Levels of Interference in Long and Short-Term Memory Differentially Modulate Non-REM and REM Sleep

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Study Objectives: It is commonly accepted that sleep is beneficial to memory processes, but it is still unclear if this benefit originates from improved memory consolidation or enhanced information processing. It has thus been proposed that sleep may also promote forgetting of undesirable and non-essential memories, a process required for optimization of cognitive resources. We tested the hypothesis that non-rapid eye movement sleep (NREMS) promotes forgetting of irrelevant information, more specifically when processing information in working memory (WM), while REM sleep (REMS) facilitates the consolidation of important information.

Methods: We recorded sleep patterns of rats trained in a radial maze in three different tasks engaging either the long-term or short-term storage of information, as well as a gradual level of interference.

Results: We observed a transient increase in REMS amount on the day the animal learned the rule of a long-term/reference memory task (RM), and, in contrast, a positive correlation between the performance of rats trained in a WM task involving an important processing of interference and the amount of NREMS or slow wave activity. Various oscillatory events were also differentially modulated by the type of training involved. Notably, NREMS spindles and REMS rapid theta increase with RM training, while sharp-wave ripples increase with all types of training.

Conclusions: These results suggest that REMS, but also rapid oscillations occurring during NREMS would be specifically implicated in the long-term memory in RM, whereas NREMS and slow oscillations could be involved in the forgetting of irrelevant information required for WM.

Keywords: reference memory, working memory, forgetting, interference, sleep, REM sleep, slow-wave sleep, oscillations


INTRODUCTION

Of all the possible functions of sleep, its role on learning and memory is certainly the most studied. Many studies have shown that brain structures engaged in mnemonic tasks can be reactivated during post-training sleep reactivation.1–5 Others have shown that memory deficits can be observed after sleep deprivation.6–10 Some interpreted these results as the positive evidence of a selective function of sleep in memory consolidation.11–13 Sleep has also been hypothesized to promote forgetting, and in particular adaptive forgetting of undesirable memories, by decreasing synaptic strength created during wakefulness.14–17 Forgetting of irrelevant information could thus occur during sleep to promote a more efficient and selective recall of more important information.

Important and relevant information are for instance those pertaining to Reference Memory (RM) that corresponds to the long-term storage of invariable information gradually acquired over many training sessions.18 In contrast, working memory (WM) depends on the short-term storage of trial-unique information.18–21 Required only temporarily, and that needs to be cleared away in order not to saturate our cognitive resources. Some authors have suggested that WM would be more a form of forgetting than a form of memory,22 and that WM and RM could simply be two antagonistic processes, one requiring forgetting and the other impaired by it.23 Whereas numerous studies suggest that the long-term storage of information in RM requires long-term synaptic potentiation (LTP), notably in the hippocampal formation,24,25 we and others have shown that hippocampal long-term depression (LTD) may function to weaken previous memory traces thereby preventing those traces from interfering with newly encoded information, in particular in tasks requiring WM.22,26 Using a transgenic mouse model, we showed that forebrain expression of an inhibitor of the protein phosphatase 2A (PP2A) constrains hippocampal LTD and forgetting.26 Inhibiting PP2A thus blocked the expression of LTD and the abilities of the mice to forget old information (concerning a platform position learned in the water maze task) that was no longer relevant. This deficit of forgetting also impaired WM abilities in a T-maze task by increasing the level of interference between trials. On the contrary, we showed that hippocampal expression of an inhibitor of the cAMP-dependent protein kinase (PKA) limits hippocampal LTP and RM, but also increases LTD, forgetting and WM abilities by decreasing the level of interference between highly identical trials of a radial maze task.23 These results thus suggest that the long-term storage of information into RM
could benefit from LTP, while forgetting and the processing of interference would depend on LTD. LTP and LTD being dependent on different neuronal firing pattern (high frequency stimulation preferentially facilitating LTP, and low frequency LTD), we hypothesized that memory is differentially modulated by the different sleep stages and their specific oscillations.

Like memory, sleep is not unitary. It has been extensively shown by our team and others that in particular rapid eye movement sleep (REMS, or paradoxical sleep) deprivation inhibits the induction or maintenance of hippocampal LTP in vivo and in vitro, whereas LTP and neuronal expression of LTP-related genes in the hippocampus could be more easily induced during REMS. In contrast, non-REMS sleep (NREMS) could favor synaptic depression. NREMS is characterized by low frequency oscillations, and several studies have shown that low frequency stimulation can induce LTD in various neuronal networks within the hippocampal pathways. Cirelli and colleagues have also shown that sleep, and in particular NREM, is associated with the upregulation of molecules implicated in LTD. In the frontal cortex, it has also been found that EPSP (excitatory postsynaptic potential) amplitude was correlated with the power of NREMS-dependent slow wave activity (SWA), and that the downscaling of EPSPs during sleep followed the decrease in SWA power. Based on these observations, the synaptic homeostasis hypothesis thus predicts that plastic processes occurring during wakefulness would be reduced (depressed or downscaled) during NREMS in order to decrease synaptic efficacy to a baseline level that is energetically sustainable and beneficial for learning and memory processes. This is how non-adaptive, “useless” or “non-usable” memory traces would be eliminated. Such hypothesis has never been tested before.

To test this hypothesis, we adopted a comparative approach by training groups of rats in three different radial maze paradigms involving or not proactive interference (Figure 1), and recorded their sleep patterns each day after training. One group of rats was thus trained in a long-term reference memory (RM) task while two other groups were trained in a WM task involving a simple delayed-non-match-to-place procedure often used to test WM abilities in primates or rodents. One of these two WM groups was trained in a WM task requiring not only the short-term storage of information relevant to an ongoing trial, but also a high level of proactive interference materialized by the repetitive presentation of similar information throughout the entire ten days of training. We previously showed that this high interference WM (HIWM) protocol required the reduction (forgetting) of this interfering information. The second WM group was trained in a low interfering WM (LIWM) protocol, so that such forgetting was less required. These three paradigms (RM, HIWM, LIWM tasks) thus tested three conditions gradually involving the adaptive forgetting of previously stored information, with HIWM training being the condition where forgetting of previous trials is the most needed in contrast to the RM task during which such forgetting is deleterious to the consolidation of information into long-term memory. However, to control for motor, motivational and emotional aspects that might be confounding factors to such a comparative approach of different cognitive abilities, we designed these three paradigms so that each day, rats in all conditions visited the same number of arms with the same time interval between each visit. This allows a clear comparison between processes requiring the long-term (RM) or short-term (WM) storage of information and those requiring the adaptive forgetting of previously stored information in WM. Our results indicate that the long-term storage of information in RM induces specific changes in the amount of REMS, but also NREMS-dependent rapid oscillations, whereas the proper treatment of memory interference and the forgetting of irrelevant information required for WM is correlated to an increase in NREMS and SWA.

