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How to cite

STERPENICH, Virginie, CERAVOLO, Léonardo, SCHWARTZ, Sophie. Sleep deprivation disrupts the contribution of the hippocampus to the formation of novel lexical associations. In: Brain and language, 2017, vol. 167, p. 61–71. doi: 10.1016/j.bandl.2016.12.007

This publication URL: https://archive-ouverte.unige.ch/unige:94302
Publication DOI: 10.1016/j.bandl.2016.12.007

Brain & Language 167 (2017) 61–71

Contents lists available at ScienceDirect

Brain & Language

journal homepage: www.elsevier.com/locate/b&l

Sleep deprivation disrupts the contribution of the hippocampus to the formation of novel lexical associations

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ARTICLE INFO

Article history:
Received 8 April 2016
Revised 19 December 2016
Accepted 20 December 2016
Available online 4 February 2017

Keywords:
Memory consolidation
Sleep
fMRI
Learning
Language
Words

ABSTRACT

Sleep is involved in the mechanisms underlying memory consolidation and brain plasticity. Consolidation refers to a process through which labile memories are reorganized into more stable ones. An intriguing but often neglected question concerns how pre-existing knowledge is modified when new information enters memory, and whether sleep can influence this process. We investigated how nonword learning may modify the neural representations of closely-related existing words. We also tested whether sleep contributes to any such effect by comparing a group of participants who slept during the night following a first encoding session to a sleep deprived group. Thirty participants were first intensively trained at writing nonwords on Day 1 (remote nonwords) and Day 4 (recent nonwords), following which they underwent functional MRI. This session consisted of a word lexical decision task including words orthographically-close to the trained nonwords, followed by an incidental memory task on the nonwords. Participants who slept detected real words related to remote nonwords faster than those related to recent nonwords, and showed better explicit memory for the remote nonwords. Although the full interaction comparing both groups for these effects was not significant, we found that participants from the sleep-deprivation group did not display such differences between remote and recent conditions. Imaging results revealed that the functional interplay between hippocampus and frontal regions critically mediated these behavioral effects. This study demonstrates that sleep may not only strengthen memory for recently learned items but also promotes a constant reorganization of existing networks of word representations, allowing facilitated access to orthographically-close words.

1. Introduction

One central question in memory research relates to how newly encoded knowledge is incorporated into preexisting networks of memory representations. This process allowing long-term retention is called memory consolidation. Substantial experimental evidence supports that sleep may represent a privileged period for memory consolidation to occur (Maquet, 2001). In particular, sleep would favor the reactivation of information previously encoded during wakefulness (Diekelmann, Buchel, Born, & Rasch, 2011). This replay of recent memories was first observed in the hippocampus (Peigneux et al., 2004; Wilson & McNaughton, 1994). Further research then showed that the hippocampal replay may trigger coordinated reactivations across those distributed cortical and subcortical circuits initially implicated when the event was memorized, whose neural representation would ultimately be strengthened (Ji & Wilson, 2007; Lansink, Goltstein, Lankelma, McNaughton, & Pennartz, 2009). This "system consolidation" involves a temporal alignment of hippocampal ripples (during which bouts of replay occur), sleep spindles, and slow oscillations (~1 Hz). In humans, slow oscillations between the hippocampus and cortical regions, in particular frontal regions would orchestrate memory transfer from short- to long-term storage (Gais et al., 2007; Lahl, Wispel, Willigens, & Pietrowsky, 2008; Sterpenich et al., 2007; Stickgold, 2005). Over the past decade or so, research in both rodents and humans has provided strong support to this model and shown in particular that the consolidation of declarative memories is improved by some form of offline memory reprocessing and concomitant neural oscillatory activity (Maingret, Girardeau, Todorova, Goutierre, & Zugaro, 2016; Marshall,

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http://dx.doi.org/10.1016/j.bandl.2016.12.007
0093-934X/

Helgadottir, Molle, & Born, 2006). Beyond its key role in the transfer of short-term memories across distributed specialized cortical sites and frontal brain regions for long-term storage, which would predominate during sleep, recent studies in the field of memory research also suggest that the hippocampus directly contributes to the integration of recently encoded knowledge, through associative processes and this region may thus subserve generalization processes as well as the emergence of more abstract representations (Davachi, Mitchell, & Wagner, 2003; Igloi, Doeller, Berthoz, Rondi-Reig, & Burgess, 2010). The hippocampus is necessary for recollection because of its unique ability to assign independent representations to even highly similar stimuli (Lacy, Yassa, Stark, Muftuler, & Stark, 2011; Yassa & Stark, 2011) through processes known as pattern separation and pattern completion. Our experimental design was however not meant to test for pattern separation (see Liu, Gould, Coulson, Ward, & Howard, 2016) and the resolution of our fMRI data would not allow for correlational multi-voxel pattern analyses across subfields of the hippocampus, believed to have distinct contributions to pattern separation/completion (e.g. Yassa & Stark, 2011).

Associative processes were studied in a paradigm in which participants had to learn novel made-up words (e.g., BANARA) that were visually close (one letter change) or "neighbors" of familiar so-called "hermit words", i.e., words initially without any such neighbors (e.g., BANANA, Bowers, Davis, & Hanley, 2005). When tested on a semantic categorization task (word referring to artefact vs. natural objects) on the next day, participants were slowed for those words which had acquired one novel neighbor. These results were interpreted as reflecting lexical competition effects, whereby a newly learned word transiently interferes with the categorization of a related word. In a study using a similar task with spoken familiar and novel words, Dumay and Gaskell (2007) demonstrated that sleep contributes to the emergence of these interference effects 12–24 h after learning, plausibly by strengthening the representation of newly learned lexical information. Moreover, the quantity of spindles during the night was also related to the degree of lexicalization (Tamminen, Payne, Stickgold, Wamsley, & Gaskell, 2010). While the results of these studies are consistent, it is however important to highlight that the delay between encoding and test was comprised between 12 and 24 h. While this rather short time interval is apparently prone to competing or interfering effects, we expect that a longer time interval (i.e. several days), allowing for the stabilization of the lexical and/or semantic changes, may eventually lead to facilitating effects. In fact, in these paradigms, lexical competition between memory elements could reflect an intermediate and possibly unstable state of memory representations, while a more integrated and better structured state of these networks of representations later in time would rather facilitate lexical access to closely related memory elements. This point is of high importance for the understanding of the impact of novel material encoding and motivated the design of our study. Additionally, facilitation could also occur due to higher perceptual priming for words when semantically and/or lexically associated with other words or nonwords (McDermott, 1997).

To account for such memory integration effects, Shohamy and Wagner (2008) developed the concept of *integrative encoding*, according to which the presence of a common feature (e.g., ***B***) between two separately encoded elements (e.g., A***B*** and ***B***C) would strengthen their association in memory and elicit a higher probability of remembering one element (A) whenever the other is presented (C). The authors further emphasized the role of the hippocampus in such generalization processes during learning and memory consolidation, also consistent with the observation that the hippocampus contributes to the integration of overlapping visual stimuli (Heckers, Zalesak, Weiss, Ditman, & Titone, 2004). It therefore appears that encoding new information in memory can both interfere with previously stored knowledge through competition (presumably at an early stage, 12–24 h after encoding) and, at some later stage of memory consolidation, facilitate the access to closely related-material through integrative memory processes (at least 2–3 days after encoding, according to our hypothesis). It is thus still not clear whether facilitating or competing behavioral effects can coexist, and/or follow a distinct deployment in time. Moreover, how sleep may influence memory integration processes underlying such behavioral effects is not yet well understood.

