

# Acute sleep loss impairs object but not spatial pattern separation in humans

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## ABSTRACT

Pattern separation allows us to form discrete representations of information in memory. Pattern separation can be measured in several domains including spatial and object-based discrimination. The brain area largely involved in this process is the dentate gyrus of the hippocampus, which has been shown to be particularly sensitive to the effects of sleep loss. However, methodology in rodent and human studies varies greatly making translational conclusions difficult. Therefore, the aim of the current study was to measure the effects of sleep deprivation on human hippocampal function, using well-validated spatial and object-based pattern separation tests. The effects of acute sleep loss were examined, as this method is frequently used in rodent research but not human studies. Results show that sleep loss impaired performance on the object-based version of the test, but not spatial pattern separation. The findings support the notion that these discrimination projections represent separate but complimentary hippocampal processes, and further elucidates how they may be discretely affected by acute sleep loss.

## 1. Introduction

Throughout everyday life an abundance of information is processed. The formation of discrete representations of this information in memory involves a process called pattern separation [1–6], which is believed to critically depend on the dentate gyrus region of the hippocampus [for a review see 7]. Pattern separation occurs when cortical information is presented to the dentate gyrus via the entorhinal cortex. Hereby, different types of information operate through distinct input pathways [8]. Spatial information enters the hippocampal loop posteriorly from the parahippocampal and medial entorhinal areas, whereas object-based information enters from the perirhinal and lateral entorhinal cortices [8]. Nevertheless, both projection pathways enable the formation of distinct representations in hippocampal area CA3 due to its attractor dynamics, i.e., a network of recurrently connected nodes whose time dynamics settle to a stable pattern [9]. However, because of the abundant recurrent collaterals, its ability to form new representations in response to weak input is limited (e.g., in case of weak cortical input). As such, the dentate gyrus constitutes an upstream layer that is able to augment minor differences between input signals before transferring

them to the associative network of area CA3 [10]. In recent years, further support for this computational framework has accumulated through rodent electrophysiological recordings and immediate-early gene imaging, as well as human functional neuroimaging [7].

Due to its central role in episodic memory formation, pattern separation is often negatively affected by conditions characterized by amnesia, including age-associated memory impairment (AAMI) and mild cognitive impairment (MCI; [11–13]), as well as post-traumatic stress disorder (PTSD; [14]). Recently, it was shown that spatial pattern separation is also impaired in non-pathological conditions in rodents such as sleep deprivation [15]. What is more, hippocampus-dependent memory formation is promoted by sleep and disrupted by sleep loss [16–18]. In addition, acute partial sleep deprivation is known to compromise (functional) neuronal connectivity in the dentate gyrus, the brain region critical for pattern separation. This has been observed after half a night of sleep loss in rodents [19] and after a full night of sleep deprivation in humans [20]. In humans, sleep loss is even emerging as a predictive marker for cognitive impairment, especially for memory deficits, due to its detrimental effects on the medial temporal lobe [e.g., 21]. However, while it is known that restricting sleep has the

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potential to aggravate existing memory problems, the specific impact of sleep deprivation on pattern separation remains unclear.

There are several reasons for this lack of clarity if and to what extent sleep loss affects pattern separation. For example, even though several tests have been developed that demonstrate reliability across species in measuring pattern separation, and are disproportionately associated with the dentate gyrus, they do not allow drawing of generalized conclusions about pattern separation abilities (e.g., spatial v. olfactory pattern separation). Even when considering hippocampal pattern separation only, different dimensions along which environmental similarity is altered are implemented that frequently tap into different cognitive domains (e.g., object v. spatial pattern separation). Together, these factors compromise drawing general conclusions. For instance, it has been shown that object and spatial mnemonic interference differentially engage lateral and medial entorhinal cortices [8]. Of these two domains and their respective pathways, object discrimination has been found to be more susceptible to mnemonic discrimination impairments. Additionally, experimental protocols to induce sleep deprivation differ greatly in methodology, duration, and, as such, societal relevance and ecological validity, thereby having major influence on study outcome [22].