METHODS

Subjects
A total of 51 Dark Agouti rats (200–250 g) were purchased from Janvier, France. They were kept in a 12/12h (07:00–19:00) light/dark cycle with ad libitum access to food and water. Rats were housed in individual cages and were food deprived and maintained at 85% of their free-feeding weight throughout the whole radial maze experiment. Three groups learned a radial maze task (high interference working memory HIWM [n = 13], low interference working memory LIWM [n = 12] or reference memory RM [n = 12] task), and a fourth group served as their respective controls (Yoked HIWM, LIWM or RM, total n = 14). All behavioral experiments were conducted from 10:00 until 12:00 each day. The animal care and treatment procedures were in accordance with the regulations of the local (Lyon 1 University CE2A-UCBL 55) and European (2010/63/EU) ethics committee for the use of experimental animals. Every effort was made to minimize the number of animals used or any pain and discomfort occurred during surgical or behavioral procedures.

Surgery and Polygraphic Recordings
Prior behavioral testing, the rats were submitted to surgical implantation of brain electrodes for sleep EEG and local field potential (LFP) recordings. They were anesthetized with Isoflurin (5% induction, 1.5–2.5% for maintenance), Kjmiflur (carprofen 5 mg/kg) and Xylocaine were injected subcutaneously before incision for analgesia. The skull was exposed, cleaned, and burr holes were drilled for the insertion of screws (0.6 mm diameter 1 mm long) for subdural EEG recordings. These screws were located over the right prefrontal cortex (AP +1; ML +1.2) and the cerebellum (reference electrode; AP, −9.0; L, −1.0). For LFP recording, a 100-µm diameter electrode (stainless steel, BioMedical Instruments, Germany) was inserted into the hippocampal CA1 region (AP, −3.3; L, 2.8; D, −2.4). Electromyogram (EMG) activity was assessed from the neck muscles by 2 wires embedded with a −1-mm diameter gold plated tin sphere. Electrodes were linked to a sub-miniature
plastic-one connector cemented to the skull. Skin was then sutured around the cement and local antiseptic was applied to avoid post-surgery infection. Then 2 mL of a 5 g/L glucose solution was injected subcutaneously. During a post-surgery recovery period of 10 days, animals were placed in a sound-attenuated, ventilated and electrically isolated chamber (60 cm side cube) and connected by a tether to a rotating connector (Plastics One Inc., CT). After recovery, animals were habituated to the radial maze apparatus for 5 days (see below). Each day after habituation or training, animals were placed in their recording chambers at 12:00, and EEG/EMG activity was amplified (1000×), filtered (0.3–500 Hz for EEG and 3–500 Hz for EMG, A-M systems) and recorded continuously using a National instrument data acquisition card (NI USB6353) and Matlab software. The signals were sampled at 2 kHz. Data were stored on a computer for off-line analysis.

**Behavioral Apparatus**

An 8-arm radial maze was used throughout the entire experiment for all tasks. The radial maze allows testing in both RM and WM in one single spatial environment and thus permits to determine a clear distinction between processes required for these different forms of memory. The apparatus consisted of an elevated radial maze.40 Eight arms (65 cm long × 12 cm wide) ended by rectangular platforms (17 cm × 25 cm) were arranged around an octagonal central platform (33 cm diameter). Each arm could be automatically moved in an upward (open) or a downward position (close) by the experimenter monitoring rat movements using a video camera above the maze while located in a room directly adjacent to the testing room.

Lowering (closing) an arm prevented access to the platform located at its end. Food rewards (Dustless Precision Pellets; Bioserve, Frenchtown, NJ) could be placed in squared food wells of 2 × 2 cm and 0.5 cm deep located on each rectangular platform. The maze was located in a room with a number of extramaze cues (e.g., door, furniture) allowing the rats to use spatial (hippocampal-dependent) memory to remember locations of food rewards. All rats’ movements in the maze were recorded for off-line examination.

**Behavioral Protocol**

Food deprived rats had to retrieve food pellets at the end of the maze’s arms using spatial navigation and distal visual cues surrounding the maze. Food deprivation was the same for all groups. Rats underwent a 5-days habituation period during which they became accustomed to the radial maze environment and learned to find rewards in the platform wells. During this habituation period, all arms were baited and rats were not authorized to return to an arm they already visited, preventing the rat to learn important aspects pertaining to the non-match rule (later used in the two WM tasks but not in the RM task). After eating a pellet in a given arm, this arm was thus closed and another arm was open in a sequential order. The route of the animal was therefore pre-randomly determined by the experimenter. At the end of this habituation procedure, rats were randomly assigned to one of the six groups (RM, YRM, LIWM, YLIWM, HIWM, and YHIWM) described below.

