Hidden memories in the sleep-deprived brain

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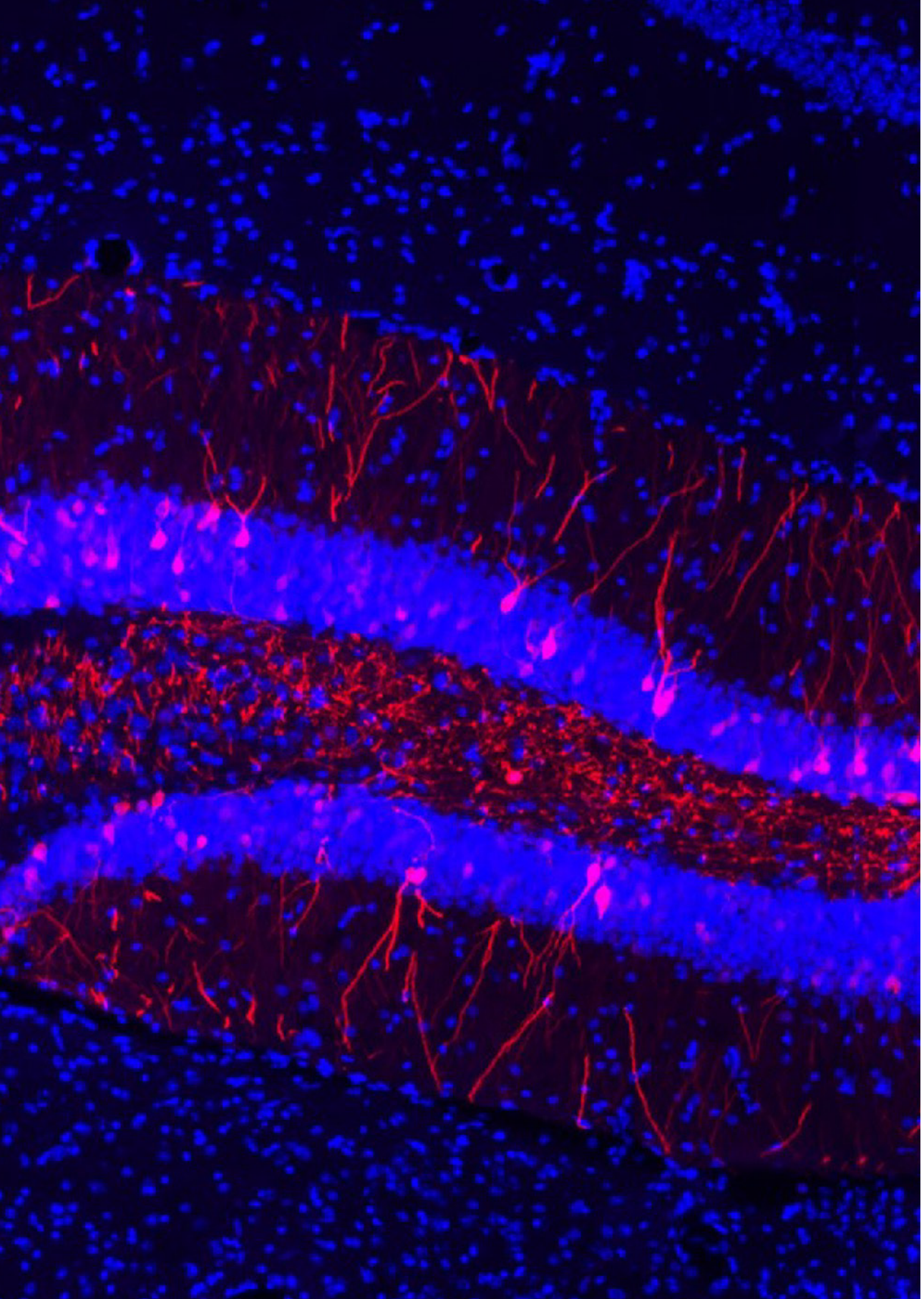

Chapter 1

General Introduction

Introduction

Memory is the process of acquiring, retaining, and retrieving information over time. This fundamental ability is present in all organisms, and is crucial for survival, as memories are providing us the capability to adapt our behavior to future events. Hence, behavior in all organisms is to a large extent guided by the retrospective use of memories. The importance of memories is becoming evident in humans when information cannot be optimally stored or retrieved anymore. Suboptimal storage and retrieval of memories can have a detrimental impact on daily functioning, and eventually reduce the quality of life. Despite the fact that memory has such an important function, the underlying biology is not completely elucidated, making it one of the most studied topics in the field of neuroscience today.

