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ORIGINAL ARTICLE

Sleep Leads to Brain-Wide Neural Changes Independent of Allocentric and Egocentric Spatial Training in Humans and Rats

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Abstract

Sleep is important for memory consolidation and systems consolidation in particular, which is thought to occur during sleep. While there has been a significant amount of research regarding the effect of sleep on behavior and certain mechanisms during sleep, evidence that sleep leads to consolidation across the system has been lacking until now. We investigated the role of sleep in the consolidation of spatial memory in both rats and humans using a watermaze task involving allocentric- and egocentric-based training. Analysis of immediate early gene expression in rodents, combined with functional magnetic resonance imaging in humans, elucidated similar behavioral and neural effects in both species. Sleep had a beneficial effect on behavior in rats and a marginally significant effect in humans. Interestingly, sleep led to changes across multiple brain regions at the time of retrieval in both species and in both training conditions. In rats, sleep led to increased gene expression in the hippocampus, striatum, and prefrontal cortex. In the humans, sleep led to an activity increase in brain regions belonging to the executive control network and a decrease in activity in regions belonging to the default mode network. Thus, we provide cross-species evidence for system-level memory consolidation occurring during sleep.

Key words: human, memory consolidation, rat, sleep

Introduction

The ability to reliably navigate to known desired locations requires the integration of spatial information from different reference frames followed by consolidation of this information to build long-term spatial maps of the surrounding environment. It has been proposed that this consolidation occurs during sleep (Girardeau and Zugaro 2011; Genzel et al. 2014; Navarro-Lobato and Genzel 2019). Two navigation strategies are thought to be used to navigate to a target in space: a place learning strategy and a response learning strategy. Place learning, which relies on the development of a spatial cognitive map containing an internal representation of relationships between distal cues, is known to be dependent on the hippocampus (Kesner et al. 1989; Morris et al. 1982; Packard and McGaugh 1996; Gahnstrom and Spiers 2020). In contrast, response learning, which relies on the location of the navigator and may involve repeated use of relatively fixed motor movements to remember the route to the target, is known to be dependent on the striatum (Packard and McGaugh 1996). During real-world navigation, information from both reference frames is integrated to form a cohesive representation of the

environment and the position of the navigator within (Andersen et al. 1997). However, one can experimentally bias the use of one strategy over the other by adopting specific training paradigms (de Bruin et al. 2001; Broadbent et al. 2020; Genzel 2020). Typically, this is done by including variable (allocentric training) versus stationary starting locations (egocentric training) within a maze, which will then bias in favor of place versus response strategies, respectively. Using allocentric and egocentric training paradigms enables the investigation of specific initial memory circuits involving the hippocampus and striatum, and their associated consolidation processes.

Sleep is important for experiences to be consolidated to form long-term memories. It optimizes the consolidation of newly acquired information and has been proposed to reorganize brain circuits at both synaptic and systems levels (Genzel et al. 2014; Navarro-Lobato and Genzel 2019). In particular, it has been proposed that memory consolidation processes associated with the hippocampus are dependent on sleep (Sawangjit et al. 2018; Schapiro et al. 2019). At a systems level, the hippocampus is thought to be initially involved in memory encoding by binding different information stored in different cortical modules into a coherent trace; over time, connections between these cortical modules strengthen and the memory thus becomes hippocampal independent (Frankland and Bontempi 2005; Squire et al. 2015). One critical mechanism underlying this process is thought to be repeated memory reactivations during non-REM sleep, which then lead to progressive strengthening of the corticocortical connections, and thus consolidation across the system (Girardeau and Zugaro 2011; Genzel et al. 2014; Maingret et al. 2016; Navarro-Lobato and Genzel 2019). These memory reactivations during sleep occur mainly during hippocampal sharp wave ripples (Girardeau and Zugaro 2011) and this may be the reason why the hippocampus plays a special role in sleep-related memory consolidation (Sawangjit et al. 2018; Schapiro et al. 2019). Considering the position of the hippocampus as a crucial hub for spatial navigation and offline consolidation processes, it may thus be proposed that, in a spatial context, learning under allocentric training conditions would benefit more from sleep compared with learning under egocentric training conditions.

In this study, we adopted a translational approach to investigate differential effects of sleep on allocentric and egocentric memory representations in rats and humans. We used the watermaze (Morris 1981), which has been a well-established paradigm used to study different aspects of spatial navigation, especially contrasting allocentric and egocentric training (de Bruin et al. 2001; Harvey et al. 2008; Ferguson et al. 2019). Further, a human analogue of the maze has been developed and there is comparable performance in behavior across both species (Schoenfeld et al. 2017; Müller et al. 2018). Using the watermaze, we tested the influence of sleep on allocentric and egocentric spatial memory training in both rats and humans and investigated the underlying neural signatures using immediate early gene expression analysis in rats and functional magnetic resonance imaging (MRI) in humans. We predicted an improvement in memory performance after sleep, especially when trained under allocentric conditions, and that sleep would lead to a brain-wide consolidation process; we report a main effect of sleep in rats and a marginal effect in humans ($P = 0.056$). Interestingly, in both rats and humans, a sleep but not wake state led to brain-wide changes of neural activity at test after both allocentric and egocentric training.

Methods and Materials

Subjects

Rats

Adult male Lister-hooded rats (Charles River, United Kingdom), aged 8–10 weeks with an average weight of 250–300 g at the start of experiments, were used. Rats were housed in groups of four per cage on a delayed day–night cycle (10 AM–10 PM light on) and had free access to food and water at all times. After arrival, rats were habituated to the housing environment for at least a week and then handled across 3 days for at least 5 min each day before watermaze habituation. A total of 45 rats were used from which 25 were used for qPCR experiments. All experimental procedures were in accordance with national Animals [Scientific Procedures] Act, 1986 and international (European Communities Council Directive of 24 November 1986[86/609/EEC]) legislation governing the maintenance of laboratory animals and their use in scientific experiments. The minimal number of rats for the necessary statistical power was used, with random assignment to groups, and minimal suffering was ensured for all experimental procedures. The experiments were approved by the UK Home Office under project license 60/4566 and by the University of Edinburgh Division of the National Veterinary Service Experimental Request Forms.

Humans

Seventy-seven neurologically healthy, right-handed male participants (age range = 18–30 years, mean = 24) were recruited for the study. Because male rats were used, only male humans were chosen for this study. Participants were recruited through the Radboud Research Participation System. All provided written informed consent prior to the start of the experiment and were paid for their participation. This study was approved by the local ethics committee (CMO Arnhem-Nijmegen, Radboud University Medical Center) under the general ethics approval ('Imaging Human Cognition,' CMO 2014/288), and the experiment was conducted in compliance with these guidelines. Exclusion criteria for the participants were 1) taking sleep medications, 2) taking regular naps, and 3) being involved in professional gaming activities. Participants were screened for these criteria before the start of the experiment. Additionally, alertness levels and sleep quality were assessed using the Stanford Sleepiness Scale and the Pittsburgh Sleep Quality Index, respectively, during the experiment session. Group values for these measures are tabulated in Supplementary Table 1. Eight subjects were excluded from the experiment due to technical issues during training or test: For five participants, the joystick was incorrectly calibrated, and for the remaining three, there were technical problems including abrupt crashing of the task environment program during the scan.

Watermaze Task—Rats

For both habituation and training, procedures were adopted from previous work (Genzel et al. 2017). Prior to the start of the main experimental session, rats were first habituated to a visual-cue version of the watermaze (diameter = 2 m) for 3 days, with four trials per day. The task was to find the submerged platform in the watermaze, indicated by a visual cue placed on top of the platform (diameter = 12 cm), while curtains surrounding the pool hid any extramaze cues. On reaching the platform, rats had to wait on the platform for 30 s before being picked up for the next trial. After habituation, rats were familiar with the procedure before training on the task began.