**Reference Memory (RM) Group**

Rats trained in the RM task had to retrieve 2 food pellets placed each day invariably in the same 2 of 8 arms for the entire 10 days of training (see Figure 1c, e.g., arms #1 and #4). A rat was thus initially placed in a pseudo-randomly chosen starting platform (on which the food well had been removed), all arms of the maze being in the upward (open) position. Once the rat has left this platform to reach a new ending platform (consisting in a “visit” or “run”), the arm leading to this new platform was lowered in order to block the rat on the platform. After consuming the food reward in the case of a correct choice, or not (in the case of an incorrect choice), the rat was placed in a transfer cage adjacent to the maze for a short intertrial delay of 15 s, then placed back into the maze for the next trial. The arms leading to the previously chosen platform(s) remained lowered (close) in order to prevent working memory use and errors. After both food pellets were retrieved, the 2 previously baited arms were re-baited and all arms were replaced in the upward (open) position. Rats underwent 8 trials (runs) per day, and the maximum score per day was thus fixed at 8 pellets eaten. The latency to choose an arm as well as the number of correct choices were scored. A third of these experimental RM rats were paired with yoked controls (YRM; n = 4) that performed the same amount of motor activity and ate the same number of pellets. These yoked controls were forced to enter into pseudo-randomly chosen arms and were either reinforced or not depending on the performance of their experimental (RM) matched rat. The starting and destination platforms varied between trials in such a way that yoked controls could not use motor memory to predict the arm location they were forced into or anticipate a reward. Using yoked controls allows the experimenter to conclude that all differences in sleep patterns observed between groups are inherent to cognitive aspects of the task and not due to emotional, motivational or locomotor effects.51

**Low Interference Working Memory (LIWM) Group**

Rats trained in the LIWM task (Figure 1d) were submitted to 4 trials per day, each consisting of a sample and a choice phase (4 trials × 2 phases = 8 runs matching the 8 runs performed by RM rats). In the sample phase, a rat was first allowed, from a pseudo-randomly chosen starting arm, to enter one pseudo-randomly chosen baited arm/platform with all other arms being lowered (closed). This rat was then returned to a transfer cage adjacent to the maze for a short delay of 15 s (same cage and delay than in the RM task). During the subsequent choice phase, and still from a pseudo-randomly chosen starting arm, the rat was allowed to visit one of 2 adjacent arms, the familiar arm that had just been visited and empty of food, or an adjacent arm (right or left chosen pseudo-randomly) containing a new food reward. The rat had to choose the novel arm in order to be positively reinforced (classical delayed non-match to place task, DNMT). Different pairs of arms were used for each trial. LIWM rats could also be matched to a yoked control group (YLIWM; n = 5). Whereas LIWM rats had to learn a DNMT rule in order to successfully complete the task, YLIWM control rats were exposed to an equal number of non-match and match trials in a pseudorandom order to make sure...
that these rats could not predict the trial outcome. They were also forced to visit only one arm during each phase of the task and were not exposed to any cognitive choice as compared to LIWM rats.

**High Interference Working Memory (HIWM) Group**
The HIWM task procedure (Figure 1e) was the same as the one described above for the LIWM task, except that the same pair of arms was used for every trial during the entire 10 days of training. This promoted a high level of interference and repetition in order to make forgetting of previous trials necessary to complete an ongoing trial.23 HIWM rats were paired with yoked (YHIWM; n = 5) controls that performed the same amount of motor activity and ate the same number of pellets (see above the YLIWM group).

**Sleep and Spectral Analysis**
The vigilance states were scored by 5-s epochs. Double-blind off-line analysis was independently carried out using the classical following criteria: for wakefulness (Wk), low voltage/fast cortical EEG and high amplitude EMG; for NREMS, high voltage (> 200 µV) slow wave EEG (1–5 Hz) and low amplitude EMG; and for REMS, low voltage and predominant theta frequency (5–10 Hz) with an absence of muscle tone.42 For sleep-wake cycle parameters, duration of each vigilance state was assessed for each hour and during the first 12 h post-training each day. These durations were expressed in minutes. For spectral analysis, EEG power spectra were computed for every 5-s epoch within the frequency range of 0–500 Hz (total spectrum) using a multitaper Fourier transform analysis with the help of the chronux toolbox43 (Chronux data analysis platform from http://chronux.org) and custom-written Matlab script (MatWorks, Inc.). The data were collapsed in 0.25 Hz bins. To prevent misinterpretation on epochs corresponding to transition phases between 2 vigilance states, the first and last epochs of REMS and the first and last 2 epochs of NREMS were omitted for the spectral analysis. Power densities obtained for each state were summed over the total band of 0–500 Hz (total power). To standardize the data, all power spectral densities at the different frequency ranges, i.e., delta δ, 0.5–5 Hz; theta θ, 5–10 Hz; sigma σ (spindles) 10–14 Hz; beta β, 14–30 Hz; and gamma γ, 30–60 Hz, were expressed as a percentage relative to the total power of the same epoch (relative spectral power). All power spectral analyses were conducted for the first hour of concatenated REMS episodes (spindles and SW-R) and the first 20 min of concatenated REMS episodes after training (rapid theta) after training but without omission of transition epochs. Recording site irregularities (broken electric contact, poor quality LFP signals or an extra-CA1 localization of a LFP electrode after electrocoagulation verification) were a priori identified and removed from local (CA1) analysis; trace without total continuity (10 days of recordings) was also excluded from oscillations analysis. For this sleep and spectral analysis, the final number of animals per group was thus n = 12 for RM and LIWM, 13 for HIWM and 14 for the control group (for oscillations and CA1 signal n = 9 for RM and LIWM, 10 for HIWM, and 13 for the control group).

**Statistical Analyses**
All data are expressed as means ± SEM, and statistical difference was assessed with probability under 0.05 after checking for normality and homogeneity of variance.

**Behavioral Performance**
Behavioral performances were analyzed using two-way ANOVAs (analysis of variance) allowing repeated measures analyses with Block (of 2 days) and Group (RM, LIWM, HIWM, and controls) as main factors (Sigmaplot). Post hoc (Scheffé) tests were further performed for particular within-group comparisons. In the RM task, the first day of rule learning was assessed by fitting performances of each rat to a classical sigmoidal curve (dose response EC50 analysis). The EC50 95% confidence interval was calculated (Sigmaplot) indicating for any rats the average period of highest increase in performance, i.e., the point in time when animals learn the rule of the RM task. This confidence interval (in days) also represents statistically the start and the end of learning. We also designed a simple Matlab routine that uses conditional operators (“if,” “then,” “else”) to virtually replicate the behavioral RM test using the same two rules as our real experiment: (1) not visiting the same arms twice unless both baited arms were visited, and (2) not going back in the starting arm. The starting arm and the visited arm were chosen randomly. The scores at the end of each session of 8 trials were recorded. This routine allowed us to calculate the chance level for the RM experiment by creating a virtual group of animals composed of the same number of individuals (n = 12) that performed completely randomly. We then compared this virtual group with our experimental RM group and performed a Man-Whitney statistical test to determine the first day of learning for RM rats, i.e., when our experimental RM group deviated from chance (virtual group performance) level. In contrast, for HIWM and LIWM (two classical delay non-match tasks), chance level was simply fixed at 50%.

