorders. Integrating these findings, this analysis identifies BMAL1-mediated oligodendrocyte dysfunction as a plausible pathway connecting sleep disruption to psychiatric risk. However, while animal models provide compelling evidence, the translational relevance to human adolescents requires further validation through longitudinal clinical studies and mechanistic investigations. Future research should prioritize direct targeting of SD-induced BMAL1 dysregulation and its downstream effects, with particular emphasis on developing personalized interventions tailored to individual circadian profiles and novel precision therapies optimized for adolescent neurodevelopmental windows.

Keywords: sleep disruption; adolescence; BMAL1; psychiatric vulnerability

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1. Introduction

Sleep disruptions (SD), frequently resulting from academic demands or workloads, significantly impair functioning, are a growing public health concern due to their profound impact on daily functioning and long-term mental health [1]. These disruptions man-ifest as difficulties falling or staying asleep, non-restorative sleep, or irregular sleep-wake patterns, all of which contribute to cognitive deficits and emotional dysregulation. Alarmingly, recent studies have found an increasing trend for the prevalence of insomnia, a disorder characterized by frequent sleep disruptions-such as trouble falling asleep, staying asleep, or waking too early-both for females and males, with adolescents being particularly susceptible. Such SD alterations in normal sleep patterns may lead to dis-comfort or impaired functioning, more severely, mood disorders [2]. A key biological pro-cess affected by these disruptions is the circadian rhythm, the biological processes that follow a

roughly 24-hour cycle, regulated by core clock genes such as Brain and Muscle ARNT-Like 1(BMAL1), which are disturbed by SD. Disruptions to these rhythms-whether from environmental, behavioral, or pathological causes-may dysregulate BMAL1 ex-pression. Altered BMAL1 expression during adolescence, a critical period of neurobio-logical and hormonal development, may contribute to the pathogenesis of severe mental illnesses, including bipolar disorder [3]. Existing clinical interventions do not yet directly target BMAL1 dysregulation. This study systematically examines the mechanistic path-ways linking adolescent sleep disruption to BMAL1-mediated circadian disturbances and in-creased psychiatric vulnerability, underscoring the need for more targeted therapeutic approaches [4]. In addition to the immediate cognitive and emotional consequences, chronic SD imposes cumulative strain on multiple physiological systems, including im-mune, metabolic, and cardiovascular networks; these systemic effects can create feed-for-ward loops that further destabilize sleep and mood regulation. During adolescence, on-going synaptic pruning, hormonal changes, and maturation of fronto-limbic circuits ren-der individuals especially sensitive to repeated sleep loss, reducing resilience and increas-ing the likelihood that transient disturbances become entrenched [5]. Environmental con-tributors—such as irregular schedules, excessive evening light exposure from screens, so-cial jetlag, and intensified academic pressure—commonly interact with genetic suscepti-bility to magnify circadian misalignment [6]. Mechanistically, BMAL1 dysregulation may alter the timing and amplitude of downstream clock-controlled genes, perturbing neuro-transmitter systems (for example, serotonergic and dopaminergic signaling), stress-re-sponse pathways (including the hypothalamic–pituitary–adrenal axis), and inflammatory cascades, all of which are implicated in mood disorder pathophysiology. Translationally, these insights argue for multimodal interventions that combine behavioral chronotherapy (sleep schedule stabilization, light exposure management), psychosocial support, and in-vestigation of chronobiotics or gene-modulatory agents that restore normal clock gene function. Future research should prioritize longitudinal adolescent cohorts, mechanistic animal models, and early-phase clinical trials to evaluate whether targeting BMAL1-re-lated pathways can prevent the progression from SD to severe psychiatric illness, and support public-health initiatives [7].

2. Increasingly Serious Sleep Problems Among Teenagers

According to the CDC, 57.8% of middle school students from the United States ex-perienced insufficient sleep, with nearly 12% sleeping less than 6 hours per night [8]. Among high school students, the figures were higher, with 72.7% reporting insufficient sleep and approximately 20% sleeping under 6 hours each night, while the American Academy of Sleep Medicine recommends that teenagers 13 to 18 years of age should sleep 8 to 10 hours per 24 hours on a regular basis [9]. This indicates a worsening situation in which teenagers are getting increasingly insufficient sleep, leading to chronic sleep dep-rivation, which has been proven to be linked with mental disorders such as major depres-sive dis-order and bipolar disorder. Beyond these alarming prevalence figures, what be-comes evident is the cumulative burden that repeated nightly sleep restriction imposes on adolescent development. Insufficient sleep compromises not only emotional stability but also memory consolidation, learning efficiency, and executive functioning, all of which are fundamental for academic performance and social adjustment. Physiological conse-quences extend to immune dysregulation, impaired glucose metabolism, and increased vulnerability to obesity and cardiovascular conditions, showing that the impact of sleep loss extends far beyond mental health alone. Moreover, the mismatch between biolog-ical sleep needs and social demands, such as early school start times, extracurricular activities, and extensive screen exposure late at night, creates a structural environ-mental barrier that amplifies the sleep crisis [10]. Importantly, longitudinal research suggests that ado-lescents who consistently experience short sleep durations are more likely to carry these

