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Circadian Disruption to Cognitive Impairment: Integrating Depression, Sleep and Immune Biomarkers

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Abstract
Circadian sleep disruption is a prominent contributor to cognitive impairment, with growing evidence pointing to the mediating roles of depressive symptoms and immune dysregulation. Psychoneuroimmunology (PNI) models indicate that irregular sleep schedules alter homeostatic sleep pressure, dysregulate the hypothalamic–pituitary–adrenal (HPA) axis, and elevate inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and cortisol (Besedovsky et al., 2019; Irwin & Opp, 2017). Depression further magnifies this pathway by promoting immune activation and reducing neurotrophic signaling, particularly brain-derived neurotrophic factor (BDNF) (Castrén & Hen, 2013). These biologically driven alterations collectively impair attention, working memory, and executive functioning (Franzen & Buysse, 2019). This narrative review synthesizes multidisciplinary evidence demonstrating how sleep irregularities lead to cognitive dysfunction through depression-mediated immune and neuroendocrine mechanisms. A biomarker-driven model is proposed to highlight inflammatory and neurotrophic pathways linking circadian disruption and cognitive decline. Understanding these pathways offers opportunities for integrative therapeutic strategies including sleep-schedule modification, anti-inflammatory interventions, and mood-focused treatments to attenuate cognitive impairment.

Keywords: circadian disruption; sleep irregularity; inflammation; C-reactive protein; interleukin-6; tumor necrosis factor-α; cortisol; BDNF; depression; cognitive impairment; psychoneuroimmunology.

1. INTRODUCTION

Circadian sleep disruption has emerged as a modifiable risk factor for cognitive decline across both clinical and community populations (Bryant et al., 2021). Neurobiological evidence indicates that irregular sleep schedules provoke chronic physiological stress, characterized by elevated inflammatory cytokines and dysregulated neuroendocrine function (Besedovsky et al., 2019; Irwin & Opp, 2017). Individuals with inconsistent or shortened sleep duration commonly exhibit impairments in attention, working memory, and executive functioning (Franzen & Buysse, 2019). Importantly, these deficits cannot be fully explained by sleep duration alone; mood disturbance and immune activation are increasingly recognized as key mediators of the impact of disrupted sleep on neural processes (Baglioni et al., 2016; Spiegelhalder et al., 2020).

From a psychoneuroimmunology (PNI) perspective, circadian disturbance disrupts restorative immune processes, promoting chronic low-grade inflammation. Elevated CRP, IL-6, and TNF-α are consistently associated with sleep disturbance and depressive symptoms (Irwin & Opp, 2017; Lasselin et al., 2021). Concurrently, reduced BDNF expression and cortisol rhythm disruption undermine neural plasticity and contribute to cognitive dysfunction (Carvalho et al., 2014; Castrén & Hen, 2013; Kim et al., 2021). These converging changes suggest that sleep-schedule disturbance initiates a biological cascade leading to cognitive deterioration. This review synthesizes evidence from sleep research, affective neuroscience, and PNI, and proposes an integrated biomarker model explaining how circadian disruption, depression, and immune dysregulation jointly shape cognitive outcomes.

2. Circadian Dysregulation and Cognitive Decline

Circadian rhythms orchestrate neuronal metabolism, synaptic pruning, memory consolidation, and glymphatic clearance of neurotoxic metabolites that accumulate during wakefulness (Walker & van der Werf, 2021). The suprachiasmatic nucleus (SCN) in the hypothalamus serves as the master clock that synchronizes these processes with the light–dark cycle. Disruption of sleep timing. through irregular bedtimes, variable wake times, or misalignment between biological and social clocks can impair hippocampal long-term potentiation (LTP), weaken synaptic plasticity, and interfere with prefrontal regulatory control (Gong et al., 2020). Experimental studies manipulating sleep timing rather than duration demonstrate that increased night-to-night variability produces cognitive deficits even when total sleep time is held constant (Chen & Chen, 2022). SCN dysfunction and mistimed light exposure further dysregulate melatonin secretion and increase oxidative stress, magnifying neuronal vulnerability (Bryant et al., 2021).

3. Depression as a Mediator Between Sleep and Cognition

Depression frequently co-occurs with insomnia and circadian misalignment and is a key mediator of sleep-related cognitive impairment (Baglioni et al., 2016; Spiegelhalder et al., 2020). Sleep disruption increases vulnerability to depressive symptoms through serotonergic imbalance, altered rapid eye movement (REM) architecture, and HPA-axis dysregulation (Treadway & Pizzagalli, 2014).

3.1 Neuroendocrine Pathway

Chronic sleep disturbance elevates nocturnal cortisol levels and blunts the normal diurnal decline, resulting in a dysregulated cortisol rhythm (Kim et al., 2021). Sustained hypercortisolemia suppresses hippocampal neurogenesis, promotes dendritic atrophy, and impairs connectivity within memory and executive networks (Carvalho et al., 2014).

3.2 Neurotrophic Pathway

Sleep disturbance and depression are both associated with reduced expression of BDNF, a key neurotrophin regulating synaptic remodeling and neuronal survival (Castrén & Hen, 2013). Reduced BDNF weakens synaptic remodeling and impairs cognitive flexibility and recall (Bjurstrom & Giridharan, 2020).

4. Inflammatory Biomarkers Linking Sleep and Cognition

Inflammation is a central biological mechanism connecting circadian disruption to cognitive function. Elevated CRP, IL-6, and TNF-α are associated with sleep irregularity, depression, and impaired cognitive functioning (Aguirre et al., 2019; Irwin & Opp, 2017).

CRP reflects chronic low-grade inflammation and correlates with fragmented sleep and cognitive slowing (Besedovsky et al., 2019).

IL-6 is highly responsive to acute sleep loss and contributes to mood dysregulation and attention deficits

(Lasselin et al., 2021).
TNF-α disrupts synaptic plasticity and slows working memory and processing speed (Gong et al., 2020).

4.1 Neuroimmune Mechanisms

Pro-inflammatory cytokines can cross the blood–brain barrier and activate microglia, altering glutamatergic signaling and disturbing network stability (Bjurstrom & Giridharan, 2020). Chronic immune activation disrupts dopaminergic and cholinergic pathways in the prefrontal cortex, impairing executive functioning and attentional control (Kim et al., 2021; Raison et al., 2013).

5. Integrated Psychoneuroimmunology Pathway

Circadian irregularity → Sleep disturbance → HPA dysregulation + ↑ cytokines + ↓ BDNF → Depression → Cognitive impairment
(Bryant et al., 2021; Castrén & Hen, 2013; Gong et al., 2020; Irwin & Opp, 2017)

6. Clinical Implications

- Prioritize sleep-schedule regularity, not only duration (Chen & Chen, 2022).
- Consider anti-inflammatory strategies such as exercise and omega-3 supplementation (Aguirre et al., 2019).
- Use chronotherapy and CBT-I to treat circadian misalignment (Spiegelhalder et al., 2020).
- Apply stress-management interventions to normalize cortisol rhythms (Kim et al., 2021).

Implement BDNF-enhancing interventions such as physical activity and antidepressants (Castrén & Hen, 2013).

7. Conclusion

Circadian disruption impairs cognition via depression-mediated immune and neuroendocrine mechanisms. Elevated inflammatory cytokines, dysregulated cortisol, and reduced BDNF are central biomarkers linking sleep disturbances to cognitive decline. Integrative therapeutic approaches targeting sleep-schedule regulation, immune signaling, and mood symptoms may meaningfully reduce cognitive impairment.
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