Research

Sleep strengthens integration of spatial memory systems

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Spatial memory comprises different representational systems that are sensitive to different environmental cues, like proximal landmarks or local boundaries. Here we examined how sleep affects the formation of a spatial representation integrating landmark-referenced and boundary-referenced representations. To this end, participants ($n = 42$) were familiarized with an environment featuring both a proximal landmark and a local boundary. After nocturnal periods of sleep or wakefulness and another night of sleep, integration of the two representational systems was tested by testing the participant's flexibility to switch from landmark-based to boundary-based navigation in the environment, and vice versa. Results indicate a distinctly increased flexibility in relying on either landmarks or boundaries for navigation, when familiarization to the environment was followed by sleep rather than by wakefulness. A second control study ($n = 45$) did not reveal effects of sleep (vs. wakefulness) on navigation in environments featuring only landmarks or only boundaries. Thus, rather than strengthening isolated representational systems per se, sleep presumably through forming an integrative representation, enhances flexible coordination of representational subsystems.

Wilson and McNaughton (1994) reported that "… information acquired during active behavior is … reexpressed in hippocampal circuits during sleep…." This observation of experience-dependent neural replay activity in the brain during slow-wave sleep (for review, see O'Neill et al. 2010) forms a keystone in our current understanding of how sleep affects memory consolidation in an active system consolidation process that involves the redistribution of hippocampal memory to extrahippocampal regions (McClelland et al. 1995; Diekelmann and Born 2010; Klinzing et al. 2019). According to theory, the emerging extrahippocampal memory representations are essentially schematic, devoid of specific context-information, and lack minute detail (Lewis and Durrant 2011; Payne 2011; Sekeres et al. 2018). Simultaneously, hippocampal replay strengthens hippocampal memory traces in the short-term following Hebbian learning, leading to improved context memory immediately after sleep compared with wakefulness (van der Helm et al. 2011; Weber et al. 2014). In the present study, we sought to test sleep's role in establishing higher-level memory representations drawing on the example of spatial memory processing.

Inspired by the strong role of the hippocampal formation in human spatial memory (Burgess 2008; Hartley et al. 2014) a number of studies examined effects of sleep specifically on spatial memory consolidation (Peigneux et al. 2004; Orban et al. 2006; Ferrara et al. 2008; Rauchs et al. 2008; Wamsley et al. 2010; Nguyen et al. 2013; Noack et al. 2017). In these studies, participants explored a virtual environment during a learning phase before retention periods of sleep and wakefulness and, later on, engaged in specific retrieval tasks that required to reach a predefined goal location in the environment as fast as possible. Results were mixed, with, some studies reporting positive effects of sleep on spatial navigation performance (e.g., Peigneux et al. 2004; Wamsley et al. 2010; Nguyen et al. 2013; Noack et al. 2017), whereas in others such sleep effect depended on the length of the retention interval (e.g., Ferrara et al. 2008), or was completely absent (Orban et al. 2006; Rauchs et al. 2008). Interestingly, in the latter studies—despite absent behavioral effects—using a 72-h retention interval between learning and retrieval testing, functional magnetic resonance imaging (fMRI) suggested that sleep favors a shift from activation of hippocampal areas toward preferential activation of striatal areas at retrieval of the relevant spatial representations.

Indeed, spatial navigation can rely on two distinct representational systems that involve as key structures hippocampal and striatal circuitry, respectively, and are also linked to different spatial frames of reference (Burgess 2008; Hartley et al. 2014). Doeller et al. (2008) showed in humans that striatal activation is linked to the processing of single proximal landmarks whereas hippocampal activation is related to the processing of spatial boundaries, and that acquisition of representations in both systems may follow different learning rules (Doeller and Burgess 2008). The subject's reliance on one or the other representation system depends on the specific navigational problem (Maguire et al. 1998; Hartley et al. 2003) as well as familiarity with the environment (Hartley et al. 2003; Iaria et al. 2003; Packard and McGaugh 1996), but both systems can also be activated in parallel and interact. For example, patients with hippocampal atrophy showed impaired memory performance not only for boundary-based but also for landmark-based navigation (Guderian et al. 2015) suggesting the presence

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of synergistic effects between the representational systems. The activation of the representational systems is presumably coordinated by the medial prefrontal cortex (Ragozzino et al. 1999; Doeller et al. 2008; Rich and Shapiro 2009), that is, a region that is not only involved in the abstraction of schema-like spatial representations (Tse et al. 2011; van Buuren et al. 2014) but, also shows neuronal reactivation during sleep (Euston et al. 2007; Peyrache et al. 2009).

In fact, there is first evidence suggesting that sleep supports the formation of abstract representations of space in particular. We found, for example, that sleep benefitted the extraction of semantic structure (regions defined by semantic category of landmarks) in a virtual navigation task (Noack et al. 2017). To date, there is no study, however, to specifically test the interaction between landmark- and boundary-referenced representations of space and their integration during sleep. Here we sought to fill this gap. Drawing on the active systems consolidation concept of sleep (Dudai et al. 2015; Klinzing et al. 2019) and on the existing literature, we followed the hypothesis that, rather than benefiting a specific spatial representation, sleep via neuronal replay primarily supports the formation of an integrative schema-like spatial representation and, thereby, improves flexibility in the use of hippocampus-based and striatum-based representations.

