A brief period of sleep deprivation negatively impacts the acquisition, consolidation, and retrieval of object-location memories

Heckman, Pim R A; Roig Kuhn, Femke; Meerlo, Peter; Havekes, Robbert

Published in:
Neurobiology of Learning and Memory

DOI:
10.1016/j.nlm.2020.107326

Publication date:
2020

Neurobiology of Learning and Memory 175 (2020) 107326

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

A brief period of sleep deprivation negatively impacts the acquisition, consolidation, and retrieval of object-location memories

Pim R.A. Heckman*, Femke Roig Kuhn, Peter Meerlo, Robbert Havekes*

Neurobiology Expertise Group, Groningen Institute for Evolutionary Life Sciences (GELIFES), University of Groningen, Groningen, the Netherlands

ARTICLE INFO

Keywords:
Sleep deprivation
Hippocampus
Object-location memory
Acquisition
Consolidation
Retrieval

ABSTRACT

Memory is a cognitive concept and refers to the storage of information over a longer time period. It exists of a series of complementary processes; acquisition, consolidation, and retrieval. Each of these processes has its own partly unique neurobiological signature. Sleep deprivation is known to impair hippocampus-dependent long-term memories. Many studies have used extended periods of wakefulness, affecting all three memory processes, thereby making it unable to determine how each of the processes is affected by sleep loss, separately. Others have extensively examined the effects on memory consolidation, showing the detrimental effect of sleep deprivation during the consolidation process on memory formation. Few studies have investigated how memory acquisition and its retrieval are affected by sleep loss. In the present study, we therefore assessed in mice how sleep deprivation negatively impacts memory acquisition, consolidation, and retrieval, in the Object Location Memory task. Mice were sleep deprived for six hours at the beginning of the light phase using the gentle handling method, 1) directly preceding the learning trial (acquisition), 2) immediately after the learning trial (consolidation), or 3) directly preceding the test trial (retrieval). Memory was assessed at either a 24-h or 1-h interval. Using this approach, we show for the first time that six hours of sleep deprivation attenuates the acquisition, consolidation, and retrieval of object-location memories in mice.

1. Introduction

Memory is the storage of information over time (McGaugh, 2000). It requires a sequence of complementary processes of acquiring, maintaining, and retrieving information. As a result, the broader concept of memory is segregated into different stages of memory referred to as acquisition, consolidation, and retrieval (Abel & Lattal, 2001; Feld & Born, 2020). Various rodent studies have shown that hippocampus-dependent memory processes are promoted by sleep and disrupted by sleep deprivation (SD) (e.g., Abel, Havekes, Saletin, & Walker, 2013; Havekes, Meerlo, & Abel, 2015; Klinzing, Niethard, & Born, 2019; Kreutzmann, Havekes, Abel, & Meerlo, 2015; Walsh, Booth, & Poe, 2011). For instance, extended periods of SD (> 24 h) showed impaired memory performance in the Morris water maze (MWM) (e.g., Cao et al., 2019; McCoy et al., 2013), contextual fear-conditioning task (CFC) (e.g., Tiba, Oliveira, Rossi, Tufik, & Suchecki, 2008), and object-location memory test (OLM) (e.g., Howard & Hunter, 2019; Lu et al., 2018). Such prolonged or chronic SD might have long-lasting effects that overlap and interfere with all different phases of memory processes, which makes it challenging to isolate the impact of SD on the different stages of memory. For this reason, many laboratories have used a single brief period of SD to examine to what extend each memory phase is affected by sleep loss. However, most of these experimental studies on brief SD have focused on memory consolidation (Havekes et al., 2015; Kreutzmann et al., 2015). To our knowledge, only few studies have examined the impact of SD on memory acquisition and retrieval (e.g., Hagewoud, Havekes, & et al., 2010; Heckman et al., 2020; Montes-Rodriguez, Rueda-Orozco, & Prospero-Garcia, 2019; Rossi et al., 2014; Shahveisi et al., 2020; Takatsu-Coleman et al., 2013). These kind of studies are important given the accumulating evidence that these different memory processes rely at least partly on distinct underlying neurobiological mechanisms, yet with a common upstream mediator (Abel & Lattal, 2001).

One-trial learning paradigms, such as the OLM and CFC, are particularly well-suited for such studies, because the timing of the intervention determines the memory stage to be affected (Abel & Lattal, 2001). Using this approach to probe the impact of SD on memory consolidation by keeping the animals awake for the first hours directly following training indicated that SD has profound effects on the consolidation of context-fear associations (e.g., Graves, Heller, Pack, &

* Corresponding authors at: Neurobiology Expertise group, Groningen Institute for Evolutionary Life Sciences (GELIFES), University of Groningen, Nijenborgh 7, 9747 AG Groningen, the Netherlands.

E-mail addresses: p.r.a.heckman@rug.nl (P.R.A. Heckman), r.havekes@rug.nl (R. Havekes).

https://doi.org/10.1016/j.nlm.2020.107326
Received 1 April 2020; Received in revised form 24 August 2020; Accepted 8 October 2020
Available online 12 October 2020

Abel, 2003; Hagewoud, Bultsma, Barf, Koolhaas, & Meerlo, 2011; Hagewoud, Whitcomb, & et al., 2010; Rosier et al., 2018; Sharma, Sahota, & Thakkar, 2020; Vecsey et al., 2009) and object-location memories (e.g., Havekes et al., 2014; Havekes, Park, Tudor, & et al., 2016; Raven, Heckman, Havekes, & Meerlo, 2019; Tudor et al., 2016). Despite these observations, to our knowledge no studies have examined the impact of SD on the acquisition and retrieval of object-location memories. Therefore, in the current study, we examined the impact of a single brief period of SD on the three stages of memory in the OLM task. Due to the (partially) overlapping or interacting mechanisms behind the three different memory processes, we hypothesize that the effect of sleep loss on each of the three memory processes separately will lead to an impairment in memory function at the behavioral level.

