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Sleep and spatial memory: Mechanisms, relationships, applications, and potential

Yuanxi Fan

Beijing City International School, Beijing, China, 100022.

2019012070@bcis.cn

Abstract. More and more attention is being paid to the study of sleep and memory because of the immense potential the field has to offer, with the majority of studies focusing on episodic and procedural memory. However, another type of declarative memory – spatial memory – is relatively lesser-known. This review discusses the scientific community's current understanding of spatial memory and its relationship with sleep using both animal and human studies as examples, exploring, in particular, existing knowledge on spatial memory, whether sleep can affect spatial memory, the nature of such a relationship, and cellular mechanisms. The discussion then moves onto some potential applications of recent findings, including actions that researchers have already taken to better incorporate the enhancing properties of sleep on spatial memory into solutions for clinical problems. The review also points out future directions for research, considering the uncertainties in sleep and memory research and the significance of investigating such topics.

Keywords: Sleep, memory, spatial memory, memory consolidation.

1. Introduction

Nowadays, the relationship between sleep and memory has become a popular topic of investigation for both researchers and consumers of scientific information, with the scientific community gradually realizing the seemingly infinite applicational potential that the subject has to offer. In recent decades, countless studies have been conducted on the effects of sleep on episodic memory and procedural memory, but compared to the relative plentitude of such research, it seems that the relationship between sleep and spatial memory – the ability to memorize the location of objects - has been less often discussed.

Despite that, the relevance of spatial memory certainly must not be overlooked; diving deep into how sleep can alter – or perhaps even enhance - spatial memory may reveal new pathways toward tackling related health issues or conducting further research. This is especially crucial because diseases involving spatial memory degradation are very prevalent in the current era, and there is also a great deal of information left for spatial memory researchers to discover. It is for this reason that this paper will synthesize and discuss what is already known about the relationship between sleep and spatial memory, as well as its potential applications and possible extensions.

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2. Basic Mechanisms of Spatial Memory

Spatial memory is defined as the ability to remember the locations of objects and landmarks long-term, which is crucial because organisms must always keep their environmental representation updated and cohesive to navigate efficiently through the intricate, ever-changing physical world.

The modern study of spatial memory from a neurobiological perspective originated largely from the discovery of hippocampal place cells by John O'Keefe and colleagues in 1971, which were found to exhibit responses when an animal reached a particular location in the environment [1-2]. Later, in 1984, James Ranck discovered head direction (HD) cells in the dorsal presubiculum of rats that were activated - in a way that mimics a compass - when the animal showed a certain directional heading [3], which inputted direction-related information into the place system [2]. More recently, May-Britt and Edvard Moser, after discovering that spatial memory relied more on the dorsal rather than the ventral hippocampus, found through further research that grid cells in the entorhinal cortex of rats fired in triangular formations in synchronization with HD cells to reflect environmental cues [4].

Now, researchers can agree that spatial memory relies largely on the medial prefrontal cortex (mPFC) and ventral hippocampus (vHPC). vHPC neurons project to the mPFC and directly influence the formation of spatial representation via the encoding and updating of spatial cues during operative memory tasks, as found in a study involving mice and delayed non-matching to place (DNMTP) tasks in a T-maze [5]. Spellman and colleagues observed that mice injected with a vHPC virus vector that ontogenetically inhibits neurons (Arch+) did not perform as well as those that did not receive the injection (Arch-), indicating that such vHPC inhibitions prevented the encoding of spatial cues necessary for productive decision-making during the DNMTS task [2].

In addition, place cells and grid cells also play essential roles in shaping the architecture of spatial representation. Hippocampal place cells fire when an animal reaches a particular location in the environment [1,6,7]. Areas in which firing rates are high are known as place fields and are usually determined by the existence of landmarks [6]. As the animal's surroundings change, its place cells' firing patterns will also change, a phenomenon known as remapping [7]. Remapping can occur as either rate remapping or global remapping. The former is triggered when nonspatial elements of an environment (e.g., the color of the wallpaper) are changed, while the latter occurs upon transition into an entirely new environment [6]. Rate remapping only changes the firing rate of place cells, whereas global remapping changes both the firing rate and place field.