**Sleep**
For sleep quantities, we used one-way ANOVAs with Group as main factor. To assess the significance of the differences between groups and how many changes are expected by chance, we calculated the significant differences from the means by bootstrap randomization tests with a confidence interval (CI) > 95%. Two-way ANOVAs on repeated measures on the
cumulative time spent in REMS on day 5 was assessed in the 4 groups of animals over the 12 h of post-training sleep using Group and Hours as main factors. Two-way ANOVAs on repeated measures on the cumulative number of events and duration of spindles and SW-Rs activity were assessed in the four groups of animals over 10 days of training using Group and Day as main factors. Post hoc (Scheffe) tests were further performed for particular within-group comparisons. Data from YLIWM, YHIWM, and YRM were pooled (as a global control) as no significant statistical differences were found between these 3 groups for all considered sleep parameters, and this group represents the comparative group.

**Correlation Analysis**

Linear regression analyses were performed to assess potential correlations existing between the vigilance state parameters (duration, number of episodes, average duration of episodes) recorded during 12 h post training (day n) and the performance of the rats on the following day (n + 1). Pearson correlation coefficient (r) was used to detect significant regressions. To assess the significance of the differences between groups and exclude a chance factor, we calculated the confidence interval (CI) > 95% by bootstrap randomization of the data and calculation of the Pearson correlation coefficients. To compare the different regressions, Fisher Z transform was calculated on the correlation coefficient to obtain a normal distribution. ANOVAs were then performed (Sigmaplot) to compare the transformed r values for the different groups.

For all oscillatory parameters (for each frequency band and transient event), the difference between the relative spectral power on one day (day n) and the relative spectral power on the next day (day n + 1) was calculated (increase or decrease in relative spectral power). Increase in performance was calculated as the difference between the performance of a given day (day n) and the performance of the same rat the day after (day n + 1). A linear regression analysis was then performed to assess correlation between behavioral performance increase (or decrease) and oscillatory parameters (increase or decrease of relative spectral power). Pearson correlation coefficient (r) was used to detect significant regressions. To assess the significance of the differences between groups and exclude a chance factor, we calculated the confidence interval (CI) > 95% or > 99% with the Bonferroni correction (1 to 0.05/5) based on comparing 5 variables (oscillations δ, θ, σ, β, γ) by bootstrap randomization of the data and calculation of the Pearson correlation coefficients. To compare the different regressions, Fisher Z transform was calculated on the correlation coefficient to obtain a normal distribution. ANOVAs were then performed (Sigmaplot) to compare the transformed r values for the different frequency bands.

**RESULTS**

**Proactive Interference Alters Working Memory Performance**

Figure 1f represents the performance of our 3 experimental groups of rats. A significant difference in performance was found between the HIWM and the LIWM groups (F1,25 = 14.17; P = 0.001). The increasing amount of interference building up after numerous trials and days in the HIWM group provoked a significant decrease in performance observed during the last days of training for rats trained in this task as compared to rats trained in the LIWM task that improved their performance over time (59.6 ± 5.7 vs 77.1 ± 4.6 on Block 4 and 69.2 ± 4.4 vs 80.2 ± 4.7 on Block 5; P < 0.05 for both blocks; see Figure 1f). This first result highlights an often overlooked issue concerning WM; more precisely, that an information supposedly stored temporarily in WM can have an impact on the long term when it becomes an interference for subsequent WM information as shown here with the decrease in performance over days (not seconds or minutes) in the HIWM group. We previously showed that forgetting such interference in this task is essential to process information in WM more efficiently. In contrast to both WM groups, RM rats gradually increased their performances across successive days to reach a level of 79% of correct choices on the last day of training (Block effect F4,44 = 38.62; P < 0.0001; see Figure 1f).