Extending previous studies looking at the effects of sleep on lexicalization (e.g. Dumay & Gaskell, 2007; Tamminen et al., 2010), here we addressed these issues by using a simple lexical (word/nonword) decision task involving familiar written words related to recently learned nonwords. Specifically, to investigate the impact of time and sleep on memory, we tested one group of participants (N = 15), who slept normally the night immediately following an initial learning session, and one group of participants (N = 15) who did not sleep during that night. All participants performed a second learning session 72 h after the first learning session, i.e., after the sleep-deprived had two recovery nights. To assess whether facilitating/competing effects on real words in the lexical decision task would implicate better consolidation of the associated nonwords, we also tested recognition memory for the nonwords. Using this experimental design, we tested (i) whether learned nonwords either facilitate or interfere with the processing of related words during the lexical decision task; (ii) how the memory for the learned nonwords and their impact on related words may vary in a time-dependent and/or sleep-dependent manner; and (iii) whether the integration of novel nonwords relies on a functionally-connected network of brain regions involving the hippocampus.

2. Material and method

2.1. Participants

Thirty normally-sighted, right-handed, healthy volunteers (20 women, 10 men, mean age 23.3 ± 4.5 years old) gave their written informed consent to take part in this fMRI study, which was approved by the Ethics Committee of the Faculty of Medicine of the University of Geneva. None of the participants had a history of neurological, psychiatric or sleep disorder. Their scores on the Beck depression scale (Steer, Ball, Ranieri, & Beck, 1997) and Beck anxiety scale (Beck, Epstein, Brown, & Steer, 1988) were within normal range. Participants with extreme morning and evening types, as assessed by the Horne-Ostberg Questionnaire (Horne & Ostberg, 1976), were not included in the study. No participant complained of excessive daytime sleepiness as assessed by the Epworth Sleepiness Scale (Johns, 1991) or of sleep disturbances as determined by the Pittsburgh Sleep Quality Index Questionnaire (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). During 7 days prior to the first visit, participants were asked to follow a regular sleep schedule (aligned to their own sleep rhythm ± 2 h), which they also kept during the next 3 days until their second visit to the laboratory. Compliance to the schedule was assessed using sleep diaries and wrist actigraphy (Actiwatch, Cambridge Neuroscience; Daqtometer by Daqtix GbR, Oetzen, Germany).

2.2. Experimental material

Nonwords were created using 144 real French words. These words were selected from a meta-analysis from Bonin et al. (2003) who investigated the concreteness, imageability, subjective frequency, and emotional valence of 866 French words, assessed by 97 native French speakers. All 144 selected words were "hermit words", i.e., without any neighbor in the French language. A neighbor is defined as a word that differs in a single letter substitution, such as "house-mouse" (Coltheart, Davelaar, Jonasson, & Besner, 1977). Subjective frequency, emotional valence, and emotional intensity of these 144 words were assessed by 9 participants who did not participate in the main experiment. We created four series of 36 words balanced in terms of letter length (5–8 letters), frequency, emotional valence, and emotional intensity. From these selected words, 144 nonwords were created by a single letter substitution method. The choice of the substituted letter was counterbalanced for each word regarding its location within the word (left or right) and vowel vs. consonant. A vowel was always replaced by another vowel, and a consonant by another consonant. This produces pronounceable words that do not break any syntactic-related rules in French. Out of the four series of nonwords, two series were used as nonwords in the learning sessions (36 in each). The words related to these nonwords were then presented in the lexical decision task, together with the hermit words from the two remaining series. The assignment of the series to each learning session was randomized across participants.

2.3. Design of the study

On the first day (Day 1), participants performed a vigilance task (see Section 2.8 below) and underwent the first encoding task (Learning 1) during which they learned nonwords (hereafter "remote" nonwords) on a computer outside of the MRI scanner (Fig. 1). Learning took place between 8 A.M. and 6 P.M. Fifteen participants were then allowed to sleep during the night immediately following Learning 1 (Sleep Group, SG, 10 women, mean age 21.5 ± 2.9 years) while 15 participants were totally sleep-deprived during that night (Sleep Deprivation Group, SDG, 11 women, mean age 25.0 ± 5.2). Both groups did not significantly differ for age, depression, anxiety, sleepiness, sleep quality, and circadian rhythms (all $p > 0.5$).

Participants from the SG went home after the first learning session, and slept normally during the following three post-learning nights under actigraphy control, as they did during the preceding week (Fig. 1). Participants from the SDG stayed awake in the laboratory during the first night following the first learning session. During this night, participants remained under the constant supervision of experimenters, and were proposed some simple activities: they played board games and cards, discussed with the experimenters, watched two movies, and went outside of the building every hour for 5–10 min. Their physical activity was maintained as low as possible and both physical activity and food intake followed a regular schedule. Every hour, participants were invited to stand up and eat a small-standardized snack. During the following day, participants were instructed to go back to their usual activities without resting sleep to avoid any nap, and then slept at home during the two remaining nights before Day 4. This procedure was used to avoid the acute effects of sleep deprivation (e.g., increased fatigue, increased impulsivity, reduced attention) that could contaminate the main results.

All participants came back to the laboratory on Day 4 at the same time of day as on Day 1 (to control for any possible circadian effect; Fig. 1). They again performed the vigilance task (see Section 2.8 below), followed by the second session of encoding (Learning 2, "recent" nonwords) on a computer outside the MRI scanner. They then went into the MRI to perform two different tasks, i.e., a lexical decision task and an incidental memory task (see below). We expected that effects of the "recent" nonwords should not differ between the groups, whereas effects of the "remote" nonwords may differ between the groups if sleep influences integration and/or consolidation processes.

2.4. Experimental tasks

2.4.1. Learning phases

On Day 1, participants had to type 36 novel nonwords presented in a black font on a light-gray background (as in all subsequent tasks; Learning 1, Fig. 1). Each nonword was repeated 10 times in random order across 10 blocks of 36 words. Each nonword was shown on a computer screen for 2.5 s and then the participant had to type it on a keyboard. If the nonword was not written correctly, it was again shown during 2.5 s, and so on until the participant wrote it without any mistake. No time constraint was imposed during this learning phase. Participants were unaware that their memory for the nonwords would be tested later during the fMRI session. On Day 4, participants performed a second learning session (Learning 2, Fig. 1) similar to Learning 1, except that 36 new nonwords were presented. Hence, nonwords learned during Learning 1 were learned 72 h before the tests in the fMRI (i.e., remote nonwords), while the nonwords learned during Learning 2 were learned 30 min before the fMRI tests (i.e., recent nonwords).

2.4.2. Lexical decision task

On Day 4 (after Learning 2 and vigilance assessment), participants were comfortably installed inside the scanner with auditory protections. During the first task, participants performed a lexical decision task aiming at testing any interfering or facilitating effect of learned nonwords on the processing of their neighboring real words (from which the nonwords were initially derived). Each stimulus was displayed during 2.5 s on a black screen. Participants had to indicate as quickly and accurately as possible whether the stimulus was a word or a nonword by pressing with their right hand a left or a right button on an MRI-compatible button box (Current Designs Inc., Philadelphia, PA, USA). The order of presentation of the stimuli was pseudo randomized across participant. A fixation cross was displayed between each trial during 1.5 s. In this task, a total of 144 words and 72 nonwords were presented. Out of the 144 words, 72 words were related to the previously learned nonwords (from which they were created by a one letter-substitution): 36 related to nonwords from Learning 1 (i.e., remote words) and 36 acquired during Learning 2 (i.e., recent words). The remaining 72 words were hermit words not related to any nonword previously learned, and were then considered as new (see Section 2.4.1 above). The 72 nonwords were derived from other French words that were transformed using the same procedure as for the learning phases. To improve the estimation of fMRI baseline activity in our analyses, we included 72 null events consisting of a 4-s gray (versus black for events) fixation cross randomly interspersed between stimulus events.

2.4.3. Memory recognition task

Explicit memory for the nonwords was tested in a second fMRI task, in which we presented only nonwords (total of 288, one at a time) to the participants. All nonwords from the learning sessions (36 remote nonwords and 36 recent nonwords) were presented, intermixed with 72 new nonwords. These new nonwords were created from real French words with the same abovementioned procedure and were never seen by the participants (neither during the lexical decision task nor during learning sessions). To ensure that recognition required the access to the exact lexical characteristics of the nonwords, 144 additional nonwords, very similar to the nonwords described above, were included in the task. These nonwords were thus derived from the 36 remote, 36 recent, and 72 new nonwords. They were created by substituting another, second letter from the nonwords. As in the lexical decision task (see above), 72 null events were randomly interspersed between stimulus events.