2. Materials and methods

2.1. Animals and housing

We conducted the studies with 36 male C57BL/6J mice (Charles River ordered at 6 weeks of age and pair-housed at arrival). Mice were individually housed one week before the start of our experiments when the animals were 9–10 weeks old. The experimental room maintained a 12 h light/12 h dark cycle (lights on 9:00–21:00) and was kept under constant temperature (22 °C ± 5 °C). Animals were housed in poly carb clear cages with a stainless-steel wired lid. The cages contained sawdust bedding and standard cage enrichment (nesting material and a cardboard roll). Chow diet and water were available *ad libitum*. All procedures were approved by the national Central Authority for Scientific Procedures on Animals (CCD) and the Institutional Animal Welfare Body (IvD, University of Groningen, The Netherlands), and conform Directive 2010/63/EU.

2.2. Experimental design

Three experiments were performed to assess the effects of SD on the three memory processes separately (12 mice for each study). In each experiment, mice were subjected to the OLM task with a learning or acquisition trial T1 and test trial T2 (see Fig. 1). In all 3 experiments the mice were subjected to 6 h of SD at a different phase of the memory process. To assess the effect of SD on memory acquisition, SD took place directly before T1 and memory was tested in T2 one hour later (experiment 1). To assess the effect of SD on memory consolidation, SD took place immediately following T1 and memory was tested in T2 the next day, 24 h after T1 (experiment 2). Finally, to assess the effect of SD on memory retrieval, SD took place immediately before T2 in mice that had been trained the previous day (experiment 3). During each of the three experiments separately, mice were tested using a repeated measures cross-over design. This means all mice were tested twice (50% SD and 50% non-SD, and vice versa) using different objects and locations. Furthermore, a recovery period of at least four days was allowed in between repeated testing sessions.

2.3. Sleep deprivation

Mice were sleep deprived during approximately the first half of the light phase. In all three experiments, mice were sleep deprived using the gentle stimulation method as described elsewhere (e.g., Havekes, Park, Tudor, & et al., 2016; Heckman et al., 2020; Raven et al., 2019). In short, animals were kept awake by gently tapping the cage, gently shaking the cage, and/or removing the wire cage top. Their bedding was disturbed only in cases when mice did not respond to tapping or shaking the cage. Importantly, we never introduce new objects, cages, clean bedding or other arousing stimuli to keep the animals awake. We have previously validated this method using EEG recordings (Meerlo, de Bruin, Strijkstra, & Daan, 2001). Furthermore, several studies have shown that the cognitive deficits and synaptic plasticity impairments as a result of SD were not caused by elevated plasma corticosterone levels or the gentle stimulation method itself (Meerlo & Turek, 2001; Ruskin, Dunn, Billiot, Bazan, & LaHoste, 2006; Tiba et al., 2008; van der Borght et al., 2006; Vecsey et al., 2009). More recently, we conducted a study in which we blocked the synthesis and release of corticosterone in mice selectively during the SD period. Using this approach, we recently showed that inhibiting glucocorticoid stress hormones does not prevent SD-induced memory deficits in the OLM task (Raven et al., 2019).

2.4. Object location memory paradigm (OLM)

The OLM task is a hippocampus-dependent spatial memory

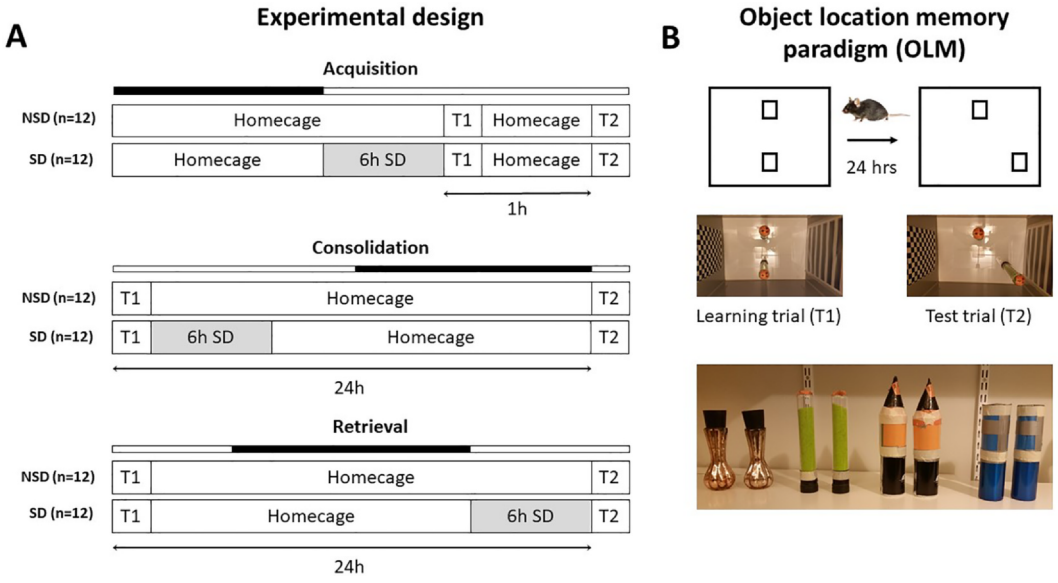

Fig. 1. Experimental design (**A**) and schematic representation of object location memory (OLM) paradigm (**B**). **A**) Outline of the temporal dynamics of SD induction to target the three different memory processes separately. For acquisition, SD was induced before the learning trial (T1); for consolidation, directly after the learning trial (T1); and for retrieval, directly preceding the test trial (T2). **B**) Overview of the arena showing a top view of one of the possible start and test positions of the objects during the learning trial (T1) and test trial (T2), respectively. Also, the 4 object pairs are shown used during the different experiments.