Based on classical amnesia studies in humans, long-term memories have been categorized into two main groups: non-declarative and declarative memories (Squire, 2004; Squire & Zola, 1996). Non-declarative memories are considered to be retrieved without consciousness awareness (Reber, 2013). For example, procedural skills, such as riding a bike or driving a car, are categorized as non-declarative memories. Declarative memories, on the other hand, are memories that are available for conscious retrieval. This category can be further subdivided into factual knowledge and episodic memories. Whereas episodic memories contain detailed information about the place (*i.e.*, spatial information) and time (*i.e.*, temporal information) of a recollection, factual knowledge is the recall of a fact without any particular context (Squire & Dede, 2015). In non-human species, declarative memories are distinguished based on the temporal and spatial information incorporated into the memory, as it remains unclear to what extent non-human species are consciously retrieving information (Allen & Fortin, 2013; Squire, 2004). Various model organisms are being used to study the neurobiological and cellular mechanisms underlying the different memory types, including non-human primates, rodents, and sea slugs (Aplysia) (Allen & Fortin, 2013).

The processing of all memory types can be subdivided into three sub-processes - encoding, consolidation, and retrieval (Abel & Lattal, 2001). During the encoding phase, the initial storage of information takes place, in which new information is translated into a biological memory trace. Subsequently, during the consolidation phase, the initial memory trace is strengthened, making it less vulnerable to disturbances and decay. Memory retrieval is related to accessing and recalling the information stored in the brain. The molecular processes underlying these three sub-processes can overlap but are in some cases selective to a specific sub-process.

Hippocampal memories

In mammals, the hippocampus is one of the most studied brain regions in relation to memory functioning. This area is located in the temporal lobe of the brain and is involved in all aforementioned sub-processes underlying declarative memory functioning (*i.e.*, encoding, consolidation, and retrieval). The first groundbreaking discovery for a key role of the hippocampus in declarative memory processing came from the study of Scovile and Milner in 1957 (Scoville & Milner, 1957). In this case report, memory was studied in the notable patient H.M., who underwent surgery involving the bilateral removal of his temporal lobe (including the hippocampus) after suffering from intractable epilepsy. Following the removal of the hippocampus and surrounding temporal cortex, patient H.M. was unable to form new episodic declarative memories (also known as anterograde amnesia). However, H.M. was still able to acquire new procedural skills and form non-declarative memories (Scoville & Milner, 1957; Squire et al., 2002). Ever since these remarkable observations, the hippocampus has attracted widespread attention and has been extensively studied in both humans and animals, providing insights into how the brain processes and stores factual, spatial, and temporal information (Jeffery et al., 2017; Tanaka & Mchugh, 2018; Voss, Bridge, Cohen, & Walker, 2017).

The hippocampus is able to connect spatial, temporal, and conceptual information, received from other brain areas such as the entorhinal cortex, into a cohesive framework that serves as a cognitive map for the storage and retrieval of memories (Tanaka & Mchugh, 2018; Voss et al., 2017). Most of the information enters the hippocampus via the perforant path (Fig. 1). This pathway originates from the entorhinal cortex and connects to the granule cells of the dentate gyrus (DG), providing the hippocampus with polymodal sensory information (Amaral, 1993). The granule cells, in turn, project their axons (mossy fibers) to the dendrites of the cornu ammonis 3 (CA3) pyramidal cells. The information is then projected to the CA1 pyramidal cells via the Schaffer collaterals and exits the hippocampus via the subiculum to the deeper layers of the entorhinal cortex (Amaral, 1993). The described information flow through the described hippocampal network is called the trisynaptic loop (Fig. 1) and is traditionally considered to be the main circuit of information processing within the hippocampus. In addition to this trisynaptic circuit, the CA3 and CA1 subregions are also innervated by the entorhinal cortex (Remondes & Schuman, 2002), illustrating that individual hippocampal subregions can also receive direct input from other brain regions.