To this end, we conducted two experiments, a Main experiment and a Control experiment, using a virtual spatial environment with one proximal landmark and a local boundary (Fig. 1) to preferentially engage striatum and hippocampus-based representational systems, respectively (Doeller et al. 2008). The Main experiment was designed to test the effect of sleep on the *integration* of landmark-referenced and boundary-referenced representations of space. To this end, participants were first familiarized with an environment featuring both a landmark and a boundary, thereby encoding both hippocampal as well as striatal representations of the environment. In order to test whether sleep enhances the integration of these representations, participants either slept or remained awake on the night after the Familiarization phase. They then learned new objects in impoverished environments featuring the same spatial cues (landmark and boundary) at the same locations but only one at a time. At a final Test session, the integration of the combined environmental layout including landmark and boundary (as presented during Familiarization before sleep) was investigated by the participant's flexibility to switch from landmark-based to boundary-based navigation in the environment, and vice versa, from boundary-based to landmark-based navigation (Fig. 1). In the Control experiment, we investigated the direct effect of postlearning sleep or wakefulness on the consolidation of spatial memory representation that were either merely boundary-

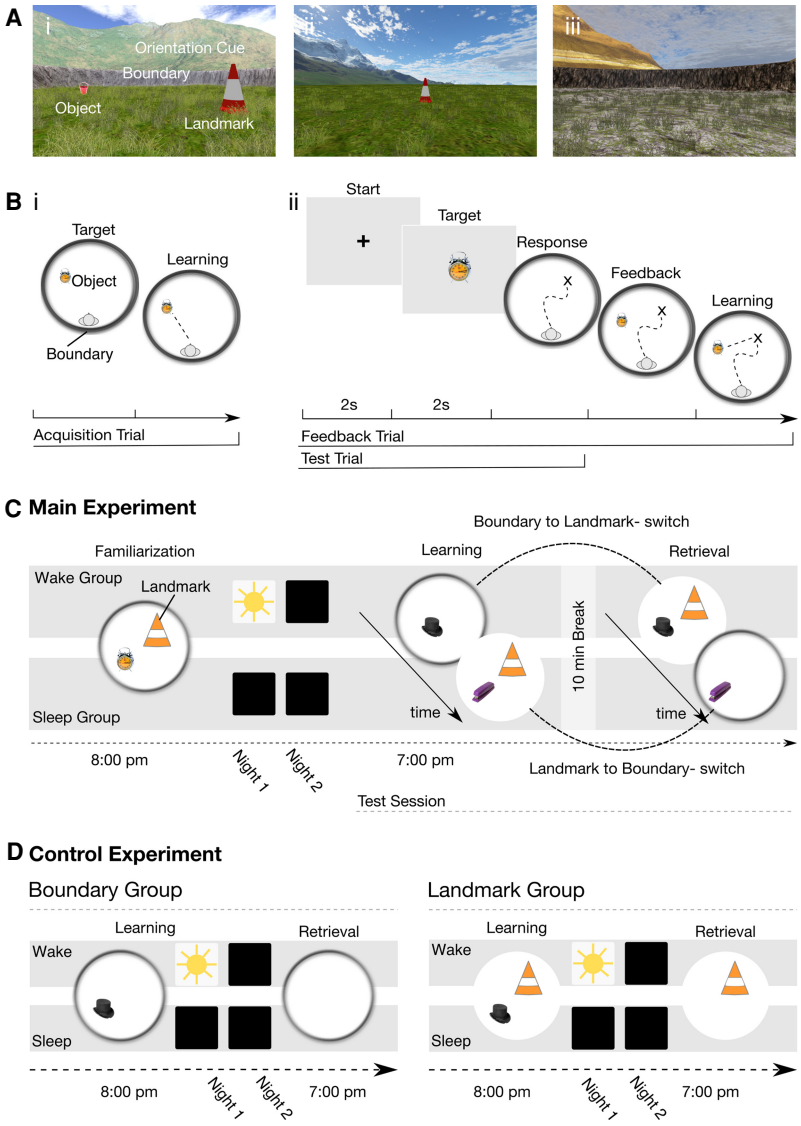

Figure 1. Task and general procedures. (*A*) Example views on the three different environments. (Panel *i*) landmark and boundary present, as used in the Familiarization phase of the Main experiment. Alpine environment (panel *ii*), and Desert environment (panel *iii*) as used in the Control experiment. (*B*) Task procedure: The task featured three different trial types in both experiments. (Panel *i*) Acquisition trials were presented at the start of Familiarization and Learning phases in both experiments. (Panel *ii*) Feedback and Test trials started with the presentation of an object on a gray screen. Participants were then placed in the experimental environment containing boundary (thick encirclement), landmarks (traffic cone) or both, and dropped the object at the location where they found it during acquisition. In Feedback trials feedback was given by presenting the object at its correct location. Participants navigated to it to collect it. (*C*) Design of Main experiment: Environment featured both landmark and boundary cues during Familiarization. The Test session comprised Learning phase and Retrieval phase. Only one spatial cue (landmark or boundary) was present during each trial of the Learning and Retrieval phase (three objects with landmark, three objects with boundary). Object reference switched from Learning to Retrieval phase: Objects presented together with the landmark during learning were presented with boundary during retrieval and vice versa. Note that a specific spatial cue was always at the same relative position when presented during Familiarization, Learning, and Test. (*D*) Design of Control experiment: Participants were randomly assigned to the Boundary or the Landmark group, whereas all participants performed in Wake and Sleep condition. Each of the two visits (sleep and wake) consisted of two sessions (learning: six Acquisition trials + four blocks and six feedback trials; retrieval: three blocks and six Test trials).

referenced or landmark-referenced, thereby controlling for general effects of sleep on spatial memory performance.

To preview our results: Whereas there was no effect of sleep on landmark- and boundary-referenced spatial memory per se in the Control experiment, sleep indeed facilitated the flexible use of different spatial retrieval cues possibly based on a superior integrated spatial memory representation.

Results

Main experiment: navigation performance

Task and procedures of the Main experiment are summarized in Figure 1. Participants of both the Sleep and Wake group, first, attended a Familiarization session that was followed by the experimental night of sleep vs. wakefulness. After another night (of normal and recovery sleep, respectively), the Test session followed that included an initial Learning phase and, 10 min later, a Retrieval phase. In the Familiarization session (before the sleep and wake intervals), the participants were familiarized with location of six real world objects in the environments that, in this session, featured both landmark and boundary cues. In the Test session (after the experimental sleep and wake intervals), the participants learned to navigate to the spatial locations of six new real-world objects but, importantly, during this Learning phase, only one of the spatial cues was present on each trial (i.e., three objects with landmark, three objects with boundary). In order to assess the participant's flexibility to switch between landmark-based and boundary-based representations, in the subsequent Retrieval phase, for each of the six objects of the Learning phase, the cue reference was switched; that is, when the participant had learned to navigate to an object based on a landmark cue during Learning, at Retrieval, he had to navigate to the location of this object based on a boundary cue, and vice versa. Whereas on trials of the Learning phase feedback was provided (Feedback trials), trials during the Retrieval phase were without feedback (Test trails). Spatial flexibility was assessed by comparing navigation accuracy at the end of the Learning phase (last 12 Feedback trials) with performance during the Retrieval phase (six Test trials).