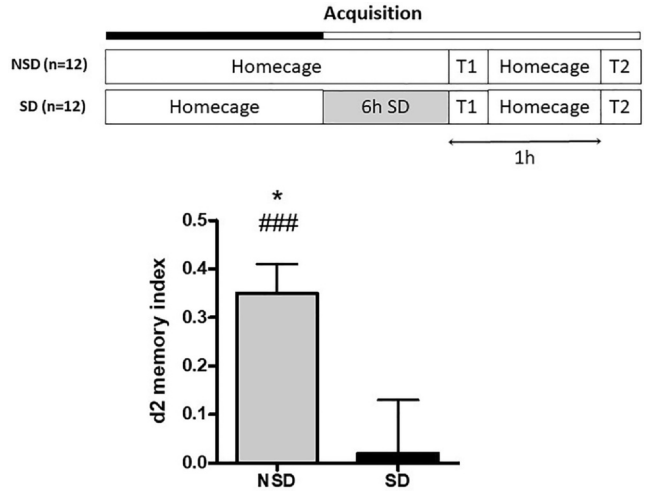

Fig. 2. Spatial memory performance measured with the Object location memory test (OLM; 24 h interval; # represents significant difference from zero (### = $p < 0.001$) by independent samples T-test (N = 12). Six hours of sleep deprivation at the beginning of the light phase directly preceding T1 impairs spatial memory performance in the OLM (24 h interval; * represents a significant difference between the non-sleep deprived and sleep deprived conditions (** = $p < 0.01$) by paired samples T-test; N = 12). SD = sleep deprived; NSD = non-sleep deprived.

paradigm (Argyrousi et al., 2019; Havekes, Park, Tudor, & et al., 2016; Oliveira, Hawk, Abel, & Havekes, 2010; Raven et al., 2019; Vanmierlo et al., 2016). The rectangular arena was made of PVC and had a length of 40 cm, width of 30 cm, and was 50 cm high. The four walls of the arena consisted of grey-colored PVC and the bottom consisted of transparent PVC. In this task, four pairs of two identical objects were used (one pair per trial). These objects were either two blue aluminum cylinders (height 12 cm and diameter 3.5 cm), two orange aluminum cylinders with tapering tops (height 12 cm and diameter at widest point 3.5 cm), two green glass cylinders (height 12 cm and diameter 2.5 cm), or two pink round vases (height 10 cm and diameter ranging from 3.5 cm at the bottom to 1.5 at the top). Inside the arena, two spatial cues were presented at opposite sides at the short walls of the rectangular arena. One cue consisted of black and white striping, while the other cue consisted of a black and white checkerboard pattern. The animals were unable to move the objects or sit on the objects.

In the present study, the task consisted of two trials of free exploration. The first trial (T1) was the learning or acquisition trial, in which two identical objects (objects A1 and A2) were placed symmetrically on a horizontal line in the arena, approximately 7.5 cm from the wall. At the start of T1, the animals were always placed in the front of the arena facing the wall, and were allowed to explore the objects for ten minutes, after which they were put back into their home cage. The second trial (T2) was the test trial and took place after a predetermined delay interval of 1 or 24 h. In this trial, one of the objects was displaced along a straight line to a position that was 15 cm away from the previous location, while the other object was placed at the similar location as during T1 (objects B and A3, respectively). The object that was moved (either left or right), the direction of movement (front or back), and the objects themselves, were all counterbalanced to avoid place and object preferences. The mice were again allowed to explore this new spatial arrangement for 10 min. Between animals and trials, the objects were cleaned with a 70% ethanol solution to avoid the presence of olfactory cues. Prior to testing animals were habituated to handling, the experimenter, and the testing arena.

The readout parameters of the OLM are referring to the exploration time for each object during T1 and T2 (Akkerman, Blokland, & et al., 2012; Akkerman, Prickaerts, Steinbusch, & Blokland, 2012). The exploration time of each object was scored manually by the experimenter, using a computer. The experimenter was blind to experimental conditions during testing and scoring. Exploration was defined as follows: directing the nose to the object at a distance of no more than 1 cm and/or touching the object with the nose. Leaning toward an object was not considered to be exploratory behavior. The exploration time (in seconds) of each object during T1 are presented as 'a1′ and 'a2′. The time spent exploring the familiar and the displaced object in T2 are represented as 'a3′ and 'b', respectively. Using this information, the following variables were calculated: T1 [e1 (=a1 + a2)], the total exploration time during T2 [e2 (=a3 + b)] and the discrimination index [d2 (=b − a3/e2)]. The d2 index is a relative measure of discrimination corrected for total exploration time and can range from −1 to 1. A significant difference from zero, *i.e.* chance level, indicates that the mice remembered the object locations from T1, and a difference from the control condition signifies an actual effect on memory performance by SD.