Therefore, the current study examined the effects of sleep deprivation on object-based and spatial pattern separation in healthy participants. We applied ‘acute sleep deprivation’, referring to short-term changes in sleep quantity, as this is more prevalent in the general population, closely resembling real-life situations. Additionally, it is often used in rodent sleep deprivation studies. Thus, the current study set out to assess whether this paradigm could be applied for humans, and whether humans would also demonstrate pattern separation deficits after one night of acute sleep deprivation. It was hypothesized that the sleep deprived subjects would perform significantly worse on spatial and object-based pattern separation than the control group.

## 2. Method

### 2.1. Participants

Fifty-four healthy adult volunteers were recruited in and around Maastricht University. Participants had to be willing to sign an informed consent form, and received compensation for their participation. To omit extreme “night owls” from participating, who would unlikely sleep before midnight regardless of experimental group allocation, we excluded anyone scoring below 42 on The Morningness-Eveningness Scale [23], indicative of a circadian rhythm classified as “evening type”. In addition, all participants were self-reportedly free of mental illness, and did not participate in shift work. In total, we recruited  $N = 54$  participants (21 males, 33 females), with ages ranging from 18 to 46 years ( $M = 22.79$ ,  $SD = 4.42$ ), and randomly assigned each participant to either the sleep deprivation or control condition (i.e., regular night of sleep). All experimental procedures were approved by the independent Ethics Review Committee Psychology and Neuroscience (ERCPN; The Netherlands). The study was conducted according to the code of ethics on human experimentation established by the Declaration of Helsinki (1964) with its latest amendments in 2013 and in accordance with the Medical Research Involving Human Subjects Act.

### 2.2. Experimental procedures

On the night before their respective test days, the sleep deprivation participants had to stay awake from 11:00 PM – 3:00 AM. All participants (SD and CON) were required to wake up at 6:30 AM. They were also asked to abstain from caffeinated or high-sugar-content food and drinks from 11:00 PM on the night before until the end of the test session, as they could diminish sleep quality [24], and may also affect alertness, learning, and memory [25]. The sleep deprivation group kept the researchers updated about their waking status through mandatory

text messages every 15 min throughout these four hours. After awakening at 6:30 AM, participants were required to send a final text message. All participants were given one hour to get ready and come to the university. Testing procedures started at 8:00 AM. In order to evaluate the sleep quality of the participants in the SD and CON group, we asked the participants to fill out the Groningen sleep quality scale questionnaire at the end of the behavioral testing.

### 2.3. Behavioral paradigms

**Spatial Pattern Separation task (SPS; [26]).** In the SPS task, 26 CON and 23 SD were tested. The task has two phases, encoding and recognition. In the encoding phase, 140 images of everyday objects are presented (duration: 2.5 s; interval: 0.5 s) across 35 distinct locations within an invisible 5x7-square grid on the screen. The tests were administered on a 17-inch CRT monitor PC using either E-Prime 3.0 (Psychology Software Tools, Pittsburgh, PA, USA) or Presentation (Neurobehavioral Systems Inc., Berkeley, CA, USA) software. Participants had to indicate whether the object belonged indoors or outdoors using the keyboard in order to facilitate spontaneous spatial encoding. Subsequently, in the recognition phase, the same images were shown either in the same location (40 images) or in a different location (100 images), as compared to the encoding phase. Using the keyboard, participants had to specify whether the location of the image is the same or different. The “different” images were displaced by either one, two, three or four grid spaces (20 stimuli for each position). There are also images (20) that were displaced from one corner to the opposite corner. Thus, the similarity of the spatial information varies, creating five levels of mnemonic interference (i.e., lure 1–5). Thus, the closer the lure is located to the originally encoded target the more difficult the discrimination performance will be. Hence, accuracy is recorded for each lure level separately. The task measures spatial pattern separation, the accurate discrimination of convergent spatial information. In healthy subjects, linear improvements can be observed as the interference level decreases, and in contrast, impairments can manifest as an absence of such improvements, as the increased bias for pattern completion hinders the ability for pattern separation even at lower levels of interference.