A one-session training design was adopted for this experiment as used previously (Genzel et al. 2017). The session consisted of eight training trials followed 20 h later by a probe trial. Rats were divided into two training groups—allocentric and egocentric. In the allocentric group, rats were placed in the watermaze from a different start quadrant on each trial and they had to reorient themselves to locate the platform. In the egocentric group, rats were placed in the watermaze from same start location each trial. For all trials, rats were introduced to the maze facing the watermaze wall. The goal location always remained the same with respect to the distal cues for each rat; only the start location differed depending on the allocentric/egocentric condition. Platform locations and start positions were counterbalanced across animals. In both training conditions, if a rat did not reach the platform by 120 s, they were guided to the location. Distal extramaze cues were present to help rats orient themselves in the watermaze. After the session, rats were randomly allocated to one of the two sleep conditions by either allowing them to sleep in allotted sleep cages or sleep deprivation by gentle handling in their home cages for 6 h after training. The sleep cages were identical to their home cages and every rat was allotted to a single cage. They were habituated to these cages before training, so it would be familiar for them to sleep in after training. Gentle handling included handling the rats occasionally, gently tapping on the cage, or removing the cover as soon as the animal started showing signs of tiredness (Genzel et al. 2017). Memory performance was tested with a single probe trial 20 h later, where rats were placed in the watermaze for 60 s with no platform present before being picked up from their current location. Swim paths were tracked using automated software (Watermaze, Watermaze Software, Edinburgh, UK [Spooner et al. 1994]). After sleep deprivation and before the test, rats were returned to their home cages and could potentially have slept. However, how long the rats slept during that period was not monitored. This was done to ensure that any behavioral or molecular effects seen were not confounded by fatigue or tiredness effects due to sleep deprivation or by direct effects of sleep deprivation on immediate early gene expression. Further, previous experiments have shown that sleep within 6 h after watermaze training is more important for memory consolidation than subsequent sleep, which cannot compensate for earlier sleep (Smith and Rose 1997; Genzel et al. 2017). For the probe trial analysis, time spent in the zone around the platform location was divided by the probe trial time (60 s), meaning that, with a zone radius of 14 cm, chance level of rat spending time in this zone was 2% with zone area/pool area. Experiments were timed such that sleep/sleep deprivation ended at lights off (thus the transition to the active period) and the test was conducted at lights on. This way, each rat had 12 h to recover from the intervention before being tested, but sleep rebound was minimized by using the active period. After the test trial, rats were sacrificed and brain regions (prefrontal cortex, striatum, and hippocampus) were extracted for qPCR analysis. In total, 45 rats were used: 20 trained under allocentric and 20 under egocentric conditions. Ten rats from each condition were allocated to either sleep or sleep deprivation, resulting in $n = 10$ per subgroup. In addition, five rats from each subgroup were randomly selected as representatives for qPCR analyses. Further, there were five home cage rats that did not undergo behavioral training and were used as home cage controls in the qPCR analysis.

RT qPCR Analysis—Rats

Analysis of qPCR was based on our previous work (Genzel et al. 2017). Briefly, rats were sacrificed 30 min after the probe test. The home cage controls were also sacrificed at the same time. We chose a neutral wake control condition (home cage), because possible alternative control conditions such as swimming in the watermaze without a platform can lead to alterations in IEG expression in association with stress or with incidental learning about the environment through exploration (Guzowski et al. 1999; Ons et al. 2004; Shires and Aggleton 2008), and these confounding factors can hinder interpretation of results (Barry et al. 2016). Furthermore, for present purposes, the critical results are the comparisons between training and sleep groups. Immediately after brain extraction, the bilateral medial prefrontal cortex, striatum, and hippocampi (both dorsal and ventral subregions were extracted as one) were dissected and flash frozen with liquid nitrogen and stored at −80°C for later processing. We focused on these brain regions since we previously showed that the hippocampus and prefrontal cortex were involved in sleep-related memory consolidation in this task (Genzel et al. 2017) and they are known to be involved in allocentric training paradigms (Kesner et al. 1989). We added the striatum because egocentric training is known to depend on the brain area (Packard and McGaugh 1996). Briefly, samples were homogenized and RNA was obtained via phenol–chloroform extraction according to the manufacturer's instructions. Next, cDNA was synthesized in vitro with use of random hexamers. Subsequently, an RT-qPCR and a comparative Ct quantitation were performed in experimental duplicates for *cFos, Arc, Zif268*, and 18S ribosomal RNA as the internal control on a StepOnePlus (Applied Biosystems, Carlsbad, United States) PCR machine. Plates were counterbalanced and amplification thresholds set manually (StepOne Software Version 2.3, Life Technologies). The amplified product size was verified using gel electrophoresis and amplification checked for primer–dimer formation and nonefficient DNase treatment. Data were normalized to the internal control 18S (also known as Rn18s, coding for ribosomal RNA47), and subsequently 'fold change' and then 'percentage change' to home cage control or other control were calculated. Percentage (%) change was used for statistical analysis and graphical presentation because fold change cannot be used for statistics and percentage change gives a more intuitive sense of effect sizes.

Study Design—Humans

The entire experimental session lasted for a maximum of 6 h and was split into three subsessions: 1) an fMRI session in which participants were trained on the task, 2) a 2.5- to 3-h interval involving either taking a nap with EEG or watching a neutral movie, followed by, 3) a second fMRI session in which participants were tested. An EEG was performed to confirm that each participant slept. The session started at noon with the participants filling in screening questionnaires and rating their alertness levels on the Stanford Sleepiness Scale. After having fulfilled all inclusion criteria, participants started the first fMRI session. This began with a T1-weighted anatomical scan, followed by a resting state scan where participants were asked to fixate on a cross projected on a screen. Next, they performed eight blocks of the training sets (allocentric/egocentric groups both alternating hidden/cued blocks). The duration

of this scan varied across participants and ended when they successfully completed all blocks. Following the task, the resting state scan was repeated and then the fMRI session ended. At the end of the first fMRI session, participants were randomly allocated to either of the two conditions—wake (watched a neutral movie for 2 h with an experimenter present to monitor that the participant stayed awake throughout) or sleep (a 1.5- to 2-h nap with polysomnography). At the end of the movie/nap, participants were asked to rate their awareness levels again on the Stanford Sleepiness Scale and then they started the second fMRI session. As with the first round, this session started with a resting state scan followed by eight blocks of the test sets (allocentric/egocentric both alternating hidden/cued blocks). The duration of this scan also varied across participants and ended when they successfully completed all blocks. Following the task, the resting state scan was repeated and then the second fMRI session ended. This marked the end of the full experimental session. Participants from the sleep condition were asked to come another day for a second session where they had to take a short nap with polysomnography (data not shown here).

Virtual Watermaze (VWM) Task—Humans

Humans were also trained in a watermaze environment, analogous to the rat task, to test spatial abilities. For this purpose, we employed a virtual watermaze (Schoenfeld et al. 2014; Schoenfeld et al. 2017), which consisted of a virtual island surrounded by four landmarks (distal cues)—a bridge, a sailboat, a wind turbine, and a lighthouse (see Supplementary Fig. 1). There was a hidden treasure box on the island, which was marked as the target location (equivalent to the platform in the water maze). The box was hidden in a fixed location in a small indentation on the virtual island surface such that it was only visible to the participants when they were close to it. This island is henceforth referred to as the 'hidden island.' The setup also consisted of another island that did not have any distal cues for orientation except for a visible colorful flag (cue) next to a treasure box, which was visible from a distance. The position of this flag changed each trial. This island is henceforth referred to as the 'cued island.' The overall task design was a block design with 8 alternating blocks of cued and hidden islands resulting in a total of 16 trials. Each trial was self-paced and ended with the participant marking the target location. There was a 15-s interval between the end of one trial and the start of the next, during which the subjects could turn around in the maze and orient themselves. The participants were allowed to freely navigate both islands with a joystick and their objective was to find the treasure box in each one and press a button on the joystick when they were in close proximity to the box. They would first encounter the cued island and had to find the visible flag. This island was used to control for motor and visual input as well as isolate memory effects in the fMRI analysis. For the encounter with the hidden island, the participants were randomly allotted to either of the training conditions—allocentric or egocentric. The participants were not aware of these two possible conditions. In the allocentric group, they would have a different start location every trial and would have to reorient themselves each time to find the target location, thereby promoting place navigation. In the egocentric group, they would have a fixed start location every trial and hence could rely on a repeated fixed movement to get to the target location in addition to using the visible cues. The main objective of the participants in both conditions was to learn the fixed location of the target box across all the trials. Finishing all 16 trials would mark the successful completion of the training set. For the test set, the island setup remained the same with one modification—the treasure box was removed from the hidden island and the participants were instructed to mark the location to the best of their knowledge, where they recalled the box to be located.

Polysomnographic Recordings

For the nap condition in the afternoon, polysomnographic recordings were obtained with a 250-Hz sampling frequency, a 0.3-Hz high-pass filter, and a 35-Hz low-pass filter (BrainAmp, Brain Products, Gilching, Germany). Thirty-two scalp electrodes were prepared including Fz, F3, F4, Cz, C3, C4, Pz, P3, P4, Oz, O1, and O2 electrode sites and referenced to the left mastoid. Additionally, horizontal and vertical eye movements (EOG), electromyogram (EMG) on the chin, and electrocardiogram (ECG) were recorded. Sleep scoring was performed by an experimenter blind to the conditions, based on EOG, EMG, and the following channels—F3, F4, C3, C4, O1, and O2 using 30-s epochs. Visual scoring of the recordings were conducted following the current, widely used American Academy of Sleep Medicine scoring rules (AASM) (Berry et al. 2012) with requirements including slow waves to occupy at least 20% of a 30-s epoch in order to be classified as Stage 3. All scoring was performed using the SpiSOP tool (https://www.spisop.org; RRID: SCR_015673).