The unique anatomical characteristics and neuronal circuit of the hippocampus depicted above, allow it to execute complex processes, which are essential for

memory functioning. For example, ample computational, electrophysiological, and human functional neuroimaging studies show that the DG is able to separate highly similar or even overlapping experiences in distinct, non-overlapping cellular representations. This ability of the DG to disentangle overlapping information into separate unique representations is called pattern separation and prevents that newly acquired information overwrites and interferes with similar previously stored information, which could lead to suboptimal memory functioning (Hainmueller & Bartos, 2020; Leutgeb, Leutgeb, Moser, & Moser, 2007). Complementary to pattern separation is the process that enables the hippocampus to generalize or complete information from incomplete representations, called pattern completion. This complex process is executed by the CA3 and allows the brain to retrieve memories from partial cues (Lee, GoodSmith, & Knierim, 2020). Thus, within the hippocampal information flow, different sub-regions can fulfill distinct functions, all contributing to proper memory functioning of declarative memories.

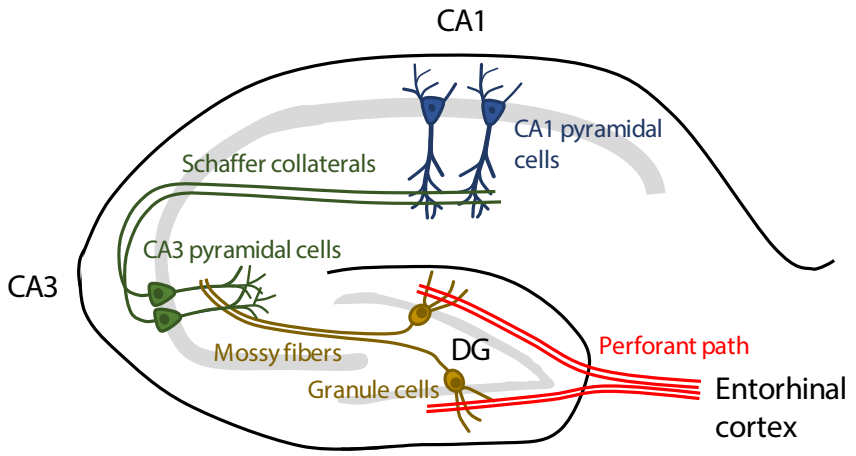

Figure 1. schematic overview of the hippocampal trisynaptic loop. This neuronal circuit connects the different subregions (DG-CA3-CA1) and is considered to be the main circuit for information processing in the hippocampus.

The molecular and cellular storage of a memory

For decades, scientists have been investigating the neurobiological basis of learning and memory to understand how the brain is able to encode, consolidate, and retrieve information. Although there is still an ongoing debate about the exact mechanisms, several essential building blocks have been identified, including the biological underpinnings of memory engrams and learning-related plasticity (Poo et al., 2016; Ryan, de San Luis, Pezzoli, & Sen, 2021). On an abstract level, the term

memory engram refers to the physical substrate of a memory as a consequence of learning-induced changes, and the term learning-induced plasticity is the general ability of the brain to change for learning processes to occur. Both memory engrams and learning-induced plasticity are necessary for the storage of information in the brain, and these terms will be explained in more detail below. Important is that this thesis will mainly focus on learning-induced plasticity occurring at the level of the synaptic connections between neurons (*i.e.* synaptic plasticity) and involves cellular and molecular changes.

Neuronal ensemble of engram cells as the physical substrate of memories

The storage of a memory starts with the integration of external information into neurons and neuronal circuits. This integration is mediated via learning-induced physical and chemical changes in neurons, leaving a persistent and unique memory trace in the brain that functions as the biological substrate for memory recall. These long-lasting learning-induced changes are collectively referred to as the memory engram (Josselyn & Tonegawa, 2020; Poo et al., 2016; Ryan et al., 2021). The term memory engram was first introduced at the beginning of the 20th century, by a German scientist named Richard Semon (Semon, 1921), but gained popularity with the emergence of new techniques in molecular and cellular biology (Liu et al., 2012; Reijmers, Perkins, Matsuo, & Mayford, 2007). To date, accumulating evidence indicates that a sparse population of neurons becomes highly active during the storage of a memory, and subsequently undergoes physical and chemical changes to serve as a biological substrate for the retrieval of the memory at a later time point. The neurons that undergo these persistent learning-induced changes are called engram cells and are together forming a neuronal ensemble, which is also activated during the retrieval of the memory. Further examination of these engram cells indicated that they are not only highly active during memory functioning, but also necessary and sufficient for storing and retrieving a memory (Frankland, Josselyn, & Köhler, 2019; Tonegawa, Liu, Ramirez, & Redondo, 2015). Therefore, there is now a consensus that the memory engram is at least partly stored in a neuronal ensemble of engrams cells, providing scientists with a framework for the investigation of the physical storage of a memory.