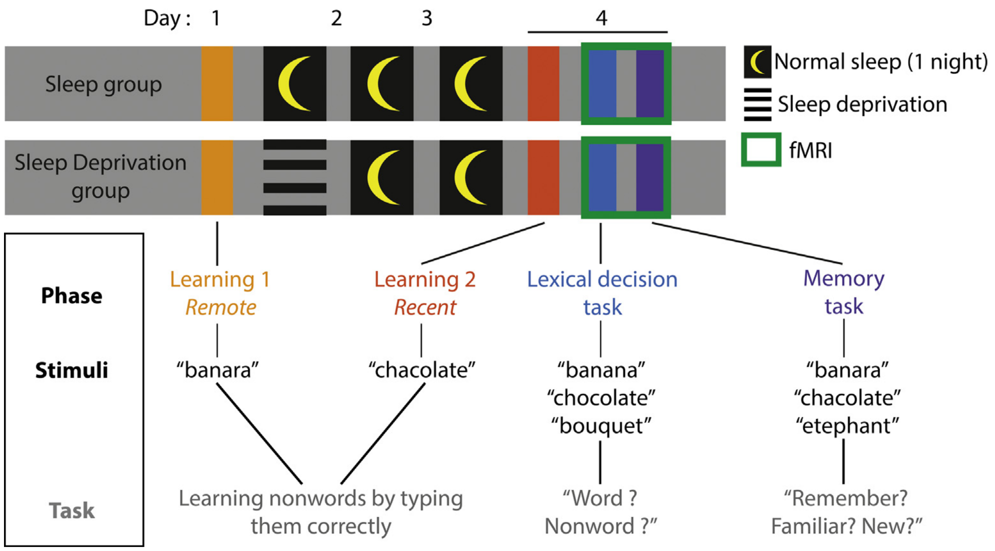

Fig. 1. Experimental design for both sleep and sleep deprivation group. Each group underwent a first learning phase before any manipulation of sleep was involved. Following this first day, the sleep group had 3 normal nights of sleep before coming again to the laboratory for the second learning and the fMRI tasks on Day 4; the sleep deprivation group was not allowed to sleep the night following the first learning, but could sleep for the following two nights. During the learning phases, participants had to type several times nonwords such as « banara » until they spell it correctly. While Learning 1 and 2 were equivalent in terms of sleep for the sleep group, the nonwords of Learning 1 could not be consolidated by sleep in the sleep deprivation group. Nonwords of Learning 1 are referred to as « Remote » while those of Learning 2 are « Recent ». The fMRI part consisted of a word-nonword lexical decision task followed by a memory task. In the lexical decision task, the stimuli consisted of words related to the nonwords learned during learning phase 1 and 2 (Remote and Recent words, respectively) as well as new words and nonwords. In the memory task, stimuli consisted of learned nonwords (both Remote and Recent) as well as new nonwords and participants had to respond by a "Remember", "Familiar" or "New" button-press.

All stimuli were presented in a pseudorandom order for 1.5 s each. The participant had to choose between three possible responses ("Remember", "Know", or "New") during this interval (maximum 1.5 s). Participants were instructed to select "Remember" if they remembered having seen the item together with contextual details (such as which learning session, or any associated thoughts at encoding). They should select "Know" whenever they had the feeling of having encoded the item or a feeling of familiarity but without being able to retrieve any further specific details. They selected "New" whenever they thought that the item had not been presented during any of the learning sessions. Responses were provided on the MRI compatible button box using the right hand. In a debriefing after the task, we asked the participants to justify their "Remember" and "Know" responses in order to ensure that they correctly understood the instructions.

2.5. Data acquisition

Data were acquired on a 3T magnetic resonance (MR) scanner (Trio, Siemens, Erlangen, Germany) using a gradient echo-planar (EPI) sequence [repetition time (TR): 2000 ms, echo time (TE): 30 ms, flip angle (FA): 80°, field of view (FOV): 192 mm, 35 transverse slices, voxel size: $3 \times 3 \times 3.6$ mm]. 585 scans were acquired for the lexical decision task, 485 for the memory task. A structural MR scan was acquired at the end of the fMRI session (T1-weighted 3D MP-RAGE sequence, TR: 1900 ms, TE: 2.32 ms, FA: 9°, FOV: 230 mm, matrix size $256 \times 256 \times 192$, TI: 900 ms, voxel size: $0.898 \times 0.898 \times 0.9$ mm). Stimuli were displayed on a screen positioned at the rear of the scanner, which the participants could comfortably see through a mirror mounted on the standard head coil.

2.6. Functional MRI data analysis

Functional MRI data were analyzed using SPM8 (http://www.fil.ion.ucl.ac.uk) implemented in Matlab (Matlab 8.4, The MathWorks, Inc., Natick, MA, 2014). Functional scans were realigned using iterative rigid body transformations that minimize the residual sum of square between the first and subsequent images. Data were then coregistered and normalized using DARTEL (Ashburner, 2007). They were processed using a two-step analysis, taking into account the intra-individual and inter-individual variance. For each task and each participant, the onset of each event/block was convolved with a hemodynamic response function (HRF). For each task, movement parameters estimated during realignment (translations in x, y, and z directions and rotations around x-, y-, and z-axes) and a constant vector were also included in the matrix as variables of no interest. The sets of voxel values obtained from the different contrasts constituted maps of t statistics [SPM(T)]. The individual summary statistical images were used in a second-level analysis, corresponding to either a random-effect or a flexible factorial design analysis (see Sections 2.6.1 and 2.6.2). Brain maps were thresholded at $p < 0.001$ (uncorrected). Small volume correction was then applied for hippocampal brain regions obtained in the lexical decision and memory task (see Sections 2.6.1 and 2.6.2). Functional statistical images of the lexical decision and memory tasks are displayed on the sample-specific ($N = 30$) mean anatomical image and brain-non-brain tissue separation was performed using Extract Brain (BET) plugin in Mango software (http://ric.uthscsa.edu/mango/mango.html, Research Imaging Institute, UTHSCSA).

2.6.1. Lexical decision task

For the lexical decision task, four trial-types were modeled at the first level: remote words (remote_W, words related to nonwords learned 3 days before), recent words (recent_W, words related to nonwords learned 30 min before), new words (new_W, words never related to learned nonwords), and nonwords. Only stimuli correctly identified as words or nonwords in the lexical decision task were modeled in these columns. Additional trials consisted of all missed items and errors and were entered as an additional regressor of no interest in the statistical design matrix. At the second-level, the Sleep factor was modeled, and contrasts of interest were assessed using a flexible factorial design with 2 (Sleep) × 3 (Condition for words only) factors. To test for the neural effects of post-learning sleep deprivation on the processing of words related to learned nonwords, we performed the following interactions: (1) [remote_W > recent_W] for [SG > SDG]; (2) [remote_W > New_W] for [SG > SDG] and (3) [recent_W > New_W] for [SG > SDG]. We performed a small volume correction ($p < 0.05$ FWE at the voxel level) using an anatomical image of the hippocampus or other brain regions as a mask, computed using the anatomy toolbox (Eickhoff et al., 2005) .

We also estimated brain activity related to words and nonwords by computing the linear contrasts [words > nonwords] and [nonwords > words], for both groups, and analyzing them in the context of a flexible factorial design with one within-subject factor.