Statistical Analysis

Repeated measure ANOVAs were run in SPSS Statistics 25 (IBM, USA) for immediate early gene expression and multivariate analysis for the sleep analysis. Univariate ANOVAs were run for the behavioral analysis. For immediate early gene analysis, within-subject factors were brain area and gene. For sleep analysis, the different sleep stages were included as different variables in the multivariate analysis. For all analyses, between-subject factors were training (allocentric/egocentric) and sleep-/wake. If sphericity was not given, Greenhouse–Geisser was used. Tests were calculated with an alpha of 0.05, but for each result, exact *P* values are reported.

fMRI Acquisition

For fMRI, functional images were acquired using ascending slice acquisition with a T2∗-weighted gradient-echo multiband echo-planar imaging sequence (Prisma 3 T, Siemens, Erlangen, Germany; 66 axial slices; volume repetition time [TR], 1000 ms; echo time [TE], 34 ms; 60° flip angle; slice thickness, 2 mm; field of view [FOV] 210 mm; voxel size $2 \times 2 \times 2$ mm). Anatomical images were acquired using a T1-weighted MP-RAGE sequence (192 sagittal slices; volume TR, 2300 ms; TE, 3.03 ms; 8° flip angle, slice thickness, 1 mm; FOV, 256 mm; voxel size $1 \times 1 \times 1$ mm).

fMRI Data Processing

Image preprocessing and statistical analysis were performed using SPM8 software (www.fil.ion.ucl.ac.uk/spm; Wellcome Trust Centre for Neuroimaging, London, United Kingdom). All functional contrast images went through the standard preprocessing steps. Images were realigned, slice-time corrected, spatially normalized, and transformed into a common space, as defined by the SPM2 Montreal Neurological Institute (MNI) T1 template. The preprocessed datasets were then analyzed using the general linear model and statistical parametric mapping

(Friston et al. 1994). The first five volumes from every dataset after preprocessing were discarded to remove nonsteady state effects. For statistical analyses, relevant contrast parameter images were generated for each participant and then subjected to a second-level GLM full factorial analysis with nonsphericity correction for correlated repeated measures. For the first-level analyses, individual contrast images for each participant were produced by comparing task-dependent activation (hidden > cued) for each session separately, with six movement parameters as regressors of no interest. Since the time taken to complete the task was not uniform across participants, we performed the first-level analysis on the activity in the first 30 s of every trial. Analyses were also done for the activity corresponding to the entire task length and are shown in the supplementary section. For the second-level analyses, these contrast images were included in a full factorial model with between-subject factors—Training (allo/ego) and Condition (sleep/wake) and within-subject factor—session (training/test). In the whole brain search, all results were collected at $P < 0.005$ uncorrected and then corrected at the cluster level to control for multiple comparisons ($P < 0.05$ FWE-cluster). To further elaborate, cluster-level correction is one of the methods used to control for multiple comparisons (Woo et al. 2014). It takes advantage of the fact that the individual voxels in the dataset are not independent of each other; instead, spatially adjacent voxels are likely to be functionally linked. So, instead of testing each voxel individually, we tested clusters of voxels for significance using a cluster-defining threshold of $P < 0.05$.

For the functional connectivity analyses between training and test sessions, we chose the medial frontal cortex (coordinates 2 10 48) as the region of interest to capture network activity. The coordinates of the region were taken from the activity analysis where we observed an increase in activity in this region after sleep. This region has been shown to be a part of the executive control network and related to goal-directed navigation (Spreng et al. 2010). A psycho-physiological interaction (PPI) analysis was performed. In general, with this analysis method, we were interested in investigating task-specific changes in connectivity between different brain regions with respect to a seed region of interest during the behavioral task (O'Reilly et al. 2012). In short, this method identifies regions in the brain that show the same modulation of the BOLD signal during the task as the seed regions and therefore these regions are assumed to be functionally correlated. The psychological variable consisted of the activity of task blocks (hidden island) in the first 30 s of each training block convoluted to the hemodynamic response. The physiological factor was the time course of a spheroid volume of interest (VOI) located in the medial frontal cortex (2, 10, 48) with a 6-mm radius. The VOI time course was extracted for each individual and adjusted for head movement. With the PPI toolbox (SPM8) the interaction value (PPI) of both factors was calculated. The PPI, VOI time course, and task timing were then included in a general linear model with the six movement parameters as regressors of no interest. For each participant, individual contrast images with the PPI activation were calculated. These contrast images were then included in a full factorial design model with the same factors as used for activity analysis. In the whole brain search, all results were collected at $P < 0.005$ and then corrected at the cluster level to control for multiple comparisons ($P < 0.05$ FWE-cluster). All data and analysis scripts will be available on the Donders Repository.

Results

Memory Performance in Rats and Humans

Both rats and humans were trained in the watermaze using a one-session paradigm to test spatial memory (Genzel et al. 2017). For rats, the task consisted of eight training trials followed 20 h later with a (no-platform) probe trial to test for long-term memory performance. Rats were divided into two training groups—allocentric and egocentric—the main difference being that that the former started each trial from a different position while the latter always started from the same point in the maze (Fig. 1A). After training, these two groups were further divided into a sleep group (allowed to sleep in assigned sleep cages) and a sleep-deprived group (sleep deprived in their home cages for 6 h after training by gentle handling, Fig. 1B) (Genzel et al. 2017). To assess memory performance, time spent in the target zone in relation to total time during the test trial was calculated. Analogous to the rat paradigm, a virtual watermaze environment was used for humans (Schoenfeld et al. 2017). The environment setting consisted of two islands—cued and hidden—to enable subsequent functional MRI (fMRI) analysis. The cued island was a brown island with no distal landmarks and contained only a visible flag (cue) next to a treasure box (Supplementary Fig. 1). The location of the flag was changed every trial and participants were instructed to scan the area to find the target. The hidden island was a green island surrounded by four landmarks and a hidden treasure box, which was the target location (analogous to the platform in the watermaze). The box was hidden in a fixed location in a small indentation on the virtual island surface such that it would only be visible to the participants when they were close to it. The overall task was run as a block design with eight alternating trials of cued and hidden island trials, resulting in a total of 16 trials (blocks for MRI analysis) that allowed us to isolate memory-specific effects excluding for general visual input and movement through the virtual world in the subsequent fMRI analysis. Each trial was self-paced and ended with the participant marking the target location. Participants could freely navigate through both islands with a joystick and their objective was to find the treasure box in each one and press a button on the joystick when they were in close proximity to the box. For the encounter with the hidden island, participants were randomly allotted to either of the training conditions, allocentric or egocentric, with either the same or changing starting position—and had to learn the location of the hidden box over trials (Fig. 1A). This training and later test sessions were conducted in the MRI scanner. After the session, participants were further grouped into the sleep (nap with polysomnography for up to 2 h 83.17 ± 3.3 min mean ± SEM, range 33.5–113.5 min; for sleep stage analysis, see Supplementary Fig. 2) or wake group. During the wake period, participants watched a neutral, nonemotional movie with an experimenter in the same room to monitor sleep/wake status and she was instructed to gently wake the participant if they fell asleep. Following the sleep/wake intervention, participants were taken back to the scanner and tested in the watermaze environment (Fig. 1B). In contrast to the rats, for which the probe trial consisted of a single trial, participants completed all eight trials again in each island to enable the correct contrast in the fMRI analysis. However, in this session, in each trial, they were instructed to mark the location of the treasure box in the hidden island to the best of their knowledge without the box being present. In humans,

memory performance was measured as latency to reach the location.

At test, the groups of rats performed above chance across both sleep and sleep-deprived groups for both allocentric and egocentric training conditions (Fig. 1C, left panel, one-sample *t*-test to chance level 2% based on zone area vs. pool area; sleep-allo $t_9 = 7.2$ $P < 0.001$, sleep-ego $t_9 = 4.3$ $P = 0.002$, SD-allo $t_9 = 2.5$ $P = 0.035$, SD-ego $t_9 = 5.3$ $P < 0.001$). However, there was a general effect of sleep and a marginally significant interaction of sleep and training condition on performance (univariate ANOVA sleep/sleep deprivation $F_{1,39} = 4.6$, $P = 0.039$, allo/ego $F_{1,39} = 1.4$, $P = 0.244$, interaction $F_{1,39} = 3.8$, $P = 0.058$). Human participants were generally better in the egocentric condition than in the allocentric condition, and there was a marginally significant effect of sleep on performance (univariate ANOVA allo/ego $F_{1,69} = 17.2$, $P < 0.001$, sleep/wake $F_{1,69} = 3.8$, $P = 0.056$, interaction $F_{1,69} = 1.6$, $P = 0.2$). In rats, the latency to reach the platform position at test showed a similar pattern to the dwell time analysis and human latency results; however, this was not statistically significant (Supplementary Fig. 3, univariate ANOVA all $P > 0.2$). In summary, there was an effect of sleep on behavior in rats with animals performing better after sleep than after sleep deprivation and the same contrast was marginally significant in humans.

