The role of sleep disturbance and inflammation for spatial memory

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ABSTRACT

Spatial memory is a brain function involved in multiple behaviors such as planning a route or recalling an object’s location. The formation of spatial memory relies on the homeostasis of various biological systems, including healthy sleep and a well-functioning immune system. While sleep is thought to promote the stabilization and storage of spatial memories, considerable evidence shows that the immune system modulates neuronal processes underlying spatial memory such as hippocampal neuroplasticity, long-term potentiation, and neurogenesis. Conversely, when sleep is disturbed and/or states of heightened immune activation occur, hippocampal regulatory pathways are altered, which - on a behavioral level - may result in spatial memory impairments. In this Brief Review, I summarize how sleep and the immune system contribute to spatial memory processes. In addition, I present emerging evidence suggesting that sleep disturbance and inflammation might jointly impair spatial memory. Finally, potentials of integrated strategies that target sleep disturbance and inflammation to possibly mitigate risk for spatial memory impairment are discussed.

1. Introduction

Spatial memory, as generally characterized by the ability to learn, store and recall spatial information, is a brain function involved in multiple behaviors such as planning a route or recalling an object’s location. Robust evidence from both animal and human studies has shown that spatial memory strongly depends on the hippocampus and associated networks (Bird and Burgess, 2008), which makes spatial memory a formidable model for translational research. The initial scientific interest in spatial memory was strongly driven by the discovery of so-called “place cells” in the hippocampus of rats. In 1971, the neuroscientist John O’Keefe published a paper, in which he reported that a specific group of hippocampal neuron cells fire at a high rate whenever a rat is in a specific place in the environment, and proposed that these “place cells” were the basis for the formation of a spatial map (O’Keefe and Dostrovsky, 1971). This work, alongside the more recent discovery of “grid cells” in the entorhinal cortex, led to the award of the 2014 Nobel Prize for Medicine or Physiology to John O’Keefe, May-Britt and Edvard Moser for their discovery of cells that constitute a positioning system within the brain (The Nobel Prize in Physiology or Medicine, 2014).

The formation of spatial memory relies on the homeostasis of various biological systems, including healthy sleep and a well-functioning immune system: while sleep is thought to promote the stabilization of initially labile spatial memory traces and their integration into neocortical networks for long-term storage (Rasch and Born, 2013), the immune system is thought to modulate the neuronal processes underlying spatial memory such as hippocampal neuroplasticity, long-term potentiation (LTP), and neurogenesis (Yirmiya and Goshen, 2011). Conversely, when sleep is disturbed and/or states of heightened immune activation occur, hippocampal regulatory pathways are altered, which - on a behavioral level - may result in spatial memory impairment. Interestingly, converging lines of research suggest that sleep disturbance and inflammation might share common biological pathways to disrupt spatial memory processes, which has clinical implications for several (neuro)psychiatric disorders associated with hippocampal dysfunction, including Alzheimer’s disease (Coughlan et al., 2018) and major depression (Gould et al., 2007; Cornwell et al., 2010).

In this Brief Review, I discuss how normal and disturbed sleep bi-directionally impacts the formation of spatial memory, and how normal and excessive activation of the immune system influences spatial
memory. Moreover, I present emerging evidence suggesting that sleep disturbance and inflammation might jointly impair spatial memory. Finally, I highlight the potentials of integrated strategies that target sleep disturbance and inflammation to possibly mitigate risk for spatial memory impairment.

2. Sleep-dependent formation of spatial memory

Sleep is a naturally occurring state of consciousness that is characterized by reduced responsiveness to external stimuli and suppressed motor activity (Krueger et al., 2016). As evaluated by an electroencephalogram (EEG), sleep can be divided into two major phases, which alternate in a cyclic manner: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. In humans, NREM sleep can further be subdivided into the stages N1, N2 and N3 of increasing depth of sleep. N3 or slow wave sleep (SWS) is defined by the deepest NREM sleep, which dominates the first half of nocturnal sleep. In turn, REM sleep is most intense during the second half of nocturnal sleep. In humans, NREM-REM cycles last between 80 and 110 min, whereas in rodents, NREM-REM cycles are compressed, lasting approximately 15 min.