Finally, a psychophysiological interaction (PPI) analysis (Friston et al., 1997) was performed to assess whether functional connectivity between the left hippocampus (resulting from the above-mentioned contrast; see Results) and some other brain regions might differ when processing remote_W as compared with recent_W. Brain regions are considered functionally connected if the signal of one or several target regions can be explained on the basis of the model originating from the signal time course in the seed region, obtained by multiplying the time series of the seed region with the specific conditions of interest. The result is an interaction between a psychological (the experimental conditions) and a physiological variable (the extracted time series in the seed region). Specifically, to extract the signal time course from the seed region in each participant, we used a sphere of 15 mm in diameter. The general linear model used for the PPI analyses includes 3 regressors: the “physiological variable” (extracted and deconvolved time series of activity in the seed region), the “psychological variable” (the comparison between the conditions, namely remote vs recent words), and the “psychophysiological interaction” (the interaction between the first two regressors) created by a point-by-point multiplication of the psychological and physiological variables. This third regressor is the one of interest, the first two regressors being included as regressors of no interest.

2.6.2. Memory recognition task

For the memory recognition task, three trial types were modeled: remote nonwords correctly remembered (remote_NW_R), recent nonwords correctly remembered (recent_NW_R), and new nonwords correctly identified as “new” (new_NW_N). An additional regressor of no interest was added, consisting of all missed items, all “know” responses, and all wrong responses (all “new” responses for learned nonwords, and all “remember” responses for new nonwords). The Sleep factor was also modeled in the flexible factorial design, yielding a 2 (Sleep) × 3 (Condition) design. The main effect of learning for nonwords ([remote_NW_R + recent_NW_R] > New_NW_N) and the effect of time for correctly remembered items (remote_NW_R > recent_NW_R) and recent_NW_R > New_NW_N were compared for the SG > SDG.

A psychophysiological interaction (PPI) analysis (Friston et al., 1997) was also performed for the memory task in order to evaluate any change of functional connectivity between the right hippocampal region (obtained from the above analysis; see Results) and some other brain regions when processing remote_NW as compared with recent_NW (see Section 2.6.1 above for the description of the PPI analysis).

2.7. Analysis of the behavioral data

2.7.1. Lexical decision task

For the lexical decision task, we computed the percentage of correct responses (words identified as words and nonwords identified as nonwords) and the reaction times (RT) between the presentation of the stimulus and the response of the participants. For the calculation of the RTs, we only considered correct responses and removed trials with extreme RTs (i.e., greater than percentile 92.5 or inferior to percentile 7.5). We computed the median RT for each category (remote_words, recent_words and new_words). Two repeated-measure ANOVAs were performed. First, the percentage of correct responses were analyzed with Word-type (word, nonwords) as within-subjects factor and Sleep (SG, SDG) as between-subjects factor. Second, RTs were analyzed with the Condition (remote, recent, new) as within-subjects factor and Sleep (SG, SDG) as between-subjects factor.

2.7.2. Memory recognition task

We computed the percentage of old nonwords correctly remembered as such (R-hits), old nonwords judged as familiar (K-hits), new items identified as old (False Alarm, R-FA) and new items identified as familiar (K-FA). We next calculated the recollection performance (R-hits minus R-FA) and the familiarity performance (K-hits minus K-FA) for each Condition (remote and recent) separately and for each group (SD and SDG) (Cairney, Durrant, Power, & Lewis, 2015). These values derive both correct and incorrect responses, so as to account for any possible response bias. We computed a 2 × 2 × 2 ANOVA with memory performance (recollection performance and familiarity performance) and Condition (remote, vs recent) as within- subjects factor and Group (SG, SDG) as between-subjects factor.

The discrimination index (d′) was also assessed separately for remote and recent conditions. Because familiarity performance was not above chance (*t*-test for both remote and recent conditions, $p > 0.05$), we computed this measure only for R response (significantly above chance, $p < 0.001$) according to the procedure of MacMillan and Creelman (1991), with R-hits, R-FA, correct rejection (new nonwords correctly identified as new) and misses (old nonwords incorrectly identified as new). The last two parameters (correct rejection and misses) were similarly used for both remote and recent d′.

2.8. Analysis of vigilance

For the Psychomotor vigilance task (PVT), we computed the mean RT for both sessions (100 trials each). A repeated measure ANOVA was performed with Session (first, second) as within-subjects factor and Sleep (SG, SDG) as between-subjects factor.

2.9. Analysis of sleep parameters

Actigraphy data were analyzed for the two nights preceding Learning 1 and the three nights between Learning 1 and Learning 2. For the deprivation night, the mean motor activity was estimated from 11 P.M. to 7 A.M., corresponding to the period during which participants stayed awake in the lab. Actigraphy data were recorded on 10 participants of the SG and 15 participants of the SDG. We performed two repeated measure ANOVAs on the number of hours of sleep estimated from the actigraphy recordings and the mean motor activity, separately, with Night (each of the 5 nights) as within-subjects factors and Sleep (SG, SDG) as between-subjects factor. Then, planned comparisons tested the group difference for each of the five nights separately.

3. Results

3.1. Sleep and vigilance

Sleep duration estimated from the actigraphy data differed between Sleep groups ($F(1,21) = 13.3$, $p = 0.002$), between nights ($F(4,84) = 30.3$, $p < 0.001$), and the interaction Group by Night was significant ($F(4,84) = 33.9$, $p < 0.001$) (Supplementary Table 1, Supplementary Fig. 1). Post-hoc tests revealed that the number of hours of sleep during the two nights before Learning 1 did not differ between groups ($p > 0.05$), as expected. Groups differed for post-learning night ($p < 0.001$), because SDG did not sleep during that night, as observed behaviorally. SDG participants slept significantly more than SG participants during the first recovery night (second night after Learning 1), suggesting a rebound of sleep after sleep deprivation ($p < 0.001$). The groups did not differ anymore for the third night after Learning 1 ($p = 0.8$), suggesting efficient sleep recovery during the first night after sleep deprivation for SDG participants.

The PVT task, an objective measure of vigilance performed before each session by all participants, showed no effect of Session ($F(1,28) = 3.75$, $p = 0.063$; Bayes factor = 1.28), no effect of Group ($F(1,28) = 3.83$, $p = 0.061$; Bayes factor = 1.21), and no interaction between Session and Group ($F(1,28) = 0.17$, $p = 0.68$; Bayes factor = 0.97; Supplementary Table 1). Altogether, these results suggest that both SG and SDG participants slept equally before both learning sessions and were in the same state of fatigue and vigilance for each session. However, it should be noted that Bayes factor values close to 1 as observed here, mean that the test was not sensitive enough.

3.2. Behavioral results for the training sessions

We calculated the mean time that subjects needed to type the nonwords during Learning 1 and 2. We observed an effect of session because all subjects were more rapid during Learning 2 than Learning 1 (mean time ± SD: SG: Sess1: 2712 ± 717 ms, Sess2: 2558 ± 642 ms, SDG, Sess 1: 2420 ± 587 ms, Sess 2: 2334 ± 635 ms, $F(1,26) = 5.17$, $p = 0.03$), but we observed no significant effect of Group ($F(1,26) = 1.16$, $p = 0.29$) and no interaction between session and Group ($F(1,26) = 0.42$, $p = 0.52$).

Because participants had to rewrite the nonword when it was wrong, we also computed the number of errors made to type the nonwords to ensure equal encoding across groups and sessions. Over the 360 nonwords per session (36 nonwords repeated 10 times each), participants performed only few errors (mean for all sessions: 5.83 ± 2.29). We observed no effect of Group (number of errors ± SD: Sleep group: Sess1: 5.00 ± 2.41, Sess2: 5.08 ± 3.63, Sleep Deprivation group: Sess 1: 7.31 ± 7.73, Sess 2: 5.94 ± 5.17, $F(1,26) = 0.79$, $p = 0.38$), no effect of Session ($F(1,26) = 0.39$, $p = 0.54$), and no interaction between Group and Session ($F(1,26) = 0.49$, $p = 0.49$). These results suggest that both groups performed similarly during learning and differences observed after sleep deprivation cannot be attributed to variations in initial encoding strength.