Experimental evidence for the storage of a memory in a neuronal ensemble largely comes from studies utilizing immediately early genes (IEGs) as a marker for neuronal activity, such as cfos and arc. As the transcription of IEGs is closely related to neuronal activity patterns, IEG mapping studies are providing a good proxy for the large-scale history of neuronal activity. The first IEG engram studies identified a stable subset of neurons (*i.e.*, neuronal ensemble) that was selectively active during both

the storage and retrieval of a specific memory, providing observational evidence for the existence of memory engram cells (Denny et al., 2014; Reijmers et al., 2007; Tayler, Tanaka, Reijmers, & Wiltgen, 2013). The second line of evidence comes from studies disrupting these tagged engram cells, leading to an impairment in subsequent memory recall. This interference with memory recall by specifically inhibiting learning-induced IEGs was firstly demonstrated by Han et al. (2007), who made use of an inducible toxin to specifically ablate engram neurons in the lateral amygdala after an auditory fear conditioning training. The ablation led to a memory impairment, supporting the necessity of the memory engram for proper retrieval. In the following years, similar findings were found in studies focusing on other brain regions including the hippocampus (Denny et al., 2014; Tonegawa et al., 2015). The most recent breakthrough in memory engram research came from the Tonegawa lab, which demonstrated that memory engrams are sufficient for memory recall (Liu et al., 2012; Ryan, Roy, Pignatelli, Arons, & Tonegawa, 2015). More specifically, based on IEG activation, the learning episode of a contextual fear conditioning trial was labeled with light-gated ion channels (*i.e.*, channelrhodopsin). The integration of this light-gated ion channel into the engram cells, enabled researchers to manipulate neuronal excitability by the use of laser light, a technique called optogenetics (Boyden, Zhang, Bamberg, Nagel, & Deisseroth, 2005). Hence, optogenetic reactivation of the fear engram in a different and safe context, led to the expression of the fear response (*i.e.*, freezing behavior), confirming that the engram is also sufficient to elicit at least some aspects of the fear memory (Liu et al., 2012).

The ability to label and manipulate memory engrams in vivo provided scientists with a great opportunity to also study memory function under suboptimal conditions such as in retrograde amnesia models (Josselyn & Tonegawa, 2020). For instance, in transgenic animal models of Alzheimer's disease and infantile amnesia, which are all characterized by amnesia, optogenetic activation of the memory engram led to a proper reinstatement of the memory (Guskjolen et al., 2018; J. Li et al., 2020; Poll et al., 2020; Roy et al., 2016). From this, we can conclude that the memory was still present in the brain even though the animal suffered from amnesia as it was unable to retrieve the memory via natural reminder cues (*i.e.*, without experimental manipulation). Similar results were found when mice were systemically treated with a protein synthesis inhibitor, immediately after the learning trial (Ryan et al., 2015). It is well-known that protein synthesis during the consolidation phase is essential for the later retrieval of the memory, and blocking this process leads to a memory impairment (Raven et al., 2020; Ryan et al., 2015). Optogenetic stimulation of the engram, however, led to the behavioral reinstatement of the memory, suggesting that the encoding of the memory survives the blockage of protein synthesis.

Together, we can conclude from these findings that memory impairments in amnesia models are not necessarily caused by the absence of the memory in the brain but seems to be more a consequence of the inability to retrieve the memory. In other words, some amnesic conditions result in a (temporarily) inaccessible memory that cannot be retrieved by natural cues. Interestingly, further examination of engram cells in amnesic-like conditions revealed that inaccessible memory engrams are often associated with a lack of change in physiological and structural properties on the neuronal and synaptic level (Pignatelli et al., 2019; Roy et al., 2016; Ryan et al., 2015).