Both NREM and REM sleep are thought to complementarily regulate different aspects of memory systems. According to the so-called “dual process hypothesis” of memory consolidation, SWS is thought to particularly promote the formation of declarative hippocampus-dependent memory (such as spatial memory), whereas REM sleep is thought to support the formation of non-declarative hippocampus-independent memory (such as procedural and emotional memory) (Ackermann and Rasch, 2014).

At a cellular level, electrophysiological animal studies, some of them dating back three decades or more, have shown that rats exhibit firing patterns in hippocampal place cells during the exploration of an environment, which are later replayed in the same order during subsequent NREM sleep (Pavlovs and Winson, 1989; Wilson and McNaughton, 1994; Kudrimoti et al., 1999; Shen et al., 1998; Skaggs and McNaughton, 1996; Ji and Wilson, 2007; Lee and Wilson, 2002). This so-called “hippocampal replay” during NREM sleep is characterized by high-frequency oscillations also known as “sharp wave ripples” (SWRs), which are thought to transfer spatial information from the hippocampus to neocortical networks for long-term storage (Buzsáki, 2015). Selective suppression of SWRs during post-learning NREM sleep, in turn, has been found to impair the formation of spatial memory in rats (Girardeau et al., 2009). Interestingly, several animal studies have shown that the exposure to various sensory stimuli during spatial learning and again during subsequent post-learning NREM sleep has the potential to augment hippocampal replay. For example, exposing rats to a sound during spatial learning and again during post-learning NREM sleep has shown to amplify the firing rate of hippocampal replay during post-learning NREM sleep (Bendor and Wilson, 2012). However, it should be noted that – in addition to NREM sleep – a small number of studies has also identified hippocampal replay during REM sleep (Louie and Wilson, 2001; Poe et al., 2000) and even during periods of quiet wakefulness (O’Neill et al., 2006; Foster and Wilson, 2006; Diba and Buzsáki, 2007). Moreover, although primarily observed in hippocampal place cells, limited data also described the occurrence of neuronal replay in subcortical and cortical brain regions, including the ventral striatum (Lansink et al., 2009) as well as the visual (Ji and Wilson, 2007), prefrontal (Euston et al., 2007), parietal (Wilber et al., 2017) and motor cortex (Ramanathan et al., 2015).

At a molecular level, sleep is thought to facilitate spatial memory processes by promoting multiple signaling pathways that regulate synaptic strength and control plasticity-related gene transcription and protein translation, such as signaling of cyclic adenosine monophosphate (cAMP), protein kinase A (PKA), mitogen activated protein kinase (MAPK), as well activity of cAMP-response element binding protein (CREB) (Havekes and Abel, 2017; Havekes et al., 2012; Prince and Abel, 2013).