3.3. Behavioral results for the lexical decision task

Performance on the lexical decision of words and nonwords was high for both groups (words correctly identified as words: SG: 95.84% ± 6.34, SDG: 97.28% ± 3.32, nonwords correctly identified as nonwords: SG: 95.93% ± 5.34, SDG: 97.59% ± 2.54) and showed no significant effect of Condition ($F(1,28) = 0.87$, $p = 0.36$), Sleep ($F(1,28) = 1.36$, $p = 0.25$), and no interaction between Condition and Sleep ($F(1,28) = 0.09$, $p = 0.76$).

We tested whether nonwords from Learning 1 or from Learning 2 would lead to a change in the processing of related real words, as measured by the RTs during the lexical decision task. An ANOVA on words correctly identified as words showed an effect of Condition (remote, recent, new; $F(2,56) = 3.95$, $p = 0.03$), no effect of Sleep (SG, SDG, $F(1,28) = 0.09$, $p = 0.77$), and no interaction between Condition and Sleep ($F(2,56) = 0.63$, $p = 0.54$). These results suggest that being part of the SG or SDG did not impact lexical decisions on words related to nonwords that were recently learned or on new words. Although the main interaction was not significant, RTs for remote words were faster than for recent and new words in the SG ($F(1,28) = 4.91$, $p = 0.035$) but not in the SDG ($F(1,28) = 1.73$, $p = 0.20$) (Fig. 2, Table 1). The observed pattern of results could suggest that sleep might facilitate the lexical access to words visually-close to nonwords learned before sleep deprivation, an effect that was prevented by sleep-deprivation.

3.4. Behavioral results for the memory task

The memory task was designed to test whether the effects observed in the lexical decision task were likely due to changes in the consolidation of the nonwords or whether these two phenomena were mainly independent. We computed a recollection index (R-hits minus R-FA) and a familiarity index (K-hits minus K-FA) as two types of memory performance for each Condition (remote, recent) and each Group (SG, SDG). A 2 × 2 × 2 ANOVA with these measures (see Methods) showed a main effect of type of memory performance ($F(1,28) = 70.8$, $p < 0.001$), due to more R than K responses (see Table 2), and a main effect of Condition ($F(1,28) = 10.4$, $p = 0.003$) because remote items were better remembered than recent ones. There was also a significant interaction between types of memory and Condition ($F(1,28) = 5.7$, $p = 0.024$), and a trend for an interaction between types of memory and Group ($F(1,28) = 3.2$, $p = 0.08$); the triple interaction between all factors was not significant ($F(1,28) = 1.8$, $p = 0.19$). Planned posthoc comparison demonstrated that SG participants has a higher recollection performance for remote nonwords than did SDG participants ($t(28) = 3.92$, $p = 0.057$), while this was not the case for recently learned nonwords ($t(28) = 1.22$, $p = 0.27$, Fig. 3). Moreover, SG participants had better recollection performance for remote than recent nonwords ($t(28) = 8.5$, $p = 0.007$) whereas, for SDG participants, remote nonwords were not discriminated significantly better than recent nonwords ($t(28) = 1.92$, $p = 0.18$). For familiarity performance, we observed no significant effect of Condition ($p = 0.60$), Group ($p = 0.11$), and no interaction between both factors ($p = 0.17$).

We performed a similar analysis on discrimination index (d') values (see Methods). This analysis confirmed a difference between remote and recent conditions ($F(1,28) = 4.87$, $p = 0.036$), because d' was better for remote than recent condition, but no Group difference ($F(1,28) = 2.35$, $p = 0.14$), and no interaction between Group and Condition ($F(1,28) = 0.59$, $p = 0.45$). Yet, replicating the results on recollection performance (see above), the difference of d' between remote and recent condition was significant for SG ($F(1,28) = 4.43$, $p = 0.04$) but not for SDG ($F(1,28) = 1.03$, $p = 0.32$) suggesting that participants of the sleep group had a better memory for the remote than recent items.

3.5. Functional MRI results for the lexical decision task

When comparing words to nonwords (only hits included), we obtained above-threshold activity in a large network including the medial frontal cortex and Wernicke's area showing a relative increase in activity for words than nonwords (Supplementary Fig. 2a and b; Supplementary Table 2). The inverse contrast yielded to large activations in the occipito-temporal and inferior frontal cortex (Supplementary Fig. 2c and d; Supplementary Table 3). These contrasts were computed for both groups taken together in order to visualize the general effect of the lexical task across groups.

To investigate the influence of remote vs. recent nonwords on the processing of related words (differing by a one-letter substitution), and the potential modulation of these effects by post-learning sleep, we contrasted remote vs. recent words (i.e., words related to remotely or recently learned nonwords) for SG vs.

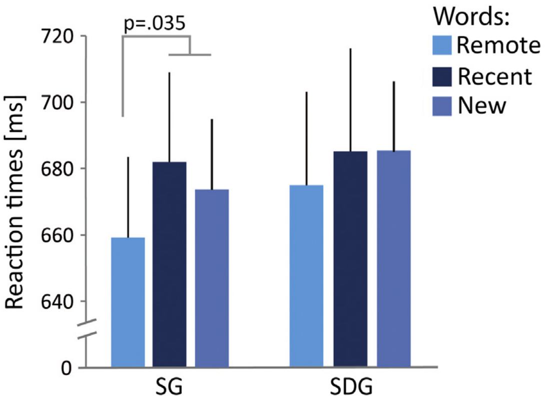

Fig. 2. Mean reaction times data for the lexical decision task. Reaction times for words related to nonwords that were learned during learning phases 1 and 2. The X axis shows the groups, the Y axis the mean reaction times in millisecond. Bars represent words related to nonwords of Learning 1 (Remote, turquoise) and Learning 2 (Recent, dark blue) and new words (New, light blue). Error bars represent one standard error of the mean. SG: sleep group. SDG: sleep deprivation group.

SDG. This contrast revealed a very specific increase of activity in the left hippocampus (MNI xyz −36 −30 −14, Z-score = 3.54, Psvc = 0.031 FWE-corrected; Fig. 4a). The extraction of beta parameters from the left hippocampus clarified the interaction between Sleep and Condition (remote vs recent) showing that this left hippocampus was more activated for remote than recent words in the SG, while the opposite pattern was observed in the SDG (t(29) = 2.87, p = 0.008; Fig. 4b). Remote compared to new words also yielded enhanced activity for the SG compared to the SDG in this same hippocampal region (t(29) = 2.56, p = 0.016) (Fig. 4b). No similar effects could be observed in the contralateral hippocampus, even at a very liberal statistical threshold of $p < 0.05$ (uncorrected). The last contrast that was tested compared Recent to New trials, revealing several subcortical regions such as the basal ganglia (putamen: MNI xyz 16 2 14, Z = 4.71, Psvc = 0.011 FWE-corrected) and lingual gyrus (MNI xyz −14 −66 6, Z = 4.33, Psvc = 0.049 FWE-corrected), but no activations were found in the hippocampi even at very low thresholds ($p < 0.05$ uncorrected). Next, we tested the functional connectivity of this hippocampal region with other brain regions using a PPI and found that functional connectivity with the left ventro-lateral prefrontal cortex (MNI xyz −34 42 −12, Z-score = 3.43; Fig. 4c) was significantly greater for the SG as compared to the SDG, and more for remote than recent items (Fig. 4d).