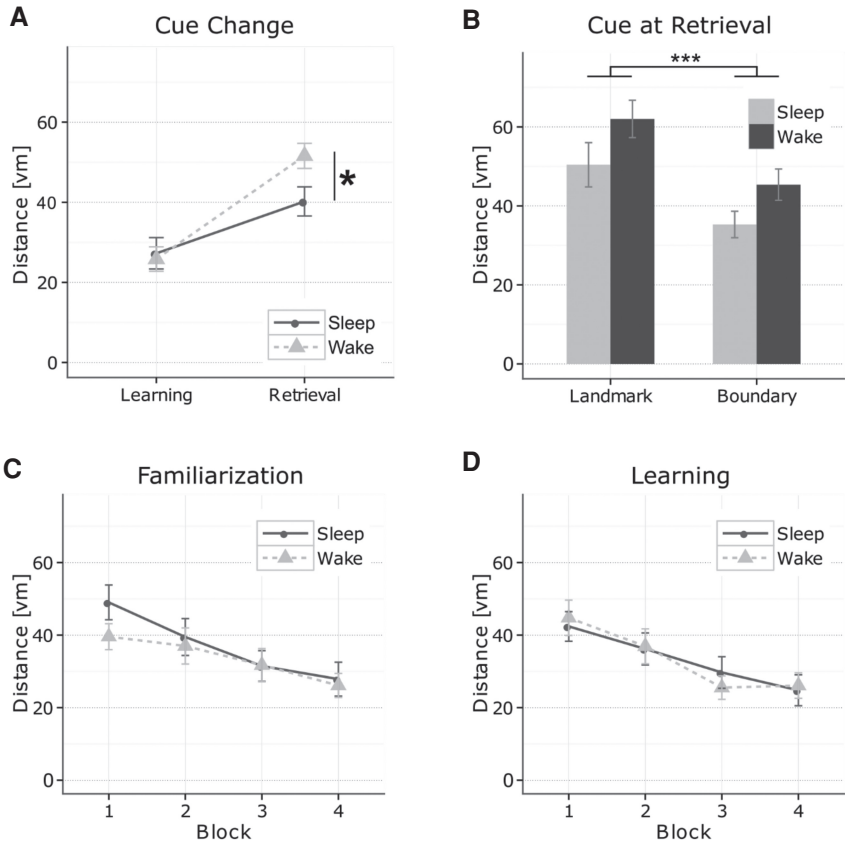

Figure 2. Main experiment. (*A*) Mean (±SEM) accuracy in navigating to target objects (in "virtual meters" [vm]) for the Sleep and Wake groups before and after spatial cue change (landmark-to-boundary switch and boundary-to-landmark switch). Learning represents averaged performance over the last 12 Feedback trials of the Learning phase and Retrieval represents performance averaged across all six Test trials of the Retrieval phase. (*B*) Cue at retrieval represents performance during retrieval for boundary and landmark separately. "Boundary" at retrieval is equivalent to landmark to boundary cue switch and vice versa "Landmark" is synonymous to boundary to landmark cue switch. Learning progress of the Sleep and the Wake group during the Familiarization phase (*C*), and the Learning phase (*D*). (Black lines and filled circles) Sleep, (gray lines and filled triangles) Wake. (*) $P < 0.05$, (***) $P < 0.001$.

In the Test session, changing the spatial cue strongly impaired navigation accuracy, $F_{(1,40)} = 71.25$, $P < 0.001$, $\eta^2_G = 0.29$ (for the comparisons between the Learning and Retrieval phase) with no general differences between sleep and wake group respectively, $F_{(1,40)} = 1.20$, $P = 0.279$, $\eta^2_G = 0.02$. However, in agreement with our hypotheses, this effect was additionally dependent on sleep and wakefulness during the experimental night, $F_{(1,40)} = 6.70$, $P = 0.01$, $\eta^2_G = 0.04$ (Fig. 2A). Participants of the Sleep group ($M = -14.77$, SEM = 4.02) were better able to deal with the cue change than participants of the Wake group ($M = -27.85$, SEM = 2.92) resulting in reliably different performance levels at retrieval, $t(40) = 2.33$, $P = 0.025$, $d = 0.73$.

In a more fine-grained analysis, we also compared the effects of sleep and wakefulness on landmark versus boundary-based spatial memory. Participant's memory retrieval was more strongly affected when the boundary cue was switched to landmark than when landmark was switched to boundary, $F_{(1,40)} = 10.86$, $P = 0.002$, $\eta^2_G = 0.04$. Whereas there was no cue-effect during the Learning phase (landmark cue: $M = 28.05$, SEM = 3.56; boundary cue: $M = 27.29$, SEM = 2.50), in the Retrieval phase, participants exhibited higher errors when navigating to boundary-learned object locations with reference to the landmark ($M = 56.08$, SEM = 3.75) than when navigating to landmark-learned object locations with reference to the boundary ($M = 40.10$, SEM = 2.66), $F_{(1,40)} = 18.55$, $P < 0.001$, $\eta^2_G = 0.14$ (Fig. 2B). However, this effect did not depend on sleep, $F < 1$. This finding is consistent with results from Doeller and Burgess (2008), who showed that due to blocking it is more difficult to acquire landmark-referenced location representations once there is a boundary related representation. Because boundary-related learning is incidental, however, boundary-related representations will be acquired even if there is a landmark-related memory representation already established.

In contrast to retrieval performance, mean navigation accuracy did not differ between Sleep and Wake groups during the preceding Learning phase $X^2(1)s < 1$. However, we found a strong

linear learning effect over the four blocks of feedback trials, $\beta = -5.99$, 95%CI = [−8.23, −3.76], $X^2(1) = 60.49$, $P < 0.001$, which was not influenced by postfamiliarization sleep or wakefulness however, $X^2(1) < 1$ (Fig. 2D). There were no differences between the frames of reference during the Learning phase, Fs < 1.