Paralleling findings from animal studies, a continuously growing body of evidence also implicates a role of sleep for the regulation of spatial memory in humans. For example, several studies have shown that the performance in a spatial task is improved across a period of post-learning sleep, as compared to a period of wakefulness (Ferrara et al., 2006, 2008; Nguyen et al., 2013; Wamsley et al., 2016; Varga et al., 2016; Noack et al., 2017; Talamini et al., 2008). Consistent with the “dual process hypothesis” of memory consolidation (Rasch and Born, 2013), considerable evidence implicates that SWS might play a particularly salient role in the sleep-dependent formation of spatial memory in humans. For example, early night sleep, which is rich in SWS, has been suggested to be especially important for the formation of hippocampus-dependent spatial memory, whereas late night sleep, which is rich in REM sleep, has been suggested to be more beneficial for non-declarative hippocampus-independent types of memory (Plihal and Born, 1999). In line with this notion, limited evidence has shown that overnight improvements in spatial performance correlate with amounts of slow wave activity (Wamsley et al., 2016; Varga et al., 2016). In addition, several imaging studies have linked sleep-dependent formation of spatial memory to increases in the activation of the hippocampus and associated networks. For example, a positron emission tomography (PET) study by Peigneux et al. found that the degree of hippocampal blood flow during post-learning SWS predicts improvement in a spatial task assessed the following day (Peigneux et al., 2004). Furthermore, a functional magnetic resonance imaging (fMRI) study by Orban et al. demonstrated that post-learning sleep promotes the integration of recently acquired spatial information into hippocampus-related networks (Orban et al., 2006). Another fMRI study by Rauchs et al. examined the effects of post-learning sleep vs. post-learning sleep deprivation on the neural substrates of spatial memory, and found that in subjects who slept after learning, spatial memory was associated with increased posterior cortical activity, while in subjects who underwent sleep deprivation after learning, spatial memory was associated with increased para-hippocampal and medial temporal activity (Rauchs et al., 2008). Interestingly, several studies have shown that hippocampal replay during NREM sleep also occurs in humans (Bragin et al., 1999; Staba et al., 2002; Norman et al., 2019; Axmacher et al., 2008), and that amounts of hippocampal replay during post-learning NREM sleep correlate with spatial memory assessed the following day (Varga et al., 2016; Moroni et al., 2014). Moreover, several studies have also examined the experimental amplification of sleep-dependent hippocampal replay in humans. Rasch et al. for example, exposed subjects to a specific smell while learning a spatial environment, and again during subsequent post-learning sleep, and found that – relative to a control condition (where no smell was presented during sleep) – re-exposure to the smell during SWS, but not during REM sleep, resulted in greater co-occurring hippocampal activation and improved spatial memory performance the following day (Rasch et al., 2007). In line with these findings, another study demonstrated that cueing recently learned spatial information with a smell during SWS activated hippocampal activity and stabilized spatial memory formation (Dietelmann et al., 2011). In addition, Rudoy et al. exposed subjects to specific sounds during the learning phase of a spatial task and again during subsequent post-learning NREM sleep, and found that upon waking, spatial memory was improved for information that was previously paired with the auditory cue, as compared to information that was not paired with an auditory cue (Rudoy et al., 2009). Finally, van Dongen et al. exposed subjects to sounds during the learning phase of a spatial task, and found that subjects who were re-exposed to sounds during subsequent SWS showed an increased activation of (para)hippocampal neurons, which also correlated with spatial memory retrieval assessed the following day (van Dongen et al., 2012).

3. Sleep disturbance and spatial memory

Sleep disturbance (i.e., difficulties falling or maintaining sleep) is a highly prevalent health complaint that occurs in more than one-third of adults in the United States (National Sleep Foundation, 2020). While
sleep disturbance has been linked to decline of various cognitive domains (Krause et al., 2017), experimental data show that the hippocampus and spatial memory are particularly vulnerable to the effects of sleep loss (Havekes and Abel, 2017). Indeed, an abundance of animal studies have shown that various forms of experimental sleep deprivation (SD), including sleep fragmentation, as well as partial and total SD, reliably induce marked deficits in hippocampus-dependent spatial memory performance (Colavito et al., 2013). In contrast to healthy sleep, SD has been shown to attenuate molecular events involved in the formation of spatial memory, such as signaling of CAMP, PKA, CREB, and mammalian target of rapamycin (mTOR) (Havekes and Abel, 2017; Havekes et al., 2012; Prince and Abel, 2013).

Importantly, limited evidence has also suggested that SD disrupts hippocampus-dependent spatial memory in humans (Ferrara et al., 2008; Peng et al., 2020). Moreover, clinical observations have documented that patients who suffer from a clinical sleep disorder often exhibit spatial memory deficits. For example, patients with insomnia, a highly prevalent sleep disorder that is characterized by interrupted, non-restorative sleep and daytime impairments in cognitive functioning, are reported to show poorer performance in a spatial task, as compared to healthy controls (Li et al., 2016; Chen et al., 2016; Khassawneh et al., 2018; He et al., 2021). Similarly, subjects with poor “insomnia-like” sleep quality are reported to perform worse in a spatial task, as compared to those with good sleep quality (Valera et al., 2016). Interestingly, a series of neuroimaging studies found that insomnia patients exhibit a reduction in hippocampal volume, as compared to healthy controls (Riemann et al., 2007; Joo et al., 2014; Emamian et al., 2021), and that poor subjective sleep quality in insomnia patients is associated with hippocampal atrophy (Joo et al., 2014; Koo et al., 2017). However, other studies have failed to demonstrate an association between insomnia and hippocampal volume (Winckelman et al., 2016; Noh et al., 2012). In addition, there is evidence that patients with sleep apnea, a condition marked by abnormal breathing during sleep, show similar deficits in spatial memory (Daurat et al., 2008; Mullins et al., 2021). As noted, the majority of prior human research has implicated a role of SWS for spatial memory formation. However, a recent study in apnea patients found that REM sleep fragmentation during post-learning sleep impaired overnight improvement in spatial memory, and that the degree of REM fragmentation correlated with poorer overnight performance (Varga et al., 2014).