**Object Pattern Separation task (OPS; [27]).** In this task, 21 CON and 19 SD participants were tested. This task has a nearly identical structure, although now each image is presented at the center of the screen. To facilitate serendipitous object encoding, one must judge whether an everyday item belongs indoors or outdoors. Subsequently, in the recognition phase, 192 images will be presented on the screen one by one (duration: 2 s; interval: 0.5 s), consisting of 64 repeats, 64 lures and 64 foils. Repeats are identical to images in the encoding phase, while lures are similar but not the same, and foils are entirely novel images. There are five different levels of lure difficulty, varying in similarity to the original image (1 = most similar, 5 = least similar), representing different levels of mnemonic interference. The participant is to indicate, using the keyboard, whether they think the pictures are “old” (repeat), “similar” (lure), or “new” (foil). Accuracy for each type of lure is again recorded separately in order to examine the linearity of performance gains as interference decreases. In addition, the task enables calculating a lure discrimination index (LDI). This is a discrimination bias score, where the individual’s tendency to erroneously call a new image ‘similar’ is subtracted from correctly calling a lure ‘similar’. This is a measure of discrimination performance, as it compares pattern completion and pattern separation tendencies. Performance on this test has been found to accurately reflect the structural and functional integrity of the dentate gyrus, and it specifically taxes object pattern separation.

### 2.4. Data analysis

A power analysis [28] based on a repeated measures within-between interaction effects, with a power of 0.90, 2 groups, 5 measurements, and

a medium effect size (Cohen's  $f$  0.25), a total sample size of 32 subjects was required. The current sample was higher than this estimated sample size indicating that the current data could be considered as a reliable sample size. All data was checked for outliers and normality. The performance in the SPS and OPS task were analyzed using a mixed repeated measure analysis (between-subjects: SD vs CON; within-subjects: 5 position/lure levels). Post-hoc analyses were conducted using a Bonferroni correction. In the OPS task, the LDI, number of correct responses for same (repeats) and foils were analyzed using an independent  $t$ -test. Effect size was reported for all effects ( $\eta^2$ ). An ad-hoc analysis was performed in order to test for possible sex differences in performance we also added Sex as a factor in the model to examine if there were any effects of Sex or interactions between SD and Sex. Of note, the number of female and male participants were relatively low and not equally distributed in both groups (CON: male  $n = 8$ , female  $n = 19$ ; SD: male  $n = 9$ , female  $n = 20$ ).

**3. Results**

**3.1. Groningen sleep quality scale**

As expected, the SD participants scored higher than CON group on this scale (See Table 1).

**3.2. Spatial pattern separation task**

Discrimination performance increased as the difference in the original and new lure position increased (analysis over 5 lure positions:  $F(4,216) = 115.6, p < 0.001, \eta^2 = 0.66$ ; see Fig. 1). Sleep deprivation did not impair the performance in this task ( $F(1,54) = 0.12, p > 0.7, \eta^2 = 0.01$ ). The discrimination performance on the different lure positions was similar for both groups (Lure  $\times$  SD interaction:  $F(4,216) = 1.06, p > 0.4, \eta^2 = 0.01$ ). There was no effect of sleep deprivation on the correct responses for the "same" position ( $t(54) = 1.58, p > 0.1$ ). No Sex, SD  $\times$  Sex or SD  $\times$  Position  $\times$  Sex interaction effects were observed (all  $F$ 's  $< 1.68, n.s.$ ).