2.5. Statistical analysis

One sample t-tests were performed in order to assess whether the d2 index for each SD condition (sleep deprived/non-sleep deprived) differed significantly from zero (chance level) in the OLM. Subsequently, paired sample t-statistics were conducted to compare means between the sleep deprived and non-sleep-deprived conditions within the same group of animals (n = 12). This was done for all three studies separately (3x n = 12; acquisition, consolidation, retrieval). Total exploration times were analyzed using paired sample t-tests.

3. Results

In the first study, we investigated the effects of SD on memory acquisition of object-location memories. We subjected mice to 6 h of SD at the beginning of the light phase directly preceding T1 (*i.e.* T1 commenced at ZT6). Because SD prior to training could potentially affect both memory acquisition and consolidation, mice were subjected to the test session at a 1-h time interval. In this way, we could exclude the occurrence of memory consolidation, a process known to be affected by SD (Fig. 3). SD preceding training resulted in an impairment during the test session (NSD = non-sleep deprived, SD = sleep deprived, n = 12; ### represents a significant difference from zero, one sample *t*-test, $p < 0.001$; Fig. 2). Furthermore, a paired sample *t*-test analyses indicated a significant difference between the SD and NSD conditions (** = $p < 0.01$; n = 12). The observed deficits were not a result of alterations in total exploration time (T1 SD = 26.3 ± 2.5 vs T1 NSD = 28.4 ± 3.0; p = 0.35, N.S.; T2 SD = 17.9 ± 1.7 vs T2 NSD = 20.4 ± 2.2; p = 0.11, N.S.)

In a second study, we examined the effects of SD on memory consolidation in the OLM task. We found that mice deprived of sleep for 6 h directly following training failed to discriminate the relocated from the non-related object during the test session 24 h after the training (NSD = non-sleep deprived, SD = sleep deprived n = 12; ### represents a significant difference from zero, one sample *t*-test, $p < 0.001$; Fig. 3). Additional statistical analyses confirmed that mice performed significantly worse under SD conditions (paired sample *t*-test, * = $p < 0.05$; Fig. 3). No differences were observed between exploration times (T1 SD = 42.9 ± 6.3 vs T1 NSD = 35.3 ± 4.4; p = 0.44, N.S.; T2 SD = 32.7 ± 2.1 vs T2 NSD = 36.3 ± 3.5; p = 0.22, N.S.). These findings confirmed our previous observations showing that memory consolidation for object-location memories is vulnerable to SD (Havekes et al., 2012; Havekes, Park, Tudor, & et al., 2016; Raven et al., 2019).

During the third study, we looked at how memory retrieval is impacted by SD. We trained mice at ZT6. The next day, SD was conducted for 6 h starting at the beginning of the light phase (*i.e.* ZT0-6) directly preceding T2. This way, we were certain to only affect the memory retrieval process and not memory acquisition and/or consolidation. SD

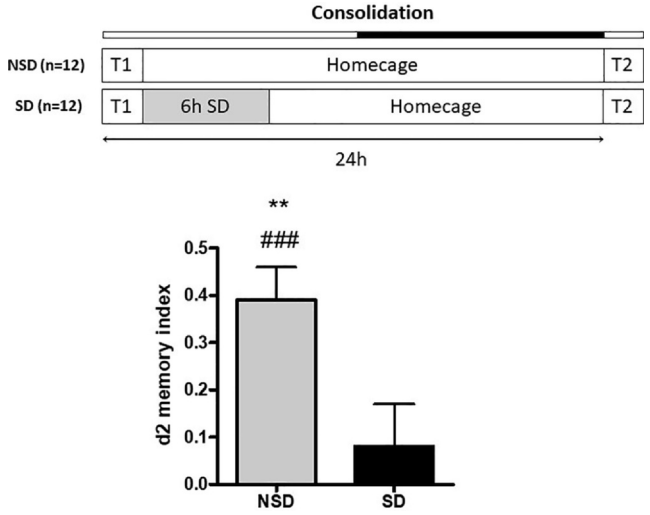

Fig. 3. Spatial memory performance measured with the Object location memory test (OLM; 24 h interval; # represents significant difference from zero (### = $p < 0.001$) by independent samples T-test (N = 12). Six hours of sleep deprivation at the beginning of the light phase directly after T1 impairs spatial memory performance in the OLM (24 h interval; * represents a significant difference between the non-sleep deprived and sleep deprived conditions (* = $p < 0.05$) by paired samples T-test; N = 12). SD = sleep deprived; NSD = non-sleep deprived.

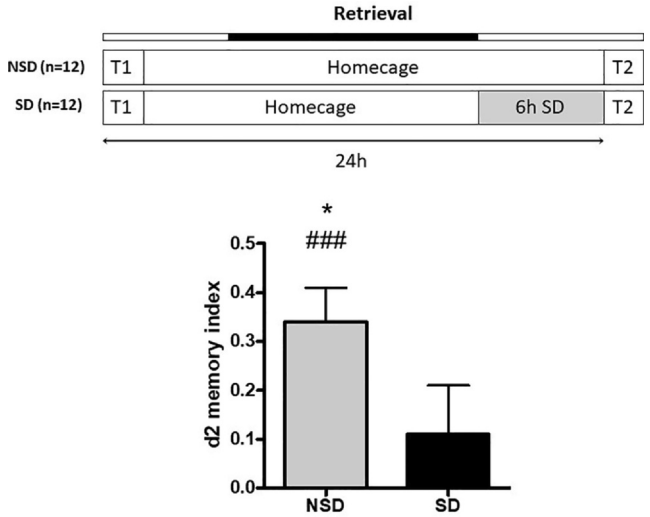

Fig. 4. Spatial memory performance measured with the Object location memory test (OLM; 24 h interval; # represents significant difference from zero (### = $p < 0.001$) by independent samples T-test (N = 12). Six hours of sleep deprivation at the beginning of the light phase directly preceding T2 impairs spatial memory performance in the OLM (24 h interval; * represents a significant difference between the non-sleep deprived and sleep deprived conditions (* = $p < 0.01$) by paired samples T-test; N = 12). SD = sleep deprived; NSD = non-sleep deprived.