**Learning the Reference Memory Task Transiently Increases the Amount of Paradoxical Sleep**

Statistically, the 95% confidence interval (4.8 to 8.8 day) calculated from the sigmoid model (EC50 analysis) shows that the 5th (4.8 exactly) day is critical for learning the RM task as the majority of RM recorded rats start to reach a score greater than half of the maximum score (> 4/8 correct trials) on that day (Figure 2b). In addition, using a simple algorithm mimicking our behavioral test (see Methods), we created a group of virtual rats that make random choices and performing at chance level—the estimated chance level was 34.2%. Compared to such a group, we found that the RM group started to have significantly higher performances (P < 0.05) on day 5. Altogether, these data show that day 5 is critical for learning the RM task. Each day after training, the rats were placed in recording chambers to assess changes in the amount of NREMS and REMS that the different types of training initiated in the rats (their sleep recordings were systematically compared to those of yoked control animals—see Methods). Interestingly, an increase in REMS was seen in the RM group on day 5 of training (P = 0.0054; Figure 2a) as compared to the day before or the day after D5. No such increase could be explained by chance alone (bootstrap verification, Figure 2a) nor was seen with NREMS (not shown). We can thus assume that the increase in REMS is observed when the rats started to integrate and memorize the RM task rule. In addition, the analysis of the cumulative curve of REMS quantity on day 5 shows that this increase in REMS began shortly after training as significant difference is observed between RM rats and controls (and the other groups) only 4 h after the end of training (P = 0.0039; see Figure 2c). Moreover, after this critical day, performance of rats trained in the RM task is correlated to the duration of REMS rapid theta activity (9–14 Hz). A significant correlation (Pearson coefficient tested; r = 0.39, P = 0.0346; Figure 2e) between the duration of rapid theta oscillations recorded during REMS post training (day n) and performance of the rats in behavioral testing on day n + 1.
Figure 1—Behavioral paradigms and performance. a–e A schematic representation of one day of training for each of the three different experimental groups. c, One daily session of RM training for a given rat. The same two arms (here 1 and 4, see b) were baited every day for each trial. Each daily session consisted of 8 trials (T1 to T8). During a given trial, the rat is able to visit one arm only. Dark represents open arms. White represents closed arms. Red represents starting arm. Circles represent food pellets (a). d, One daily session of LIWM training. Each day consisted of 4 trials (T1 to T4). Each trial (T) consisted of 2 phases. This task is a “delayed non-match to place” task during which the animal must memorize a position in space (acquired during the sample phase) and retain this information for a short time (15 seconds). To obtain the food reward during the choice phase, the animal must remember the information stored and visit a different place (arm) in space. In this task, different pairs of arms are used for each trial, so that forgetting of previous trials is not necessary in order to have good performance on an ongoing trial. e, One daily session of HIWM training. This task is also a “delayed non-match to place” task except that the same pair of arms is used every day for each trial. Consequently, the trials are very similar to each other and it is therefore necessary to forget/ignore previous trials (e.g., T1 and T2) in order to have good performance on an ongoing trial. f, One daily session of HIWM training. This task is also a “delayed non-match to place” task except that the same pair of arms is used every day for each trial. Consequently, the trials are very similar to each other and it is therefore necessary to forget/ignore previous trials (e.g., T1 and T2) in order to complete an ongoing trial (e.g., T3). f, Proactive interference induces a decrease in performance in WM. Percentage of correct choices ± SEM per Block of 2 days in the RM (dark triangles, n = 12), LIWM (white circles, n = 12) and HIWM (gray circles, n = 13) tasks. ANOVAs revealed a significant Group effect ($F_{2,34} = 33.25; P < 0.0001$), a significant Block effect ($F_{4,136} = 9.12; P < 0.0001$), as well as a significant Group × Block interaction ($F_{8,136} = 7.07; P < 0.0001$). Post hoc analyses revealed that RM rats significantly improved their performance over time ($F_{4,44} = 38.62; P < 0.0001$), while LIWM rats showed a decrease in performance over days ($F_{4,112} = 7.07; P < 0.0001$). Post hoc analysis revealed that HIWM rats significantly improved their performance over time ($F_{4,112} = 38.62; P < 0.0001$) and reached 79% correct choices on the last block of training. In WM groups, we investigated how proactive interference affected learning. At the beginning of training, both LIWM and HIWM groups started at almost 70% of correct choices. Overall, rats kept high scores throughout the entire experiment, but HIWM rats showed a decrease in performance over days. On the other hand, scores of LIWM rats slightly increased with time and reached 80% on block 5. Post hoc analysis revealed difference ($P < 0.05$) between groups (Pairwise comparison HIWM vs LIWM #, vs RM*). More importantly, a significant difference in performance was observed at the end of training between LIWM and HIWM rats ($P = 0.020$ on B4 and $P = 0.048$ on B5).
Figure 2—Modeling of performances and transient increase in REMS shortly after training in the reference memory task. a, Quantitative variations of sleep states in RM (n = 12, dark bars), LIWM (n = 12, white bars), HIWM (n = 13, light gray bars) and control (n = 14, hatched bars) rats. Data are expressed as mean ± SEM (min) over the 10 days of training. A transient increase of REMS was seen in the RM group on day 5 of training (P = 0.0054 vs Control group). To assess the significance of the differences between groups, we used a bootstrap procedure to construct a 99% confidence interval for the 5th day (gray area). The increase in REMS seen in RM on day 5 is not comprised in this interval and may not be explained by chance alone. b, The first day of rule learning was assessed by fitting performances of each rat to a classical sigmoidal curve (dose response EC50 analysis). The 95% confidence interval was calculated (gray area, from 4.78 to 8.62) indicating the highest increasing period for performances, i.e., the period when animals learn more. Note that the start of this area corresponds to a score significantly different (*P < 0.05) from the calculated chance (black line average of a virtual group of 12 animals ± SEM in gray). The first day of learning was thus determined as the 5th (4.78 exactly [see above]) day of training. c, Mean cumulative duration (±SEM) of REMS during the 12 hours following day 5 of training. ANOVAs revealed a significant Group effect (F3,47 = 3.15; P = 0.036) as well as a significant Group × Hour interaction (F13,517 = 1.994; P = 0.0012). Post hoc analyses indicate that the significant increase of REMS quantity appeared on the 4th hour of recording (*P < 0.05, RM vs Control or LIWM or HIWM). d, Sample of CA1 recording showing detected rapid theta activity using a threshold of mean + 2 SDs (red line) from the filtered (lower; 9–14 Hz) CA1 (upper) trace. e, Performance of rats trained in the RM task is correlated to the duration of REMS rapid theta activity. A significant correlation (Pearson coefficient tested; r = 0.39, P = 0.0346) between the duration of rapid theta oscillations recorded during post training (day n) REMS (20 minutes concatenated) and performance of the rats (RM task) on day n + 1 was seen after the 5th day of training.
The Processing of Interference in WM Is Associated with an Increase in NREMS Quantity and Slow Wave Activity

No noticeable change in sleep patterns was specifically observed in the 2 WM groups (see Figure S1 in the supplemental material). However, we asked whether there was any correlation between the time spent in NREMS on a given day (day n) and the performance in HIWM the day after (day n + 1). As hypothesized, NREMS amount during the 12 h post training (day n) were positively correlated to the level of performance of rats trained in the LIWM task (see Figure 1). No such correlation was found at the end of training, with REMS duration or in the other groups.

The observations of rats trained in the HIWM task (see Figure 3a) is thus superior to these values and out of a 99% CI. Moreover, at the end of training, when the performance of rats was maximum and equivalent to the performance of rats trained in the LIWM group (see Table 1), suggesting that NREMS increases the cumulative number of spindles.