patterns into adulthood, thereby establishing a trajectory of heightened risk for psychiatric disorders and chronic physical illnesses [11]. These findings underscore an urgent public health priority: aligning school schedules, family routines, and digital media use with evidence-based recommendations, while also developing interventions that target not only sleep hygiene but also circadian alignment and stress reduction to effectively mitigate the long-term risks associated with adolescent sleep insufficiency [12].

3. Adolescent Vulnerability to Psychiatric Disorders

In a period with ongoing Prefrontal Cortex(PFC) and Hippocampus development, synaptic pruning and oligodendrocyte(OL) maturation continue until teenagers reach adult synapse density in late adolescence. That is why adolescents are especially vulnerable during such a period. Sleep disruptions(SD), like other kinds of stressors, such as exposure to alcohol, during this sensitive phase, can impair PFC and Hippocampus maturation, potentially affecting gene expression patterns, including circadian clock genes like BMAL1, therefore increasing susceptibility to psychiatric disorders. This vulnerability is not only structural but also functional, as the PFC is essential for executive control, decision-making, and emotional regulation, while the hippocampus is central to memory consolidation and spatial learning [13]. When these brain regions are repeatedly challenged by insufficient or fragmented sleep, their developmental trajectories may be altered in ways that are difficult to reverse. For example, prolonged sleep loss has been shown to disrupt synaptic plasticity, reduce neurogenesis within the hippocampal dentate gyrus, and impair myelination processes mediated by oligodendrocytes, all of which are critical for the maturation of efficient neural circuits [14]. Moreover, changes in BMAL1 expression caused by SD may cascade into dysregulation of downstream molecular pathways, influencing neurotransmitter systems such as dopamine and serotonin that are already undergoing reorganization during adolescence. The combined effect of disrupted maturation, impaired neurochemical balance, and maladaptive gene expression patterns increases the probability that transient developmental stress will evolve into enduring psychiatric vulnerability. Taken together, these insights suggest that adolescence represents a window of heightened neurobiological sensitivity where the interaction between sleep quality, environmental stressors, and molecular regulators of circadian rhythms plays a decisive role in determining long-term mental health outcomes.

4. The Impacts of Sleep Disruptions on BMAL1 Expression

When the circadian rhythm(CR) acts normally, CLOCK/BMAL1 heterodimers activate Per, Cry, and Rev-erbα/β genes during the day. Fittingly, PER/CRY proteins accumulate and inhibit CLOCK/BMAL1 at night, creating a 24-hour oscillation. Conversely, when CR is disrupted, shifted light/dark cycles desynchronize the Suprachiasmatic Nucleus and peripheral clocks such as the PFC and Hippocampus, which leads to direct dysregulation of core clock genes [15]. Specifically, BMAL1 mRNA rhythms become phase-shifted and abnormally amplified at night when compared to normal levels, while other clock genes lose their rhythmic expression patterns. This loss of synchronization is more than a molecular anomaly; it has downstream consequences for neuronal excitability, synaptic plasticity, and hormonal secretion patterns. For instance, misalignment between the central pacemaker in the Suprachiasmatic Nucleus and peripheral oscillators in cognitive and emotional brain regions disrupts the temporal coordination of neurotransmitter release, thereby altering dopaminergic, serotonergic, and glutamatergic signaling. These disruptions can impair learning, emotional regulation, and stress reactivity, domains that are especially sensitive during adolescence. In addition, abnormal amplification of BMAL1 expression at night can interfere with metabolic homeostasis by altering the timing of glucose and lipid metabolism, creating a physiological state that further destabilizes brain function [16]. Evidence from animal studies suggests that circadian misa-

lignment also heightens vulnerability to oxidative stress and inflammatory responses, amplifying the risk of long-term neural damage. Thus, the breakdown of rhythmic gene expression should be understood as a multifaceted biological disturbance that compromises both neural circuitry and systemic physiology, providing a mechanistic link between environmental perturbations such as irregular sleep and the emergence of psychiatric and metabolic disorders [17].