4. Immune-mediated regulation of spatial memory

Although previously considered an immune-privileged site, it is now well-established that the brain is strongly interlinked with the immune system, and that immune-mediated processes contribute to the regulation of multiple brain functions (Dantzer, 2018). While under normal, quiescent conditions, the immune system promotes remodeling of neural circuits that underlie spatial memory, including hippocampal neuroplasticity, LTP, and neurogenesis, excessive activation of the immune system has shown to impair various aspects of hippocampal functioning and related behaviors (Yirmiya and Goshen, 2011). Animal models have provided insight in several pathways through which the immune system communicates with the brain (as reviewed previously (Dantzer et al., 2008)): for example, peripheral pathogen-associated molecular patterns (PAMPs) and cytokines activate afferent nerves which project to the brain; in turn, PAMPs stimulate macrophage-like cells expressing Toll-like receptors (TLRs) in the circumventricular organs and the choroid plexus to produce pro-inflammatory cytokines, which subsequently can enter the brain; moreover, the blood-brain-barrier actively transports various immuno-modulatory molecules in and out of the brain, while peripheral immune cells have also been shown to traffic to the brain’s vasculature and parenchyma. Of note, excessive activation of these immune-to-brain pathways invokes so-called “sickness behavior”, a constellation of behaviors, including loss of appetite, fatigue, social withdrawal and increased pain, that is thought to facilitate recuperation and recovery from illness and disease (Dantzer and Kelley, 2007).

Importantly, when the peripheral inflammatory signals reach the brain, resident microglia in the brain are activated, which leads to reduced neurogenesis by suppressing neuronal stem cell proliferation, increasing apoptosis of neuronal progenitor cells, and decreasing survival of newly developing neurons and their integration into existing neuronal circuits, with deleterious consequences for hippocampal neuroplasticity and spatial memory processes (Chenshokova et al., 2016). For example, numerous animal studies have consistently demonstrated that administration of lipopolysaccharide (LPS), a bacterial agent that reliably induces TLR-4-mediated production of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF-α) (Schedlowksi et al., 2014; Akira and Takeda, 2004), impairs the ability to form spatial memory (Shaw et al., 2001; Arai et al., 2001; Sparkman et al., 2005a, 2005b; Dinel et al., 2014; Valero et al., 2014; Anaegoudari et al., 2016; Abareshi et al., 2016; Tanaka et al., 2006; Zhao et al., 2019). Similarly, also intracerebroventricular injection of pro-inflammatory cytokines has been shown to impair spatial memory processes (Gitzl et al., 1993; Gibertini et al., 1995; Song and Harrobin, 2004), while superfusing hippocampal brain slices with pro-inflammatory cytokines is reported to inhibit hippocampal synaptic strength and LTP (Katsuki et al., 1990; Bellinger et al., 1993). In addition, an array of genetic studies yielded compelling evidence that transgenic mice with hippocampal over-expression of IL-1 (Moore et al., 2009; Hein et al., 2010) or TNF-α (Fiore et al., 2000) exhibit impaired spatial memory performance, while knockout-mice lacking IL-6 (Braida et al., 2004) or TNF-α (Golan et al., 2004) show improved spatial memory performance. Intriguingly, the impairing effects of inflammation on hippocampus-dependent spatial memory are thought to be modifiable, as indicated by several animal studies which demonstrated that exposure to anti-inflammatory agents attenuates the adverse effects of inflammation on spatial memory, and even improves spatial memory (Ormerod et al., 2013; Wadhwa et al., 2017a; Cui et al., 2008; Marchalant et al., 2008; He et al., 2011; Kumar et al., 2018). Whereas the vast majority of prior research on inflammation and spatial memory has focused on experimental animal models, less is known about the role of inflammation for spatial memory in humans. Yet, limited evidence indicates that the excessive activation of the inflammatory response also impairs spatial memory processes in humans. For example, clinical observations have shown that patients with an inflammatory disease, such as rheumatoid arthritis (Chaurasia et al., 2020; Petra et al., 2020) or multiple sclerosis (Brochet and Ruet, 2019), show greater difficulties in memorizing and recalling spatial information, as compared to healthy controls. Moreover, in a recent placebo-controlled study (Harrison et al., 2014), healthy subjects underwent a PET scan and a spatial memory task before and after an inflammatory challenge (i.e., intramuscular typhoid vaccination). In this study, subjects showed an impaired performance of spatial memory following the inflammatory challenge, an effect that was mediated by alterations of brain activity in the temporal lobe. In another placebo-controlled study (Reichenberg et al., 2001), healthy subjects received an intravenous injection of LPS, which caused a disruption of figural memory (a memory form functionally related to spatial memory), and these LPS-induced memory impairments correlated with systemic concentrations of TNF-α. However, in contrast to these findings, a recent placebo-controlled study found that treatment with minocycline, a centrally penetrating antibiotic with anti-inflammatory properties, in fact, resulted in an improvement of spatial memory performance (Berens et al., 2020).