The place-modulated grid cells exist abundantly in layer II of the medial entorhinal cortex (MEC) and fire in fields arranged as periodic hexagonal lattices, which tesselate to form units of equilateral triangles [6][8]. Grid cells exhibit 3 parameters: the grid phase, or the coordinates of the grid vertices; the grid frequency, or the spacing of the hexagonal fields; and the positioning of the grid axes [8]. Grid cells differ from place cells in that unlike place cells, whose firing combinations differ depending on the environment, grid cells exhibit consistent activity and clusters' relative firing locations across various environments [8]. Within clusters, relative phase differences are typically maintained in the face of environmental changes.

3. The Effects of Sleep on Spatial Memory

Whether sleep presents strong effects on spatial memory has been a popular topic of research for decades. A 1994 study by Wilson and McNaughton - in which the researchers recorded hippocampal place cell activity during spatial behavioral tasks and pre- and post-task slow-wave sleep - has already shown that memories form during activeness are re-expressed in the hippocampus during sleep [9][10]. Indeed, many later studies have also shown that such a conclusion also applies to spatial memory. Nowadays, researchers are concerned not just about the stimulation of cerebral systems but also about the cellular mechanisms that occur in those systems during sleep.

3.1. Animal Research

First and foremost, research on animal models has suggested that sleep indeed does have effects on spatial memory. For instance, a 2013 study by McCoy et al. performed chronic sleep restriction (CSR)

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on rats to record the effects of CSR on the recalling of spatial memory during a water maze task [11]. CSR consisting of 18 h/day of total sleep deprivation (SD) was implemented for 5 days, beginning on the day before day 1 of training and ending with the probe trial to test spatial memory recall. The researchers found that acquisition training was not hindered by CSR, but recall of the platform during the probe trial was impaired, as seen in the substantially longer period taken by the CSR rats to enter the platform zone and the platform-containing quadrant [11].

Incorporating previous findings into their interpretation, the researchers explained that adenosine, an inhibitory neuromodulator, may have mediated the observed behavioral effects [11]. Upon the experimental extension of wakefulness in rats, adenosine levels have been observed to increase in the basal forebrain [11-12]. Furthermore, adenosine inhibits cholinergic neuronal projections from the basal forebrain to the frontal cortex, which are known for their responsibilities in not only attention but also cognitive processes such as memory [11,13], indicating that adenosine may have modulated post-CSR amnesia in the sleep-deprived rats [11]. In addition to adenosine, other neurotransmitters such as serotonin, dopamine, and norepinephrine are also known to mediate sleep characteristics and are being extensively examined for their potential effects on memory and other higher cognitive activities [11].

3.2. Human Research

Likewise, in studies focusing on human participants, researchers found that spatial memory is processed during the asleep state in humans, particularly during NREM sleep [14]. Peigneux and colleagues used cerebrospinal blood flow measurements to show that during post-route-learning slow wave sleep (SWS), the hippocampal regions activated during route learning in a virtual town were reactivated. The researchers estimated the regional cerebral blood flow (rCBF) as an indicator of local synaptic activity in 3 participant groups: (1) during training for a topographical memory task requiring participants to navigate through a complex 3-D virtual town; (2) during all stages of post-navigation nocturnal sleep (SWS, stage 2, REM, and wakefulness); and (3) during all stages of nocturnal sleep without training. The researchers also (4) obtained rCBF data from a prior study [15] that collected measurements during all stages of nocturnal sleep after training for a procedural serial reaction time (SRT) task. The experimental data reflected no significant differences in the sleep characteristics of groups 2 and 3, indicating that any change in brain activity would've been due to pre-sleep training. Groups 2, 3, and 4 all exhibited similar results, increased activity in the bilateral hippocampal formation and parahippocampal gyrus during post-training SWS, stage 2 sleep, and REM sleep compared to during wakefulness. Activity in the bilateral hippocampus and parahippocampal gyrus was higher during SWS than during REM sleep. Subsequent interaction analyses showed that in group 2 vs. 3 interactions (both SWS vs. wakefulness and SWS vs. REM sleep), activity was increased in the right hippocampal and parahippocampal regions for trained subjects during SWS.

4. Implications of Current Findings

With a myriad of discoveries being made, what implications are there to notice and utilize? Given that spatial memory can be seen in action in many aspects of daily life, many researchers are interested in the applicational aspect of the relationship between sleep and spatial memory, in hopes that it can be incorporated into clinical contexts and future research, respectively, solve health-related problems and propel the advancement of extensive research. To see progress in the aforementioned fields, however, an enduring series of questions must be answered: what effect does sleep have on the processing of spatial memory? Is it an enhancement of some sort? What are the mechanisms of said effect? If sleep can indeed strengthen some aspect of spatial memory, then certainly there must be ways to harness this relation for the benefit of humanity.