5. BMAL1 Dysregulation and Risk for Psychiatric Disorders

Over-expressed BMAL1 levels in PFC and Hippocampus at night directly contribute to increased psychiatric disorder risks: Nighttime BMAL1 peaks suppress OL maturation genes, including Cnpase, Mobp, Mag, etc, and inhibit the AKT/mTOR pathway, which is critical for OL differentiation. These result in the production of fewer mature OLs and reduced myelination in mood-related brain regions. Insufficient production of mature OLs compromises myelin repair and maintenance and accumulates damage to white matter integrity, and disrupts communication in emotional processing networks [18]. The demyelination due to BMAL1 dysregulation also aligns with human studies linking OL dysfunction to most of the major mental illnesses and depression, and anxiety-like be-haviors. Beyond these direct effects, impaired oligodendrocyte differentiation alters axonal conduction velocity and reduces synchrony across distributed neural circuits, which is particularly detrimental for brain regions like the PFC and hippocampus that rely on efficient information transfer for working memory, decision-making, and emo-tional regulation. Furthermore, inhibition of the AKT/mTOR pathway not only interferes with OL development but also broadly impacts cellular growth, protein synthesis, and energy metabolism, amplifying neuronal vulnerability to stress. Animal models have demonstrated that chronic BMAL1 overexpression disrupts myelin thickness and induces behavioral phenotypes resembling anhedonia, cognitive inflexibility, and heightened anxiety, reinforcing the causal role of circadian gene dysregulation in psychiatric risk. In parallel, neuroimaging studies in humans have revealed reductions in white matter integrity in adolescents and young adults with sleep disturbances, suggesting that these molecular and cellular alterations translate into clinically observable structural abnor-malities [19]. Taken together, these findings emphasize that BMAL1 overexpression creates a cascade of deficits at genetic, cellular, circuit, and behavioral levels, making it a crit-ical target for mechanistic research and the development of therapeutic strategies aimed at preserving oligodendrocyte function and white matter health in vulnerable populations [20].

6. Potential Interventions to Alleviate Sleep Disruption and Its Consequences

Emerging empirical findings suggest that multiple intervention strategies are capable of moderating detrimental clinical outcomes associated with adolescent sleep disruption (SD). However, the effectiveness of the available methods is varied, and most of the interventions are yet to be further supported by empirical evidence. At present, available interventions can be broadly categorised into pharmacological and chronobiological domains, each addressing distinct facets of the sleep-circadian-psychopathology axis [21].

Pharmacological interventions demonstrate particular promise by virtue of their capacity to modulate endogenous circadian pathways. Melatonin agonists, for instance, have been shown in animal models of chronic sleep deprivation to upregulate BMAL1 expression, thereby attenuating cognitive impairment through a reduction in oxidative stress in hippocampal and prefrontal regions. In adolescents with delayed sleep-wake phase disorder, low-dose melatonin significantly improves sleep onset latency; however, the intervention's direct influence on BMAL1 rhythms in humans remains to be elucidated. Supplementary concerns include observations that sustained high-dose treatment with melatonin antagonists may paradoxically disrupt circadian regulation.

From a chronobiological perspective, timed light exposure constitutes an efficacious strategy for re-aligning circadian rhythms by suppressing melatonin secretion, thereby

imparting indirect effects on the regulation of BMAL1-driven transcriptional activity. Endogenous adolescent sleep patterns have been linked to significant increases in sleep duration and daytime alertness with delayed or modified school start times that are synchronised with endogenous adolescent sleep patterns. In contrast, evening "digital curfews" designed to restrict blue light exposure from screens have been shown to mitigate further circadian disruption by curbing unwanted phase delays.

To date, the majority of interventions remain under-evaluated for their specific effects on adolescent BMAL1 expression. Phenotypic heterogeneity-manifested through differing circadian chronotypes-further complicates the formulation of universally applicable recommendations. Consequently, longitudinal investigations combining polysomnography with molecular profiling, such as BMAL1 expression assays, should be prioritized for identifying the adolescents who benefit most from each strategy. Absent such evidence, a personalised, multimodal approach-integrating chronobiological and pharmacological modalities-constitutes the most pragmatic path forward for mitigating SD's cascading effects on mental health.

7. Conclusion

Chronic sleep disruption(SD) impairs BMAL1's regulation of OL maturation and myelination, particularly in mood-related circuits like the PFC and hippocampus. These disruptions, compounded by developmental vulnerabilities in adolescence, may escalate long-term psychiatric risk. While current findings underscore the need for public health measures to protect adolescent sleep, future work should explore BMAL1-targeted therapies and biomarkers to identify at-risk individuals. Ultimately, recognizing sleep's role in circadian myelination reframes it not just as a restorative process but as an active safeguard against mental illness. Currently existing intervention methods, including pharmacology and chronobiology, are capable of mitigating certain parts of SD's physiological and psychological effects on human bodies. However, future explorations in other approaches are required to directly address SD-induced BMAL1 dysregulation and linked effects. They should invest more in investigating personalized intervention strategies based on individual circadian phenotypes and exploring novel methods to enhance the precision and effectiveness of sleep-related treatments during critical neurodevelopmental periods, in other words, adolescence.

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