Learning-induced synaptic plasticity

Synaptic plasticity refers to the ability to change the synaptic strength between two interconnected neurons (Kandel, 2015). Firstly, alterations in synaptic strength can be established via the modification of existing synaptic connections (*i.e.*, synaptic weight). Secondly, new synaptic connections can be created or existing synaptic connections can be removed (*i.e.*, synaptic (re)wiring) (Chklovskii, Mel, & Svoboda, 2004). Both processes enable the brain to modify the strength of information flow and are suggested to occur simultaneously in response to memory processes (Chklovskii et al., 2004; W. Li, Ma, Yang, & Gan, 2017; Ryan et al., 2021; Yang et al., 2014).

Donald Hebb firstly proposed that activity-dependent synaptic plasticity might serve as a cellular mechanism for memory functioning in 1949 (Hebb, 1949). He postulated that synaptic strength grows as a result of persistent or concomitant activation of the pre-and post-synaptic neuron, resulting in stronger and more efficient signal transmission. The discovery of long-term potentiation (LTP) in hippocampal slices supported Hebb's theory of synaptic plasticity as a cellular mechanism for learning and memory (Bliss & Gardner-Medwin, 1973; Bliss & Lomo, 1973). Related to this, Bliss and Lomo demonstrated that a brief high-frequency pre-synaptic activation leads to long-lasting enhanced signal transmission at the post-synaptic site (Bliss & Lomo, 1973). Thereafter, other forms of synaptic plasticity have been identified, including long-term depression (LTD) which causes a reduction in synaptic strength (Dudek & Bear, 1992). The fact that synaptic plasticity in the hippocampus is critical for learning and memory processes has later been supported by in vivo studies showing that in the CA1, LTP is induced by subjecting an animal to a hippocampus-dependent learning task (Gruart, Muñoz, & Delgado-García, 2006; Whitlock, Heynen, Shuler, & Bear, 2006). To date, there is a consensus that memory function relies upon changes at the synaptic level, sculpting neuronal connections (Baltaci, Mogulkoc, & Baltaci, 2019).

Synaptic plasticity is mediated by structural changes as it includes the physical modification of the synaptic contact sites. Within the synapse, neurotransmitters are released from the pre-synaptic axonal terminals and bind to post-synaptic receptors on the dendrites. These post-synaptic receptors are found on small dendritic protrusions, called spines. The abundance and structural morphology of spines are often investigated in relation to synaptic plasticity, because it provides an indication of the amount of post-synaptic receptors available (Chidambaram et al., 2019; Segal, 2017; van der Zee, 2015). Furthermore, changes in spine abundance and morphology are rapidly initiated upon learning and LTP (Engert & Bonhoeffer, 1999; Nikonenko, Jourdain, Alberi, Toni, & Muller, 2002; Segal, 2017). Based on their morphology, spines are classified into five main categories: filipodia, mushroom spines, thin spines, branched spines, and stubby spines. Whereas filipodia and thin spines are characterized by a relatively thin neck and small head, mushroom spines have a large head/neck ratio. Stubby spines lack a distinctive head, while branched spines are characterized by two necks and heads (van der Zee, 2015). The head's size is the most determining factor for synaptic transmission as it contains all the molecular machinery, such as receptors (Kopec, Real, Kessels, & Malinow, 2007; Maiti, Manna, Ilavazhagan, Rossignol, & Dunbar, 2015). Hence, mushroom spines are considered to be indicative of a strong and robust post-synaptic response as they have a relatively large head size (Kopec et al., 2007; van der Zee, 2015). Filipodia, and to some degree also thin spines, are considered to be very dynamic and involved in the formation of new connections (Portera-cailliau, Pan, & Yuste, 2003; Ziv & Smith, 1996). Altogether, the characterization of different spine types can provide valuable information about the structural and functional plasticity of the synapse.