impaired object location memory performance leading to a significant difference between the NSD and SD group (NSD = non-sleep deprived, SD = sleep deprived, n = 12; ### represents a significant difference from zero, one sample *t*-test, $p < 0.001$; Paired sample *t*-test, * = $p < 0.05$; Fig. 4). Again, the effects of SD before retrieval could not be attributed to effects on exploration times (T1 SD = 19.1 ± 4.4 vs T1 NSD = 18.0 ± 1.7; $p = 0.56$, N.S.; T2 SD = 15.5 ± 1.0 vs T2 NSD = 17.5 ± 2.3; $p = 0.66$, N.S.).

4. Discussion

In the current study, we investigated the effect of SD on the acquisition, consolidation, and retrieval of object-location memories. We showed that all three memory processes can be negatively affected by SD independently. To this end, we induced sleep loss either directly before learning, immediately after learning, or directly proceeding memory retrieval. To exclude the possibility that SD affected both acquisition and consolidation, we used a 1-h interval during the test of the effects on the acquisition process. This window is too short for consolidation to contribute to the behavioral performance because effects of SD on consolidation occur one to four hours after training (Bollen et al., 2014; Prince et al., 2014). These previously published findings exclude the possibility that our findings in the acquisition experiment are due to effects of sleep deprivation on consolidation.

However, when applying SD during acquisition, it is challenging to fully separate the negative impact on memory retrieval. This is a general limitation when assessing the impact of sleep loss on short-term memory, which may always be a mix of acquisition and retrieval processes. This way, memory impairment observed at the behavioral level can validly be assigned to the impact of sleep loss on molecular processes related to memory acquisition or retrieval.

The three different memory processes of acquisition, consolidation, and retrieval have (partially) overlapping or interacting neurobiological mechanisms (Abel & Lattal, 2001). Although different downstream effector molecules are involved in each of the memory processes, studies have pointed to cyclic adenosine monophosphate (cAMP) a potential common upstream mediator (e.g. Argyrousi et al., 2019; Bollen et al., 2014; Heckman et al., 2020; Rutten, Prickaerts, & Blokland, 2006). As such, cAMP signaling is known to be essential for memory consolidation (Bourtchouladze et al., 2006). Early work indicated that a brief period of SD at the beginning of the light phase increases levels of the protein PDE4A5 in the mouse hippocampus, which subsequently leads to a decrease in local baseline cAMP levels (Vecsey et al., 2009). As a result, activity of the cAMP-protein kinase A (PKA)-cAMP response element binding protein (CREB) pathway is suppressed leading to decreased hippocampal neuroplasticity (Vecsey et al., 2009). To examine whether misregulation of neuronal cAMP signaling in the hippocampus could be responsible for the effects SD on memory consolidation, Havekes et al. (2014) used a viral approach to modulate neuronal cAMP signaling. Using this chemogenetic/viral approach, the authors showed that transiently increasing cAMP levels in mouse hippocampal excitatory neurons during SD prevents memory consolidation deficits in the OLM task. As such, these results indicate that decreased cAMP signaling in hippocampal excitatory neurons is indeed part of the underlying mechanism through which sleep loss affects spatial memory function. As mentioned previously, less is known regarding the molecular machinery through which SD could affect memory acquisition. It has been shown that cAMP is able to improve the process of memory acquisition upon stimulation (Argyrousi et al., 2019; Bollen et al., 2014; Rutten et al., 2006). This can potentially be linked to underlying pre- or postsynaptic mechanisms. Presynaptically, it is thought to be due to a stimulatory effect on cholinergic transmission by enhancement of cholinergic turnover (Imanishi et al., 1997) as well as stimulation of glutamate release (Rodriguez-Moreno & Sihra, 2013). Furthermore, elevated intracellular cAMP levels are thought to excite noradrenergic and dopaminergic (Schoffelmeer, Wardeh, & Mulder, 1985) neurotransmitter systems and thus increasing their availability, hence also enhancing synaptic transmission. The second mechanism relates to postsynaptic cAMP-activated PKA, which plays a key role in the induction of long-term potentiation (LTP) and long-lasting neuronal changes. Downstream of cAMP-PKA, it is known that the formation of new memories involves fast, basic excitatory synaptic transmission provided by ionotropic receptors (Abel & Lattal, 2001). Among these receptors, the ionotropic glutamate receptors, *i.e.* the 2-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors

(AMPARs) and N-methyl-d-aspartate receptors (NMDARs), are critical for place and grid cell formation in the enthorinal cortex necessary for spatial memory formation, *i.e.* acquisition (e.g., Allen et al., 2014; Sanderson et al., 2007). Interestingly, it has been shown by multiple groups that these ionotropic glutamate receptors in the hippocampus and entorhinal cortex are sensitive to sleep loss (e.g., Dubiela et al., 2013; Hagewoud, Havekes, & et al., 2010; Xie et al., 2016, 2015). Memory retrieval is the least examined memory process in light of the mechanism by which SD can negatively affect the different memory stages (Alvarenga et al., 2008; Montes-Rodriguez et al., 2019). It has been shown that SD before memory recall, impaired the retrieval of fear memories and that this effect was accompanied by a lack of the otherwise observed increase in c-Fos activity (Montes-Rodriguez et al., 2019). However, the reduced c-Fos activity was only observed in the basolateral amygdala, not in the hippocampus (Montes-Rodriguez et al., 2019). In the previous paragraph, we mentioned a potential involvement of ionotropic glutamate receptors during memory retrieval. Where both AMPARs and NMDARs seemed to be involved in the acquisition process, for memory retrieval it is shown that blocking the NMDARs in the hippocampus does not disrupt the successful recollection of previously established spatial memories (Steele & Morris, 1999). Nevertheless, 4 h of SD directly before the retention trial of the MWM did increase surface expression levels of GluN1 and GluN2B with no effect on GluN2A (Xie et al., 2016). The AMPARs, on the other hand, do seem to be affected as 4 h of SD directly before the retention trial of the MWM strongly reduced surface expression of GluA1, while simultaneously increasing GluA2 and GluA3 levels (Xie et al., 2016). Whether these effects are mediated through cAMP signaling remains to be seen. Importantly, effects of SD on the molecular mechanisms of each of the three memory processes can result in a deficit at the behavioral level.

Taken together, we showed for the first time how six hours of SD using the gentle handling method, can negatively affect the three memory processes of acquisition, consolidation, and retrieval separately. One limitation of the current study is that the observation were restricted to object-location memories in mice. In future studies, it will be important to determine whether these findings extend to other memory paradigms and species.

CRediT authorship contribution statement

Pim R.A. Heckman: Conceptualization, Methodology, Formal analysis, Investigation, Writing - original draft, Writing - review & editing. **Femke Roig Kuhn:** Investigation. **Peter Meerlo:** Conceptualization, Methodology, Supervision, Writing - original draft, Writing - review & editing. **Robbert Havekes:** Conceptualization, Methodology, Supervision, Project administration, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

None.

References

Abel, T., Havekes, R., Saletin, J. M., & Walker, M. P. (2013). Sleep, plasticity and memory from molecules to whole-brain networks. *Current Biology, 23*, R774–R788.

Abel, T., & Lattal, K. M. (2001). Molecular mechanisms of memory acquisition, consolidation and retrieval. *Current Opinion in Neurobiology, 11*, 180–187.

Akkerman, S., Blokland, A., Reneerkens, O., van Goethem, N. P., Bollen, E., Gijselaers, H. J., ... Prickaerts, J. (2012a). Object recognition testing: Methodological considerations on exploration and discrimination measures. *Behavioural Brain Research, 232*, 335–347.

Akkerman, S., Prickaerts, J., Steinbusch, H. W., & Blokland, A. (2012b). Object recognition testing: Statistical considerations. *Behavioural Brain Research, 232*, 317–322.

Allen, K., Gil, M., Resnik, E., Toader, O., Seeburg, P., & Monyer, H. (2014). Impaired path integration and grid cell spatial periodicity in mice lacking GluA1-containing AMPA receptors. *Journal of Neuroscience, 34*, 6245–6259.

Alvarenga, T. A., Patti, C. L., Andersen, M. L., Silva, R. H., Calzavara, M. B., Lopez, G. B., ... Tufik, S. (2008). Paradoxical sleep deprivation impairs acquisition, consolidation, and retrieval of a discriminative avoidance task in rats. *Neurobiology of Learning and Memory, 90*, 624–632.

Argyrousi, E. K., Heckman, P. R., van Hagen, B. T., Muysers, H., van Goethem, N. P., & Prickaerts, J. (2019). Pro-cognitive effect of upregulating cyclic guanosine monophosphate signalling during memory acquisition or early consolidation is mediated by increased AMPA receptor trafficking. *Journal of psychopharmacology (Oxford England)* 269881119885262.

Bollen, E., Puzzo, D., Rutten, K., Privitera, L., De Vry, J., Vanmierlo, T., ... Steinbusch, H. M. (2014). Improved long-term memory via enhancing cGMP-PKG signaling requires cAMP-PKA signaling. *Neuropsychopharmacology, 39*, 2497–2505.

Bourtchouladze, R., Patterson, S. L., Kelly, M. P., Kreibich, A., Kandel, E. R., & Abel, T. (2006). Chronically increased Gsalpha signaling disrupts associative and spatial learning. *Learning & Memory, 13*, 745–752.

Cao, Y., Li, Q., Liu, L., Wu, H., Huang, F., Wang, C., ... Li, Q. (2019). Modafinil protects hippocampal neurons by suppressing excessive autophagy and apoptosis in mice with sleep deprivation. *British Jornal of Pharmacology, 176*, 1282–1297.

Dubiela, F. P., Queiroz, C. M., Moreira, K. D., Nobrega, J. N., Sita, L. V., Tufik, S., & Hipolide, D. C. (2013). AMPA receptors mediate passive avoidance deficits induced by sleep deprivation. *Behavioural Brain Research, 257*, 189–196.

Feld, G. B., & Born, J. (2020). Neurochemical mechanisms for memory processing during sleep: Basic findings in humans and neuropsychiatric implications. *Neuropsychopharmacology, 45*, 31–44.