5. Converging pathways

Although prior work examined the role of sleep disturbance and inflammation for spatial memory primarily in separate studies, emerging lines of research implicate that sleep disturbance and inflammation might jointly impair spatial memory processes. Under normal conditions, sleep and immunity share a reciprocal relationship, such that activation of the immune system alters sleep dynamics, while sleep plays a pivotal role.
especially salient for older adults, a population that is particularly known for risk factors for the development of major depression (Irwin and Piber, 2010). Finally, a conceptual model in which sleep disturbance and inflammation contribute to the pathophysiology of Alzheimer’s disease (Coughlan et al., 2018), a disease that is thought to contribute to the pathophysiology of Alzheimer’s disease in the preclinical stages (Coughlan et al., 2018). In turn, accumulating evidence implicates that the inflammatory signals generated in periphery alter activity of brain regions and neurotransmitter systems involved in the regulation of sleep (Irwin, 2019).

Interestingly, compelling data from animal models implicate inflammation as a mechanistic pathway linking sleep disturbance to spatial memory impairment. Work in rodents, for example, has shown that SD induces hippocampal inflammation, as indexed by increased concentrations of IL-6 and microglia activation in the hippocampus (Yin et al., 2017). Of note, a recent mechanistic animal study by Wadhwa et al. (2017b) showed that SD induces an increase in pro- and decreases in anti-inflammatory cytokine expression, along with deficits in spatial memory. In their study, Wadhwa et al. demonstrated that spatial memory deficits correlated with concentrations of IL-1, IL-6, and TNF-α in both hippocampus and plasma, implicating that SD-induced deficits in spatial memory are attributed to an up-regulation of neuroinflammation. As part of their study, Wadhwa et al. also exposed their test animals to an anti-inflammatory agent, which not only decreased pro- and increased anti-inflammatory cytokine levels in the hippocampus and plasma, but also promoted neurogenesis and ameliorated SD-induced impairments in spatial memory. In line with these findings, a conceptually-related study by the same group found that the inhibition of microglial activation with an anti-inflammatory agent attenuates the impairing effects of SD on hippocampal neurogenesis and spatial memory (Wadhwa et al., 2017a).

Given the reciprocal interactions between sleep disturbance and inflammation, their individual associations with spatial memory impairment, and the converging evidence that inflammation might mediate the link between sleep disturbance and spatial memory deficits, both factors — sleep disturbance and inflammation — might act in concert to jointly impair spatial memory processes. Indeed, if healthy sleep and immune function positively regulate spatial memory, and if experimental and naturalistic sleep disturbances as well as inflammatory states impair spatial memory, then the co-occurrence of sleep disturbance and inflammation might activate a converging pathway to impair spatial memory. Thus, individuals who simultaneously experience sleep disturbance and heightened states of inflammation might be particularly at risk to develop spatial memory impairment. Indeed, such conceptual approach in which sleep disturbance and inflammation mutually interact and jointly disrupt spatial memory has implications for various health outcomes. For example, both sleep disturbance and inflammation are thought to contribute to the pathophysiology of Alzheimer’s disease (Irwin and Vitiello, 2019), an illness characterized by hippocampal neurodegeneration as well as spatial memory loss. Interestingly, a recent study by Coughlan et al. showed that individuals at risk to develop Alzheimer’s disease exhibit altered spatial navigation patterns before the onset of any memory complaints, which suggests that spatial behavior could be used as a cost-effective cognitive biomarker to detect Alzheimer’s disease in the preclinical stages (Coughlan et al., 2018).