4.1. Determining the Nature of the Relationship between Sleep and Spatial Memory

A study by Noack and colleagues [16] explored the very basics of this topic – whether post-training sleep can enhance spatial navigation – by examining the effects of sleep on spatial representation that involved the integration of landmark- and boundary-referenced representations by focusing specifically on the hippocampus- and stratal-based systems. Hippocampus- and striatal-mediated encoding of spatial representation was encouraged in the participants (n = 42) as they familiarized themselves with an environment that contained both a landmark and a boundary. The participants then either slept or remained awake the night after familiarization and were afterward exposed to impoverished environments containing the same landmark and boundary, in which they were tasked to learn about novel objects. The researchers found that participants who engaged in post-familiarization sleep utilized spatial retrieval cues more flexibly based on a “superior integrated memory representation” [9]. Based on this, the researchers proposed that sleep affects the integration of the hippocampus-based and striatal-based systems via the establishment of a coordinating representation that mediates interactions between the two systems [9][16].

These findings are significant because they support that post-training sleep can indeed benefit navigation. To extend upon this, the next step would be to investigate the underlying neurological mechanisms behind this enhancement.

4.2. Mechanisms of the Enhancing Properties of Sleep

Other studies have reinforced the aforementioned findings and looked deeper into this topic by identifying the type of brain activity apparent during the sleep-propelled consolidation of spatial memory. Wamsley and colleagues approached the objective by recruiting participants (n = 53) for a hippocampal-mediated virtual maze-learning task to examine whether a daytime nap can enhance navigation performance across a single day [17]. The researchers hypothesized that post-learning sleep would enhance retest performance and indeed, performance did improve for participants assigned the post-learning sleep condition [17]. The researchers also observed, however, that performance was dependent on prior experience with 3D games, as seen in results obtained from a self-report 5-point scale.

Despite this, the study still offers valuable insights regarding the specific electrophysiological features of sleep that may contribute to the enhancement of spatial memory. The researchers designed the study so that the daytime nap consisted of mainly NREM sleep as opposed to REM sleep [17]. Following this logic, any sleep-dependent improvements in maze performance can be confirmed as a result of post-learning sleep. In particular, a robust correlation was observed between considerable improvements during retest and delta band (1-4 Hz) electroencephalogram (EEG) activity during stage 2 NREM [16]. It is also worth mentioning, though, that baseline performance in the maze task correlated strongly with EEG delta power during post-learning sleep, indicating that pre-sleep task performance – or intensive pre-sleep learning in general – is a contributing factor towards subsequent sleep characteristics [17-18]. Either way, increased delta EEG power may foster effective interactions between the hippocampus and neocortex during post-learning NREM sleep, reactivating neural pathways and consolidating learning-related memories [17].

4.3. Potential Applications of Relevant Findings

The above research reflects the tremendous applications of sleep as a tool for enhancing spatial memory, presenting sleep as a potential solver of various real-world problems. The beneficial properties of sleep can be applied in both clinical and research contexts to, respectively, serve those struggling with spatial memory degradation and establish a robust foundation for future research in the field of sleep and spatial memory.

From a clinical standpoint, it is hopeful that sleep can be incorporated into therapeutic strategies targeting diseases that involve the degradation of spatial memory to, at the very least, alleviate symptoms and by extension increase patients' quality of life, lessening the impairment their conditions have on daily activities. For instance, since memory consolidation happens primarily during sleep, methods such as targeted memory reactivation (TMR) have been developed as a means of strengthening memories during sleep [19], effectively utilizing the enhancing properties of sleep to an advantage. So far, TMR has already been shown to improve declarative memory [19,20], and subsequent research has also revealed the possibility that TMR may also be able to enhance other memory types, including spatial

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memory [19]. However, researchers also must overcome a plethora of limitations to ensure the effectiveness of their experiments. TMR requires the presence of experimenters to monitor the sleep activities of the patient and present them with certain cues [19], meaning that the patient must sleep in an environment different from that in the typical bedroom, which may have unwanted effects on sleep characteristics. The effects of multi-session TMR have also largely been left undiscovered due to logistical difficulties, making it difficult to determine the practicality of TMR in clinical settings [19].

