

Influence of Circadian Rhythm on Learning and Memory

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Abstract. Circadian rhythms are regulated by the suprachiasmatic nucleus (SCN) in the hypothalamus and are critical for coordinating physiological and cognitive functions. Although a great many studies have centered on the role of sleep in memory, this paper concentrates on the independent role that the circadian rhythm itself plays in learning and memory. This study combines data from animal models (e.g., Siberian hamsters, mice) and human populations, combining behavioral tests (e.g., new object recognition tasks), electrophysiological recordings, and molecular mechanism studies. The results show that loss of SCN rhythm impairs memory function dependent on the hippocampus, even when sleep timing is not altered. SCN dysfunction also has an impact on long - term potentiation (LTP) in the hippocampus and the expression of core clock genes. In humans, the disruption of circadian rhythms, which is caused by shift work or aging, is closely associated with decreased attention and memory. Interventions such as light therapy and regulation of GABA pathways have been found to help restore cognitive function. The findings highlight the importance of circadian stability for memory and support its use as a potential therapeutic strategy direction.

Keywords: Circadian rhythms, Memory consolidation, Suprachiasmatic nucleus, Hippocampus, Cognitive neuroscience

1. Introduction

Circadian rhythms are a biological rhythm that repeats about every 24 hours. It regulates important physiological behaviors such as sleep, eating, hormone production and cognitive activity. This rhythm is mainly dominated by the suprachiasmatic nucleus (SCN) located in the hypothalamus, which regulates the biological clock according to external light signals and thus maintains the stability of the circadian rhythm [1]. Although a great many studies have demonstrated that sleep plays a crucial role in memory consolidation [2], an increasing amount of evidence indicates that circadian rhythms per se play an important part in learning and memory, even without any alteration in the length of sleep. As an important structure in the brain that is responsible for spatial and declarative memory, there exists a functional connection between the hippocampus and the SCN at the levels of nerve and hormone. Recent experiments have shown that disruption of SCN rhythms can impair hippocampal-related learning and lead to a decline in long-term enhancement (LTP), a physiological marker of neuroplasticity and memory coding [3,4]. The emergence of these memory impairments is not contingent upon sleep deprivation; rather, it is directly associated with

the disruption of rhythmic central function. A profound understanding of the mechanism by which circadian rhythm influences learning is not only conducive to comprehending the mechanism of memory formation from the perspective of basic neuroscience, but also of great significance for practical applications. For example, night shift workers, students with irregular schedules, and older adults with neurodegenerative diseases often experience varying degrees of cognitive impairment due to circadian rhythm disturbances. This paper will explore the potential mechanisms by which circadian rhythms regulate memory formation, synthesize animal and human research evidence, and discuss current and possible future interventions to mitigate memory deficits caused by rhythm disturbances.

2. Biological mechanisms of circadian influence on memory

Circadian rhythms modulate memory through circuit-level and molecular mechanisms. At the heart of this regulation is the SCN which acts as the brain's master clock. While the SCN does not participate directly in memory formation, it communicates to cognitive circuitry, especially to the hippocampus through hormonal pathways, modulation via neurotransmitters, as well as through intermediate hypothalamic structures where the SCN sends projections.

One suggested route is that the SCN may indirectly modulate hippocampal function via hypothalamic relays, e.g., subparaventricular zone (sPVz) and dorsomedial hypothalamus (DMH). These regions mediate arousal and autonomic rhythms and may serve as intermediaries through which the SCN (suprachiasmatic nucleus) exerts modulation on cortical and limbic activity. In addition, orexin-expressing neurons in the lateral hypothalamus could connect circadian and cognitive processes, especially those related to wakefulness and attention. Melatonin secretion has been also attributed to regulating hippocampal neuroplasticity by influencing sleep timing in rodents[5], although this process may not be present in all rodent strains, such as C57BL/6J.

As shown in Figure 1, the SCN receives photic information from the retina through the retinohypothalamic tract (RHT) and projects through a multi-synaptic pathway to hypothalamic nuclei involved in sleep-wake regulation, including the VLPO, TMN, and PVN. These nuclei might then modulate the hippocampus via diffuse modulatory systems or circadian-timed hormone secretion. Although the anatomical connectome between SCN and hippocampus is not well characterized, strong evidence supports functional regulation by rhythmic changes in hippocampal LTP and clock gene transcription[6,7].