In addition, sleep disturbance and inflammation are also well-established risk factors for the development of major depression (Irwin and Piber, 2018), a disease that — in turn — has been associated with impairments in hippocampus-dependent spatial memory (Gould et al., 2007; Cornwell et al., 2010). Finally, a conceptual model in which sleep disturbance and inflammation jointly contribute to spatial memory impairment might be especially salient for older adults, a population that is particularly known to exhibit sleep disturbance (Li et al., 2018), increased inflammatory activity (Franceschi et al., 2000; Campisi, 2013; Franceschi and Campisi, 2014; Kennedy et al., 2014; Piber et al., 2019) and deficits in spatial memory (León et al., 2016; Korman et al., 2019; Moffat et al., 2001; Foster et al., 2012). However, to evaluate this proposed model, further research is needed. Indeed, future research could experimentally test the separate and joint effects of experimental SD and exposure to LPS on spatial memory, or evaluate the longitudinal contributions of sleep disturbance and inflammation to spatial memory impairment and associated (neuro)psychiatric diseases. Moreover, future research could also examine whether a conceptual approach differentially affects the individual stages of spatial memory (i.e., acquisition, consolidation, recall) or even other memory functions and cognitive domains, such as procedural and verbal memory, attention, executive functioning, mood regulation and social/emotional processing, which have previously been shown to be vulnerable to both sleep (McCoy and Strecker, 2011) and inflammation (Boilen et al., 2017).

6. Interventions targeting sleep disturbance and inflammation

Given the separate and joint contributions of sleep disturbance and...
improves sleep quality and duration (Dolezal et al., 2017), while data from randomized controlled trials showed that physical exercise improves spatial memory (ten Brinke et al., 2015) and even increases hippocampal volume (Erickson et al., 2011). In addition, a large body of evidence indicates that specific foods, such as whole, plant-based foods, have the potential to reduce inflammatory activity (Ricker and Haas, 2017), while accumulating evidence indicates that dietary habits also influence sleep physiology (St-Onge et al., 2016; Frank et al., 2017). Finally, limited data from both animal (Ross et al., 2009; Zhao et al., 2017; Henry and Stoner, 2011; Rendeiro et al., 2013) and human studies (de Vries et al., 2020) have suggested that shifts in dietary habits might also impact spatial memory processes.

7. Conclusion

In the present article, I summarized converging pathways by which sleep disturbance and inflammation impair spatial memory (Fig. 1). While most of our mechanistic understanding on the role of sleep disturbance and inflammation for spatial memory comes from animal studies, less is known about the joint contributions of sleep disturbance and inflammation to spatial memory processes in humans. As shown in Fig. 2, there are several pathways that could potentially be targeted to possibly mitigate risk for spatial memory impairment. However, further research is needed to evaluate the separate and joint contributions of sleep disturbance and inflammation to spatial memory impairment in humans, specifically in older adults - a population well-known to show a high prevalence of sleep disturbance, increased levels of inflammation, and spatial memory deficits and related diseases. Indeed, gaining insight into how specific aspects of sleep disturbance and inflammation influence spatial memory processes could direct the development of interventions that target the pathways between sleep disturbance, inflammation, and spatial memory impairment. Such precision in the characterization of sleep and inflammatory profiles might have the potential to refine and augment treatments of health outcomes associated with spatial memory impairment.

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**Fig. 2.** A schematic overview of the contributions of sleep and immune function to spatial memory in models of health and disease. **Abbreviations:** SWS = slow wave sleep; REM = rapid eye movement sleep; LTP = long-term potentiation; CBT-I = cognitive behavioral therapy for insomnia; MBI = mind body interventions.
Declaration of competing interest

I have no conflicts of interest to report.

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