3.6. Functional MRI results for the memory task

The behavioral results for the lexical decision task (Fig. 2) converged with the fMRI data (greater hippocampal activity for remote vs. recent words discrimination in the SG; Section 3.4 above) to suggest that nonwords learned during the Learning 1 underwent greater consolidation in the SG compared to the SDG. In the memory task, we thus expected that regions known to be involved in memory processes may also show enhanced activity for remote nonwords. By contrasting remote to recent nonwords for the SG vs. SDG, we found a selective increase of activity in the right hippocampus (MNI xyz 30 −10 −20, Z-score = 3.19, P_{SVC} = 0.039 FWE-corrected; Fig. 5a). Beta parameters extracted from this region clarified the observed interaction (Fig. 5b), with increased activity in the right hippocampus for remote compared to recent nonwords in the SG, while the inverse pattern was observed in the SDG ([Remote > Recent] for [SG > SDG]: t(29) = 2.47, p = 0.020) (Fig. 5b). This pattern of activation could not be observed in the contralateral hippocampus, even at a low ($p < 0.05$) threshold. Finally, Recent compared to New for the SG > SDG trials revealed activity in posterior visual cortices (middle occipital gyrus: MNI xyz 22 −80 48, Z = 4.38, Psvc = 0.008 FWE-corrected; precuneus: MNI xyz −30 −92 20, Z = 3.99, Psvc = 0.035 FWE-corrected), but again no activity in the hippocampi or frontal brain areas, even at a very low threshold ($p < 0.05$ uncorrected).

We then investigated functional connectivity with the right hippocampus across the whole brain and found increased connectivity with several frontal regions, including the medial prefrontal (MPFC; MNI xyz 40 42 −6, Z-score = 4.41) and ventro-lateral prefrontal cortex (VLPFC; MNI xyz −6 38 12, Z-score = 3.63) (Fig. 5c). Functional hippocampal-frontal connectivity was enhanced in the SG as compared to the SDG when processing remote vs. recent nonwords (Fig. 5d), highlighting the role of these regions in memory processes.

4. Discussion

In this study, we investigated the impact of sleep on the formation of novel lexical associations. Specifically, we studied how the acquisition of novel nonwords may alter lexical access to visually similar real words, how sleep may affect this process, and how both effects converge to modulate activity and connectivity across memory circuits in the human brain. We show that (1) the consolidation of nonwords is enhanced by a full night of sleep (as measured by recollection performance (R-hits – R-FA) and d′), (2) consolidated nonwords facilitate the access to related real words (as indexed by faster reaction times), and (3) hippocampal and prefrontal regions act in concert to mediate these behavioral effects.

We used an experimental paradigm that allows assessing the influence of adding a new neighbor to a hermit word on the lexical access to the latter. Hermit words have the particularity to be relatively isolated in the mental lexicon (they have no neighbors). They have been shown to be more rapidly detected in a categorization task (in our study, this interaction was however not significant), as compared to a word with many neighbors interacting as competitors in the decision (see Bowers et al., 2005). Such competing effects of neighbors have been exploited as a tool to investigate the potential remodeling of lexical networks, with the following assumption: adding a neighbor (or competitor) to a hermit target word would interfere with the subsequent lexical access to the target word. Moreover, the memory trace of the neighbor needs to be sufficiently robustly incorporated into memory networks to affect the processing of the target word. Several studies provided support to both facilitation and interference hypotheses by showing that the acquisition of new neighbors interferes with categorization and phonological processing of target words, and that this effect emerges after a period of consolidation that includes a post-learning night of sleep (Bowers et al., 2005; Dumay & Gaskell,

Table 1
Reaction times for the lexical decision task (mean of all subjects ± SEM (N = 30), median for each subject, removing percentile 7.5–92.5 ms).

	Remote words	Recent words	New words	Nonwords
Sleep	659.2 ± 22.3	681.9 ± 28.9	671.6 ± 23.2	844.5 ± 33.6
Sleep deprivation	675.1 ± 28.24	685.3 ± 29.4	685.6 ± 26.5	918.9 ± 29.4

Table 2
Memory performance for the memory task for all items (percentage ± SEM; N = 30).

	Sleep	Sleep deprivation
Remember response		
Remote nonwords (R-hits)	78.9 ± 5.6	63.1 ± 5.9
Recent nonwords (R-hits)	68.3 ± 6.3	58.0 ± 5.4
New nonwords (R-FA)	3.8 ± 1.3	2.9 ± 1.5
New nonword related to remote nonword (FA)	15.4 ± 2.7	10.8 ± 2.0
New nonword related to recent nonword (FA)	10.9 ± 2.1	10.4 ± 2.2
Familiar response		
Remote nonwords (K-hits)	11.1 ± 4.8	22.0 ± 4.9
Recent nonwords (K-hits)	14.1 ± 4.4	20.6 ± 4.0
New nonwords (K-FA)	12.9 ± 4.2	9.2 ± 2.1
New nonword related to remote nonword (FA)	18.6 ± 4.9	14.1 ± 2.7
New nonword related to recent nonword (FA)	14.8 ± 5.0	9.7 ± 2.8
New response		
Remote nonwords (Miss)	5.2 ± 1.3	7.7 ± 2.1
Recent nonwords (Miss)	11.9 ± 2.9	9.7 ± 2.1
New nonwords (CR)	79.5 ± 5.6	81.2 ± 3.7
New nonword related to remote nonword (CR)	60.1 ± 6.7	61.3 ± 4.6
New nonword related to recent nonword (CR)	68.6 ± 6.7	68.1 ± 5.1
Discrimination index		
D′ for remote nonwords	3.7 ± 0.2	4.2 ± 0.3
D′ for recent nonwords	3.2 ± 0.3	4.0 ± 0.4
Recollection performance		
Remote nonwords	75.1 ± 5.3	60.2 ± 5.3
Recent nonwords	64.5 ± 6.5	55.2 ± 5.1
Familiarity performance		
Remote nonwords	−1.7 ± 6.9	12.8 ± 5.0
Recent nonwords	1.2 ± 5.3	11.5 ± 3.9

Note: Percentage values do not include omissions of response, which are not reported in the table.

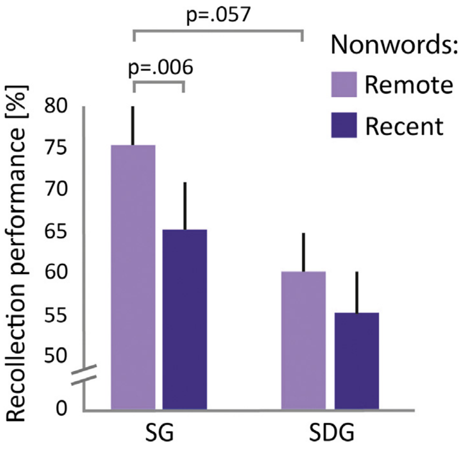

Fig. 3. Recollection performance for "Remember" responses during the memory task. Recollection performance calculated as percentage of R-hits minus percentage of R-false alarms for the SG and SDG group. Nonwords from Learning 1 (remote) are shown in pale purple, and from Learning 2 (recent) in medium purple. Error bars represent one standard error of the mean. SG: sleep group. SDG: sleep deprivation group.

2007; Gaskell & Dumay, 2003; Tamminen et al., 2010). There are several key differences between those studies and our study: (1) we tested the impact of visually-similar neighbors (vs. similar-sounding spoken words (Dumay & Gaskell, 2007; Tamminen et al., 2010)); (2) we assessed lexical facilitation using a lexical decision task (vs. a semantic categorization task (Bowers et al., 2005)), and (3) we tested for the first time the impact of a full night of sleep deprivation (versus no direct manipulation of sleep (Bowers et al., 2005; Gaskell & Dumay, 2003)) as opposed to a comparison between intervals with nighttime sleep and daytime wakefulness (Dumay & Gaskell, 2007; Tamminen et al., 2010). Unlike in our study, these previous studies found inhibitory effects of new nonword neighbors on the processing of related words after a period of consolidation. Yet, even if this difference could be attributed to the process targeted during testing or to lower-level perceptual priming processes, these findings were interpreted as consistent with a more effective lexicalization for the nonwords after a delay including a night of sleep, much like we propose here.