To tackle these problems, automated TMR systems have been developed to support relevant therapies at home, with an example being SleepStim developed by Whitmore and colleagues [19]. TMR itself operates by utilizing cues that are associated with learning episodes during NREM sleep [21]. The SleepStim system includes a smartwatch that collects data related to movement and heart rate, as well as a smartphone containing audio cues. SleepStim uses a machine-learning model to identify periods of deep sleep, with auditory cues presented during appropriate sleep periods. Through extensive natural experimentation, the researchers concluded that low-stimulus TMR during undisrupted sleep can reliably enhance spatial memory [19].

Such findings offer a great deal of potential, as they suggest the possibility of incorporating TMR into a home environment, allowing sleep- and memory-related therapy to occur outside of hospitals. This, ideally, will greatly enhance the effectiveness of the therapeutic strategy in which TMR is involved and by extension benefit the health of the individual receiving the treatment. To convert TMR into an accessible solution to health problems, additional research is needed to determine the efficacy of different cue types, as well as whether other sleep characteristics – such as dream content and non-phase-locked entrainment – can be affected by TMR [19].

SleepStim also establishes a foundation for future research, providing opportunities for researchers to explore the undiscovered applications of TMR, which could allow for the application of such a method in the curing of other sleep disorders such as parasomnias, as well as the strengthening of other memory types. This is just one example of how researchers from various fields are collaborating to find applications for scientific discoveries and inventions – such progress is happening in diverse ways in the research of sleep and spatial memory, as well as in the study of other memory types.

4.4. Future Directions for Research

Despite the tremendous progress that has already been made, there still exists a myriad of unknowns. For example, many of the aforementioned studies were not designed to explore whether spatial memory consolidation is exclusive to sleep [14]. In the case of procedural memories, evidence of pre-sleep preconsolidation has been recorded [14], but researchers have yet to verify the existence of this phenomenon with spatial memory. Perhaps there is also a large portion of spatial memory processing that occurs in a less-often-studied phase of sleep or even during wakefulness, but more investigation is needed to pinpoint the timing of such activities and their cellular mechanisms.

In addition, sleep may not be the only physiological process that plays a major role in processing and consolidating spatial memory. Previous research has revealed the inhibitory effects of circadian arrhythmia on declarative memory, in which GABAergic hippocampal inhibition is increased [22]. With that said, looking further into the relationship between circadian rhythms and spatial memory may also offer valuable insights, as this could not only pave the way for further research but also enhance the accuracy of clinical diagnoses and treatments in the case of diseases that involve symptomatic spatial memory impairment.

Above are just two of the many pathways that future research could take to yield new findings that could potentially benefit both the clinical and research aspects of sleep and memory neuroscience. With the rapid pace at which discoveries are being made, more and more clarity will come with our understanding of sleep, spatial memory, and the mechanisms and applications of their relationship.

5. Conclusion

In conclusion, prior studies have already determined a relationship between sleep and spatial memory, and in most cases, researchers have found that sleep can enhance spatial memory in both animal and human models. This consolidation process occurs mainly during NREM sleep, but whether it is exclusive to NREM or even sleep is still unknown. So far, it is known that increased EEG power and the neurotransmitter adenosine may both mediate interactions between the hippocampus and other brain structures, reactivating neural pathways that were strengthened during pre-sleep navigation training. Such findings have already been applied to solve real-world problems in both clinical and research settings, with the SleepStim system being an example of the enhancing properties of sleep on spatial memory being incorporated into accessible TMR in home environments.

In the future, more research is needed to better identify spatial memory consolidation that occurs outside of NREM sleep, as well as other physiological processes that may also affect spatial memory [14,22]. This will unlock new potential in terms of the application of sleep and memory research.

Admittedly, this review is also not an comprehensive evaluation of the current state of sleep and memory research. Indeed, this review has discussed the known mechanisms and applications of sleep's enhancement of spatial memory, but to gain a deeper understanding of the exact cellular mechanisms behind this relationship, additional resources must be considered. Though this review pinpoints the potential neuromodulators and brain structures that are active during the sleep-driven consolidation of spatial memory, it did not explain the details of how these factors interact – an area of improvement that could be targeted in future writings. Still, this review provides the fundamental information needed to better understand how sleep affects spatial memory, and how such a relationship can be applied to tackle real-life problems in both the medical field and research.

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