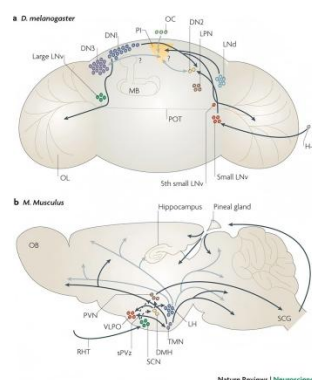


Figure 1: Schematic illustration of circadian circuitry in (a) fruit fly and (b) mouse brain. While connections between clock neurons and memory centers (e.g., mushroom bodies) are established in *Drosophila*, the mammalian SCN influences the hippocampus

primarily through intermediate hypothalamic regions and neuromodulatory pathways[6,7]

At the molecular level, the major components of core clock genes, such as BMAL1, CLOCK, PER1/2, and CRY1/2, are rhythmically expressed in the hippocampus and have an influence on synaptic plasticity. For example, deletion of BMAL1 was shown to disrupt LTP and compromise memory consolidation [8]. These genes govern the generation of transcriptional loops that impact neurotransmission, such as GABAergic and glutamatergic signaling, which are crucial for learning.

In *Drosophila*, an invertebrate, the connections between rhythm neurons and memory centers, such as the mushroom body, are clearer. As shown in Figure 1a, these rhythm neurons receive light input and send time signals to downstream neural circuits. In contrast, Figure 1b shows that the connections between SCN and memory-related structures in mammals are more indirect, and the specific mechanisms are still being further explored [5].

3. Experimental evidence

3.1. Animal studies

In rodents, experimental studies have shown that a functional circadian system is required for hippocampal-dependent memory formation, regardless of sleep [3], as well as the metabolism of certain nutrients [4]. Ruby et al. [3] employed a dark disruptive phase shift (DPS) protocol in Siberian hamsters (*Phodopus sungorus*), resulting in a complete annulment of circadian rhythmicity with no loss of sleep quantity. The protocol involved a light pulse during the night (ZT12-X) followed by a 3-hr delay in the light–dark (LD) cycle. Control hamsters exhibited strong circadian activity patterns, whereas DPS-treated animals were arrhythmic after a few days (Figure 2A–B).

Neurocognitive test using the Novel Object Recognition (NOR) task. Performance, defined as the discrimination index (DI), reflecting a preference for the novel over the familiar object (ssc.tamc.edu.tw), was used to determine memory. As shown in Figure 2C, control animals demonstrated robust recognition memory at a 60 min delay ($P < 0.001$), whereas arrhythmic animals did not discriminate the novel object at 20 or 60 min ($P > 0.05$), but performed normally at 0-minute delay. The data indicates that short-term memory preservation is intact but memory consolidation and retention are disrupted in the absence of functional SCN.

The performance also differed throughout the circadian cycle. Control animals tested at a range of Zeitgeber Times (ZT; Fig. 2D) showed a time-of-day dependent change in DI, while arrhythmic animals showed no significant performance at any time point. This data highlights that circadian phase, not simply sleep status, modulates memory function.

More work by Snider et al. supports these behavioral results at the neural level. Using electrophysiological recordings, they found that LTP, a cellular correlate of memory, was significantly reduced in arrhythmic animals, but LTP was restored following SCN ablation[6]. This shows that the SCN itself, when dysfunctional, actively disrupts hippocampal plasticity and that its removal can relieve this inhibition.

Pharmacological manipulation also provides insight into SCN-cognition interaction. Colas et al. [4] showed that pentyleneetetrazole (PTZ)-induced GABA_A receptor blockade restores the memory of a Down syndrome mouse model. Similarly, Ruby et al. [3] reported that PTZ administration significantly promoted NOR performance in arrhythmic hamsters across a broad background of ongoing circadian disruption. This indicates that excessive inhibitory output from the SCN may

provide an inhibitory effect on cognitive circuits, and it is worth investigating this pathway for therapeutic purposes.

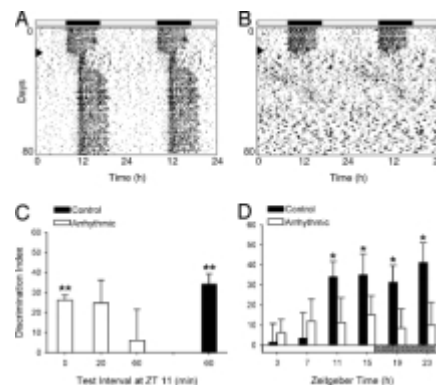


Figure 2: Circadian disruption impairs object recognition in hamsters. (A) Control hamster with stable circadian rhythm[3]. (B) DPS-treated arrhythmic hamster. (C) Discrimination index (DI) across different delays (0, 20, 60 minutes) at ZT 11. (D) DI across different circadian phases (ZT 3–23); performance is disrupted in arrhythmic animals

3.2. Human studies

The research also supports the significant role of circadian rhythm regulation in human cognitive function. Valdez et al. found that attention, working memory, and executive function have obvious time - related effects, usually peaking in the morning and evening [9]. These patterns are in line with the circadian rhythm in the body, not just with the waking hours.