Retrieval-Induced IEG Expression Analysis in rats

After establishing the behavioral effect of sleep, we next tested the neural effects of sleep. For this, in rodents, we measured the retrieval-induced expression of immediate early genes. More specifically, we measure expression of *Arc*, *cFos*, and *Zif268* in the prefrontal cortex, striatum, and hippocampus. Immediate early genes expression can be used as an index for neuronal activation (Jones et al. 2001; Fleischmann et al. 2003; Korb and Finkbeiner 2011; Genzel et al. 2017). In a full model including gene and brain area as within-subject factors, and sleep and training type as between-subject factors, there was a significant effect of sleep and gene and an interaction between training type (allo/ego) and brain area and an interaction between gene and brain area (repeated measure ANOVA sleep $F_{1,16} = 8.5$, $P = 0.01$; training type × brain area $F_{2,33} = 4.1$, $P = 0.026$; gene $F_{2,32} = 4.7$, $P = 0.016$; gene × sleep $F_{2,32} = 3.1$, $P = 0.061$; gene × brain area $F_{2.6,42.3} = 3.7$, $P = 0.023$; other $F < 1.9$ $P > 0.13$; Fig. 2). Next, two separate repeated measure ANOVAs were run with the same factors, but now separately for the sleep and sleep deprivation groups. For the sleep deprivation groups, there was an interaction between training and brain area ($F_{2,16} = 4.66$ $P = 0.046$), which was not significant for the sleep groups ($F_{2,16} = 1.49$ $P = 0.28$). An interesting pattern emerged in which sleep led to an increase in gene expression in all brain areas (prefrontal cortex, hippocampus, and striatum), whereas after sleep deprivation, there was only increased gene expression in the hippocampus in the allocentric group and in the striatum for the egocentric group (one-sample *t*-test to 0 indicated change to home cage, all significant $P < 0.032$, see Fig. 2, all nonsignificant $P > 0.22$, all genes included in one analysis per group and brain area). Thus, brain-wide activation for task-solving was seen only after sleep and was independent of allocentric or egocentric training conditions. In contrast, if animals were sleep deprived after training, task-solving was associated only with those brain areas known to be necessary for each training type: striatum for egocentric and hippocampus for allocentric.

Effect of Sleep on Brain Activity in Humans

Next, to assess the neural correlates of sleep on spatial memory under allocentric and egocentric training in humans, we analyzed the MRI BOLD images acquired during the training and test session. In both sessions, participants completed eight training trials to fixed treasure in the hidden island under either allocentric or egocentric conditions as well as eight trials to navigate to a visible flag in the cued island, where the position of the flag changed from one trial to the next. Thus, the first-level contrast was between the hidden and cued islands to enable isolation of memory encoding and retrieving specific effects while controlling for general task properties, such as joystick movement and visual input. Only the first 30 s of each trial were included in the analysis, to control for the fact that each trial length was different due to the self-pacing of the trial, and that there was a difference in average latency at test over the groups (mean 42.5 s; range 15.8–110.6 s). However, when the whole trial periods were included, the general pattern of results was unaffected (see Supplementary Figs 5 and 6). Only when participants slept between training and test were significant changes seen in BOLD activity, with increased activity in the medial and lateral frontal cortices, anterior and posterior parietal cortices, the visual cortex, and cerebellum and a decreased activity in the mPFC, precuneus, and hippocampus (Fig. 3 shows the contrast between training and test for sleep in both training groups; for sleep allocentric and sleep egocentric separately, see Supplementary Figs 4 and 6). All results were collected at uncorrected $P < 0.005$ and then corrected at the cluster level to control for multiple comparisons with $P < 0.05$ FWE (GLM full-factorial model with within-subject factor training-test and between-subject factor allo–ego and sleep–wake). It is noticeable that brain areas that had an increase due to sleep belong to the executive control network, which is related to goal-directed behavior (Gruber and Goschke 2004) and spatial memory (Maguire et al. 1998). In contrast, brain areas that had a decrease belong to the default mode network, which is associated with spatial memory (Spiers and Maguire 2007; Doeller et al. 2010; Brodt et al. 2016; Cowan et al. 2020; Navarro-Lobato and Genzel 2020).

The same contrasts for the wake subjects showed no significant voxels when looking at increase and decrease from training to test (both for each training group separately as well as for the combined wake group). However, when signal change at the peak voxel for each cluster was extracted for each group separately, similar changes to those in the sleep groups were observed for the wake egocentric group, even though they were not significant in a whole brain analysis (also not observed when uncorrected $P < 0.005$). Additional contrasts were run to determine further differences between allocentric and egocentric changes across wake. Following allocentric training (but not egocentric), the same brain areas that had higher activation between training and test during sleep were also more active at test between participants who slept and those that did not (allo sleep > allo wake at test, Supplementary Fig. 7). Furthermore, there was no significant interaction of sleep versus wake and training to test changes when including both egocentric and allocentric or if only egocentric participants were included. However, this same interaction (sleep/wake and training/test) was significant if only allocentric participants were included, with areas belonging to the executive control network showing increases in the sleep but not wake group (allo sleep training < allo sleep test and allo wake training > allo wake test, Supplementary Fig. 8).

