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NLM Special Issue on Sleep and hippocampal function

Sleep is one of biology's greatest mysteries. Animals and humans spend a significant portion of their lives asleep, yet its functions remain largely unknown. Many cognitive functions that rely on the hippocampus are facilitated by sleep and impaired by sleep deprivation or disturbance. Hippocampal circuit function appears to be particularly vulnerable to sleep loss. Understanding the special role of sleep in hippocampally-mediated cognitive processes, and in hippocampal circuit function, activity, and plasticity is essential for discerning how sleep affects cognition in the healthy brain. Furthermore, because sleep is adversely affected in a wide range of neurocognitive, neuropsychiatric, and neurodevelopmental disorders – from Alzheimer's disease and dementia to autism spectrum disorders and schizophrenia – clarifying how it affects basic neurobiological processes related to cognition may have major implications for treatment strategies. In this special issue, we have curated studies focused on both human subjects and animal models, which address how sleep and sleep loss affect the hippocampus and the cognitive functions it mediates.

Neurobiological features of sleep conducive to hippocampal memory consolidation:

Sleep and wake are characterized by state-specific changes in neuronal activity, electrophysiological properties, and molecular events both in the synapse and the nucleus. In the first paper of this special issue, Navarro-lobato and Genzel (Navarro-Lobato & Genzel, 2018) provide an overview of these changes and associated up and down states that can be observed within a sleep cycle. The authors then explore how these molecular and physiological changes could contribute to the consolidation of information in hippocampal and cortical circuits.

Recent studies examining interaction between the hippocampus and prefrontal cortex have raised questions regarding how activity within and communication between these regions contributes to information storage. Tang and Jadhav (Tang & Jadhav, 2018) provide an overview of recent literature and underscore the importance of sharp wave-ripples in hippocampal-cortical communication during both wakefulness and sleep. Skelin and colleagues (Skelin, Kilianski, & McNaughton, 2018) review qualitative and quantitative features of hippocampal oscillations and hippocampal communication with cortical and sub-cortical structures in the context of memory storage. Their review highlights reactivation of ensembles of neurons during sharp wave-ripples in sleep that were activated in these structures during prior waking experience.

Various hypotheses exist about the role of sleep in memory processing. Some data support a role for sleep in actively forgetting irrelevant information, whereas other studies suggest a role for sleep in extracting and consolidating the most salient features (*i.e.*, the “gist”) of prior experiences. Theoretical models have allowed researchers to test these hypotheses' predictions for comparison with empirical data.

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Rennó-Costa and colleagues (Renno-Costa, da Silva, Blanco, & Ribeiro, 2018) provide an outline of recent advances in the use of models to test the role of sleep in memory processes.

Specific aspects of information encoding and subsequent rehearsal may contribute to sleep-dependent memory processing. Alger and colleagues (Alger, Chen, & Payne, 2018) conducted a study comparing emotional and neutral memories, which were either ‘cued to be remembered’ or ‘cued to be forgotten’ across the day, and with or without subsequent sleep. Memory for negative information, ‘cued to be remembered’, was positively correlated with the relative amount of slow-wave sleep during a nap, while memory for negative information, ‘cued to be forgotten’, was negatively correlated with greater sleep spindle activity. Gideon Rothshild (Rothschild, 2018) examines how hippocampal and cortical circuits incorporate information from multiple sensory modalities during experiences into long-term memories. The review proposes a model in which the cortex is a “fast learner”, which supports and modulates hippocampally-mediated memory consolidation. Such a model may provide insight into memory biasing (*e.g.*, using sensory cues) during sleep. Oyanedel *et al.* (Oyanedel, Sawangjit, Born, & Inostroza, 2018) subjected rodents to two different learning paradigms (“what-where-when” and “what-where-which”), related to different aspects of episodic memory. While sleep was important for the consolidation in both the tasks, the benefit of sleep for memory consolidation was most prominent in the task, which included a temporal component (*i.e.* the “what-where-when” paradigm).