All Types of Training Increase the Cumulative Time of Sharp Wave Ripples while Reference Memory Training Specifically Increases the Cumulative Number of Spindles

Sleep oscillatory activities have been found relevant for learning and memory processes. During NREMS, sharp waves corresponding to depolarizing events superimposed with fast ripple activity (100–300 Hz) form sharp wave ripples (SW-R) events in the CA3 and CA1 regions. Recent studies showed that SW-Rs are critically involved in the replay of hippocampal activity and in the consolidation of hippocampal-dependent memories during sleep, the selective suppression of SW-Rs during sleep periods resulting in a decrease in memory performance. We analyzed high frequency events from the CA1 LFP recordings and using a threshold of mean ± 2 SDs, and found 2713 ± 44 SW-R epochs per 60 min of NREMS recording, lasting 30.1 ± 0.7 ms in average. Although no statistical changes in the number of SW-R epochs (Figure 5b) was observed between groups, a significant cumulative increase in the duration of these epochs was observed (Figure 3e). We have assessed potential correlation existing between sleep parameters and the performance on the day before sleep recording (day n). Statistical analyses failed to reveal any significant correlation between these factors. The maximum r calculated was 0.17 with a P value equal to 0.34 (NREMS quantity vs performance in HIWM group).

Slow wave activity (SWA) during NREMS has been hypothesized to be linked with synaptic strength increase during previous waking period. On the other side, synaptic down-scaling during NREMS is coupled with a decrease in SWA. We then asked if SWA may promote reduction of proactive interference, and found that an increase in delta power (0–5 Hz) on the EEG signal during NREMS could predict an increase in performance of rats in the HIWM task over 2 consecutive days (Figure 4a). In contrast, in the LIWM task such a positive correlation was not observed (see Table 2). Next, given that these spatial tasks implicate the hippocampus, we carried out the same analysis on LFP signals and found that a positive correlation exists between the increase in delta power in the CA1 area and the increase in performance of rats trained in the HIWM task suggesting that, during NREMS, local process in the hippocampus could be involved (Figure 4b). As we did for NREMS (see above), to verify the significance of our observed correlations (both with EEG or CA1 traces), we compared them to those obtained when the data were randomized 100 times. Our significant r values are again out of the 99% CI suggesting that the correlations found between SWA and behavioral performance did not arise by chance only. Moreover, we confirmed with a test for equality of slopes that the correlations between the progression in performance and SWA increase are statistically different between HIWM and LIWM groups (F_{1,179} = 18.32; P < 0.0001) for EEG and F_{1,140} = 10.274; P = 0.0017 for CA1 signal. Strikingly, no such correlation was found for the other groups of rats or for any other frequency band during NREMS (see Figure 4c and 4d and Table 2) or for all frequency band during REMS suggesting that, as predicted, a reduction of proactive interference in a spatial WM task depends on a very specific increase in SWA.

### Table 1—Correlation between performance of rats and sleeps amount showed by the regression coefficient and the Pearson probability of significance (in parentheses).

<table>
<thead>
<tr>
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<th>1st 4 Days</th>
<th>Last 4 Days</th>
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<tbody>
<tr>
<td>NREMS RM</td>
<td>0.180 (0.24)</td>
<td>-0.028 (0.87)</td>
</tr>
<tr>
<td>LIWM</td>
<td>-0.198 (0.20)</td>
<td>-0.072 (0.63)</td>
</tr>
<tr>
<td>HIWM</td>
<td>0.657 (&lt; 0.01)</td>
<td>0.218 (0.14)</td>
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Correlation between NREMS or REMS amounts recorded during 12 hours post training (day n) and performance of rats in behavioral testing on day n + 1. A significant correlation between NREMS duration and performance was seen at the beginning of training (first 4 days see Figure 3) when performance was maximum and equivalent to performance of rats trained in the LIWM task (see Figure 1). No such correlation was found at the end of training, with REMS duration or in the other groups.

The results showed that SW-Rs are critically involved in hippocampal-dependent memories during sleep, the selective suppression of SW-Rs during sleep periods resulting in a decrease in memory performance. We analyzed high frequency events from the CA1 LFP recordings and using a threshold of mean ± 2 SDs, and found 2713 ± 44 SW-R epochs per 60 min of NREMS recording, lasting 30.1 ± 0.7 ms in average. Although no statistical changes in the number of SW-R epochs (Figure 5b) was observed between groups, a significant cumulative increase in the duration of these epochs was observed (Figure 3e). We have assessed potential correlation existing between sleep parameters and the performance on the day before sleep recording (day n). Statistical analyses failed to reveal any significant correlation between these factors. The maximum r calculated was 0.17 with a P value equal to 0.34 (NREMS quantity vs performance in HIWM group).

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seen over days in all experimental groups (Figure 5c) as compared to controls. This increase was particularly prominent for HIWM rats (P = 0.0311), and more discrete for RM and LIWM rats, only occurring on the second, third, and eighth days (P < 0.05 vs control). This result suggests that SW-R could be involved indiscriminately in the storage of spatial information.

Figure 3—Performance of rats trained in the HIWM task is correlated to NREMS amount. Correlation between NREMS or REMS recorded during 12 hours post training (day n) and performance of the rats in behavioral testing (HIWM task) on day n + 1. a, A significant correlation (Pearson coefficient tested; r = 0.33, P = 0.0006) between NREMS duration and performance was seen during the 10 days of training. No such correlation was found with REMS duration (b) or in the other groups (Table 1). c, A more pronounced and clear significant correlation (r = 0.66, P < 0.0001) between NREMS duration and performance was seen at the beginning of training (first four days). No such correlation was found during the last four days of training (e) or with REMS duration (d, f).
NREMS spindle oscillations are other transient events that have been shown to be important for learning and memory processes (for review see 31). Notably, rats present increases in sleep spindles (10–14 Hz) density after a passive avoidance training51 or after an odor-reward association learning.52 Using a threshold of mean ± 2 SDs for the 10–14 Hz band, we found 549 ± 34 spindle epochs (per 60 min of NREMS recording), lasting 709 ± 7 ms in average for all groups of trained rats. Although no statistical changes in the mean duration of spindle epochs (Figure 6c) was observed between groups, a significant cumulative increase in the number of these epochs was seen over days in the RM group (Figure 6b) as compared to controls (P = 0.0239), potentially confirming the role of spindle activity in the long-term consolidation of information.