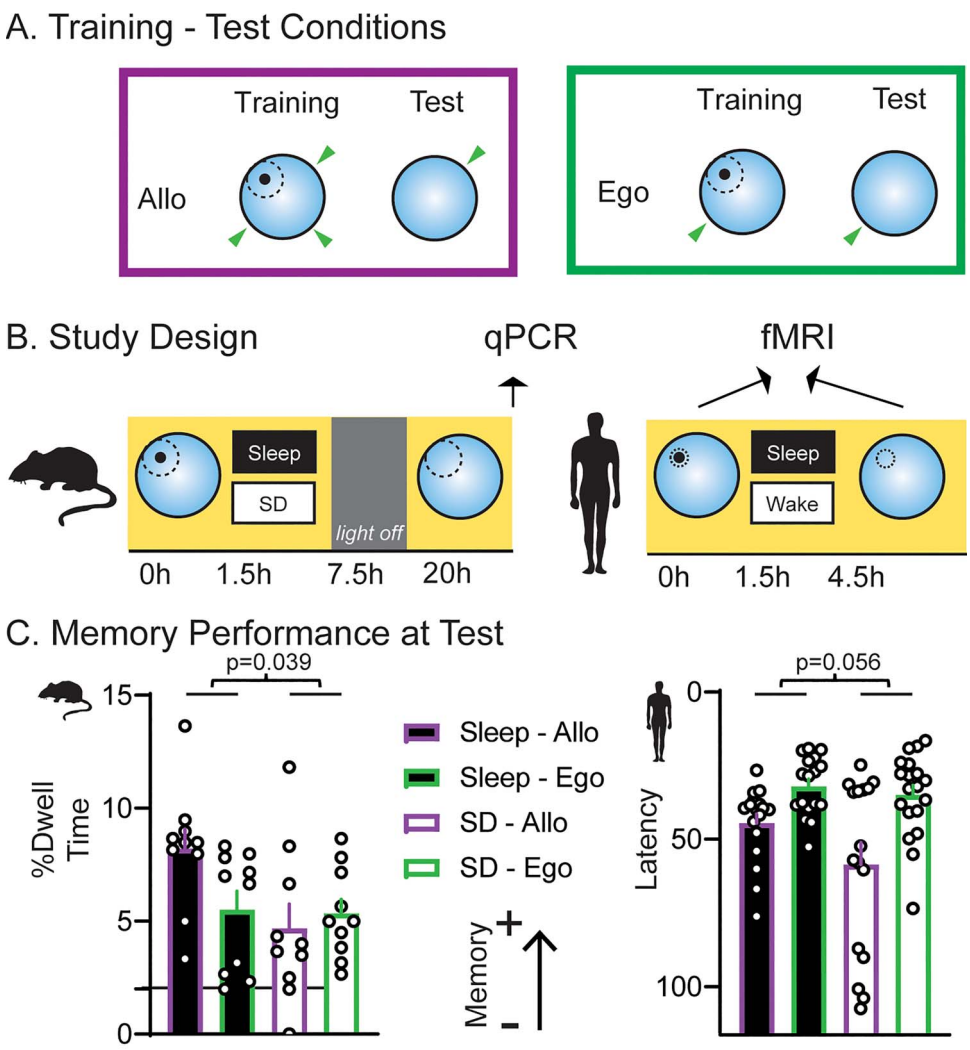

Figure 1. Study design and memory performance. (*A*) The training-test conditions. The left panel shows the allocentric condition during which both rats and humans started from different locations on every training trial. In contrast, during the egocentric condition, the starting location remained the same for every training trial (right panel). (*B*) Shows the study design for rats (left) and humans (right). Rats and humans were divided into two groups based on the training condition (allo/ego) and underwent a single-day training protocol in the watermaze with eight training trials. After training, each group was subdivided into two additional groups: sleep (allowed to sleep individually in sleep cages with video monitoring) and sleep-deprived (SD) group (sleep deprived for 6 h after training by gentle handling in the home cage) in rats and sleep (a nap with polysomnography for up to 2 h; for sleep stages, see Supplementary Fig. 2) and wake (watched a neutral movie for 2 h) in humans. Overall, there were four groups each of rats and humans: sleep–allocentric ($n = 10$), sleep–egocentric ($n = 10$), SD–allocentric ($n = 10$), SD–egocentric ($n = 10$) in rats and sleep–allocentric ($n = 17$), sleep–egocentric ($n = 16$), wake–allocentric ($n = 16$), wake–egocentric ($n = 19$) in humans. Sleep/SD in rats ended when the light-on period switched to the light-off period. Rats from all groups were tested the next day at the onset of the light-on period with a probe trial in the watermaze (no platform present). 30 minutes after the test trial, rats were sacrificed and brain regions were collected (prefrontal cortex, hippocampus, and striatum) for qPCR analyses on retrieval-induced expression of different immediate early genes. Humans from all groups were tested after the sleep/wake session in the watermaze environment with fMRI. (*C*) Behavioral results of the rats (left) and humans (right). All groups of rats performed above chance level (one-sample *t*-test to chance level, which was 2% based on zone area vs. pool area and indicated by the line) and those animals that slept after training showed significantly better performance in dwell time (higher values indicate better memory) than awake animals. Human participants, who took a nap between training and test, showed marginally significantly better memory performance compared with those that stayed awake (lower latency values indicate better memory, axis reversed to allow for comparison to rat data therefore better performance is still up). The purple bar contours represent the allocentric condition and the green contours represent the egocentric condition. The black and white filled bars for both colors correspond to sleep and sleep-deprived (SD) groups, respectively. Error bars are SEM.

In summary, we observed a change in the whole brain that was independent of training after sleep, which was not present after being kept awake. More specifically, we observed a shift in brain activation after sleep with higher activity in regions belonging to the executive control network and lower activity in regions belonging to the default mode network, including the hippocampus. Similar changes were observed in the egocentric wake group, but these were much weaker and were not statistically significant. Further, these changes were absent in the allocentric wake group.

Functional Connectivity Changes in Humans

Areas that had increased activity belong to the executive control network and areas that had decreased activity are associated with the default mode network. Thus, we next investigated

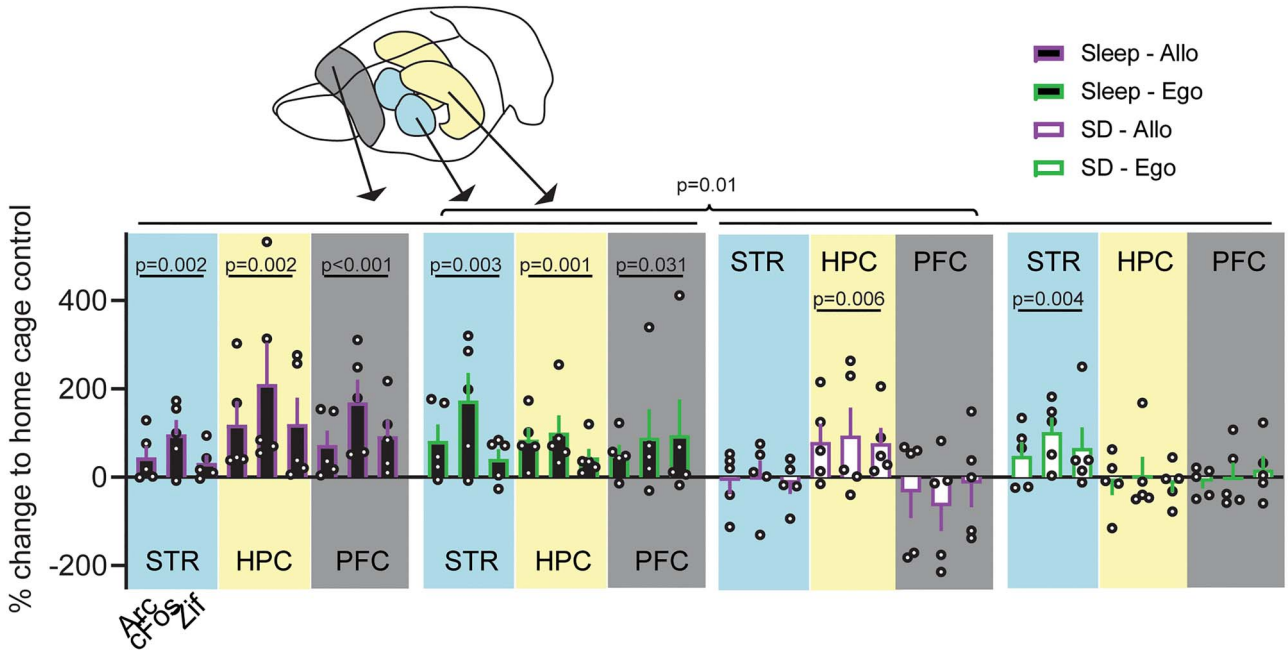

Figure 2. Memory retrieval in rats. Gene expression profile for immediate early genes *Arc*, *cFos*, and *Zif268* (represented as % change in relation to home cage controls) across different brain regions for all groups of rats. Prefrontal cortex (PFC) in gray, striatum (STR) in blue, hippocampus (HPC) in yellow. There was an overall effect of sleep ($P = 0.01$), with sleep groups showing higher gene expression levels. Separate repeated measure ANOVAs for sleep deprivation and sleep groups showed a significant brain area × training type interaction only after sleep deprivation and not after sleep. Further, one-sample *t*-test to 0 (which tests for change in gene expression in comparison to home cage controls) showed that the sleep groups had higher gene expression in all three brain areas than the home cage. Under sleep deprivation, the allocentric group had higher gene expression only in the hippocampus and the egocentric group had higher only in the striatum in comparison to home cage (nonsignificant $P > 0.22$, significant effects shown above, data for each brain area includes each gene separately. Of note, if Bonferroni correction applied with $0.05/12 = 0.00417$, the results for PFC in sleep–ego and HPC SD–allo would not pass significance). Purple bar contours are used for the allocentric condition and the green contours for the egocentric condition. The black and white filled bars for both colors correspond to sleep and sleep deprived (SD) group, respectively. Error bars are SEM.

functional connectivity changes during task execution by conducting a psychophysiological interaction (PPI) analysis. Led by the activity analysis, we focused on the medial frontal cortex as region of interest (ROI −2 −10 48). This ROI is a key hub of the executive control network, related to goal-directed behavior (Spreng et al. 2010). As with the activity analysis, we only included the first 30 s of each trial and all results were collected at uncorrected $P < 0.005$ and then corrected at the cluster level to control for multiple comparisons with $P < 0.05$ FWE (GLM full-factorial model with within-subject factor training-test and between-subject factors allo–ego and sleep–wake). At test, in contrast to training, the medial frontal cortex was functionally less connected to areas known to be part of the default mode network but again, only for those participants that slept and not those that stayed awake (inferior parietal cortex, precuneus, prefrontal cortex, and hippocampus; Fig. 4). Furthermore, for both sleep and wake groups, the cerebellum was decoupled from the medial frontal cortex (for wake contrast, see Supplementary Fig. 9). As with the activity analysis, we extracted the change in functional connectivity for the peak voxel in each cluster for each group separately.

The decreased functional connectivity and thus decoupling between the main hub of the executive network and default mode network parallel the finding in the activity analysis where increased activity was observed in the former and decreased activity was observed in the latter network, in the sleep but not wake group.

Discussion

In this study, we investigated the effects of sleep and no sleep on allocentric and egocentric memory representations in rats and humans using the watermaze. Overall, memory was intact—the subject/participant knew where the goal was—independent of training condition or if subject/participant slept or stayed awake between training and test. However, in both rats and humans, sleep led to better memory performance compared with sleep deprivation (of note, in humans, the effect was only marginally significant with $P = 0.056$). This effect of sleep was numerically larger in the allocentric training group; however, the interaction between sleep and condition was only marginally significant in rats ($P = 0.058$) and not significant in humans.

To investigate effects on brain activity, two different methods were used in the different species: In rats, we measured retrieval-induced immediate early gene expression in the hippocampus, striatum, and prefrontal cortex in comparison to home cage controls. In contrast, in humans, we compared the MRI BOLD signal at training and test. These analyses showed, in rats and humans, a change in activity across multiple brain regions that was observed after sleep for both allocentric and egocentric training conditions, which was not present in the wake group.