While our results are in apparent contradiction with competition models, which state that word recognition involves a competition between similar lexical items (e.g., Luce & Pisoni, 1998; Marslen-Wilson, 1987; McClelland & Elman, 1986), models from memory research proposed that encoding stimuli with shared features may trigger an integrative (or generalization) process that would then facilitate the recollection of such associated stimuli, a mechanism that relies on the hippocampus (e.g., Shohamy & Wagner, 2008). Importantly, previous studies have demonstrated that sleep contributes to memory integration effects. For example, Ellenbogen, Hu, Payne, Titone, and Walker (2007) demonstrated that a period of sleep helps creating inferences between related items. Using semantically related words, it has also been demonstrated that both accurate and false recollections may be enhanced after sleep, as compared to sleep deprivation (Darsaud, Dehon, et al., 2011) or as compared to an equivalent period of wakefulness (Payne et al., 2009). The hippocampus contributed to the recollection of both correct and false memories, suggesting that sleep favors the system-level reorganization of all semantically-related information (Darsaud, Dehon, et al., 2011). Moreover, sleep was found to interact with reward to selectively enhance the long-term integration of associative memories, which were also remembered with higher subjective confidence (Igloi, Gaggioni, Sterpenich, & Schwartz, 2015). Other capacities that rely on the formation of new links across items or concepts, such as finding a hidden solution to a problem ("insight"), are favored by a period of sleep (as compared to sleep deprivation (Darsaud, Wagner, et al., 2011; Wagner, Gais, Haider, Verleger, & Born, 2004)). Hence, the notion that sleep promotes the emergence and consolidation of new associations across related items fits well with the results of the present study. Indeed, we show that lexical access to a target word is improved by the acquisition of an orthographically-similar nonword, which would lower the activation threshold of the target word through associative or integrative processes. We also demonstrate here that the consolidation of the nonword representation is strengthened by a period of sleep following the learning phase (i.e., increased recollection performance and better discrimination index, d′, for remote nonwords). These findings suggest that facilitated lexical access requires a stable representation of related items. Because the main sleep by condition interaction was not significant, these results should be taken with caution. It is however still fair to observe that the present findings are in accordance with an integrative account of sleep-related memory consolidation for associative or partially overlapping information, while they specifically also reveal the impact of new learning on existing knowledge. Interestingly, the pattern of behavioral results across the lexical decision and memory tasks emphasize an advantage for remote material for the SG as compared to the SDG. Note that all these observations are also consistent with the theory proposed by Lewis and Durrant (2011), according to which the replay of related memories during sleep selectively strengthens shared elements, and thus actively contributes to schema formation and the addition of new knowledge to existing schemata. We can speculate that in our experiment, sleep fostered integrative processes

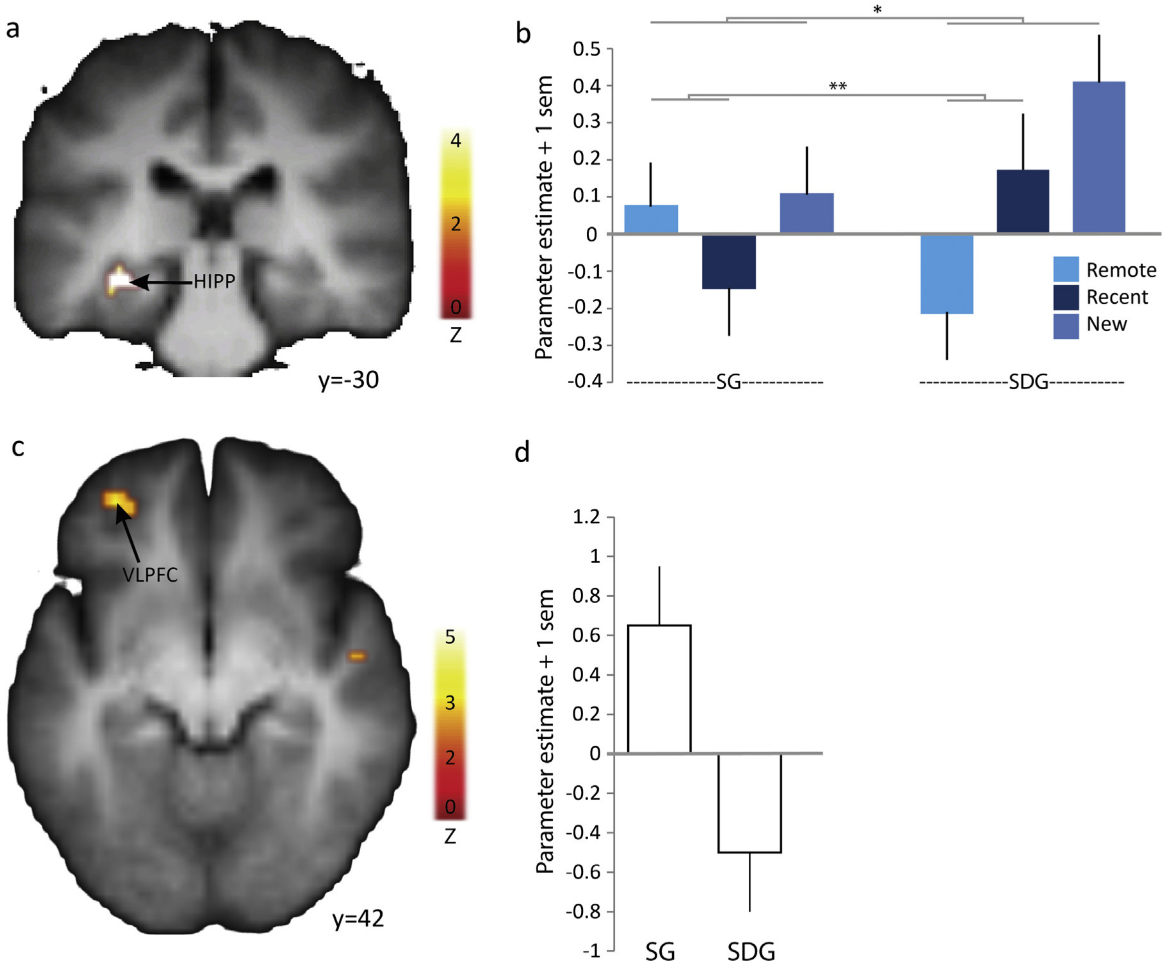

Fig. 4. Neural activity and psychophysiological interactions for remote compared to recent words, for sleep compared to sleep deprivation group in the lexical decision task. (a) Increased activity in the left hippocampus (MNI xyz: −36 −30 −14) for remote compared to recent words and for the sleep compared to the sleep deprivation group. (b) Percentage of signal change in the left hippocampus (MNI xyz: −36 −30 −14) for all conditions (Remote: turquoise; Recent: dark blue; New: medium blue) and both groups. (c) Psychophysiological interactions taking the left hippocampus (MNI xyz: −36 −30 −14) as seed, showing functional connectivity with the left ventro-lateral prefrontal cortex (MNI xyz: −34 46 −12). (d) Percentage of signal change in the left ventro-lateral prefrontal cortex (MNI xyz: −34 46 −12) showing higher activity for sleep as compared to sleep deprived participants. SG: sleep group; SDG: sleep deprivation group. HIPP: hippocampus; VLPFC: ventro-lateral prefrontal cortex. Error bars signal 1 standard error of the mean. Activations are displayed on the mean structural image of our 30 participants (15 of the sleep, 15 of the sleep deprivation group). $^{*}p < 0.05$. $^{**}p < 0.01$.

through the offline coactivation of the newly learned nonword and the related pre-existing word, which would give the associate (e.g., the pre-existing word in our experiment) a more accessible status in memory. Indirect support for this suggestion comes from a previous report showing a correlation between the quantity of spindles (which promote memory replay during sleep) and the degree of lexicalization for spoken verbal material (Tamminen et al., 2010). However, even though a facilitation effect of learning was observed significantly in the SG and not in the SDG, the pattern of reaction times was similar for both groups. One possible interpretation could be that sleep deprivation postpones, rather than fully suppresses, the incubation-like period for lexicalization processes taking place preferentially during sleep. To address this issue, future studies may for example test participants at more than one time-point, from immediately after sleep deprivation (however with the potential confound of reduced vigilance and attention) to several days after.