At a molecular level, synaptic plasticity requires the activation of several signaling molecules and molecular pathways (Baltaci et al., 2019). Within the hippocampus, cyclic adenosine monophosphate (cAMP) and protein kinase A (PKA) play a crucial role in plasticity processes. They initiate various molecular pathways, leading to transcriptional and structural changes important for memory functioning (extensively reviewed by Kelly, 2018). More specifically, cytosolic levels of cAMP increase after a Ca+2 influx, which in turn results in the activation of many downstream targets, including PKA (the cAMP-dependent protein kinase). Upon activation, PKA is then able to phosphorylate several downstream target proteins, such as the transcription factor CREB. When CREB is phosphorylated (pCREB), it promotes the transcription of many plasticity-related genes (Athos, Impey, Pineda, Chen, & Storm, 2002). Another important downstream target of the cAMP-PKA pathway is cofilin which is an acting-binding protein that disassembles actin filaments, the structural foundation of spines. PKA attenuates cofilin activity via the phosphorylation of LIM kinase (LIMK), which in turn phosphorylates cofilin (pcofilin), making it inactive. Therefore, activation of the cAMP-PKA-LIMK pathway ultimately results in the inactivation of cofilin, and is able to indirectly regulate neuronal communication via the cofilin-mediated structural build-up or breakdown of spines (Borovac, Bosch, & Okamoto, 2018; Havekes et al., 2016). Because cAMP has such a crucial role in plasticity-related molecular processes, cAMP-degrading enzymes, such as cAMP-degrading phosphodiesterases (PDEs), are essential mediators in learning-induced plasticity (Kelly, 2018). Thus, it is clear that cAMP and its initiated molecular pathways are underlying important learning-induced plasticity processes, including structural modifications of the synapse.

Altogether, memory engrams and learning-induced synaptic plasticity are both considered to be essential mechanisms for memory function. However, only a handful of studies investigated the relationship between the two mechanisms, revealing an interesting interaction; hippocampal memory engram cells have an increased synaptic potentiation compared to non-engram cells (Ryan et al., 2015). Moreover, engram-specific synaptic plasticity seems to be initiated by hippocampal learning and dependent upon protein synthesis. Indeed, the treatment with a protein synthesis blocker (*i.e.*, anisomycin) immediately after the training abolished all the consolidation-initiated synaptic changes in engram cells (Ryan et al., 2015). In line with these findings, Choi and colleagues found an increase in the number and size of spines in CA1 cells after a hippocampal learning task, particularly in engram neurons that were predominantly connected with other engram neurons (Choi et al., 2018). Interestingly, it seems that enhanced synaptic connectivity (*i.e.*, increase in synaptic gain) in engram cells is in particular essential for the retrieval of a memory – and not for long-term storage. Hence, memory engram cells that lack synaptic enhancements cannot be naturally retrieved (Roy et al., 2016; Ryan et al., 2015), but optogenetic stimulation results in the instant behavioral reinstatement of the memory (Roy et al., 2016; Ryan et al., 2015). These studies imply that engram-specific synaptic plasticity takes place during the consolidation window of a learning episode, and is required for the proper natural retrieval of a memory.

Sleep & Memory

Sleep is conserved across all organisms and is a reversible state with reduced motor activity, loss of consciousness, and reduced responsiveness to external stimuli. In mammals, the initiation of sleep is determined by two processes, a sleep-dependent process which refers to the build-up of sleep need as time being awake, and a sleep-independent process which depends upon the internal circadian rhythm (Borbély, 1982). Critically, this latter process is determined by internal self-sustaining oscillations of clock genes with a cycle of approximately 24 h (Takahashi, 2017).

Although there is still no consensus about the precise overarching purpose of sleep, it is clear that sleep has a beneficial role in memory processes and cognition (MacDonald & Cote, 2021). Indeed, a wealth of studies in various species including humans demonstrated that sleep after a learning episode significantly facilitated the recall of declarative and non-declarative memories (reviewed by MacDonald & Cote, 2021; Rasch & Born, 2013; C. Smith, 2001).

Sleep deprivation & Memory

In contrast to the beneficial effects of sleep, a lack of sleep has a detrimental effect on a wide array of cognitive processes, including memory functioning. Unfortunately, sleep deprivation (SD) is becoming more prevalent in our modern 24/7 society due to factors such as higher working loads, more shift working and increasing exposure to psychosocial stressors (Chattu et al., 2018). Concerning memory functioning, human and animal studies revealed that hippocampus-dependent memories are in particular vulnerable to sleep disturbances (Kreutzmann, Havekes, Abel, & Meerlo, 2015). Experimental rodent studies during the last decades found that SD severely impacts hippocampal functioning and underlying synaptic processes via structural and molecular alterations (Raven, Van der Zee, Meerlo, & Havekes, 2018).