Cognitive impairments are well documented in populations experiencing chronic circadian disruption, including shift workers. Wright et al. [10] showed that although total sleep time is comparable, shift workers have deficits in short-term memory, attention, and information processing speed. These impairments are associated with circadian misalignment, rather than sleep deprivation per se [11].

Another relevant context in which circadian dysfunction affects cognition is aging. Mander et al. [12] found that aged individuals with impaired SCN output exhibited simultaneous deficits in sleep quality and hippocampal function. These findings were further expanded by Hood and Amir [13], who provided compelling evidence suggesting that SCN degeneration during aging is partly responsible for defects in circadian stability and memory, exacerbating neurodegenerative processes.

4. Consequences and interventions

Timed circadian disruption is an increasingly recognized contributing risk factor to cognitive decline across populations, including shift workers, adolescents sleeping out of rhythm, and elders. Such outcomes may be attributed not only to an inadequate amount of sleep time but also to the desynchrony between internal circadian timing and external demands.

Effects of circadian disruption on cognition are most prominently seen in the context of shift work. Workers on the night or rotating shifts usually show a desynchrony between their endogenous circadian pacemaker and the imposed work–sleep schedule. Even when total sleep time is controlled for, this results in cognitive deficits in attention, working memory, and decision-

making speed[14]. These results indicate that circadian misalignment, but not sleep deprivation per se, is a significant contributor to impaired cognitive functioning in shift-working populations.

Circadian disruption is also a strong contributor to cognitive decline during aging. In older individuals chronobiological deficits include attenuated SCN output, diminished amplitude rhythms, phase delays of core body temperature and melatonin secretion[13]. These physiological changes correlate with impaired memory, especially on hippocampal dependent tasks. In fact, longitudinal studies examining older healthy individuals have reported associations between long-term circadian disruption and higher β -amyloid deposition and accelerated memory impairments[15]. These findings underscore the relevance of maintaining circadian integrity to cognitive health across the lifespan.

Considering the negative implications of circadian disruption, several intervention strategies have been devised to reduce its effect on cognition. The most powerful of these is light therapy, especially the use of short-wavelength (blue) light. Sleepless: The scope of blue light evidence is limited to insomniacs, and waking it during the ultra morning or early day can improve both alertness and cognitive ability, even in blinds who cannot consciously see[16]. These effects are mediated by melanopsin-containing retinal ganglion cells that project directly to the SCN, reinforcing an increasing recognition of the role of circadian mechanisms in the control of cognition.

A second strategy is the use of chronobiotic agents, including melatonin and its agonists, that may manipulate the timing of circadian rhythms. Melatonin, taken when used properly and at the right time, has had some success in treating jet lag, shift work disorder, and delayed sleep phase syndrome, with indirect benefits for mood and cognitive clarity[17]. Yet in older adults, reduced endogenous production and end organ desensitization may limit the efficacy of melatonin.

In addition to pharmacological and photic manipulations, behavioral strategies are also key elements in circadian alignment. Regular sleep - wake schedules, physical activity during the daytime, and exposure to natural light will enhance circadian entrainment and help strengthen cognitive resilience. These methods are of great significance for older adults, as the restructuring of lifestyle could counteract the degradation of endogenous rhythms [18].

In conclusion, circadian disruption represents an apparent danger to learning and memory; however, multiple types of non-invasive and low-risk interventions, especially those that involve light exposure or behaviour timing, can remedy rhythm-cognition misalignment. As contemporary lifestyles increasingly disrupt biological timing systems, these findings hint at a means of safeguarding and enhancing cognitive performance across all ages.

5. Conclusion

Circadian rhythms, maintained by the suprachiasmatic nucleus (SCN), are critical for sleep, hormone release, and cognition. This review elucidated the evidences from both animal and human studies that indicate that circadian rhythmicity, independent of sleep duration, is essential for learning and memory. SCN dysfunction leads to impairments in hippocampal-dependent memory performance and synaptic plasticity and restoration of circadian integrity improves cognitive outcomes. These findings emphasize the brain's reliance on internal timing strategies to support memory consolidation and attentional control.

However, this review must not be without limitations. While this work strongly implicates circadian rhythms in memory formation, the actual number of studies addressing the causal role of circadian rhythms in memory formation is still relatively small. Many of these findings rely on specific animal models like Siberian hamsters or genetically engineered mice, which might not translate perfectly to us. Furthermore, differences in experimental protocols between studies

complicate the investigation of subjective circadian effects unconformity with alternate factors, including stress or sleep disruption.

Future research needs to utilize heterogeneous populations and standardized methods to expand the evidence. Understanding how circadian oscillators interact with cognitive circuits at the molecular level is able to reveal new therapeutic targets. Ultimately, a better understanding of how these circadian rhythms regulate memory will be crucial for formulating strategies to delay cognitive decline across all ages.

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