Graves, L. A., Heller, E. A., Pack, A. I., & Abel, T. (2003). Sleep deprivation selectively impairs memory consolidation for contextual fear conditioning. *Learning & Memory, 10*, 168–176.

Hagewoud, R., Bultsma, L. J., Barf, R. P., Koolhaas, J. M., & Meerlo, P. (2011). Sleep deprivation impairs contextual fear conditioning and attenuates subsequent behavioural, endocrine and neuronal responses. *Journal of Sleep Research, 20*, 259–266.

Hagewoud, R., Havekes, R., Novati, A., Keijser, J. N., Van der Zee, E. A., & Meerlo, P. (2010a). Sleep deprivation impairs spatial working memory and reduces hippocampal AMPA receptor phosphorylation. *Journal of Sleep Research, 19*, 280–288.

Hagewoud, R., Whitcomb, S. N., Heeringa, A. N., Havekes, R., Koolhaas, J. M., & Meerlo, P. (2010b). A time for learning and a time for sleep: The effect of sleep deprivation on contextual fear conditioning at different times of the day. *Sleep, 33*, 1315–1322.

Havekes, R., Bruinenberg, V. M., Tudor, J. C., Ferri, S. L., Baumann, A., Meerlo, P., ... Abel, T. (2014). Transiently increasing cAMP levels selectively in hippocampal excitatory neurons during sleep deprivation prevents memory deficits caused by sleep loss. *Journal of Neuroscience, 34*, 15715–15721.

Havekes, R., Canton, D. A., Park, A. J., Huang, T., Nie, T., Day, J. P., ... Baillie, G. S. (2012). Gravin orchestrates protein kinase A and beta2-adrenergic receptor signaling critical for synaptic plasticity and memory. *Journal of Neuroscience, 32*, 18137–18149.

Havekes, R., Meerlo, P., & Abel, T. (2015). Animal studies on the role of sleep in memory: From behavioral performance to molecular mechanisms. *Current Topics in Behavioral Neurosciences, 25*, 183–206.

Havekes, R., Park, A. J., Tudor, J. C., Luczak, V. G., Hansen, R. T., Ferri, S. L., ... Radwańska, K. (2016b). Sleep deprivation causes memory deficits by negatively impacting neuronal connectivity in hippocampal area CA1. *Elife, 5*.

Heckman, P. R. A., Roig Kuhn, F., Raven, F., Bolsius, Y. G., Prickaerts, J., Meerlo, P., & Havekes, R. (2020). Phosphodiesterase inhibitors roflumilast and vardenafil prevent sleep deprivation-induced deficits in spatial pattern separation. *Synapse (New York, N.Y.), e22150*.

Howard, K. A., & Hunter, A. S. (2019). Immediate and long-lasting cognitive consequences of adolescent chronic sleep restriction. *Behavioral Neuroscience, 133*, 461–466.

Imanishi, T., Sawa, A., Ichimaru, Y., Miyashiro, M., Kato, S., Yamamoto, T., & Ueki, S. (1997). Ameliorating effects of rolipram on experimentally induced impairments of learning and memory in rodents. *European Journal of Pharmacology, 321*, 273–278.

Klinzing, J. G., Niethard, N., & Born, J. (2019). Mechanisms of systems memory consolidation during sleep. *Nature Neuroscience*.

Kreutzmann, J. C., Havekes, R., Abel, T., & Meerlo, P. (2015). Sleep deprivation and hippocampal vulnerability: Changes in neuronal plasticity, neurogenesis and cognitive function. *Neuroscience, 309*, 173–190.

Lu, C., Wang, Y., Lv, J., Jiang, N., Fan, B., Qu, L., ... Liu, X. (2018). Ginsenoside Rh2 reverses sleep deprivation-induced cognitive deficit in mice. *Behavioural Brain Research, 349*, 109–115.

McCoy, J. G., Christie, M. A., Kim, Y., Brennan, R., Poeta, D. L., McCarley, R. W., ... Strecker, R. E. (2013). Chronic sleep restriction impairs spatial memory in rats. *NeuroReport, 24*, 91–95.

McGaugh, J. L. (2000). Memory–a century of consolidation. *Science, 287*, 248–251.

Meerlo, P., de Bruin, E. A., Strijkstra, A. M., & Daan, S. (2001). A social conflict increases EEG slow-wave activity during subsequent sleep. *Physiology & Behavior, 73*, 331–335.

Meerlo, P., & Turek, F. W. (2001). Effects of social stimuli on sleep in mice: Non-rapid-eye-movement (NREM) sleep is promoted by aggressive interaction but not by sexual interaction. *Brain Research, 907*, 84–92.

Montes-Rodriguez, C. J., Rueda-Orozco, P. E., & Prospero-Garcia, O. (2019). Total sleep deprivation impairs fear memory retrieval by decreasing the basolateral amygdala