Control analyses also confirmed that Sleep and Wake groups did not differ during the Familiarization phase before the nocturnal sleep and wake intervals (and before allocation of subjects to the two groups), in absolute performance, $X^2(1) < 1$, or in the rate of learning over the four blocks, $X^2(1) = 2.60$, $P = 0.107$; both groups showed clear linear learning across the blocks, $\beta = -7.59$, 95%CI = [−9.14, −4.98], $X^2(1) = 58.76$, $P < 0.001$ (Fig. 2C).

We also analyzed the time the participants took for each trial. There were no differences in navigation time between the Sleep and Wake groups at the Familiarization, Learning, or Retrieval phase, Fs < 1. Across both groups, participants who took more time to navigate were also more accurate during the Familiarization phase, $r = -0.43$, $P = 0.005$, 95%CI = [−0.65, −0.14], as well as during the Learning phase, $r = -0.40$, $P = 0.009$, 95%CI = [−0.63, −0.11]. We also observed a general reduction in navigation time across blocks of the Familiarization, $F_{(3,120)} = 8.19$, $P < 0.001$, $\eta^2_G = 0.04$, and Learning phase, $F_{(2.47,98.77)} = 14{,}44$, $P < 0.001$, $\eta^2_G = 0.07$.

Main experiment: sleep and control tests

To control for potential nonspecific effects of sleep and nighttime wakefulness that may account for behavioral performance differences on the basis of alertness or vigilance we ran additional control analyses. Subjects of the Sleep group slept on average 526 min on the night after the Familiarization phase. On the following night (before the Test session) the Wake group recovered sleep, and consequently slept longer ($M = 580$, SEM = 11.24) than the Sleep group ($M = 463$ min, SEM = 21.09), Welch's $t(29.20) = -4.88$, $P < 0.001$, $d = 1.55$. This difference in sleep duration did not translate into subjective feelings of sleepiness during learning and retrieval (as measured by the SSS), where both groups reported the same levels of sleepiness (Sleep: $Mdn = 2$, range = [1, 4]; Wake: $Mdn = 3$, range = [1, 5]). Both objective measures of vigilance (PVT) and word fluency indicated a trend for better performance in the Wake than in the Sleep group. Waking participants reacted slightly faster than sleeping participants (PVT: M = 294 ± 4.16 msec vs. 305 ± 5.89 msec; $t(40) = 1.89$, $P = 0.066$) and similarly, waking participants generated slightly more words than the Sleep group ($M = 22 \pm 1.13$ words vs. 18 ± 1.08, $t(40) = -1.95$, $P = 0.058$).

Note that we did not observe any correlations between measures of sleep duration, sleepiness, vigilance, word fluency, or operation span on the one hand and the target measures of navigation during learning or retrieval on the other hand ($|r| < 0.23$, $P > 0.13$).

Control experiment: navigation performance

It could be argued that the effect of sleep on the flexible use of landmark or boundary cues for successful navigation resulted from separate effects of sleep on each of the two kinds of representations, that is, on landmark-referenced and boundary-referenced representations, respectively, rather than from an effect of sleep enhancing an integrative representation over both subkinds of spatial representations. To investigate such separate effects of sleep on spatial memory performance, in a Control experiment, a Learning session for boundary-referenced and landmark-referenced learning of object-locations, respectively, took place before the experimental night of sleep and wakefulness, respectively. Retrieval was tested 47 h later (after another night of normal and recovery sleep, respectively) using the same spatial cue reference as during Learning (see Fig. 1D for the design of the Control experiment).

Object location memory became less accurate over the retention interval ($M_{\text{encode-retrieve}} = -2.48$ vm, SEM = 1.02), $F_{(1,38)} = 7.29$, $P = 0.01$, $\eta^2_G = 0.07$, irrespective of whether participants slept or stayed awake during the postlearning night, $F < 1$. We found a general effect of the spatial cue type, $F_{(1,38)} = 7.76$, $P = 0.008$, $\eta^2_G = 0.14$, such that participants navigated to boundary-referenced objects less accurately ($M = 32.68$ vm, SEM = 4.33) than to landmark-referenced objects ($M = 18.86$ vm, SEM = 2.51). (Note that the difference in cue type was unexpected and not found in the original publication of the task paradigm [Doeller and Burgess 2008].) Changes in memory accuracy over the retention period did not depend on the spatial cue however, $F_{(1,38)} = 1.17$, $P > 0.250$, and again, we did not observe a specific effect of sleep or wakefulness on the consolidation of boundary-referenced or landmark-referenced object locations, $F < 1$ (Fig. 3).

Analyses of performance over familiarization blocks showed that both tasks were sensitive to training: Both groups (Landmark and Boundary) linearly improved their navigation performance with practice, $\beta = -3.64$, 95%CI = [−6.14, −1.06], $X^2(1) = 35.66$, $P < 0.001$, irrespective of the Landmark/Boundary group, Sleep/Wake condition, or their interaction, $X^2(1)$s < 1 (Fig. 3). On the other hand, there was no further learning during the Retrieval blocks, showing that participants maintained their performance levels over the three Retrieval blocks irrespective of group (Landmark and Boundary) or condition (Sleep and Wake), $X^2(1)$s < 1. Additional analyses of design variables showed that female ($M = 31.15$, SEM = 4.10) participants displayed less accurate navigation performance than male participants ($M = 19.82$, SEM = 3.00), $F_{(1,36)} = 4.98$, $P = 0.032$, $\eta^2_G = 0.014$. In addition, there was a main effect of session, $F_{(1,36)} = 5.13$, $P = 0.03$, $\eta^2_G = 0.018$, with performance being better in visit 2 ($M = 24.98$, SEM = 2.90) compared with visit 1 ($M = 30.22$, SEM = 2.67). Finally, there was a main effect of environment $F_{(1,32)} = 8.48$, $P = 0.006$, $\eta^2_G = 0.027$, with the desert ($M = 30.11$, SEM = 2.81) environment being more challenging than the alpine ($M = 25.08$, SEM = 2.77) environment (see Materials and Methods for details). Importantly, accounting for the effect of