The impact of SD on hippocampus-dependent memories has been experimentally investigated in a variety of behavioral learning paradigms, including the object-location memory (OLM) task. In the OLM task, rodents are first subjected to a training trial in which they are allowed to freely explore objects in an open box. Thereafter, in the testing trail, one of the objects is moved to a new location. Due to the natural tendency of rodents to explore novelty, they will be able to discriminate the relocated object in the testing trial only if they have a proper memory of the training trial. The detection of the relocated object requires the integration of detailed spatial and contextual information, and, therefore, relies strongly upon the hippocampus (Aggleton & Nelson, 2020; Migues, Wong, Lyu, & Hardt, 2019). Six hours of SD prior to the training trial leads to a failure in discriminating the relocated object 24 hours later (Heckman, Roig Kuhn, Meerlo, & Havekes, 2020), indicating that SD interferes with the encoding of the memory. Similarly keeping the animals awake for 6 hours post-training or pre-testing leads to a failure to discriminate the relocated object (Havekes et al., 2014, 2016; Heckman et al., 2020), illustrating that SD is also able to disrupt the consolidation and retrieval of hippocampal memories, respectively. In accordance with these findings, SD also impairs memory performance in other hippocampus-dependent memory tests such as the contextual fear conditioning test (Graves, Heller, Pack, & Abel, 2003; Hagewoud et al., 2010; Vecsey et al., 2009). Hippocampus-independent memories, however, are to a lesser extent impaired by SD (McDermott et al., 2003; Carlyle Smith & Rose, 1996), confirming the vulnerability of the hippocampus compared to other brain regions. In conclusion, there is a substantial amount of literature that highlights the detrimental effect of a brief episode of enforced wakefulness (*i.e.*, 5-6 h) on hippocampal memory functioning, and these animal studies are providing a robust foundation for a more in-depth investigation of the cellular and molecular underpinnings which will be discussed in more detail below.

Examination of hippocampal slices of sleep-deprived animals showed that SD interferes with LTP (Campbell, Guinan, & Horowitz, 2002; Marks & Wayner, 2005; McDermott, Hardy, Bazan, & Magee, 2006; Vecsey et al., 2009). Both 12 hours of prolonged wakefulness as well as 5 hours, lead to a deficit in LTP (Campbell et al., 2002; Vecsey et al., 2009). Further examination revealed that SD also affects synaptic plasticity processes that underly LTP and memory functioning (reviewed by Frank Raven et al., 2018). More specifically, a reduction in the overall number of spines was observed in the CA1 and DG of the hippocampus when animals were sleep deprived for 5 to 6 h (Havekes et al., 2016; Noorafshan, Karimi, Kamali, Karbalay-Doust, & Nami, 2018; Raven, Meerlo, Zee, Abel, & Havekes, 2019). Inspection of the different hippocampal subregions showed that all spine subtypes were attenuated in the CA1, while in the DG there was only a reduction observed in branched and thin spines (Havekes et al., 2016; Raven et al., 2019). Interestingly, opposing findings were found in the study of Gisabella and colleagues, showing that SD leads to an increase in synaptic connections in the CA1 (Gisabella, Scammell, Bandaru, & Saper, 2020). However, the underlying cause of this discrepancy remains a question, and might, for example, be related to partial sampling of specific spine subtypes or dendritic branches. Nevertheless, SD appears not to impact the structural plasticity in the CA3 area of the hippocampus (Havekes et al., 2016). These findings suggest that SD does not equally impact the hippocampus, but leads to subregion and spine-specific effects. In accordance with most of the findings, a more prolonged enforced wakefulness of 24 h also led to a reduction in the overall number of spines in the CA1, while no changes were observed in the prefrontal cortex (Acosta-peña et al., 2015; Wong, Tann, Ibanez, & Sajikumar, 2019). Important to note is that the structural changes in the CA1 were reversed after 3 hours of recovery sleep, suggesting that (recovery) sleep has opposing effects (Havekes et al., 2016). In summary, it seems that both short and longer periods of extended wakefulness impact various aspects of neuronal functioning in the hippocampus including LTP and the abundance of spines.