The hippocampus has been designated to be a good candidate for the gradual encoding of new information without deteriorating neocortical networks of representations (McClelland, McNaughton, & O'Reilly, 1995). This hypothesis fits well with the activation of the dorsal hippocampus that we observed for the remote condition during the lexical decision task for the participants who were allowed to sleep, and with enhanced dorsal hippocampal-prefrontal functional connectivity. Moreover, sleep is known to favor the transfer of information from the hippocampus to the neocortex, predominantly during slow wave sleep (Diekelmann et al., 2011). Further supporting this notion, during the memory task, we observed that the dorsal hippocampus was more active for recognized remote nonwords than recognized recent nonwords, but only for participants who were allowed to sleep the night following the first learning session. Simultaneously, the hippocampus was found to modulate the activity of the MPFC and VLPFC for the sleep group. It is interesting to note that the hippocampal activity was not increased when processing words related to recently learned nonwords (but instead regions involved in reading verbal material, such as the visual cortex and putamen; (Oberhuber et al., 2013)), nor during the recollection of recent nonwords. This pattern of results confirms that differences in hippocampus activity are selectively observed for remote stimuli. Taken together, our data support that sleep strengthens the interplay between the hippocampus and cortical areas (mainly the prefrontal cortex), as already observed for word pairs learning (Gais, Lucas, & Born, 2006) and picture learning (Sterpenich et al., 2009; Takashima

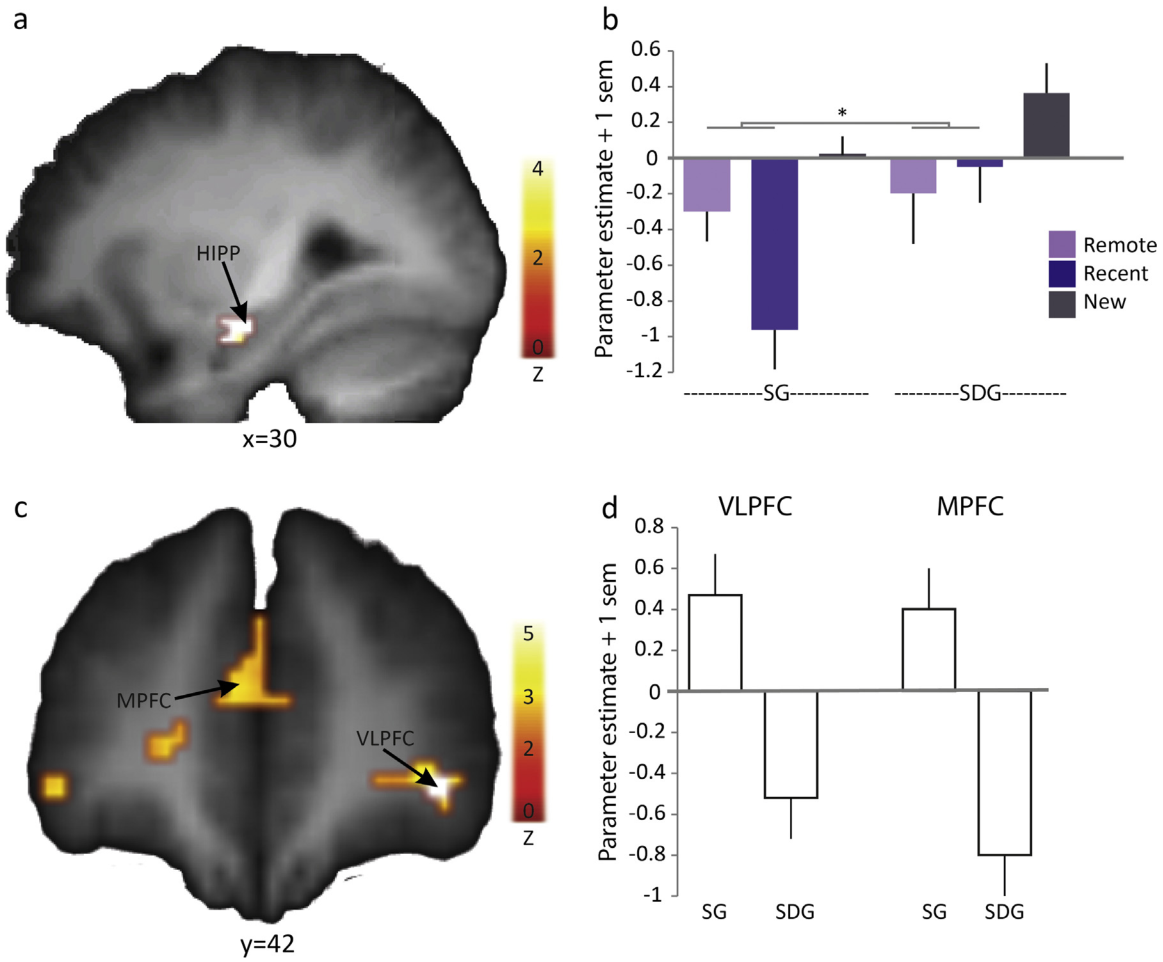

Fig. 5. Psychophysiological interactions and neural activity for remote compared to recent nonwords, for sleep compared to sleep deprivation group in the memory task. (a) Increased activity in the right hippocampus (MNI xyz: 30 −10 −20) for remote compared to recent nonwords and for sleep compared to sleep deprivation group. (b) Percentage of signal change in the right hippocampus (MNI xyz: 36 −10 −20) for all conditions (Remote: pale purple; Recent: medium purple; New: dark purple) and both groups. (c) Psychophysiological interactions taking the right hippocampus (MNI xyz: 30 −10 −20) as seed, showing functional connectivity with the left ventro-lateral prefrontal cortex (MNI xyz: 40 42 −6) and the medial prefrontal cortex (MNI xyz: −6 38 12). (d) Percentage of signal change in the left ventro-lateral prefrontal cortex (MNI xyz: 40 42 −6) and the medial prefrontal cortex (MNI xyz: −6 38 12) showing higher activity for sleep as compared to sleep deprived participants. SG: sleep group; SDG: sleep deprivation group. HIPP: hippocampus; MPFC: medial prefrontal cortex; VLPFC: ventro-lateral prefrontal cortex. Error bars signal 1 standard error of the mean. Activations are displayed on the mean structural image of our 30 participants (15 of the sleep, 15 of the sleep deprivation group). $^{*}p < 0.05$.

et al., 2006). In these studies, the prefrontal cortex was also identified as a key structure for long-term storage.

5. Conclusion

Our findings suggest that sleep may potentially favor a remodeling of lexical representations after the learning of novel words. Here we directly assessed the role of sleep by using a sleep deprivation protocol. Our results first confirmed that sleep deprivation interfered with the consolidation of recently encoded nonwords. Second, we showed that sleep facilitated (while sleep deprivation prevented) the identification of target words orthographically related to consolidated nonwords. This pattern of results suggests that sleep fosters memory integration processes, whereby related items become more tightly connected, so that the activation of one item makes related items more easily accessible in memory. Third, and consistent with recent theoretical accounts of learning overlapping information (integrative encoding (Shohamy & Wagner, 2008)) or cognitive schemata (Lewis & Durrant, 2011), our fMRI data demonstrate that the hippocampus is a major site for such memory integration processes, also recruiting strong functional connections with the prefrontal cortex. Thus, beyond its active role in the consolidation of memory for specific items or events, sleep is also involved in the emergence of novel associations. By promoting an adaptive local remodeling of memory representations, sleep may hence provide a favorable condition for the modular architecture of brain functions to be expressed and reinforced.

Acknowledgement

We thanks Richard Gaskell for his helpful comments during the elaboration of the study. This work was supported by the Swiss National Science Foundation (grants: 310000-114008 and 320030-159862) and by the National Center of Competence in Research (NCCR) Affective Sciences financed by the Swiss National Science Foundation (No 51NF40-104897).

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bandl.2016.12.007.

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