**DISCUSSION**

Many authors have suggested that sleep is beneficial to memory consolidation.11,46,53,54 Others have hypothesized that sleep may promote forgetting,14,15,55,56 but it has rarely been shown.57 This work represents the first comparative study, using a single spatial environment—a radial maze—aimed to assess how different cognitive processes involving the long-term consolidation of information or in the contrary forgetting, can influence sleep patterns in the rat. We found that RM training involving the long-term storage of spatial information lead to a transient increase in REMS the day the animals reach a significant level of performance. In contrast, we found that the reduction of proactive interference in a HIWM task previously shown to depend on hippocampal LTD-dependent forgetting52 is linked to an increase in NREMS quantity and SWA. These results seem to confirm Giuditta’s sequential hypothesis of the function of sleep proposed two decades ago,38 stating that, after learning, NREMS would consist in the weakening of non-adaptive (useless) memory traces, while REMS would deal with the storage of the remaining memory traces into long-term memory.

It has long been hypothesized that REMS promotes learning and memory by facilitating consolidation of newly acquired information into long-term storage58,59 (but see also 60). Notably a specific increase in IEG expression occurs in REMS specifically in cerebral cortices under the control of the hippocampus. These findings suggest that the consolidation of spatial traces requires a migration during REMS from the engaged hippocampus in waking to the cerebral cortex.31,32,61 In addition, it has been shown that training in various memory tasks transiently increases REMS amount within a short time window, during which consolidation is sensitive to REMS loss.62–64 Such transient increase in REMS reported by Hennevin and colleagues65 was observed before the stabilization of performance, when learning approached asymptote. After that, when the task was mastered, this transient REMS increase dissipated and REMS returned to baseline. Our results confirm such findings as we found that training rats in a RM task transiently increases REMS, possibly when rats trained in this task mastered the RM task rules on day 5. In contrast, no increase in NREMS was found in RM trained rats, nor in REMS or NREMS in rats trained in WM or control tasks, suggesting that REMS may be specifically linked to the consolidation of information into long-term storage, whenever this information is consolidated (the day the animal learn the information to be consolidated; here, on day 5 for most subjects).

Expression of the immediate-early gene Egr1 (also known as Zif268/Krox-26), a marker of synaptic plasticity,66 was found to be increased in hippocampal and neocortical neurons when exploration of a novel environment or the induction of LTP were followed by REMS (but not NREMS).31,67 We have recently found that REMS amounts modulate hippocampal Egr1 expression, LTP and the consolidation of contextual information acquired during fear conditioning.28,29,33,68 Therefore, it is reasonable to assume that the increase in REMS transiently seen in rats trained in the RM task induces the same changes

<table>
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<tr>
<th>Table 2</th>
<th>An increase in delta power is correlated to an increase in performance over two consecutive days of HIWM training.</th>
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<tbody>
<tr>
<td></td>
<td>RM</td>
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<tr>
<td></td>
<td>NREMS</td>
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<tr>
<td>EEG</td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>-0.009 (0.95)</td>
</tr>
<tr>
<td>θ</td>
<td>-0.007 (0.96)</td>
</tr>
<tr>
<td>σ</td>
<td>-0.105 (0.45)</td>
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<tr>
<td>β</td>
<td>0.082 (0.55)</td>
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<tr>
<td>γ</td>
<td>0.148 (0.28)</td>
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<tr>
<td>CA1 LFP</td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>0.083 (0.56)</td>
</tr>
<tr>
<td>θ</td>
<td>0.149 (0.30)</td>
</tr>
<tr>
<td>σ</td>
<td>0.200 (0.16)</td>
</tr>
<tr>
<td>β</td>
<td>-0.060 (0.67)</td>
</tr>
<tr>
<td>γ</td>
<td>0.214 (0.13)</td>
</tr>
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</table>

A positive correlation was found (r = 0.454, P = 0.027 and r = 0.405, P = 0.011 from EEG and CA1 LFP recordings respectively) between Delta band spectral power increase (calculated as the difference between the relative spectral power on one day [day n] and the relative spectral power on the next day [day n + 1]) and performance increase (calculated as the difference between the performance of a given day [day n] and the performance of the same rat the day after [day n + 1]) for rats trained in the HIWM task (see also Figure 4). No such correlation was found with the other frequency bands, in REMS or in the LIWM or RM groups.
providing a cellular and molecular ground for consolidation of important information required for solving the RM task the day following the increase in REMS. Many studies showed a post-learning REMS increase. However, in most of these REMS studies the learning is brief and definite (i.e., fear conditioning, inhibitory avoidance) compared to the present RM task. In our case, learning of the RM task is incremental with gradual acquisition of task-related information that may lead to different reorganization of REMS dynamics during the 10 days of training. Recent articles suggest another possible interpretation for REMS increase. REMS and theta oscillations could play an important role in excitatory homeostasis in the hippocampus. The present data and our result showing a positive correlation between RM performance and the duration of rapid theta may indeed suggest a REMS homeostatic process needed to recalibrate cortical networks after the rule learning. This could limit an overflow of hippocampal networks and reset these networks for another RM task.

In contrast to REMS, NREMS is known to be a non-permissive sleep stage for hippocampal LTP induction, and it has been suggested that NREMS, characterized by low frequency oscillations, facilitates instead the induction of LTD. Cirelli and colleagues have thus shown that sleep is associated with the upregulation of molecules implicated in LTD. Such molecules include protein phosphatases such as calcineurin (PP2B) or PP1 that have been shown to be involved in forgetting and WM. NREMS is also associated with higher levels of insulin, which promotes the internalization of glutamate AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors that is essential for the expression of LTD. In addition, in vivo and in vitro studies have shown that NREMS could induce LTD in the CA3 and CA1 hippocampal regions by internalization of specific AMPA receptors subtypes. We and others previously showed that inhibiting the protein phosphatase PP2A decreases the internalization of these AMPA receptors and the expression of NMDAR-dependent hippocampal LTD. Blocking such LTD results in an increase in behavioral flexibility and WM performance in a T-maze task, suggesting that NMDAR-dependent LTD is required for behavioral flexibility and may act by weakening previously encoded memory traces when new information is learned.