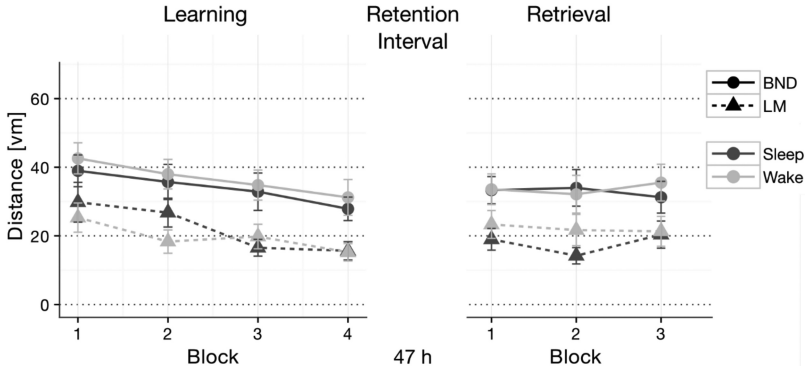

Figure 3. Results Control experiment. Mean (±SEM) accuracy in putting target objects back (in "virtual meters" [vm]) during the 24 Feedback trials of the four Learning blocks and the three Retrieval blocks in the Boundary (solid lines and circles) and the Landmark (dashed line and triangles) group during the Sleep (black) and Wake (gray) condition. Because sleep order (Sleep first/Wake first) was counterbalanced between participants, all data points include individual navigation performance of participant's first and second visit to the laboratory.

these variables statistically, did not influence the general outcome pattern reported above.

Control experiment: sleep and control tests

Analyses of sleep and vigilance showed that in the Sleep condition participants slept 455 min (SEM = 13.52) during the experimental sleep night (after Learning). During the second night after Learning participants slept longer in the Wake ($M = 640$ min, SEM = 20.05) compared with the Sleep ($M = 480$ min, SEM = 13.05, $t(39) = 7.12$, $P < 0.001$) condition, recovering lack of sleep from the experimental night. This difference in sleep duration during recovery sleep was paralleled by a difference in subjective sleep quality, where participants reported better sleep quality during the recovery night of the Wake ($Mdn = 4.47$, range = [1, 5]) than the Sleep condition ($Mdn = 4.17$, range = [1, 5]; $V = 5.5$, $P < 0.01$). However, there was no difference in how "well-rested" they felt in the morning after the recovery night (Wake: $Mdn = 3.6$, range = [1, 5]; Sleep: $Mdn = 3.62$, range = [1, 6], $P > 0.250$) or in how sleepy they felt during the Retrieval session (Wake: $Mdn = 3$, range = [1, 5]; Sleep: $Mdn = 3$, *range* = [1, 6], $P > 0.250$). The self-reports of sleepiness were complemented by objective measures of vigilance. Median reaction times in the PVT ($M = 300$ ms, SEM = 3.58) did not differ between the Sleep and Wake condition, respectively, $t < 1$. Despite comparable levels of vigilance, participants generated more words in the Wake condition ($M = 18.95$, SEM = 0.81) than in the Sleep condition ($M = 17.55$, SEM = 0.68; $t(39) = -2.22$, $P < 0.01$)

Discussion

Spatial navigation in complex environments is typically supported by different representational subsystems that can be activated in parallel and can cooperatively or competitively interact (Burgess 2008; Hartley et al. 2014). These conditions make it difficult to determine how sleep improves spatial navigation performance and might also explain the mixed outcome of previous studies on this matter (Peigneux et al. 2004; Orban et al. 2006; Rauchs et al. 2008; Wamsley et al. 2010; Nguyen et al. 2013; Noack et al. 2017). Against this backdrop, the central aim of our study was to disentangle the specific effects of sleep on two dissociable representational subsystems, that is the hippocampus-based and striatal-based system, in isolation as well as on their integration. We propose that the latter is achieved through sleep by building a coordinating representation that mediates the interaction between the representational subsystems of interest (Dudai et al. 2015). Indeed, our finding that sleep facilitates the flexible transfer of object locations between two spatial reference frames on the basis of presleep spatial experiences finds its parallels in a study of cross-modal memory transfer (Durrant et al. 2016), where learning of auditory statistical regularities transferred to the visual domain over a 24-h period including sleep but not over a 30-min period including wakefulness only. Investigating integration of different memory systems, Schönauer and Gais (2017) showed that sleep supports cooperative retrieval of implicit and explicit memory content in a feedback-driven classification task. Using structural equation modeling, these investigators found (across subjects) negative correlations between implicit and explicit recall at the immediate post-test and after a wake retention interval but slightly positive correlations after sleep. This result suggests that waking participants relied on either implicit or explicit memory at retrieval whereas in the sleeping participants this competitive retrieval pattern disappeared. Thus, evidence converges on the view on sleep favoring the integration of different sensory domains as well as implicit and explicit memory systems (Lewis and Durrant 2011; Stickgold and Walker 2013; Wilhelm et al. 2013; Sawangjit et al. 2018; Schapiro et al. 2019). Our finding of a stronger integration between landmark-referenced and boundary-referenced representation systems after sleep might therefore be considered another example of a general principle of how sleep transforms memory representations.

Importantly, different from other studies on the sleep-dependent integration of memory systems (e.g., Wilhelm et al. 2013; Durrant et al. 2016; Schönauer and Gais 2017), participants in the Main experiment both learned and retrieved object locations after sleep. That is, we did not investigate the effect of sleep on object-location memory per se but on the formation of a general representation of the environment including a combination of landmark-based and boundary-based references. Note that such more general schema-like representation can affect memory processing on all levels, encoding, consolidation, and retrieval (Tse et al. 2011; van Kesteren et al. 2012; Preston and Eichenbaum 2013; van Buuren et al. 2014). It might therefore surprise that sleep did not also improve encoding of object-locations during the Feedback trials of the Learning phase in the Main experiment as well as in the Retrieval phase of the Control experiment. However, these conditions did not require to switch between representational systems—a specific novel object could be retrieved within one of the two representational subsystems of interest here. Because we observed a specific effect of sleep on the transfer-condition but not on the direct retrieval conditions, we would argue that the effect of sleep is primarily on forming a general schema-like representation with only indirect effects on the representational subsystems themselves. This does not mean that sleep, in general, does not favor effects of prior knowledge on post-encoding stages of memory processing. However, depending on the contextual conditions during encoding, such effect might or might not express itself at the behavioral level (Orban et al. 2006; Rauchs et al. 2008).