More specifically, after sleep in rats, there was an increase in retrieval-induced gene expression in all three tested brain areas (hippocampus, striatum, and prefrontal cortex), which was independent of allocentric or egocentric training conditions. In

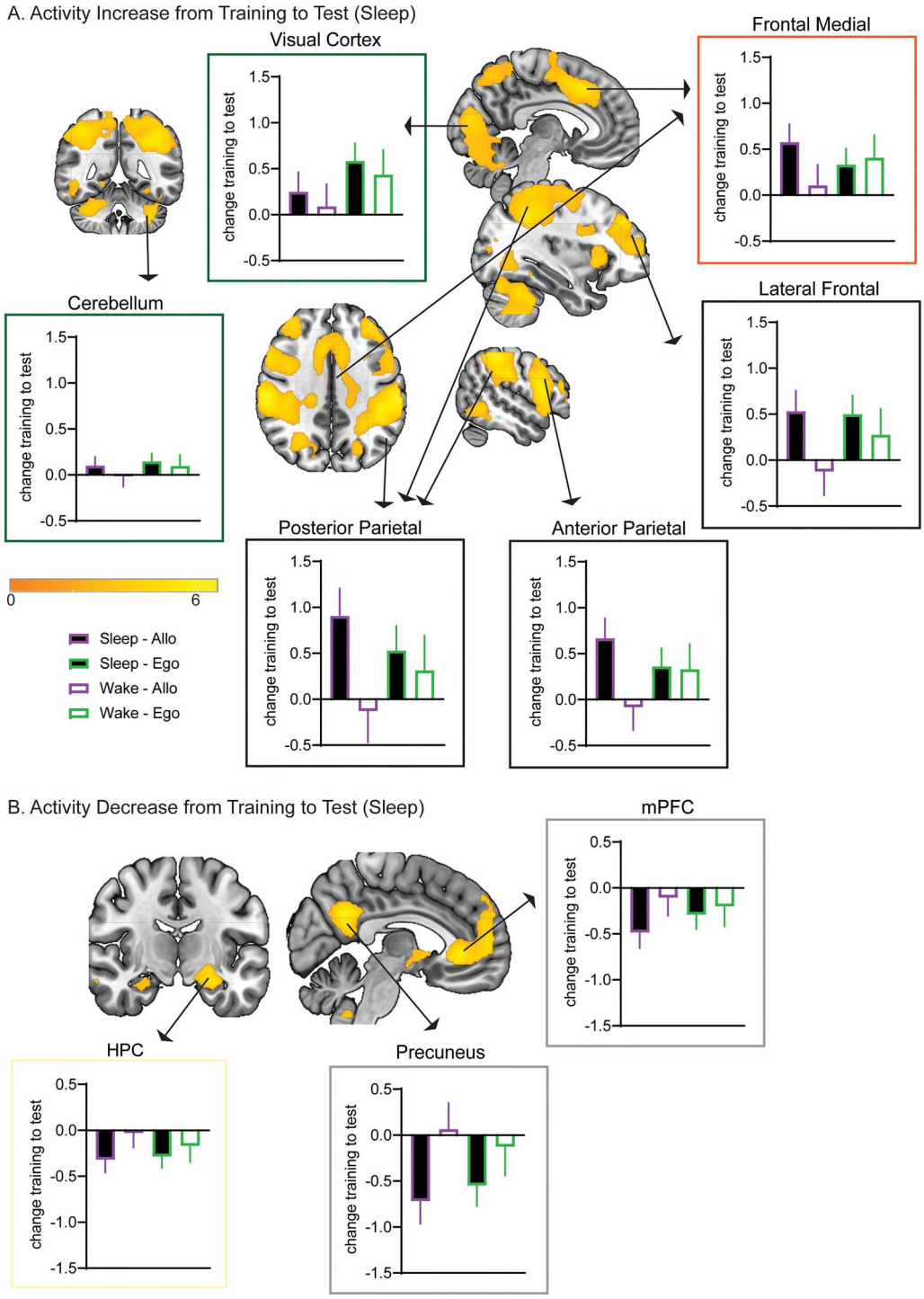

Figure 3. fMRI activity analysis in humans. (*A*) Brain maps showing changes in activity from both sleep groups (test more so than training, $P < 0.05$ FWE-cluster corrected). Bar graphs are extracted for each subgroup for the peak voxel of each cluster. An increase in activity was observed in the medial and lateral frontal cortex, anterior and posterior parietal cortex. Increases were also observed in a part of the visual cortex and cerebellum. This activity increase was similar across both training conditions over sleep (maps for each group, see Supplementary Figs 4, 5, 7 and 8). In contrast, after wake the whole brain analysis maps were empty. However, the peak voxel activity extraction indicates that egocentric wake did show similar changes to sleep, even if the smaller change and larger variability in this group precluded statistical significance on the whole brain level. (*B*) Brain maps show the changes from both sleep groups (test less than training, $P < 0.05$ FWE-cluster corrected) and bar graphs are extracted for each subgroup for the peak voxel of each cluster. A decrease in activity was observed in the medial prefrontal cortex (mPFC), precuneus, and hippocampus (HPC). The purple bar contours are used for the allocentric condition and the green contours for the egocentric condition. The black and white filled bars for both colors correspond to sleep and sleep-deprived (SD) group, respectively. Error bars are 95% confidence interval. For detailed statics on each cluster, see Supplementary Tables 2 and 3.

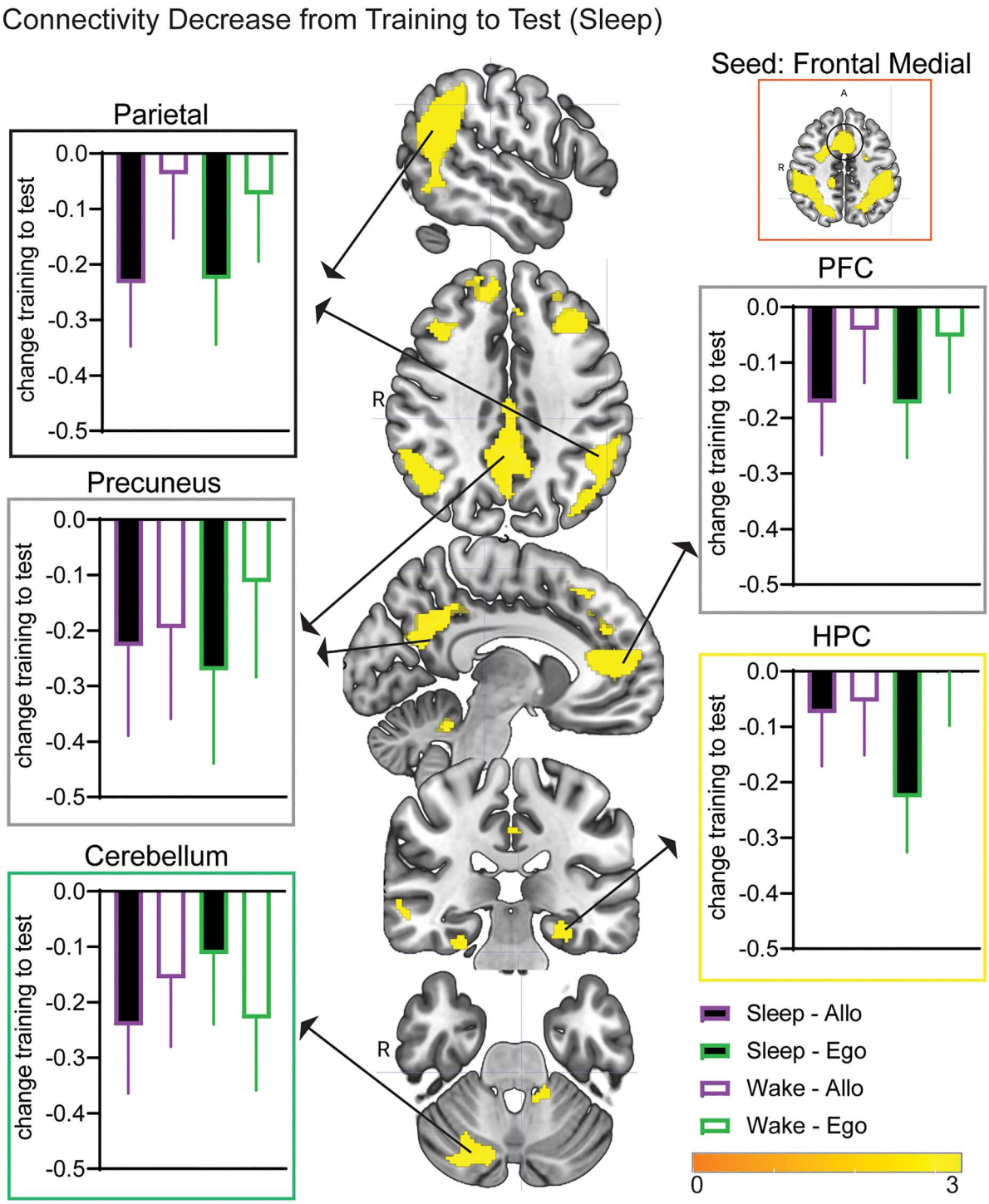

Figure 4. fMRI connectivity analysis (PPI) in humans with medial frontal ROI. Brain maps showing changes from both sleep groups (test less than training, $P < 0.05$ FWE-cluster corrected). Bar graphs are extracted for each subgroup for the peak voxel of each cluster. There was a significant decrease in connectivity in the frontal medial cortex with the prefrontal cortex (PFC), hippocampus (HPC), the precuneus, and the inferior parietal cortex from training to test (see Supplementary Table 4). These regions are known to be part of the default mode network. Additionally, there was also a significant decrease in functional connectivity with the cerebellum for both sleep and wake groups (wake contrast in Supplementary Fig. 9). Purple bar contours are used for the allocentric condition and the green contours for the egocentric condition. Black and white filled bars for both colors correspond to the sleep and sleep-deprived (SD) groups, respectively. Error bars are 95% confidence interval.

contrast, when rats were sleep deprived after training, task-solving was associated with increased gene expression only in those brain areas known to be necessary for each training type: the striatum for egocentric and the hippocampus for allocentric strategies.