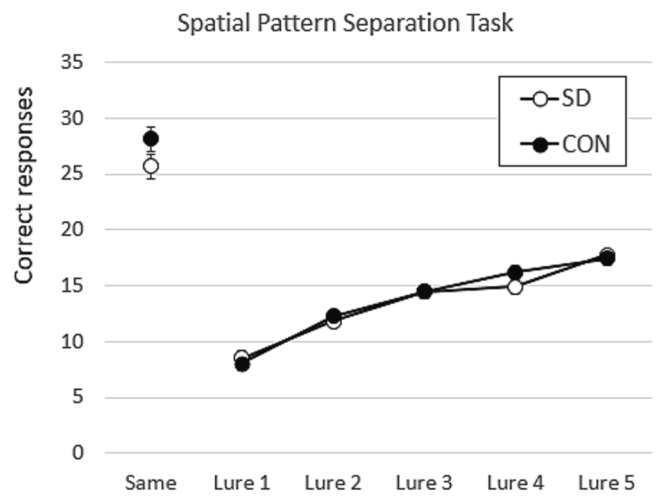
**3.3. Object pattern separation task**

Average performance in the object pattern separation task for each group is displayed in Fig. 2 for the same stimulus and each lure level. The SD group had less correct responses when they had to recognize the same picture ( $t(45) = 2.11, p < 0.05, \eta^2 = 0.15$ ). Analyzing the performance over the different lure conditions, the between-subjects analysis showed that the sleep deprivation impaired the overall discrimination performance ( $F(1,44) = 4.69, p < 0.05, \eta^2 = 0.09$ ). Similar to the spatial pattern separation task, the level of similarity of the lure was related to the discrimination performance (analysis over 5 lure positions:  $F(4,180) = 55.75, p < 0.001, \eta^2 = 0.55$ ). A larger difference from the original picture was associated with a better performance. There was no interaction between the Lure and SD ( $F(4,180) = 1.59, p > 0.19, \eta^2 = 0.03$ ). A Bonferroni post-hoc comparison for group means for each lure resulted in differences for lures 2, 4, and 5. The LDI also showed that the SD group performed worse than the CON group (see Table 1). The SD group scored higher on the foils as compared to the CON group (see Table 1). No Sex, SD  $\times$  Sex or SD  $\times$  Position  $\times$  Sex

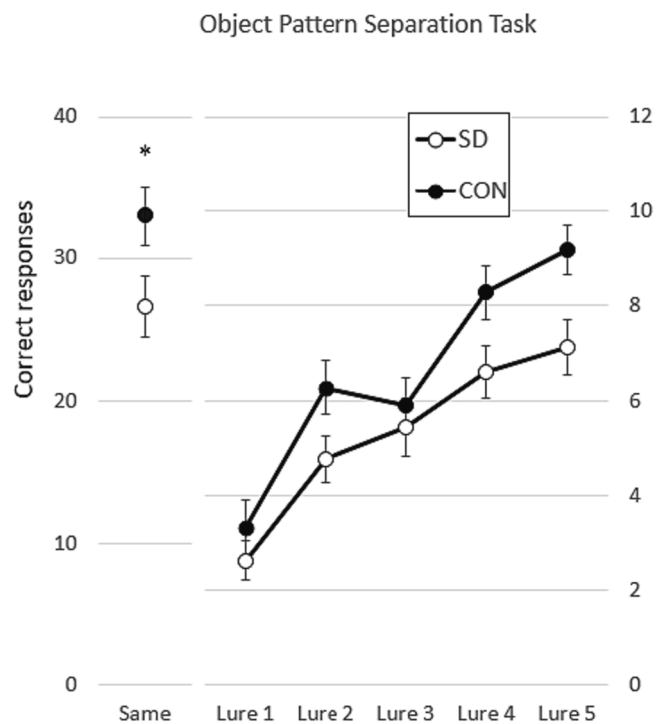
**Table 1**

Means and SEMs of the Groningen sleep quality scale, Lure discrimination index (LDI), and number of correctly detected foils in the object pattern. \*:  $p < 0.05$ , \*\*:  $p < 0.01$ .

	SD	CON	$t$ -test
Groningen sleep quality scale	7.6 (0.42)	3.5 (0.39)	$t(54) = 7.32^{**}$
Lure discrimination index (LDI)	29.0 (3.23)	70.5 (1.79)	$t(45) = 10.84^{**}$
Correct foils	8.4 (1.31)	4.8 (0.68)	$t(45) = 2.40^*$



**Fig. 1.** Number of correct responses per condition in the spatial pattern separation task. The number of trials was different for 'Same' (40 trials) than for each 'Lure' (20 trials). Data represent the mean ( $\pm$ SEM).



**Fig. 2.** Number of correct responses per condition in the object pattern separation task. The number of trials was different for 'Same' (65 trials) and each 'Lure' category (13 trials). Note that the scale for 'Same' and 'Lures' is different (left y-axis and right y-axis, respectively). Data represent the mean ( $\pm$ SEM). \*:  $p < 0.05$ .

interaction effects for all variables were observed (all  $F$ 's  $< 0.89, n.s.$ ).

**4. Discussion**

The aim of the current study was to delineate to which degree spatial and object pattern separation would be impacted by acute sleep loss in humans. To this end, we employed two well-validated pattern separation paradigms in human subjects for each dimension. To resemble real-life situations more closely and translate animal study design to humans, participants were sleep deprived using "acute" and "partial" sleep deprivation. This means sleep depriving participants for one night

(acute) and only half the night (partial). Participants were found to successfully engage in both object-based and spatial pattern separation as indicated by the performance in control condition, where group performances per mnemonic interference level show a steady increase in correct performance with increasing difference between original and lure items. Object pattern separation performance was found to be impaired after acute sleep loss. Conversely, we did not observe an impairment in spatial pattern separation after acute sleep loss.