Successful retrieval of object locations under conditions of a switched spatial frame of reference, as observed during the Retrieval phase of the Main experiment, can also originate from an improved retrieval operation per se, rather than from strengthened and more effective spatial schema representations. Sleep deprivation is known to impair prefrontal cortical executive functions including retrieval operations (e.g., Durmer and Dinges 2005) but also affective states and hippocampus-dependent memory (e.g. Krause et al. 2017). This potential confound can be excluded for three reasons in the present study: First, we did not observe a sleep effect in the Control experiment, where memory retrieval in the wake condition should also suffer from the general impacts of sleep deprivation, which it did not. Second, the Retrieval phases of both experiments were scheduled such that all subjects had a night of normal sleep before, that is, subjects of the Wake group had recovered sleep before testing. Third, we examined sleepiness and executive control functions on several additional tests (PVT, word fluency test). However, none of these measures revealed any Sleep/Wake-group related difference and none correlated with target measures of spatial navigation, which safely excludes this type of confound. Still, it could be argued that sleep deprivation—that is, keeping participants awake at night—might adversely affect the consolidation process itself; for example, by enhancing levels of so-called stress hormones. Compared with nocturnal sleep, nocturnal wakefulness is indeed associated with enhanced levels of catecholamines, cortisol, and especially cortisol is well known to affect hippocampal consolidation processes (Wilhelm et al. 2011; Kelemen et al. 2014; Bennion et al. 2015). However, beyond the fact that the state of waking is inevitably linked to increased levels of such hormones, it is to emphasize that the increase typically observed when humans are asked to stay awake the night, is very mild (though statistically significant) and does by far not reach the levels observed in experimental stress conditions (e.g., Lange et al. 2003; Rasch et al. 2007). Nevertheless, future studies using

different designs (e.g., split night, cuing, or pharmacological interventions) might help to further disentangle effects of (experimentally established) wakefulness from potential stress-related confounds. Our Control experiment was designed to examine the direct effects of sleep (vs. wakefulness) on spatial memory. It is important to note that the conceptual differences between these two experiments—namely participants explicitly learning object-locations before sleep in the Control experiment whereas implicitly learning the environmental layout featuring landmark and boundary in the Main experiment—implicated differences in design. As we intended to prevent participants from seeking explicit strategies to integrate the landmark and boundary cue during Familiarization in the Main experiment, repeated testing (as would have been required for a Sleep/Wake within-subject design) was impossible and the number of Test trials at Retrieval was limited to one per object. These limitations did not hold for the Control experiment and we were therefore able to manipulate sleep and wakefulness during the experimental nights within participants and to conduct three blocks of Test trials during Retrieval. In addition, as a consequence of the lower power in the Main experiment, we drew a gender-homogenous sample for the Main experiment whereas male and female participants were tested in the Control experiment. Together these measures improved power and generalizability of the Control experiment at the cost of direct comparability.

Interpretation of our results depends on the assumption that object locations relative to landmarks are differently processed than object locations relative to local boundaries and that these systems constitute different frames of reference, which together form a coherent representation of the environment. This assumption is strongly supported by lesion-studies in animals (Packard and McGaugh 1996; Pearce et al. 1998) and virtual navigation studies in humans (Doeller et al. 2008). Nevertheless, the absence of a direct test for this assumption in this study can be considered a limitation. In addition, the degree to which each reference-system contributes to the formation of an integrated representation remains debated as there is evidence showing that allocentric relations between object locations can be better inferred after landmark-referenced spatial learning rather than boundary-referenced learning (Zhou and Mou 2016) and boundary-referenced information can be acquired after landmark-referenced learning but not vice versa (Doeller and Burgess 2008). Our data are in line with these previous observations insofar as we found a corresponding asymmetry in our data where the landmark-to-boundary switch was more difficult for our participants than the boundary-to-landmark switch.

Referring to our sleep-related hypotheses the fact that sleep was not assessed polysomnographically can also be considered a limitation. The latter is crucial for future investigations of the active systems consolidation of spatial memory representations, as it specifically posits a role of slow wave sleep in memory transformation (e.g. Klinzing et al. 2019), whereas others emphasize the role of REM sleep specifically for memory integration (e.g. Payne 2011; Walker and Stickgold 2010).

Our results extend previous findings on sleep's role in spatial memory formation by showing that sleep improves the integration and flexible use of representations in two different spatial reference systems. We propose that this effect is conveyed by sleep supporting the formation of a general schema-like representation presumably involving prefrontal cortical areas.

Materials and Methods

Participants

Because the size of effects of sleep on navigation performance greatly varied among previous studies, we determined sample size based on general assumptions rather than specific a priori expectations of the size of the effect. That is, we sampled 42 participants (all male, mean age 24.2 yr, range: 20–33 yr) in the Main experiment in order to reliably detect even small sleep × spatial cue change interaction effects, $\eta_p^2 > 0.05$, at a Power of 0.95. In the Control experiment Power was further increased by sampling 45 participants (23 female, mean age 28.8 yr, range 19–31yr) in a pure repeated measures design. The additional inclusion of women, here might represent a limitation. However, exploratory analysis of the gender factor did not reveal significant effects, relevant to the present study. Data from five participants of the Control experiment were excluded from analysis because of a lack of compliance to the study protocol (overnight wakefulness in the Sleep group $n = 4$, extended daytime nap in the Wake group $n = 1$). Another seven participants took a short nap during the day after the wake night possibly reducing the impact of the sleep manipulation. Control analyses excluding these participants, revealed essentially identical results. We therefore decided to report results including these participants. All participants had normal or corrected-to-normal vision and reported no history of sleep disturbance or mental disease, and low video gaming experience. Participants were instructed to abstain from caffeine, alcohol, and nicotine over the entire course of the study. Participants gave written informed consent and were paid for their participation. The study was approved by the ethics committee of the Medical Faculty of the University Tübingen.