On the opposite, we showed that inhibition of protein kinase A (PKA) leads to an increase in hippocampal LTD, cognitive flexibility and WM performance, specifically when repetitive information (proactive interference) are presented as it is the case in a HIWM task. Performance in this task may thus depend on molecular mechanisms of LTD that are modulated by NREMS and SWA. Indeed, we observed a positive correlation between performance in this task and SWA power immediately after training. Given that experiments suggest that an increase in SWA is linked to an increase in synaptic efficacy, we would now have to examine if this task is associated with an immediate increase in synaptic plasticity followed by a homeostatic decrease in synaptic efficacy during NREMS.

This forgetting function of NREMS is of course in stark contrast with the many studies suggesting the consolidation function of NREMS. Nevertheless, as we have said earlier, post-training sleep reactivation of brain structures engaged in mnemonic tasks, as well as memory deficits observed after sleep deprivation, can also be seen as the positive evidence of a selective forgetting function of sleep. Forgetting is essential to our daily lives. By promoting forgetting, NREMS may sort information important to be consolidated from the one to be discarded. This hypothesis is in agreement with recent findings. Rauchs and colleagues have studied the impact of total sleep deprivation on directed forgetting. Directed forgetting is an experimental approach consisting in presenting “to be remembered” and “to be forgotten” information that

Figure 4—An increase in delta power is correlated to an increase in performance over two consecutive days of HIWM training. a, A positive correlation was found (r = 0.454, P = 0.027) between Delta band spectral power increase (calculated as the difference between the relative spectral power in EEG recordings on one day [day n] and the relative spectral power on the next day [day n + 1]) and performance increase (calculated as the difference between the performance of a given day [day n] and the performance of the same rat the day after [day n + 1]) for rats trained in the HIWM task. b, Same analysis as in a based on intrahippocampal CA1 local field recordings; a positive correlation was found (r = 0.405, P = 0.011) between Delta band spectral power and performance increases for rats trained in the HIWM task. c, In color scale (red p = 0; blue p = 1), the Pearson correlation coefficients for each regression curve showed that the increase in the delta band spectral power is the only oscillation variable correlated to the increase in performance in the HIWM task. The Fisher tests for equality of slopes (with bracket in the right) between each frequency band showed that the positive correlation between the increase in delta power spectrum and the increase in performance was significantly different from all increases in other frequency band and performance. d, Same analysis as in c based on intrahippocampal CA1 local field recordings; Pearson correlation coefficients show significance only in the delta band and Fisher test for equality of slopes indicates the positive correlation in delta band statistically different from the other frequency band correlations in the HIWM task (see also Table 2 for the other tasks and REMS).
allows to selectively decrease or increase the strength of individual memory traces according to the instruction provided at learning. The authors found that human participants to this study remember more “to be forgotten” items after sleep deprivation than after a normal night of sleep suggesting that sleep promotes the erasure of irrelevant information. Although this work does not conclude on the nature of the sleep phase involved in forgetting, our data suggest that NREMS, and more specifically SWA, might be responsible for such a process.

In 2006, Born and colleagues have shown that transcranial stimulation of endogenous slow oscillation during NREMS in humans not only boosted SWA, but also improved memory performance in a declarative memory test.82–84 They recently tried to replicate these findings in rodents trained in a radial maze experiment.85 Surprisingly, the authors found that boosting SWA during NREMS did not improve the rats’ performance in RM, but in WM. In fact, when examining their data more closely, it becomes clear that boosting SWA reduced the increase of WM errors (possibly due to interference) that was observed in their control group during the first four days of training. Like rats trained in our HIWM task, this control group’s WM performance deteriorated over days. Rats trained in delayed non-match to place tasks displayed a high percentage of correct responses from the first blocks of training. This immediate learning of the delayed-non-match rule is certainly due to innate spontaneous alternation, a behavior that naturally causes rodents to choose a different option (visit arm #2) than one previously adopted (visit arm #1) and in consequence to alternate exploration between two open arms.86 This tendency to spontaneously alternate between radial maze arms facilitates correct non-match responses. Nevertheless, spontaneous alternation requires memory storage of the previously visited arm in order to alternate to a different arm, and has long been shown to be dependent on the hippocampal formation.
Most interestingly, while LIWM rats kept high scores throughout the entire experiment, HIWM rats showed a decrease in their performance over the course of training. This decrease is attributed to the high level of interference and repetition present in the HIWM task. This modification in WM performance due to the ever-increasing buildup of proactive interference has already been observed in previous studies using similar radial maze paradigms. This result highlights an often overlooked issue concerning WM; more precisely, that information supposedly stored temporarily in WM can have an impact on the long term when it becomes an interference for subsequent WM information. This deleterious impact of previously stored information on WM would, however, be blocked by boosting SWA, a result in agreement with our present data and the hypothesis that SWA could indeed be required for the processing of interference in WM.

SWA is a cardinal feature of NREMS. However, other higher frequency oscillations characterize NREMS. For instance, NREMS-dependent hippocampal reactivation is suggested to occur mainly during bursts of activity known as sharp-wave ripple events (SW-Rs). Girardeau and colleagues found that a selective elimination of SW-Rs during post-training NREMS resulted in performance impairment in rats trained in a radial maze on a RM task similar to ours. These results thus suggest that NREMS, with its SW-Rs, may also facilitate memory consolidation through a different mechanism than SWA. High-frequency oscillations during NREMS may thus facilitate LTP and, by so, the storage of spatial information.
We can thus hypothesize that during NREMS, information of memory during sleep. Notably in humans, reactivation of memory during sleep. That is why our results suggest a specific role of SW-Rs in spatial memory formation (Figure 5).

SW-Rs are often associated to NREMS spindles that have been shown to play a key role in learning9 and in the reactivation of memory during sleep. Notably in humans, reactivation of memory during sleep. That is why our results suggest a specific role of SW-Rs in spatial memory formation (Figure 5).

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DISCLOSURE STATEMENT

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