In detail, the object-based pattern separation task employs five lures (1–5) with higher numbers indicating less similarity between objects when comparing items from learning trials to test trials. The main effect of lure type for the object-based version shows that with increased dissimilarity between items, the performance increased. This is represented by the correct indication of the item as “similar” by the participant. This shows successful engagement in the task by the participants and the occurrence of pattern separation. The main effect of sleep loss indicated that object pattern separation is sensitive to acute sleep loss. The effect is independent of the level of dissimilarity as all levels of mnemonic interference (lures) are affected. On the other hand, in the spatial pattern separation task, the two groups did not perform differently. However, the task appears sensitive to changes in mnemonic interference, as the different lure types elicited different levels of accuracy irrespective of experimental sleep conditions. This confirms the successful implementation of the task and the occurrence of pattern separation in healthy adults within the spatial domain.

The discrepancy between the effects of sleep deprivation on object-based and spatial pattern separation performance is likely to be explained in terms of a different sensitivity to sleep loss of the complementary but distinct neural networks underlying the two types of pattern separation paradigms. It is known that object-based v. spatial information follows different processing pathways within the hippocampal networks [8,29,30]. Acute sleep deprivation may have more effect on the perirhinal cortex, responsible for object or item information, projecting mostly to the hippocampus via the lateral entorhinal cortex. Projections from the parahippocampal cortex to the medial entorhinal cortex, deliver contextual and spatial information, which might be less sensitive to acute sleep loss. Similar differences in sensitivity to acute sleep loss in mice have been observed for different hippocampal subregions [19,31–33]. This also supports the view that these networks function in parallel but might be responsible for different processes [34–43].

Although significant efforts have been undertaken to map the role of hippocampal subregions as well as the medial temporal lobe, during pattern separation, studies specifically addressing the impact of sleep loss are lacking. Nevertheless, a search for similar, related studies shows a similar trend is observed during aging for object-based decline over spatial discrimination, further substantiating the hypothesis of differences in network susceptibility [44]. Also, object-based pattern separation, measured using a similar version of the task discussed in the current work, was stabilized after sleep but diminished after wakefulness [45]. These findings were related to EEG oscillatory parameters of non-REM sleep, serving as markers of sleep-dependent memory consolidation and hippocampal reactivation. However, despite the comparison of sleep vs the absence of sleep (testing during daytime), this is not similar to the loss of sleep (i.e., sleep deprivation) as induced in our study. Finally, a study investigating the effects of present vs absence of sleep on a similar object-based pattern separation task, showed that after a period of wakefulness the participants had fewer correct responses when tested after a twelve-hour delay [46]. Again, this is absence of sleep during daytime testing is not equal to sleep deprivation or sleep loss, but results are in line with our current data.

Previous rodent studies have reported sex differences in pattern separation performance attributed to differences in factors like neuronal connectivity, network activation, adult neurogenesis, and immediate early gene expression [47,48]. Such a sex effect was not observed in the current study. It must be noted that this was an ad hoc analysis, and that

the gender distribution was unequal across groups. Thus, the power of this analysis was limited, rendering any conclusions on this finding uncertain and in need of further research.

Taken together, the current study investigated the effects of acute sleep loss on object-based and spatial pattern separation. Interestingly, acute sleep deprivation showed different effects within the two pattern separation domains potentially related to the fact that both discrimination projections represent separate but complimentary hippocampal processes, the mechanisms of which are only starting to be explored.

## 5. Author contributorship

PH conceived the study; PH and AB designed the experiments with input from MJ, KP and JS; MJ, KP and JS conducted the experiments; AB, MJ, KP, and JS analyzed the data; PH, AB, MJ, KP and JS interpreted the results; PH, AB, MJ, KP and JS wrote the manuscript; PH and AB supervised the work.

## Conflict of interest

None to declare.

## CRediT authorship contribution statement

**Arjan Blokland:** Conceptualization, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Meyra Jackson:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Kia Puustinen:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Jens Soeterboek:** Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Project administration. **Pim R.A. Heckman:** Conceptualization, Formal analysis, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

## 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.

## Data availability

Data will be made available on request.

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