Virtual environment and spatial navigation cues

We used a virtual reality environment adopted from Doeller et al. (2008). The environment was implemented using the UnrealEngine 2 runtime software (Epic Games) and consisted of a grassy plane surrounded by a distant mountain landscape, which provided directional but no distance information, such that successful navigation based on the landscape alone was impossible. We used three different mountain landscapes all created with Terragen 3 (The Planetside Software): one in the Main experiment (the same as used in Doeller et al. 2008) and two other newly created landscapes in the Control experiment. The two new landscapes in the control experiment provided similar directional information (through sun and distant mountains) but differed strongly in surface characteristics. One landscape resembled an alpine setting with green grass and snowy mountains; the other one resembled a dry desert setting (see Fig. 1A). The two new landscapes were created to minimize learning effects over the repeated sessions in the Control experiment. The order of landscape type was counterbalanced with all other experimental between-subjects factors (Sleep/Wake order and Landmark/Boundary cue order; see below) of the Control experiment, such that each landscape type was equally often paired with sleep/wakefulness and Landmark/Boundary cue.

Depending on the experimental condition, one or two proximal cues were added to the environment: There was either a rocky circular wall extending roughly 180 virtual meters (vm), a traffic cone, or both. The circular wall served as experimental boundary and the traffic cone served as experimental landmark. Both cues were rotationally symmetrical and therefore did not provide any directional information.

Task and trial structure

The general task of both experiments was to learn and retrieve the spatial locations of images of real-world objects within the virtual environment. Both experiments comprised three different trial types: Acquisition trials, Feedback trials, and Test trials (see Fig. 1B), whereas the exact scheduling and the specific design of these trials depended on the experiment and on the experimental condition (see below). Each experiment started with a set of six Acquisition trials where participants initially saw the objects and their corresponding locations in the arena. One image of a real-world object was displayed at a specific location in the arena and the participants had to navigate toward it from variable starting points and to "pick it up" by moving over it. Then the next trial

started until all six objects were picked up once. After participants had seen all objects at their corresponding locations, a set of 24 Feedback trials (four blocks of all six objects in random order) followed. Each Feedback trial included a cued recall part and a subsequent feedback part. The trials started with the presentation of a fixation cross. Next, one object was presented centrally on a gray background for 2 sec before participants were placed at variable starting points in the arena with the instruction to move to the location, where they had encountered this object previously and then press the space bar. Once the participants pressed the space bar or 45 sec had passed without any response, the feedback part started: The object was presented at its correct location and the participants had to move to it to start the next Feedback trial. Finally, a set of Test trials followed. Depending on the experimental condition the number of Test trials was six (Retrieval phase of Main experiment) or 18 (Retrieval phase of Control experiment). The structure of Test trials was similar to the cued recall part of the Feedback trial (i.e., no feedback was given at the end of the trial).

Participants were rewarded for good navigation performance during all Feedback and Test trials. Depending on the distance between their response location and the correct location, they received zero, one, two, or three points (i.e., indirect feedback was given also during the Test trials). Points cumulated over the course of the experiment and the total score translated into bonus payment (maximal amount = 10€ during each retrieval session) at the end of the experiment. Reward was given to increase the compliance of our participants during the task and to increase the relevance of the acquired memories, which was expected to further strengthen the effect of sleep (Stickgold and Walker 2013).

Main experiment: design and procedure

The Main experiment was designed to investigate the effect of sleep on the formation of an integrated representation of space featuring landmark and boundary cues (Fig. 1C). To this end, participants were randomly assigned to the Sleep group ($n = 22$) or the Wake group ($n = 20$). This was done because the effect of crucial experimental manipulation (i.e., the unexpected spatial cue change) cannot be repeated within participants. Unequal group sizes resulted from invited participants not coming to the laboratory. Note that the groups did not differ in working memory capacity (absolute Ospan Sleep: $M = 44.76$, SEM = 0.71, Wake: $M = 45.95$, SEM = 0.744), $t(39) < 1$).

Participants of both the Sleep and Wake group came to the laboratory twice (a Familiarization session and a Test session) with a 47-h interval comprising the experimental night and an additional night in between. The Familiarization session started at 8:00 p.m. and featured six real-world objects with the combined environment in six Acquisition + 24 Feedback trials. Note that this session was intended to familiarize the participants with the general layout of the environment including the proximal landmarks and the local boundary. Locations of the six familiarized objects were not tested during the test session. Group membership (Sleep/Wake) was disclosed to the participants after the end of familiarization. Members of the Sleep group were asked to sleep at home and members of the Wake group stayed in the laboratory until the next morning at 8 a.m. During the nocturnal vigil, they watched animal documentaries and, on two occasions, went for a short walk in the park together with the experimenter. Light snacks (pretzels, fruit) were offered twice during the night. When leaving the laboratory, participants were instructed to follow their regular sleep schedule, not to take any afternoon naps, to abstain from caffeine, alcohol, and nicotine, and to go to bed for recovery sleep the next evening. All participants were asked to wear actimeters (Actiwatch, Respironics). The Test session started at 7:00 p.m. 47 h after the beginning of the Familiarization session, and involved again six Acquisition and 24 Feedback trials for six new objects, which were now presented together with either the proximal landmark (three objects) or the local boundary (three objects). The capability to switch between landmark-based and boundary-based representations of the environment was assessed in the six final Test trials (one for each object), where the spatial cue for each object was exchanged. (Each object was retrieved only once because we expected that participants would form new representations of object-locations at each retrieval trial; that is, we tried to prevent that participants would draw on their memory of previous retrieval trials rather than on their memory representations from Learning and Familiarization.) That is, those three object locations that were learned relative to the proximal landmark were now tested in the presence of the local boundary and, vice versa, those locations that were learned relative to the local boundary were now tested in the presence of the proximal landmarks. Both sessions included assessment of vigilance and sleepiness (see below for a description of the control tasks) besides the navigation task. In addition, the Familiarization session included assessment of working memory capacity and familiarization with the handling of the task using another virtual environment with different spatial layout (e.g., a square boundary), objects, proximal landmarks (a bush instead of a traffic cone), and distal landmarks. Familiarization with this practice environment was terminated as soon as participants felt confident with the task handling and signaled understanding of the task (typically after ~10 min).