In humans, fMRI analyses only showed statistically significant changes between training and test in participants that slept and not those who stayed awake. Significant increases were observed in activation in areas associated with the executive control network (such as the superior posterior parietal cortices and frontal medial cortex) and significant decreases in areas associated with the default mode network (hippocampus, mPFC, and precuneus). Extracting activity changes for the peak voxel in each cluster for each group revealed that there was similar changes in the egocentric wake condition as in both sleep groups; however, these changes were neither visible nor significant in the whole brain analysis (also uncorrected $P < 0.005$). Furthermore, only in the allocentric training groups was there a significant difference between wake and sleep at test in addition to a significant interaction between wake/sleep and training/test. Functional connectivity analyses during the task with PPI revealed a functional decoupling of the frontal medial cortex—the key hub of the executive control network—with areas of the default mode network.

Thus, across both species, we observed brain-wide changes following sleep, which were similar for both allocentric and egocentric training. In contrast, being awake led to differential effects across training conditions.

Differences between Species

With these results, it is important to consider the inherent, unavoidable between-species differences that are present, firstly, in behavior and, secondly, in the source of the neural activation measure and baseline contrast.

With regard to behavior, species will naturally differ in their awareness of the principle that they were being tested. Humans were aware that the testing session would not have a treasure reward at the goal and they needed to mark where they expected the goal to be. In contrast, rats would simply be searching for a place to rest within the pool. After not finding the platform in the correct location during the test, they would naturally search the rest of the pool in addition to repeatedly returning to the former platform location. To facilitate analysis, the tests themselves also differed between species. In humans, we ran eight test trials to allow for fMRI analysis. In rats, we only had one test trial. In rats, repeated test trials would have led to extinction and, therefore, less goal-searching behavior. This was not an issue in humans since they were aware of the nature of the test and, therefore, did not expect the goal to be visible.

The method of measuring neural activity also differed between species. In rats, we measured retrieval-induced changes in gene expression of immediate early genes in the hippocampus, striatum, and prefrontal cortex in contrast to home cage controls. Immediate early genes are expressed more in those cells that are especially active at a given moment and can thus be used to test for activity related to memory retrieval (Genzel et al. 2017). The rat data then highlight which brain areas were more active during memory retrieval in comparison to behaviors in home cage controls, and therefore, these areas are also generally associated with task-solving. We chose a neutral wake control condition (home cage), because possible alternative control conditions such as swimming in the watermaze without a platform can result in alterations in IEG expression in association with stress or with incidental learning about the environment through exploration (Guzowski et al. 1999; Ons et al. 2004; Shires and Aggleton 2008), and these confounding factors can hinder interpretation of results (Barry et al. 2016). But therefore, it is still important to keep in mind that results presented here could be influenced by the process of swimming. For humans, we measured BOLD responses both during encoding and retrieval phases of task and the results focus on relative changes in regions active during each of the sessions. However, the prime measure is relative since we first create contrasts of regions active during hidden versus cued island and then on the second level changes from first session to the second one. Further, while the BOLD signal is also known to measure brain activity, it is based on blood oxygenation changes and is thus a more indirect measure than the gene expression used in rats. The main difference in the results between species would be that for rats, the expression levels are compared with those in home cages, whereas for humans, the comparison is memory specific (cued vs. hidden island) and between sessions (within subject).

It is thought that the role of sleep in systems consolidation processes and underlying mechanisms is fairly conserved across both rodents and humans even though they have not been directly compared until now. With regard to the watermaze, several human analogue virtual maze environments have been developed to study mechanisms underlying spatial navigation and, more recently, to better understand the role of allocentric and egocentric learning strategies (Rodriguez 2010; Schoenfeld et al. 2014; Schoenfeld et al. 2017; Müller et al. 2018). With these limitations in mind, our discussion here will focus on a rough comparison of differences observed across training types and sleep groups and focus less on direct between-species comparisons.

Sleep and Egocentric versus Allocentric Training

Sleep is crucial for offline consolidation processes and strengthening memories. The proposed key underlying mechanism is neural reactivation wherein neural activity present during encoding reemerges during non-REM sleep (Girardeau and Zugaro 2011; Genzel et al. 2014). These reactivation events have been shown to occur mainly during hippocampal high-frequency burst oscillations, referred to as sharp wave ripples (Dupret et al. 2010; Girardeau and Zugaro 2011). Results collected from anesthetized macaque recordings showed these ripples to be closely associated with robust increases in cortical activation and suppression of activity in the thalamus and other subcortical structures. Another study demonstrated an increase in activity exclusively in the default mode network following the hippocampal sharp wave ripples (Logothetis et al. 2012; Kaplan et al. 2016), indicating a link between default mode network level fluctuations and behaviorally relevant hippocampal circuit dynamics. Furthermore, offline consolidation processes are thought to involve a dialog between the hippocampus and cortex via hippocampal sharp wave ripples in combination with neocortical slow oscillations and sleep spindles, which should stabilize labile memory traces in the cortex leading to systems consolidation (Schabus et al. 2007; Girardeau and Zugaro 2011; Schreiner et al. 2015; Squire et al. 2015; Maingret et al. 2016; Noack et al. 2017; Navarro-Lobato and Genzel 2019; Genzel 2020). Considering the crucial role of the hippocampus in spatial navigation and allocentric learning (O'keefe and Nadel

1978), it has thus been proposed that memories encoded with allocentric training, known to depend on the hippocampus, would benefit more from sleep (Sawangjit et al. 2018; Schapiro et al. 2019). In contrast, egocentric learning is dependent on the striatum and thus consolidation of these memories should be less dependent on sleep (Packard and McGaugh 1996; Genzel 2020). Several studies do provide evidence for this dissociation (Hagewoud et al. 2010; Albouy et al. 2015; Viczko et al. 2018). Sleep has also been shown to enhance the semantic explicit knowledge of routes navigated in a virtual spatial environment (Noack et al. 2017). Hagewoud et al. (2010) reported that depriving rodents of sleep after learning a plus maze led to a shift from a preferred place learning strategy, preferred by animals that were allowed to sleep, to a response learning; this was accompanied by a respective shift from hippocampal to striatal levels of retrieval-induced pCREB. In humans, several studies have investigated the use of allocentric versus egocentric strategies using virtual maze environments. Iglói et al. (2009) showed that subjects could spontaneously switch between allocentric and egocentric navigation strategies when engaged in a task, thereby acquiring different knowledge types in parallel. This ability to switch between strategies however was shown to be reduced in patients with Alzheimer's disease (Morganti et al. 2013) accompanied by degeneration in the hippocampus and retrosplenial cortex in these patients. On similar lines, Bohbot et al. (2004) reported an impaired ability in using the allocentric strategy in subjects with lesions in the medial temporal lobe. These studies further validated the role of hippocampus in place learning and striatum in response learning. Several other studies (Albouy et al. 2015; Viczko et al. 2018) further tried to disentangle the effect of sleep on memory processing using these strategies. They used motor-sequence tasks, like the finger tapping sequence task, which was designed in a way that one could test both allocentric and egocentric memory representations of a learned motor sequence. After training on a sequential finger tapping sequence, participants were tested on their ability to recall motor or spatial representations of the sequence with the same hand, but with the hand bottom up and keypad turned upside down. The egocentric or motor representation corresponded to the internal features and tested for movement-based learning (e.g., left little to index finger tapping transition would remain left little to index finger tapping transition). The allocentric or spatial representation corresponded to the global features and tested for spatial-based learning (e.g., left little to index finger tapping transition would change to left index to little finger tapping transition, so same spatial sequence requiring subjects to produce different sequence of finger movement). These studies showed an improvement in performance for the allocentric strategy following sleep, in contrast to the egocentric memory expression, which was maintained after sleep deprivation (Albouy et al. 2015; Viczko et al. 2018).

While similar effects were numerically visible in the behavior in our study where allocentric training groups had larger differences between sleep and wake, statistical analysis did not confirm this dissociation between sleep and training strategy. In both rats and humans, there was a main effect of sleep (but only marginally significant with $P = 0.056$ in humans). In rats, the interaction between sleep and training type did show a marginally significant effect ($P = 0.058$), but in humans, this interaction was not significant.