Hippocampus-specific neurobiological effects of sleep vs. sleep loss:

As mentioned in the previous paragraphs, sleep and wake are characterized by state- and region-specific changes in neuronal activity. Delorme and colleagues (Delorme, Kodoth, & Aton, 2018) examined how sleep and sleep deprivation affected transcription and translation of the plasticity-related immediate early gene *Arc* in different brain circuits. Whereas brief sleep deprivation in mice minimally affects *Arc* mRNA in areas CA3 and CA1, it significantly decreases *Arc* mRNA and protein expression in dentate gyrus granule cells. In contrast, in neighboring cortical areas, *Arc* expression is increased, rather than decreased, after sleep deprivation - both at the mRNA and protein level. Raven *et al.* (Raven, Meerlo, Van der Zee, Abel, & Havekes, 2018) also examined how sleep deprivation affects dentate gyrus granule cells in mice, but focused on anatomical changes. The authors showed that a brief period of sleep deprivation reduces dendritic spine numbers in these neurons. Together, these findings underscore the idea that sleep deprivation does not affect the brain uniformly, and can have particularly detrimental effects (*e.g.*, for synaptic plasticity) in the hippocampus.

Oliveira *et al.* (Oliveira, Oliveira, & Hipolide, 2018) examined the impact of multiple days of sleep deprivation and altered adenosine A1

receptor signaling on hippocampus-dependent vs. striatum-mediated learning. Performance in both tasks was negatively impacted by sleep deprivation. However, A1 receptor inhibition prevented impairments in striatum-mediated, but not hippocampus-dependent, learning. At the molecular level, A1 receptor inhibition prevented the sleep loss-induced decrease in cAMP/PKA signaling in the striatum, but not in the hippocampus. Together, these findings underscore the hippocampus-specific impacts of sleep deprivation.

Malerba and Bazhenov (Malerba & Bazhenov, 2018) present a model of how the CA1-CA3 network orchestrates sharp wave-ripple activity during slow wave sleep. The model suggests a critical role for excitatory synaptic activity in reactivating ensembles in both regions, but with different dynamics (i.e., of sharp waves in area CA3 and ripples in CA1). These dynamics promote a differential role for synaptic inhibition in modulating ensemble reactivation in the two areas, and promote greater spike sequence specificity CA3. The model also demonstrates how encoding of spatial information drives synaptic changes in the hippocampus during wake, leading to ensemble reactivation in this region during subsequent sleep.

Sleep and hippocampally-mediated memory in central nervous system disorders:

It is increasingly recognized that sleep loss and/or sleep fragmentation may contribute to cognitive impairments associated with many nervous system disorders. Dufort-Gervais and colleagues (Dufort-Gervais, Mongrain, & Brouillette, 2018) review existing literature to examine the bidirectional relationship between changes in sleep and altered hippocampal beta amyloid load, a common feature of Alzheimer's disease. Sex differences also greatly affects the risk for Alzheimer's disease, with women having a two-fold greater risk after the age of 75. Baker and colleagues (Baker et al. 2018) summarize sex steroid-dependent aspects of sleep-dependent memory processing, and propose a series of testable predictions to define how sex steroids modulate sleep-dependent memory consolidation in adulthood. Van Someren and colleagues (Van Someren et al. 2018) explored the relationship between sleep fragmentation and medial temporal lobe atrophy, using actigraphy and magnetic resonance imaging. They found that sleep fragmentation accounted for almost 20% of the variance in medial temporal lobe atrophy, whereas aging accounted for only 15%. These findings highlight the exciting possibility that some forms of neurodegeneration may be prevented by improving sleep quality.

Using two mouse models for phenylketonuria (PKU) on different genetic backgrounds, Van der Goot et al. (van der Goot et al. 2018) tested whether PKU alters microglia activation, which is commonly associated with sleep deprivation. The authors found a background-specific increase in total microglial numbers, and in microglial activation, that was independent of high phenylalanine levels or disturbed sleep.

Leerssen and colleagues (Leerssen et al. 2018) used functional magnetic resonance imaging to assess how functional connectivity between brain areas was altered in insomnia patients. The authors observed stronger functional connectivity between the hippocampi and the left middle frontal gyrus in patients with more severe insomnia and worse sleep quality. Intriguingly, this particular connection is part of a circuit that activates with maladaptive rumination and deactivates with sleep.

Looking in hospital nurses working day or night shifts, Molzof et al. (Molzof et al. 2019) studied how the misalignment of core body temperature affected cognitive capacity. Their data indicate that circadian disruption and reduced sleep quality predict poorer performance on

cognitive tasks relying on the hippocampus.

Among children with neurodevelopmental disorders, there is a high rate of reported sleep and circadian disruption. Barone et al. (Barone, Hawks-Mayer, & Lipton, 2019) review neurodevelopmental disorders with well-defined molecular genetics, emphasizing that studies of sleep in these patient populations presents a unique opportunity to elucidate the role of sleep and circadian rhythms in cellular mechanisms of neurodevelopment, neuroplasticity, and cognition.

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