Control experiment: design and procedure

The ontrol experiment (Fig. 1D) was designed as a conceptual control of the assumption that the results of the Main experiment reflected a general beneficial effect of sleep on the spatial memories itself that were encoded prior to sleep, rather than on memory integration. We therefore tested whether sleep had a direct effect on landmark-referenced as well as boundary-referenced spatial representations of objects as encoded before sleep and wakefulness. In addition, the Control experiment aimed at alleviating some of the design restrictions inherent to the Main experiment. Specifically, with regard to the sleep/wake comparison we, here, used a within-subject comparison, which is more sensitive than the between-group comparison that we used in the Main experiment to exclude transfer effects (e.g., of cue switch strategies) between the conditions. For similar reasons, in the Control experiment the number of test trials could be distinctly increased to enhance sensitivity of the memory measurement. Thus, in the Control experiment, participants were randomly assigned to either the Boundary group ($n = 20$, 10 men) where they learned (before sleep or wakefulness) the objects relative to a local boundary, or to a Landmark group ($n = 20$, 9 men) where participants learned the spatial locations of the objects relative to a proximal landmark ($n = 20$, 10 men). (Landmark group: $M = 41.05$, SEM = 3.72; Boundary group: $M = 39.10$, SEM = 4.01; $t(38) < 1$).

Sleep and wakefulness were manipulated according to a within-subject crossover design. This means, each subject participated in two conditions, a Sleep condition and a Wake condition, with the order of conditions counterbalanced across participants (Sleep first: $n = 20$; Wake first: $n = 20$). Similarly, the environment order was counterbalanced between participants (Desert first: $n = 20$; Alpine first: $n = 20$), such that Sleep/Wake condition and Environment condition were fully crossed. The interval between a participant's two conditions was at least 2 wk.

For both the Sleep and Wake conditions, the participant came to the laboratory for a Learning and a Retrieval session, which were separated by a 47-h Retention interval comprising a first experimental night and a second night. The Learning session started at 8:00 p.m. and involved the learning of new object locations within unfamiliar virtual environments in six Acquisition trials and 24 Feedback trials (see Fig. 1B). The Retrieval session started at 7:00 p.m. and involved retrieval of the previously learned object locations in 18 Test trials (see Fig. 1B,D).

At the end of the Learning session of the first visit to the laboratory it was disclosed whether participants pertained to the Sleep or Wake condition. Procedures were then identical to the Main experiment: In the Sleep condition, participants went home to sleep the next two nights according to their regular schedule, whereas—in the Wake condition—they stayed in the laboratory until the next morning at 8:00 a.m. watching animal documentaries, having light snacks and going on a walk on two occasions. When leaving the laboratory, all participants were equipped with actimeters (Actiwatch, Respironics) to monitor compliance with the sleep

instructions, and for objective assessment of activity and rest periods. Assessment of control tasks was similar to the procedures described for the Main experiment (see above).

Sleep and control tests

During all sessions, participants rated their subjective sleepiness using the Stanford Sleepiness Scale (SSS). They also performed on the psychomotor vigilance test (PVT) and on a German version of the word fluency test (Regensburger Wortflüssigkeitstest [RWT]). The PVT is a high signal-load simple reaction time task where participants have to repeatedly respond as quickly as possible to the start of a digital counter. We used median reaction time as dependent measure. The word fluency test assesses the process of retrieving information from long-term memory and is also sensitive to sleep loss (Horne 1988). It requires the participant to produce as many words as possible within 90 sec, starting with a given letter ("P" or "M"). Because there are only two validated parallel versions of the RWT, participants of the Control experiment performed on it only during the Retrieval sessions.

Sleep duration was assessed after both nights of the retention phase. Sleep durations were obtained by assessment of the actimeter data. When data were not available (e.g., due to device malfunctioning), sleep durations were taken from standardized self-reports (SF-A/R).

Working memory capacity as a control marker of general memory performance was tested at the beginning of the first visit to the laboratory using an automated version of the operation span task (Ospan; Unsworth et al. 2005; Conway et al., 2005). This task involves the presentation of a series of letters in alternation with simple math problems [e.g. $(2 \times 3) + 2 = ?$]. Participants have to solve the problems and judge the correctness of one presented solution (e.g., 8) before retrieving the letters in the order they were presented. Letter set size ranged between three and seven letters. Three sets of each set size were presented in random order. The sum of all letters in correctly recalled sets (Ospan score) was used as dependent variable.

Data reduction and analyses

Statistical analyses of the navigation task focused on the distance (in virtual meters) between the participant's response and the correct locations. In addition, duration of navigation per trial was assessed. Before the analyses, time out trials (>45 sec) were removed. The average number of time out trials was 1.4 trials per participant (range: 0–10) and did not differ between groups, $X^2(1) = 1.83$, $P = 0.18$, or phases, $X^2(2) = 1.36$, $P = 0.50$.

Analyses of Variance (ANOVA) were performed with ezANOVA (ez; Version 4.2-2) implemented in R (https://www.R-project.org). Single comparisons were conducted using two-tailed Student's *t*-test on aggregated data, if not stated otherwise. Violations of normality and equality of variances were tested using Shapiro–Wilk test and Levene's test, respectively. Effect sizes of simple between group comparisons were estimated using Cohen's *d* for unequal group sizes. Effect sizes of single ANOVA effects were estimated using generalized Eta-Square, η^2_G. To test for the linear change in navigation performance over blocks, we used a linear mixed model implemented in the lme4 package (lme4; Version 1.1-8). Linear mixed effects modeling of single trial data was additionally applied to confirm ANOVA results in cases where cells contained different numbers of data points (e.g., different trail numbers during the Learning phase). These analyses indeed revealed results identical to the ANOVA results reported here.

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