At a molecular level, SD alters a variety of signaling molecules and related pathways, including those important for hippocampal memory processes. Extensive research

showed that SD reduces the cAMP levels in the hippocampus (Vecsey et al., 2009). As described earlier, cAMP initiates several molecular pathways, including the PKA-LIMK-cofilin pathway that ultimately leads to structural changes via the stabilization or breakdown of dendritic spines. As such, SD lowers the pcofilin/cofilin ratio in the hippocampus, indicating relatively more active (non-phosphorylated) cofilin, which disassembles the spine filaments (Chen, Rex, Casale, Gall, & Lynch, 2007). The direct influence of the cAMP-PKA-LIMK-cofilin pathway during SD was further investigated by virally injecting a catalytically inactive version of the phosphodiesterase 4A5 isoform (PDE4A5) in the hippocampus, thereby locally preventing the degradation of cAMP (Havekes et al., 2016). Blocking PDE4A5 function normalized pcofilin/cofilin levels in sleep deprived mice and prevented hippocampal memory deficits. The same study examined the direct role of cofilin in SD by virally injecting a mutant inactive form of cofilin in the hippocampus, which locally shuts down the activity of cofilin hippocampal excitatory neurons. Blocking cofilin function not only made memories resilient to sleep deprivation, but also prevented the reduction in dendritic spines (Havekes et al., 2016). Together, these findings show that SD impacts hippocampal memory functioning via altering the cAMP-PKA-LIMK-cofilin pathway, which directly influences structural plasticity. Another molecular consequence of the attenuated cAMP levels is the change in CREB-mediated transcription, as pCREB levels were found to be reduced after enforced wakefulness (Hagewoud et al., 2010; Vecsey et al., 2009). Lastly, also other cAMP-independent molecular pathways seem to be vulnerable to SD. For instance, sleep loss hampers the kinase complex mammalian target of rapamycin complex 1 (mTORC1) mediated protein synthesis in the hippocampus, having an impact on synaptic consolidation processes, including a long-lasting form of LTP (Tudor et al., 2016). In addition to the abovementioned mentioned impact of SD on molecular processes in neurons, sleep loss-induced cognitive deficits may also be mediated via non-neuronal alterations, such as astrocyte activity (Halassa et al., 2009; Vecsey, Halassa, Haydon, & Abel, 2011).

Overall, it is clear that SD has a detrimental impact on hippocampal function and memory processes. Most studies investigated the impact of SD on hippocampal memory processing with emphasis on processes involved in synaptic plasticity. However, due to the broad and severe impact of SD on the brain, it is not unlikely that other not (yet) identified mechanisms also play a role in the cognitive deficits caused by SD. Clock genes, for example, might mediate SD-induced cognitive deficits as they are modulating both sleep and memory processes in the brain. Whereas learning-induced plasticity (*e.g.*, synaptic plasticity) has been extensively investigated in the context of SD, other prominent mechanisms, such as memory engram cells, have, remarkably, never been investigated in relation to sleep loss. The investigation of memory engrams in other amnesia models has led to several novel insights, even providing new strategies to overcome memory deficits (Roy et al., 2016). Therefore, further investigation of SD should include both the examination of learning-induced plasticity processes, as well as other mechanisms like memory engrams.

Outline thesis

The general aim of this thesis was to further investigate the detrimental impact of SD on hippocampal memories and underlying biological processes by examining plasticity-related processes as well as novel mechanisms, such as memory engrams. Therefore, in this thesis, we first further investigated the effects of SD on synaptic plasticity in more detail. As such, in the second chapter, we took a closer look at how SD impacts structural plasticity by examining hippocampal spine subtype- and branch-specific alterations after 5 h of SD. This in-depth investigation also elucidated to a large extent the underlying cause of the seemingly opposing effects of SD on synaptic plasticity found in other studies (*i.e.*, Gisabella et al., 2020). In chapter three, we examined the consequences of SD during the consolidation phase on memory and, importantly, on memory engrams. More specifically, we used optogenetic approaches to investigate whether memories are still stored in the brain despite being consolidated under sleep deprivation conditions. Based on the results of the optogenetic reactivation studies, we investigated whether the detrimental impact of SD on hippocampal memories can also be rescued via boosting the retrieval process with the systemic treatment of a PDE4-inhibitor. Lastly, in chapter three we artificially reactivated memory engram cells in combination with systemic PDE4-inhibitor treatment to make hippocampal memories more accessible for natural retrieval (*i.e.*, without experimental manipulation) after SD. In chapter four we mapped the immediate-early gene activity in the hippocampus after the exposure to different degrees of spatial novelties. As such, we aimed to investigate the neuronal plasticity mechanisms in the hippocampus underlying the processing of spatial novelties. The fifth chapter is a comprehensive overview of the role of clock genes in SD, memory, and stress. In this chapter, we provided insight in how clock genes might mediate the interaction between the different processes, including their role in SD-induced memory deficits. The last chapter consists of a summary of the main findings and a general discussion.

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