activity. *Brain Research, 1719*, 17–23.
Oliveira, A. M., Hawk, J. D., Abel, T., & Havekes, R. (2010). Post-training reversible inactivation of the hippocampus enhances novel object recognition memory. *Learning & Memory, 17*, 155–160.
Prince, T. M., Wimmer, M., Choi, J., Havekes, R., Aton, S., & Abel, T. (2014). Sleep deprivation during a specific 3-hour time window post-training impairs hippocampal synaptic plasticity and memory. *Neurobiology of Learning and Memory, 109*, 122–130.
Raven, F., Heckman, P. R. A., Havekes, R., & Meerlo, P. (2019). Sleep deprivation-induced impairment of memory consolidation is not mediated by glucocorticoid stress hormones. *Journal of Sleep Research, e12972*.
Rodriguez-Moreno, A., & Sihra, T. S. (2013). Presynaptic kainate receptor-mediated facilitation of glutamate release involves Ca2+-calmodulin and PKA in cerebrocortical synaptosomes. *FEBS Letters, 587*, 788–792.
Rosier, M., Le Barillier, L., Meunier, D., El Yacoubi, M., Malleret, G., & Salin, P. A. (2018). Post-learning paradoxical sleep deprivation impairs reorganization of limbic and cortical networks associated with consolidation of remote contextual fear memory in mice. *Sleep, 41*.
Rossi, V. C., Tiba, P. A., Moreira, K. D., Ferreira, T. L., Oliveira, M. G., & Suchecki, D. (2014). Effects of sleep deprivation on different phases of memory in the rat: Dissociation between contextual and tone fear conditioning tasks. *Frontiers in Behavioral Neuroscience, 8*, 389.
Ruskin, D. N., Dunn, K. E., Billiot, I., Bazan, N. G., & LaHoste, G. J. (2006). Eliminating the adrenal stress response does not affect sleep deprivation-induced acquisition deficits in the water maze. *Life Sciences, 78*, 2833–2838.
Rutten, K., Prickaerts, J., & Blokland, A. (2006). Rolipram reverses scopolamine-induced and time-dependent memory deficits in object recognition by different mechanisms of action. *Neurobiology of Learning and Memory, 85*, 132–138.
Sanderson, D. J., Gray, A., Simon, A., Taylor, A. M., Deacon, R. M., Seeburg, P. H., ... Bannerman, D. M. (2007). Deletion of glutamate receptor-A (GluR-A) AMPA receptor subunits impairs one-trial spatial memory. *Behavioral Neuroscience, 121*, 559–569.
Schoffelmeer, A. N., Wardeh, G., & Mulder, A. H. (1985). Cyclic AMP facilitates the electrically evoked release of radiolabelled noradrenaline, dopamine and 5-hydroxytryptamine from rat brain slices. *Naunyn-Schmiedeberg's Archives of Pharmacology, 330*, 74–76.
Shahveisi, K., Farnia, V., Khazaie, H., Ghazvini, H., Nozari, M., & Khodamoradi, M. (2020). Novel object recognition memory in REM sleep-deprived rats: Role of the cannabinoid CB1 receptor. *Behavioural Brain Research, 381*, 112311.
Sharma, R., Sahota, P., & Thakkar, M. M. (2020). Sleep loss immediately after fear memory reactivation attenuates fear memory reconsolidation. *Neuroscience, 428*, 70–75.
Steele, R. J., & Morris, R. G. (1999). Delay-dependent impairment of a matching-to-place task with chronic and intrahippocampal infusion of the NMDA-antagonist D-AP5. *Hippocampus, 9*, 118–136.
Takatsu-Coleman, A. L., Zanin, K. A., Patti, C. L., Zager, A., Lopes-Silva, L. B., Longo, B. M., ... Frussa-Filho, R. (2013). Short-term sleep deprivation reinstates memory retrieval in mice: The role of corticosterone secretion. *Psychoneuroendocrinology, 38*, 1967–1978.
Tiba, P. A., Oliveira, M. G., Rossi, V. C., Tufik, S., & Suchecki, D. (2008). Glucocorticoids are not responsible for paradoxical sleep deprivation-induced memory impairments. *Sleep, 31*, 505–515.
Tudor, J. C., Davis, E. J., Peixoto, L., Wimmer, M. E., van Tilborg, E., Park, A. J., ... Gatti, E. (2016). Sleep deprivation impairs memory by attenuating mTORC1-dependent protein synthesis. *Science Signaling, 9*, ra41.
van der Borght, K., Ferrari, F., Klauke, K., Roman, V., Havekes, R., Sgoifo, A., ... Meerlo, P. (2006). Hippocampal cell proliferation across the day: Increase by running wheel activity, but no effect of sleep and wakefulness. *Behavioural Brain Research, 167*, 36–41.
Vanmierlo, T., Creemers, P., Akkerman, S., van Duinen, M., Sambeth, A., De Vry, J., ... Prickaerts, J. (2016). The PDE4 inhibitor roflumilast improves memory in rodents at non-emetic doses. *Behavioural Brain Research, 303*, 26–33.
Vecsey, C. G., Baillie, G. S., Jaganath, D., Havekes, R., Daniels, A., Wimmer, M., ... Kim, S. S. (2009). Sleep deprivation impairs cAMP signalling in the hippocampus. *Nature, 461*, 1122–1125.
Walsh, C. M., Booth, V., & Poe, G. R. (2011). Spatial and reversal learning in the Morris water maze are largely resistant to six hours of REM sleep deprivation following training. *Learning & Memory, 18*, 422–434.
Xie, M., Li, C., He, C., Yang, L., Tan, G., Yan, J., ... Hu, Z. (2016). Short-term sleep deprivation disrupts the molecular composition of ionotropic glutamate receptors in entorhinal cortex and impairs the rat spatial reference memory. *Behavioural Brain Research, 300*, 70–76.
Xie, M., Yan, J., He, C., Yang, L., Tan, G., Li, C., ... Wang, J. (2015). Short-term sleep deprivation impairs spatial working memory and modulates expression levels of ionotropic glutamate receptor subunits in hippocampus. *Behavioural Brain Research, 286*, 64–70.