Interestingly, the neural effects did not confirm this dissociation either. In both rats and humans, a brain-wide change was seen across sleep but not wake, which was the same in both training conditions. Thus, while the prediction from the theory was that only hippocampal dependent memories would benefit from sleep, perhaps the different memory systems may be more interrelated than previously thought, especially during sleep. Another study (Orban et al. 2006) confirms some of our findings wherein subjects from sleep and sleep-deprived groups show equal performance levels with behavior but exhibit differences at the network level, with sleep leading to reorganization of the brain networks. The ventral striatum has been proposed to integrate inputs from the hippocampus, prefrontal cortex, and related subcortical structures to construct outcome predictions and stimulate goal-directed behavior (Pennartz et al. 2011; Pezzulo et al. 2014). Further, while memory reactivations are most known for hippocampal systems, Pennartz and colleagues have shown memory reactivations in the striatum, which were in close temporal association with hippocampal ripples (Pennartz et al. 2004; Lansink et al. 2009; Pennartz et al. 2011). Other recent studies also indicate that the interaction between the place and response learning memory systems is a lot more complex than the notion of having a hippocampus-independent response memory and striatum-independent place learning system (Iglói et al. 2010; Ferbinteanu 2020; Gasser et al. 2020). Interestingly, even within the hippocampus, there is evidence of lateralization of function with the right hemisphere contributing to place learning and the left hemisphere involved in temporal processing of the memory sequences (Iglói et al. 2010). Therefore, perhaps it is less surprising that we see brain-wide neural changes after sleep in both allocentric and egocentric training conditions. These findings fit well with the proposed role of sleep for systems consolidation, and thus, perhaps consolidation of memories is independent of learning strategy and this allows flexibility and adaptability for future use (Girardeau and Zugaro 2011; Maingret et al. 2016; Navarro-Lobato and Genzel 2019; Genzel 2020).

One point to be considered here is that, in theory, rats and humans could use the allocentric strategy to solve the maze even in the egocentric training condition since the goal was always at the same location with respect to the cues. However, if this did occur, then the differences we see in the wake groups would not be explained. Further, in this experiment, the rats were only sleep deprived for 6 h after training but potentially could have slept after this period and before test. This was done to decrease the effect of sleep deprivation and fatigue on memory retrieval per se and since previous experiments have shown that sleep within 6 h after watermaze training is more important for memory consolidation than subsequent sleep, which cannot compensate for earlier sleep (Smith and Rose 1997; Genzel et al. 2017). Our findings confirm that it is the initial sleep that is important for memory consolidation.

Immediate Early Gene Expression Results in Rodents

We know from rodent research that during learning, neuronal populations in different brain regions are recruited, leading to a learning-specific up-regulation of plasticity markers such as immediate early genes (IEG) in these regions. One can use the same markers at retrieval to measure which brain areas are involved in this process (Jones et al. 2001; Fleischmann et al. 2003; Korb and Finkbeiner 2011; Genzel et al. 2017). Here, we found an increase of retrieval-induced expression of IEGs in rats in the prefrontal cortex in addition to an increase in the hippocampus and striatum for both training conditions following

sleep. These findings fit well with the proposed role of prefrontal cortex in offline consolidation processes, during which salient information across multiple episodes is thought to be abstracted to build semantic memory networks (Frankland and Bontempi 2005; Maingret et al. 2016; Navarro-Lobato and Genzel 2019). Additionally, we also observed an increase in expression in the hippocampus and striatum in both training conditions for the sleep groups. This is in line with several previous reports (Guzowski et al. 2001; Feldman et al. 2010), which have shown increased levels of IEG expression in the hippocampus following successful memory performance in the watermaze. Guzowski et al. (2001) mapped IEG expression in rats trained in either an allocentric or egocentric condition and found similar expression profiles in the hippocampus for both conditions. There is also evidence supporting the potential use of both strategies to some extent for navigating efficiently in the maze (Harvey et al. 2008).

For the sleep-deprived groups, we only saw a localized IEG increase in the hippocampus and striatum when trained under allocentric and egocentric conditions, respectively. These results fit well with the original finding that place learning is known to be dependent on the hippocampus (Kesner et al. 1989). In contrast, response learning is known to be dependent on the striatum (Packard and McGaugh 1996). Therefore, after sleep deprivation, brain areas that are necessary for each training type should still show activation even if no additional recruitment of other brain areas can take place, such as after sleep. These results also fit well with Hagewoud et al.'s (2010) study, in which sleep deprivation led to a shift from place learning to a response learning strategy, which was accompanied by a shift from hippocampal to striatal levels of retrieval-induced pCREB.

Lastly, regarding the results above, it must be noted here that we extracted the entire hippocampal tissue to test for gene expression. However, it is well known that different subregions of the hippocampus, primarily the dorsal and ventral hippocampus, contribute to different functions. For example, the dorsal region is involved in spatial memory processes (O'Keefe 1976; Moser et al. 1995) and the ventral region is more involved in stress regulation and emotional memory processes (Kjelstrup et al. 2002). It could thus be speculated that our gene expression findings in the hippocampus would be more pronounced if we focused on only the dorsal part of the hippocampus. Across multiple studies, the role of dorsal hippocampus in spatial navigation and map-based learning has been extensively investigated, so one may expect a stronger effect of sleep on gene expression if only this specific subregion was analyzed.

fMRI Results in Humans: Executive Control Network

Our fMRI results show a dynamic interaction between areas of the executive control network and the default mode network over sleep across both training conditions. We observed an increase in activity in areas belonging to the executive control network and a decrease over sleep in areas belonging to the default mode network, which includes the hippocampus.

The executive control network is active during attention-demanding visuospatial tasks, goal-directed behaviors, and navigation and the parietal cortex is particularly implicated in playing a critical role in sensorimotor integration and activities of higher cognitive function (Gilmore et al. 2015). The posterior parietal cortex is of particular interest with respect to spatial navigation tasks and calculating route-centric information with respect to a target location. Using information from different sensory inputs, it produces an egocentric frame of the local environment where the target is located and provides appropriate motor coordinates required for making directed movements (Andersen et al. 1997; Spreng et al. 2010). Multiple studies in primate and rat models have also indicated a role of the posterior parietal cortex in encoding route progression during navigation under both allocentric and egocentric conditions and adapting to external environments and maintaining an internal cognitive map of self-position in space (McNaughton et al. 1994; Driscoll et al. 2017). This is also the case when tests are in virtual environments (Harvey et al. 2012). The posterior parietal cortex serves as a cortical integration site for hippocampally generated allocentric spatial information and egocentric spatial orientation to permit goal-directed navigation (Whitlock et al. 2008; Calton and Taube 2009; Nitz 2012; Khodagholy et al. 2017). Furthermore, memory reactivations during sleep have been observed in the parietal cortex in addition to the prefrontal cortex (Peyrache et al. 2009; Wilber et al. 2017) and both brain areas show high-frequency oscillations during non-REM sleep co-occurring with hippocampal ripples (Khodagholy et al. 2017). Consistent with these findings, we observed an increase in activation in the posterior parietal cortices across both training conditions after sleep.

fMRI Results in Humans: Default Mode Network

In regard to the changes observed in areas of the default mode network, much evidence has pointed to the importance of the hippocampus and medial temporal lobe structures including the prefrontal cortex and precuneus (also known as the retrosplenial cortex [van Heukelum et al. 2020]) in spatial navigation in both human and rodent models (Maguire et al. 1998; Peigneux et al. 2004; Epstein 2008; Whitlock et al. 2008). Furthermore, the default mode network is functionally modulated by sleep, with persistent functional connectivity during light sleep, and sleep spindles in particular, and a gradual decoupling with deep sleep (Schabus et al. 2007; Horovitz et al. 2009; Larson-Prior et al. 2009; Spoormaker et al. 2010; Andrade et al. 2011). Thus, this network could potentially play a role in offline consolidation processes coordinating the systems-wide consolidation process during sleep (Spreng et al. 2013; Brodt et al. 2016; Cowan et al. 2020; Genzel 2020; Navarro-Lobato and Genzel 2020). Recent evidence in rodents shows the co-occurrence of cortical high-frequency oscillations in default mode network areas including the posterior parietal cortex with hippocampal ripples, during non-REM sleep (Khodagholy et al. 2017). This may be the mechanism by which memories are consolidated from the initial hippocampal storage to downstream areas, such as the posterior parietal cortex, via cortical default mode network areas (Genzel 2020). This may also be the mechanism underlying our findings, where we see a shift in activity with a decrease in activity in regions belonging to the default mode network, which is perhaps an intermediate storage, and an increase in the goal-directed network, including the parietal cortex, over sleep.

Conclusion

In summary, across both species and training conditions, we observed brain-wide changes at the time of retrieval following sleep, which were not present after sleep deprivation. This fits to the main effect we found of sleep on behavior, even though in humans this effect only reached marginal significance ($P = 0.056$). Thus, we provide cross-species evidence for

the proposed function of sleep for brain-wide consolidation of memories proposed by Marr (1970).

Supplementary Material

Supplementary material can be found at *Cerebral Cortex* online.

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